Editors
Fatma Nur TAKI
Sabri KOÇER
Resul BÜTÜNER

NEW GENERATION TECHNOLOGIES AND SUSTAINABILITY IN HEALTH :

CURRENT STUDIES

ISRES Publishing

Editors
Fatma Nur TAKI
Sabri KOÇER
Resul BÜTÜNER

NEW GENERATION TECHNOLOGIES AND SUSTAINABILITY IN HEALTH :

CURRENT STUDIES

ISRES Publishing

New Generation Technologies and Sustainability in Health:Current Studies

Edited by

Assist. Prof. Dr. Fatma Nur TAKI
Necmettin Erbakan University,
Seydişehir Kamil Akkanat Faculty of Health Sciences
Department of Physiotherapy And Rehabilitation, Konya, Türkiye
Email: ftaki@erbakan.edu.tr

Prof. Dr. Sabri KOÇER
Necmettin Erbakan University,
Faculty of Engineering
Department of Computer Engineering, Konya, Türkiye
Email : skocer@erbakan.edu.tr

Engineer, MSc. Resul BÜTÜNER
Ministry of National Education,
Directorate General for Innovation and Educational Technologies, Ankara, Türkiye
Email : resul.butuner@eba.gov.tr

Language Editors
Lecturer Ceren DOĞAN
School of Foreign Languages, Necmettin Erbakan University, Konya, Türkiye
Email : cerendogan@erbakan.edu.tr

ISRES Publishing

New Generation Technologies and Sustainability in Health:Current Studies

Editors

Fatma Nur TAKI

Sabri KOÇER

Resul BÜTÜNER

This book was typeset in 10/12 pt. Times New Roman, Italic, Bold and Bold Italic.

New Generation Technologies and Sustainability in Health:Current Studies

Published by ISRES Publishing, International Society for Research in Education and Science (ISRES). Includes bibliographical references and index.

ISBN

978-625-6959-39-2

Date of Issue

December, 2024

Contact

Askan Mah. Akinbey Sok. No: 5/A Meram/Konya/Türkiye
isresoffice@gmail.com
www.isres.org

Preface

The emergence of new generation technologies heralds a transformative epoch in the domain of healthcare. These advancements, encompassing artificial intelligence, wearable health devices, and other innovative solutions, not only enhance medical capabilities but also promote sustainability within global health systems. Confronted with pressing challenges such as aging populations, escalating healthcare expenditures, and the imperative to address environmental sustainability, the integration of advanced technologies into healthcare practices has transitioned from being a mere option to an essential requirement.

New Generation Technologies and Sustainability in Health : Current Studies is published from the selected papers invited by the editors.All submissions are reviewed by at least two international reviewers. The purpose of the book is to provide the readers with the opportunity of a scholarly refereed publication in the field of New Generation Technologies and Sustainability In Health.

This edition includes sections from the New Generation Technologies and Sustainability In Health of used in today's technology. It synthesizes a range of perspectives, presenting pioneering research, forward-thinking applications, and actionable solutions aimed at fostering a healthcare landscape that is more efficient, equitable, and environmentally sustainable.

We hope that this volume serves as a valuable resource for academics, practitioners, and students alike, inspiring further exploration and fostering interdisciplinary collaboration in medicine and healthcare innovation.

New Generation Technologies and Sustainability in Health : Current Studies is published by ISRES Publishing.

We wish you a pleasant reading.

December, 2024

Assist. Prof. Dr. Fatma Nur TAKI

Necmettin Erbakan University

Prof. Dr. Sabri Sabri KOÇER

Necmettin Erbakan University

Engineer, MSc. Resul BÜTÜNER

Ministry of National Education

Table of Contents

Citation

Takı, F. N., Koçer, S. & Bütüner, R. (Eds.). (2024). *New Generation Technologies and Sustainability in Health : Current Studies.* ISRES Publishing.

Managing Editors

Fatma Nur TAKI, PhD, is an Assistant Professor at Necmettin Erbakan University in Konya,Türkiye. She holds a PhD in medical physiology from Necmettin Erbakan University. Her main areas of interest are muscle contraction, cell signaling, physiotherapy and rehabilitation.
E-mail: ftaki@erbakan.edu.tr, **ORCID:** 0000-0003-1548-7213

Sabri KOÇER, PhD, graduated from the Department of Electrical Engineering of Selcuk University. He completed his master's and doctoral degrees at Gazi University. He is currently working at the Computer Engineering department of Necmettin Erbakan University, Faculty of Engineering. he has studies in the fields of electronics, computers, telecommunications, signal processing and biomedicine.
Email: skocer@erbakan.edu.tr, **ORCID:** 0000-0002-4849-747X

Resul BÜTÜNER is a Computer Teacher at the Ministry of National Education in Ankara, Türkiye. He has a master's degree in Computer Engineering from Necmettin Erbakan University. His main areas of interest are artificial intelligence, robotic coding, data mining, and augmented reality applications. He is an instructor in the field of Robotic coding within TUBITAK. He continues to write a book in the field of robotic coding at the Ministry of National Education. He worked as a coordinator in projects related to student education.
E-mail: resul.butuner@eba.gov.tr , **ORCID:** 0000-0002-9778-2349

In This Book

Chapter 1

The term "robot nurse" refers to robotic systems that aim to improve the quality of patient care, reduce the workload of nurses, and reduce work risks and errors. Robot nurses that move in a straight line, have wheels, are simple in appearance and have limited capabilities are being replaced by impressive machines with human-like shapes and features, and with capabilities such as perception, learning, analysis and solution generation using artificial intelligence algorithms. This section of the book defines robot nurses and discusses their possible functions for the present and future. The rest of the section discusses the advantages and disadvantages of robot nurses, gives examples of robot nurses, and lists current issues being discussed on the subject. In spite of the fact that the problem of labor shortage in the health sector has been persistent from the past to the present, the risks and intensity of work in the sector are reflected in the performance of health professionals; revolutionary technological developments make it impossible for members of the nursing profession to remain indifferent to the subject of robotic nurses. Faced with this reality, we hope that the section you are about to read on robot nurses will support your specific level of knowledge.

Chapter 2

This chapter discusses the development of a model for early detection of Parkinson's disease using artificial intelligence and machine learning techniques. The model, developed using the XGBoost algorithm, achieved an accuracy rate of 94.87%. The chapter highlights how the model performs well on new datasets, maintaining high accuracy. The potential applications of this technology in the healthcare sector and the importance of early diagnosis are emphasized, demonstrating its critical role in improving patient outcomes and enhancing the effectiveness of treatment strategies.

Chapter 3

Regenerative medicine, particularly stem cell therapy, represents a revolutionary approach in treating previously incurable diseases. This review examines the current state of stem cell research, including embryonic, adult, and induced pluripotent stem cells, and their therapeutic applications in neurological, cardiovascular, and hepatic conditions. While clinical applications show promising results in tissue regeneration and organ repair, significant challenges remain, including cell purity maintenance, immunological rejection, and ethical considerations. Despite these obstacles, stem cell therapy continues to advance, offering hope for sustainable therapeutic solutions. This review highlights both the potential and limitations of stem cell applications in modern medicine, emphasizing the need for continued research and technological development for optimal clinical outcomes.

Chapter 4

Developmental Dysplasia of the Hip (DDH) is a prevalent pediatric condition requiring early detection to prevent severe long-term consequences. This review explores the application of machine learning (ML) technologies to improve the accuracy and reliability of DDH diagnostics, which traditionally rely on subjective methods. Synthesizing findings from 45 studies published between 2016 and 2024, the review highlights the methodologies, outcomes, and clinical implications of ML-driven solutions, including deep learning models, automated imaging systems, and hybrid frameworks. These innovations demonstrate significant potential in reducing diagnostic variability, enhancing early detection, and improving treatment outcomes for infants. However, challenges such as dataset diversity and clinical validation persist. This comprehensive overview emphasizes the transformative impact of ML on pediatric orthopedics and outlines future research directions for broader implementation.

Chapter 5

This study aims to evaluate the performance of machine learning models in breast cancer diagnosis. The dataset includes a dataset of clinical characteristics related to breast cancer diagnosis. The models used in the study include Random Forest, Decision Tree, Naive Bayes, Gradient Boosting, AdaBoost and Bagging. First of all, the data set was converted to a suitable format for machine learning models and divided into training-test data sets. Then, different models were trained and evaluated on the test dataset. Accuracy values and confusion matrices were calculated and visualized for each model. Performance metrics include accuracy, precision, recall, F1 score, and ROC AUC. These metrics were used to evaluate the classification abilities of the models. The ROC curve of each model was also plotted and the ROC AUC values were reported. The results show that different models can be used successfully in breast cancer diagnosis. However, it has been observed that models such as Gradient Boosting and AdaBoost exhibit higher performance than others. These findings suggest that machine learning models can be used effectively for breast cancer diagnosis and may be helpful in clinical applications.

Chapter 6

This section reviews research on the use of Platelet Rich Plasma (PRP) in reproductive medicine, focusing on its potential to improve endometrial thickness, implantation rates and ovarian function in women with infertility. Increasing Endometrial Thickness: PRP shows potential to increase endometrial thickness in women with thin endometrium (<7 mm). PRP treatment stimulates the proliferation and regeneration of endometrial cells through growth factors and cytokines, leading to a thicker and more receptive endometrium. Improvement of Ovarian Function: PRP can rejuvenate and improve ovarian function, especially for women with low ovarian reserve, such as those with primary ovarian insufficiency (POI) or poor ovarian response (POR). Improving Implantation Success: PRP may increase the likelihood of embryo attachment to the uterus by increasing endometrial receptivity. This is particularly advantageous for women who experience recurrent implantation failure (RIF), as improved receptivity can help overcome this significant obstacle. Gene Expression and PRP: PRP may influence endometrial receptivity by regulating the expression of implantation-related genes such as COX-2, TP53, ER-α and ER-β, and progesterone receptors. Conclusion: PRP therapy shows promise in improving key aspects of reproductive health, including endometrial thickness, ovarian function and implantation success. Continued research is needed to optimise treatment protocols and develop personalised approaches, to ensure the effective and safe use of PRP in improving fertility and reproductive outcomes.

Chapter 7

Data science provides a powerful analysis tool for identifying threat patterns and predicting potential attacks based on historical data of cybersecurity incidents. This section will focus on how data science approaches are integrated into critical security structures such as intrusion detection systems (IDS) and intrusion prevention systems (IPS) used to detect and prevent cyber threats. In this context, important techniques such as machine learning, big data analytics, and anomaly detection methods will be detailed. The aim of the section is to understand the critical role of data science techniques in cybersecurity and to demonstrate how these techniques are applied in practice. At the same time, it is aimed to inform readers about the current state of cybersecurity analytics and to provide a glimpse into where this field may evolve in the future.

Chapter 8

In the 21st century, education models have evolved into a quite different dimension in accordance with the digital age. This dimension is a dimension that reveals this new perspective on education and brings lifelong sustainability with a wide variety of information from different channels. With this approach in education, the concept of learning has replaced the classical concept of teaching and the student has been put at the center of education.

In this context, education programs have evolved from the traditional behaviorist approach to the learner-centered constructivist approach. In constructivism, accessing knowledge is a process that is at the center of the individual and regulated by his/her experiences. In this context, the content of learner-centered education programs has progressed towards the direction where traditional, classical narratives are abandoned, the learner is more active, problem solving skills are developed and group work is effective. In the learner-centered education approach, the learning process is considered as a complex process. However, it is thought that informing trainers about this system will facilitate the process. In this process, the trainer should prepare the training program with the role of facilitator and guide and draw the framework in this direction. In this constructivist model, the trainer is expected to be open to innovations, to have a digital and technical infrastructure and to be able to apply them . These changes in education have revealed the importance of training of trainers.

In conclusion the importance of learner-centered education models in sustainable medical education and the superiority of their advantages over their disadvantages are obvious. It is very important for physician candidates to be well-equipped physicians. We believe that with this enriched medical education curriculum, physician candidates will be trained as better equipped and more self-confident physicians.

Chapter 9

Traditional and Complementary Medicine practices are becoming more widespread in Türkiye every passing day. This situation has resulted in regulations on many issues such as which professions can perform these practices, the minimum education standards that people must have, and the indication areas of the practices. Although the Ministry of Health does its part, the Council of Higher Education and Universities don’t take sufficient action, which causes the academic staff not to be formed. Detection, reasons, discussion and solution of the problems that arise in practice will ensure that traditional and complementary medicine is established on healthier scientific foundations.

Chapter 10

Cancer treatment should be multifaceted and include etiologic factors, tissue oxygenation disorders, ascites, toxicity and complementary methods that should be used to eliminate them. Only in this way, with a multidisciplinary approach, can we come up with the right approach to cancer, which we call the king of diseases.

Phytotherapeutic plants have anti-inflammatory effects and are used for anti-inflammatory purposes in cancer treatment. Ozone increases chemo-radiosensitivity by increasing oxygenation. Thus, it increases the effectiveness of chemoradiotherapy and reduces side effects such as fibrosis formation and polyneuropathy in the long term.

With this book chapter, we aim to position phytotherapy and ozone therapy, which are traditional treatment methods applied in addition to conventional treatments of cancer, one of today's biggest health problems and one of the most common causes of death, to eliminate the side effects of toxic chemotherapy drugs, to solve personal problems, to ensure the sustainability of treatment. For this purpose, we want to develop a new perspective on cancer treatment by increasing the inclusion of traditional treatment methods in the treatment algorithm, which are not emphasized in conventional medical treatments, but which patients and their relatives learn by researching the treatments of previously treated cancer patients.

Chapter 11

Acupuncture, a traditional treatment method that has been known since ancient times, continues to be widely used today. This treatment, which has been used since ancient times, is performed by needling specific acupuncture points using special and sterile disposable needles. And bioresonance is a complementary therapy method to classical medicine. It is based on the principles of Chinese traditional medicine, quantum medicine and new discoveries of biotechniques. This chapter provides a comprehensive overview of the anatomical locations of key acupuncture points, including back-shu, front-mu, he-sea, yuan-source, tonification, and sedation points. Additionally, it introduces bioresonance therapy, highlighting its principles and potential applications in clinical practice.

Chapter 12

Traditional and Complementary Medicine practices are becoming more widespread in Türkiye every passing day. This situation has resulted in regulations on many issues such as which professions can perform these practices, the minimum education standards that people must have, and the indication areas of the practices. Although the Ministry of Health does its part, the Council of Higher Education and Universities does not take sufficient action, which causes the academic staff not to be formed. Detection, reasons, discussion and solution of the problems that arise in practice will ensure that traditional and complementary medicine is established on healthier scientific foundations.

Chapter 13

Acupuncture is a method of needling and can be used to treat many diseases such as chronic pain. Needling the acupuncture point activates the transmission from the brain to the spinal nucleus, thalamus, sensory cortex, periacuaductal neurons and activates the pain control system. Acupuncture stimulation stimulates endorphinergic and encephalinergic neurons, which are associated with the cortex and hypothalamus. Through synaptic connections, serotonergic neurons in the bulb are activated. It should be recognized that the basic law of homeopathy, the law of similimum, means that the frequencies of the homeopathic remedies match the frequencies of the patient. The disease-causing photons are canceled or missing photons are added by the resonance effect until the normal frequency pattern is restored. The aim of this book chapter is to describe the combined use of acupuncture and homeopathy in chronic neuropathic pain.

Chapter 14

This chapter delves into the application of artificial intelligence techniques within the domain of medical image processing. As a fundamental pillar of modern healthcare, medical imaging serves as an essential tool in critical areas such as early disease detection, treatment planning, and patient monitoring. By integrating artificial intelligence and deep learning, these processes can achieve greater precision and efficiency, ultimately enhancing the quality of healthcare services. This section explores the impact of artificial intelligence and deep learning methods on medical image processing, highlighting current applications and future directions. The chapter aims to provide valuable insights and practical examples for academics, researchers, and healthcare professionals, enabling them to better understand advancements and practices in this innovative field.

Contributors

Assist. Prof. Dr. Fatma Nur TAKI
Necmettin Erbakan University,
Seydişehir Kamil Akkanat Faculty of Health Sciences
Department of Physiotherapy And Rehabilitation, Konya, Türkiye

Research Assist. Fatma Nur UZUN
Kütahya Health Sciences University,
Faculty of Engineering and Natural Sciences,
Department of Computer Engineering Kütahya, Türkiye

Lecturer İbrahim YILDIZ
Necmettin Erbakan University,
Health Services Vocational School, Konya, Türkiye

Assist. Prof. Dr. Elif GÜLBAHÇE MUTLU
KTO Karatay University,
Faculty of Medicine,
Department of Medical Biology, Konya, Türkiye

Assist. Prof. Dr. Hatice Nur ŞEFLEK
KTO Karatay University,
Faculty of Medicine,
Department of Medical Histology and Embryology, Konya, Türkiye

Kartal DERİN
SmartPro Technology, AI Department, İstanbul, Türkiye

Assist. Prof. Hayriye Dilek AKDOĞAN
İzmir Bakırçay University, Faculty of Medicine,
Department of Medical Education, İzmir, Türkiye

Assist. Prof. Dr. Hayriye ALP
Necmettin Erbakan University,
Nezehat Keleşoğlu Faculty Of Health Sciences,
Department Of Physiotherapy And Rehabilitation, Konya, Türkiye

Şerife AYDIN
Necmettin Erbakan University,
Institute of Health Sciences,
Department of Physiotherapy And Rehabilitation Thesis Master's Student, Konya, Türkiye

Dr. Ayşe Gamze ÖZCAN
Selçuk University,
Faculty of Medicine, Department of Anatomy, Konya, Türkiye

Specialist Doctor İsmail ESEOĞLU
Dokuz Eylül University,
Department Of Medical Services And Techniques Anesthesia Program, İzmir, Türkiye

Assist. Prof. Dr. İbrahim ÇETİN
Necmettin Erbakan University,
Seydişehir Kamil Akkanat Faculty of Health Sciences
Department of Surgical Nursing, Konya, Türkiye

Dr. Eralp KUYUCU
Söke Fehime Faik Kocagöz State Hospital,
GETAT Units, Aydın, Türkiye

Physiotherapist Osman Doğukan KÜREKCİ
Necmettin Erbakan University,
Institute of Health Sciences,
Department of Physiotherapy And Rehabilitation Master's Degree Student , Konya, Türkiye

Dr. Hasan EGE
Istanbul Arel University,
Department of Physiology, Faculty of Medicine, Istanbul, Turkiye

Research Assistant Dr. Oğuzhan EKİCİ
Istanbul University-Cerrahpaşa,
Department of Physiology, Cerrahpaşa Medical Faculty, Istanbul, Turkiye

Lec. Dr. Musa ÇANKAYA
Necmettin Erbakan University
Seydişehir Vocational School of Health Services,
Department of Therapy and Rehabilitation, Konya, Turkiye

Physiotherapist Pariya POURİYAMANESH
Necmettin Erbakan University,
Institute of Health Sciences,
Department of Physiotherapy And Rehabilitation Master's Degree Student, Konya, Türkiye

Mevlüt Can ADIYAMAN
KTO Karatay University,
Department of Computer Engineering. Konya, Türkiye.

Şeyma Nefise SATICI
Boğaziçi University,
Master's Degree Student,
Institute of Data Science and Artificial Intelligence,

Muhammed Furkan DARILMAZ, MD.
Aksaray Training and Research Hospital,
Orthopedic and traumatology surgeon

Asst. Prof. Hüseyin Oktay ALTUN
Boğaziçi University,
Institute of Data Science and Artificial Intelligence

Yunus Emre GÖKTEPE
Necmettin Erbakan University,
Faculty of Seydisehir Ahmet Cengiz Engineering,
Department of Computer Engineering

Assist. Prof. Dr. Yusuf UZUN
Necmettin Erbakan University,
Faculty of Seydisehir Ahmet Cengiz Engineering,
Department of Computer Engineering

The Robot Nurses

İbrahim ÇETİN

Necmettin Erbakan University

To Cite This Chapter

Çetin, İ. (2024). The Robot Nurses. In F. Nur Takı, S. Koçer, & R. Bütüner (Eds.), *New Generation Technologies and Sustainability in Health:Current Studies* (pp. 1-15). ISRES Publishing.

Introduction

Robotic technology continues to develop over time. Humanoid or various forms of robots are increasingly being used in many sectors, including construction, agriculture, automotive, military and healthcare. Although human-robot interaction is a relatively new field of robotic technology, it is developing as a versatile and comprehensive research and design activity. This interaction has accelerated the entry of robotic technology into the health sector (Sheridan, 2016). While technological breakthroughs continue to increase, the developments put forward also affect the structure and organization of the health sector. The use of robots with artificial intelligence in health services is a concrete indicator of the potential of technological breakthroughs in the health sector. In the health sector, where tolerance to errors is extremely limited, the ability of robots to perform various tasks and procedures efficiently and safely can be described as a robotic revolution in service delivery. This revolution experienced today is a first and has no previous example. It was impossible for technological developments not to be reflected in the field of nursing, which is a part of the health sector, and the expected happened. Various nursing practices began to be transferred to robot nurses with the technological revolution. The development of more complex artificial intelligence algorithms has made it possible for machines to make critical decisions and coordinate patient care in healthcare today. Technological developments that are increasingly felt have brought human nurses and their practices into question. While the nursing discipline examines the professional integration of technology on the one hand, it has also begun to work to answer the question of what human nurses can do in the future to stay current in healthcare (Pepito & Locsin, 2019).

Functions and Advantages of Robot Nurses

Robot nurses are assistive devices equipped with artificial intelligence and robotic technologies that can perform various tasks performed by human nurses. Robot nurses help the people they provide care to, real nurses, and other healthcare team members (Ohneberg et al., 2023; Robert, 2019; Huang et al., 2011). Robot nurses provide various advantages for both patients and nurses and support care. Therefore, although there are some hesitations, robot nurses and robotic nursing seem to be accepted for both sides of nursing care (patient and nurse). Nurses do not think that they will lose their jobs because of their robot colleagues. On the contrary, they have the opinion that they can benefit from them for boring routines and laborious physical tasks. At this point, before moving on to the developments in robot nurses, let's focus on the concept of robotic nursing and the functions of robot nurses. Robotic nursing is a programmable, autonomous, mobile robot design that aims to assist nurses in hospitals and other healthcare facilities in performing their duties. Essentially, they are not designed with the purpose of replacing human nurses (Kumar, 2018). A study supporting the definition of robotic nursing in this study was published in 2023. The research, which took the form of a systematic literature review, identified 39 different robotic systems to assist with care. 55% of the identified systems are in the testing phase and 29% are in the development phase, and more than half are designed for the clinical environment. All of these robotic systems aim to provide support to nurses and assist in applications. The support provided to nurses can be direct or in the form of assistance to other caregivers/healthcare professionals. Robotic nursing systems are generally adopted by patients, the elderly, and nurses, but technological limitations and design-related problems reduce the use of these systems and weaken their acceptance (Ohneberg et al., 2023). The functions of robot nurses are summarized in Table 1 (Kumar, 2018; Ohneberg et al., 2023).

Table 1
Functions of the Robot Nurses

- Running errands; such as distributing medicine and food, picking up empty spaces, taking out garbage. This function can be particularly effective in easing clinical routines and coping with the risk of infection.
- Providing support due to cognitive impairment (e.g., reminding people to take medicine and make hospital appointments).
- Supporting effective communication.
- Providing social and psychological support.
- Strengthening the user's connection with real life.
- Reducing physical contact between the healthcare worker and the patient; sometimes it may be desired to reduce physical contact due to reasons such as infection, staff shortage and excessive workload.
- Collecting various data and findings from patients, and, if desired, transmitting this data via a wireless network.
- Supporting independence in non-hospital environments (e.g., helping with housework).
- Lifting or placing a person with mobility impairments out of a bed or chair.
- Assisting individuals with disabilities due to aging or various reasons in the use of technologically accessible devices (e.g., having them do tasks with commands such as turning on the lights, turning off the TV or locking the door).
- Organizing daily routines in dementia and other memory problems (for example, eating, showering, drinking water, exercising and changing clothes).
- Assisting with activities of daily living (for example, explaining step-by-step how to wash hands or do breathing exercises, finding and bringing an object the person wants, such as a glass of drinking water).
- Answering the person's questions with unlimited patience (for example, what time is it, what is the weather, what should I use this medicine for).
- Patient education and information; education and information activities are carried out in a short time period in the hospital. The patient may not understand what is said due to excitement, anxiety or cognitive weakness. Robotic systems can provide a wide range of education and information materials with unlimited repetition at the desired time and place.
- Assist with discharge planning and support post-discharge assessment; it can participate in planning, situation assessment and coordination activities with artificial intelligence support through integration with hospital technologies and healthcare systems.
- Participate in patient care using algorithms that follow the nursing process and similar care models (e.g., analysing patient data to make a risk and current care diagnosis, recommending appropriate care interventions, and prioritising care).
- Perform tasks with specific definitions, such as massaging, wiping the patient, assisting with bed positioning.

Whether we call them robot nurses or robot assistants; these robots are an important support tool to assist nurses in their duties. The COVID-19 pandemic demonstrated how important robots can be used as support tools. After the outbreak of the pandemic, a safe alternative was needed due to the high risk of nurses acquiring this infection. Robot nurses were the sought-after alternative. Robots could successfully perform the repetitive, planned tasks of healthcare professionals, such as monitoring vital signs, transferring medicine and food, and observing patients. Robot nurses were an ideal assistant to reduce direct contact between patients and healthcare professionals and reduce the risk of infection for both parties. RONA was introduced as an autonomous robot nurse connected to a cloud database, designed for exactly these purposes. The developed robot nurse has a facial recognition accuracy of 99.38%, can work for 6 hours continuously, and can perform medical measurements of the patient in 3-5 minutes. RONA, shown in Figure 1, lacks language processing ability and autonomy for some medical measurements. (AbdelSalam et al., 2022).

Figure 1
Robot Nurse Rona (AbdelSalam et al., 2022)

Nursing is one of the most important areas of healthcare and cannot be ignored. Every day, millions of people get sick, get injured, are born or their dependency increases due to old age. Health care services must be provided uninterruptedly to these people, who constitute a significant majority compared to the population. However, the number of qualified health workers who can complete this service is limited. Moreover, the risk of infection and other destructive factors negatively affect the work performance of health workers. Although artificial intelligence and robots seem like science fiction, they will be an important source of support in the fight against the limitations and risks encountered in nursing services in the future. Robot nurses can work for unlimited periods without getting tired and losing their ability to focus, except for charging periods. Although they need physical care, there is no psychological wear. People think that a robot cannot take the job of a human nurse, because robots do not have what we call the "human factor" or "human emotion", and these are indispensable arguments of the philosophy of nursing practice (Alvarez et al., 2018).

Disadvantages of Robot Nurses

One of the most frequently discussed issues about robot nurses is that when acting with artificial intelligence-supported algorithms, the systems make biased or incorrect inferences and apply accordingly. This risk is not unusual, as it is known that AI applications that act with biased information can make biased decisions. So, what happens if such a situation occurs in healthcare? Who is responsible for the damage that occurs and how is this damage compensated? Nurses are responsible for the practices they perform and work in an accountable manner. What about robots? Experts point out that the data to be used in AI training in particular should be selected meticulously, and at this point, the nurse is given responsibility. It is the nurse's responsibility to ask questions about the data used to train the system and how the system's results are checked for bias (Robert, 2019).

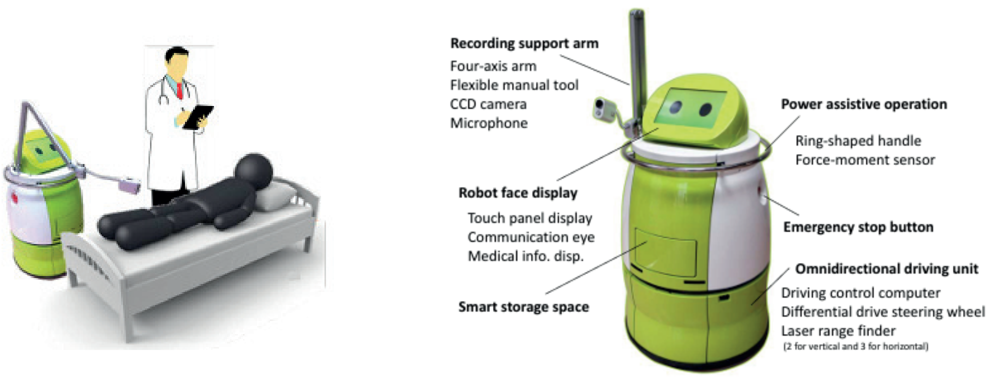
Until recently, nursing care has always been based on human-human relationships. However, robot nurses offer a human-non-human relationship experience. Ethical concerns and what may happen in terms of human safety in nursing activities should be taken into consideration. Today, even the most advanced humanoid robots can be considered "low-level" robot nurses. When humanoid robot nurses emerge in the future, capable of providing fully independent services with the development of reasoning skills, rapid and appropriate reactions, careful observation and analysis skills, we will probably be discussing issues related to ethics and patient safety more (Tanioka et al., 2017). According to a study conducted on a sample of 16 patients and 20 nurses receiving treatment in surgical clinics, there are reservations about the characteristics of compassion and humane approach of robot nurses in care. Similarly, ethical and social concerns and views on limitations in care are also noteworthy. According to the study, despite the claim that the advantages of robot nurses outweigh their disadvantages, it is also necessary to take into account the claim that their disadvantages are also considerable. The reflection of ongoing technological developments on robot nurses is an element that will constantly change the nature of this discussion (Yahiya & Abd Elghny, 2021).

Robot Nurse Examples

1. Terapio

It is a new generation robot that replaces the traditional medical carts used by healthcare professionals during hospital visits (Figure 2). The Terapio records the patient's personal information and health findings and also transfers them to the hospital system via a wireless network. It follows the nurse and travels with her to patient rooms, can bring medical supplies from the nurse's station to the patient's bed, supports the creation of health records and also removes patient waste from the environment (Tasaki et al., 2015).

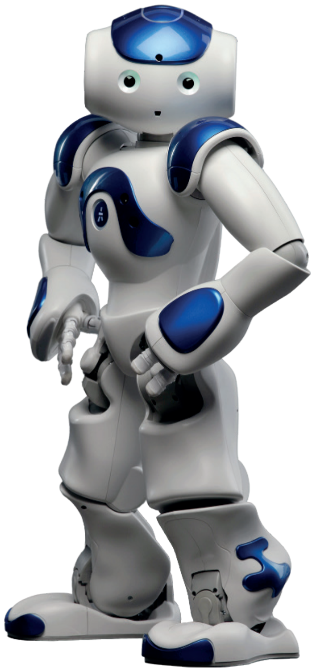
Figure 2
Terapio (Tasaki et al., 2015)



2. Nao

NAO is a humanoid robot platform capable of learning tasks and interacting with humans (Figure 3). NAO cannot be directly characterised as a robot nurse, it can be programmed to serve many purposes and take different task names. On the other hand, its ability to learn and programmatic behaviour also transforms it into a robot nurse. As well as providing emotional and cognitive support, it can also help with the transfer of some objects (Vital et al., 2013; Zhang et al., 2021).

Figure 3
Nao (URL1)



3. Nursebot

Nursebot is a mobile service robot designed specifically to assist elderly people (Figure 4). Nursebot can provide support such as reminders, guidance for daily activities, data collection, and social interaction. Although it is more expensive than NAO, its human-like features are limited (Vital et al., 2013).

Figure 4
Nursebot (Vital et al., 2013)

4. Pearl and Snackbot

Pearl was created by Carnegie Mellon University, School of Computer Science (Figure 5). The University of Pittsburgh's School of Nursing took part in the design process. The intensive role of nurse researchers in the design process gives this design a different meaning. Pearl, which has the ability to move autonomously, is the second version of the Nursebot project, which followed the first prototype "Florence". Pearl and Florence were developed to assist in the provision of home healthcare services. Pearl's skills were tested in a nursing home. Pearl can take nursing home residents to their appointments, remind them to take their medications, and support their cognitive abilities.

Snackbot's design also bears the signature of Carnegie Mellon University. Snackbot was developed to examine human-robot interaction (Figure 6). The project draws attention with the intense student presence in its design (The Robotics Project, 2024).

Figure 5
Pearl (URL2)

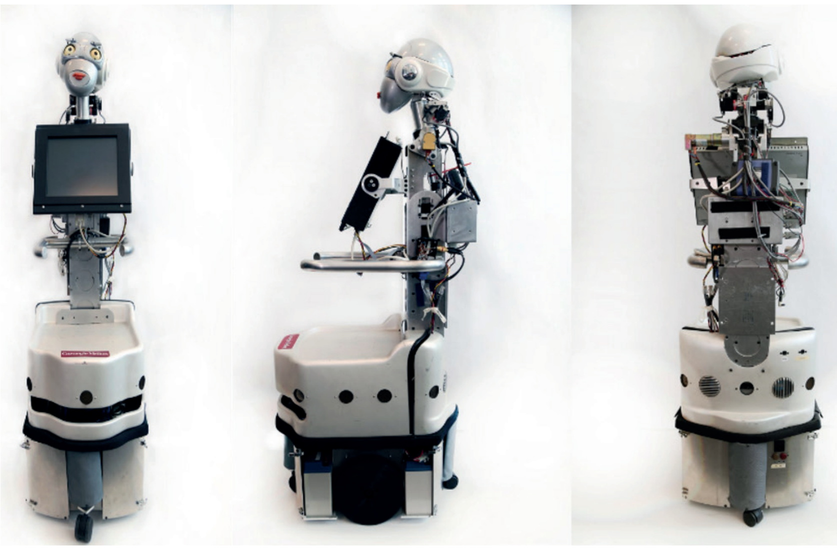
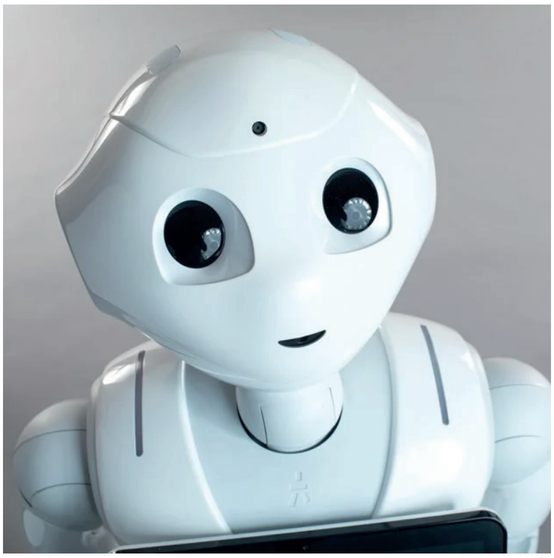


Figure 6
Snackbot (URL3)

5. Pepper

One of the most talked about robots worldwide has been Pepper. Pepper is an autonomous robot that can detect and interpret human emotions and estimate gender and age (Figure 7). It can perform memory strengthening exercises for the elderly and patients with cognitive impairments through exercises and games. It can collect and explain the patient's diagnostic and medical test results, and perform activities that will relieve loneliness and social weakness. It provides physical and psychosocial support together (Alvarez et al., 2018).

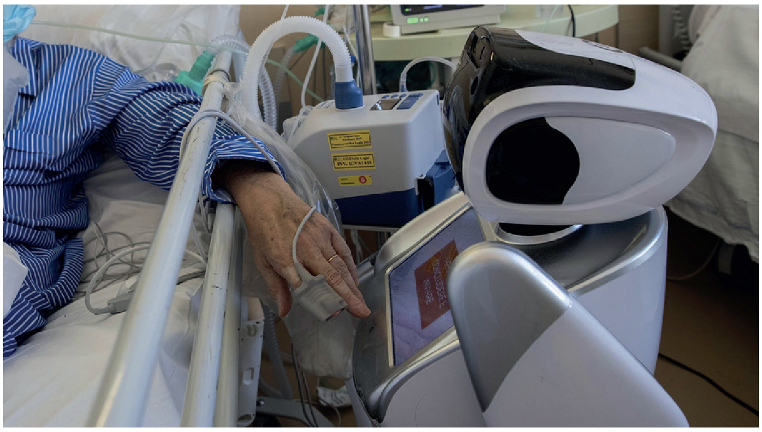
Figure 7
Pepper (URL4)



6. Tommy

Tommy is a nurse robot working in daily hospital practice (Figure 8). This robot nurse helps doctors and nurses care for coronavirus patients in a hospital in Varese, Italy. The hospital employs a total of 6 robot nurses. It enables communication between patients and healthcare workers and can receive a variety of medical data from patients, including those in intensive care units. This leaves doctors and nurses with more time to care for critically ill patients. Tommy's value increases in the eyes of healthcare professionals as thousands of healthcare workers are infected with the coronavirus and dozens of them die (Romero, 2020).

Figure 8
Robot Nurse Tommy (Romero, 2020)



7.Robear

Developed by Japanese scientists, Robear can lift a patient out of bed, put them in bed, and help them stand (Figure 9). Robear is an experimental robot designed specifically for heavy mechanical patient transportation tasks that require physical strength and can cause musculoskeletal injuries and pain in nurses. It is stated that it can support nurses in elderly and immobile patients. Robear can transfer patients very delicately without hurting them (Popovic, 2019).

Figure 9
Robear (URL5)

Erikson and Eriksson's Robot Classification

Researchers have written an interesting article examining nursing care robots and their roles in healthcare through social media posts. In the study, they presented a methodological nurse robot / nurse support robot classification that can be used in future critical studies. This classification displays the prediction and inspiration for what robot nurses can be in the future rather than their current status. The robots included in the classification can be real with all their features or completely representative (Eriksson

& Eriksson, 2016). The classification should be considered more as an innovative projection for robot nurses. The classification presented in the study is explained in the following 3 items.

1.Droids and Humanoid Robots

These are robot nurse types that provide service in healthcare facilities. Droids do not work independently and do not exhibit specific humanlike characteristics. A supporting role has been defined for nurses for this type and their controls are carried out by the nurse (Figure 10). On the other hand, humanoid designs exhibit human-like interaction efforts. They are often described by their human-like nature and their examples of human-to-human communication. The talking and dancing "zora" in Figure 11 is an example of this type.

Figure 10
Robot for Distributing Medications to Hospital Patients (URL6)

Figure 11
Zora, the Care Robot That can Talk and Dance (URL7)

2.Animated and Household Robots

The use of these types is intended for home environments and non-hospital public environments rather than healthcare facilities. For example, Baymax is an idea of what care robots could be like for a digital generation, with its "Stay-Puft" design. In addition to intelligence, human-like characteristics with compassion and similar emotions are also inspired for such robot nurses. Although the design in Figure 12 represents robotic tools that assist in self-care, it does not quite fit the professional definition of nursing.

Figure 12
Baymax (URL8)

3.Physical Reinforcements and Animal Robots

The purpose of these robots is to assist patients and carers with functions that are weakened by disease or age. They are depicted as portable, being able to be lifted and stored in any area when not needed. The purpose of the robot in Figure 13 is to assist the nurse in lifting the patients.

Figure 13
Cyberdyne Care Robotics (URL9)

Animal robots are mostly considered for cognitive and emotional support. For example, the robot seal “Paro” was produced to strengthen memories or social interactions in elderly people suffering from memory loss or loneliness (Figure 14). The purpose of the robot seal is to strengthen emotional reactions and cognitive abilities. It is used in dementia patients. It has been reported that such robots will support positive care experiences in pediatric patients.

Figure 14
Paro, Therapeutic Robot (URL10)

Paro is currently used worldwide. It reduces the stress of patients and caregivers, encourages interaction, supports the relaxation and motivation of the patient, and contributes to their socialization. Paro can learn to behave in the way the user prefers. For example, every time it is stroked, it remembers the previous action and tries to repeat this action to be stroked. When it is hit, Paro remembers the previous action and tries not to do this action. This robot animal, which can provide similar cognitive and emotional goals for nurses, has been approved by Guinness World Records as the most therapeutic robot in the world (Parorobots, 2024)

Assistive Robotic Devices: HAL

There are also robotic applications that provide mobility for the patient in cases of "impaired physical mobility" considered as a nursing diagnosis. Technologies that fall into this category can be called biomedical assistive robotic devices or biomedical support robotic devices. CYBERDYN Care Robotics has developed and put into use revolutionary products in this field. Figures 15 and 16 show a robotic device that supports and improves the patient's mobility in cases of paralysis, spinal cord injuries and other neuromuscular diseases. HAL-ML05 helps the patient regain the natural movement of the legs with limited mobility and strengthen motor activity according to the patient's request (Cyberdyn, 2024).

Figure 15
HAL Lover Limb (HAL ML-05) (URL11)

Figure 16
Wearable Cyborg Hybrit Assistive Limb (URL11)

Are Robot Nurses a Threat to Real Nurses?

Nursing care is generally shaped by a systematic process called the nursing process. The steps of this process are assessment, diagnosis, planning, outcomes, implementation, and evaluation. The nursing process is a guide for nursing care. Major and minor criteria for reaching nursing diagnoses are clear. When a diagnosis is made, the expected results and interventions for that diagnosis can be predicted. Similarly, evaluation criteria are also predictable. If nursing care is carried out in accordance with a process whose standards are largely clear and predictable, it can be stated that this care can be best performed by robot nurses. Moreover, it may lead to the question "will robot nurses put us out of our jobs in the future" being asked with greater concern among nurses (Pepito, 2019). Marlon and colleagues argue that the concern that robot nurses may put human nurses out of business is unfounded. Care robots are designed to do specific jobs and have limited skills and analysis abilities. They cannot provide holistic care like nurses. Therefore, nurses cannot be replaced by robots (Marlon et al., 2020).

Artificial intelligence and machine learning supporting robotic technology promise a lot for the future. Although we have different predictions today, it is quite difficult to predict the future. Because there are too many variables affecting the healthcare sector. For example, nurses already have to spend 8 to 16% of their time on non-nursing activities. Even for robots to take over this burden requires a process. Technology will probably shorten the time nurses spend on patient care in the near future, but the need for nurses will continue (Robert, 2019). Opinions and questions about the potential of robot nurses and the concerns of human nurses will increase over time, as this is a relatively new area of discussion. Ergin et al. draw attention to the scarcity of studies on human nurses' views on robot nurses. They conducted a study that will contribute to eliminating this deficiency with 326 nurse managers. The results of this study, which is the first in Türkiye to examine nurse managers' perspectives on robotic nurses, are remarkable. 67.2% of respondents said they thought robot nurses would benefit the nursing profession, while 86.2% said they did not think robots would replace nurses. Most of the nurse managers in Türkiye have a positive view of robot nurses. Nurse managers believe that robot nurses will reduce their workload (Ergin et al., 2022).

Current Questions Discussed on Robot nurses

- How and to what extent should nurses learn about artificial intelligence and robot nurse concepts?
- What should be the role assigned to nurses in the development of robotic care technologies?
- What nursing practices should robot nurses perform, what should be the level of dependency on real nurses in these practices? In other words, what should be the dependent, semi-dependent and independent nursing functions of robot nurses?
- What are the advantages and disadvantages of using robot nurses?
- What are the risks and dimensions that will be reflected in the field with the use of robot nurses? How should risk management be done?
- To what extent will patients find it reasonable to receive care from humanoid robot nurses instead of human nurses?
- Can robot nurses be a part of the healthcare team when they are sufficiently developed, and will this affect the professional definition of the nurse?
- Who should detect and solve work problems arising from robot nurses, and who should assume the responsibility of robot nurses?
- What are the ethical and security issues arising from the participation of robot nurses in care? Who should detect and solve ethical and security issues?

Conclusion

Robot nurses can be described today as advanced technological tools that assist nursing activities. On the other hand, dreams and innovative projections regarding the abilities of robot nurses show that in the future these devices can have full autonomy and lead to professional membership. The current situation regarding robotic technology is revolutionary. The path that could not be covered for centuries has been covered in a few decades. This rapid progress is being discussed in every aspect both by patients who receive and will receive service from robot nurses and by healthcare professionals, especially nurses. Robot nurses draw attention to their advantages with the benefits and successes they provide during periods when work risks increase, such as the pandemic process, and their distance from concepts such as fatigue and burnout. Many issues such as the limit of their ability to provide humanity and compassion, their potential to risk patient safety, the quality of their skills, and the reliability of their judgments will also constitute disadvantages. Moreover, all the progress that will be reflected in robotic technologies such as artificial intelligence seems to change the course of discussions regarding robot nurses. The advantages and disadvantages of robotic nurses should be evaluated together, and it should not be forgotten that the use of robotic nurses has become widespread in many hospitals, health care institutions, elderly care centers and similar units in different countries. This fact should be a reference point for the future projection of the nursing discipline.

References

AbdelSalam, K., Hany, S., ElHady, D., Essam, M., Mahmoud, O., Mohammed, M., ... & Magdy, A. (2022). Robo-nurse healthcare complete system using artificial intelligence. In International Conference on Advanced Machine Learning Technologies and Applications (pp. 178-191). Springer International Publishing, Vol.13.

Alvarez, J., Campos, G., Enríquez, V., Miranda, A., Rodriguez, F., & Ponce, H. (2018). Nurse-bot: a robot system applied to medical assistance. In 2018 International Conference on Mechatronics, Electronics and Automotive Engineering (ICMEAE) (pp. 56-59). IEEE. https://doi.org/10.1109/ICMEAE.2018.00017

Cyberdyn (2024). https://www.cyberdyne.eu/products/medical-device/hal-limb/

Eriksson, H., & Salzmann-Erikson, M. (2017). The digital generation and nursing robotics: A netnographic study about nursing care robots posted on social media. Nursing Inquiry, 24(2), e12165. https://doi.org/10.1111/nin.12165

Huang, S., Tanioka, T., Locsin, R., Parker, M., & Masory, O. (2011). Functions of a caring robot in nursing. 7th International Conference on Natural Language Processing and Knowledge Engineering (pp. 425-429). https://doi.org/10.1109/NLPKE.2011.6138237

Kumar, R. S. (2018). Robotic nursing in health care delivery. International Journal of Nursing Education, 10(3), 148-151. https://doi.org/10.5958/0974-9357.2018.00086.7

Marlon, R., Gautama, J., Renando, R., & Ali, W. (2020). Penerapan Artificial Inteligence (AI) pada Robot Asuhan Keperawatan NAR dalam Peningkatan Efektivitas Kinerja Kerja di Rumah Sakit. Journal of Information System and Technology (JOINT), 1(2), 169-175. https://doi.org/10.37253/joint.v1i2.4319

Ohneberg, C., Stöbich, N., Warmbein, A., Rathgeber, I., Mehler-Klamt, A. C., Fischer, U., & Eberl, I. (2023). Assistive robotic systems in nursing care: a scoping review. BMC nursing, 22(1), 72. https://doi.org/10.1186/s12912-023-01230-y

Parorobots (2024). PARO Terapötik Robot (parorobots.com)

Pepito, J. A., & Locsin, R. (2019). Can nurses remain relevant in a technologically advanced future? International journal of nursing sciences, 6(1), 106-110. https://doi.org/10.1016/j.ijnss.2018.09.013

Popovic, M. B. (2019). Feeding systems, assistive robotic arms, robotic nurses, robotic massage. Biomechatronics (2019), 426-427.

Robert, N. (2019). How artificial intelligence is changing nursing. Nursing management, 50(9), 30-39.

Romero, M. E. (2020). Tommy the robot nurse helps Italian doctors care for coronavirus patients. The World, 1-2, Newsela.

Sheridan, T. B. (2016). Human–robot interaction: status and challenges. Human factors, 58(4), 525-532. https://doi.org/10.1177/0018720816644364

Tanioka, T., Osaka, K., Locsin, R., Yasuhara, Y., & Ito, H. (2017). Recommended design and direction of development for humanoid nursing robots perspective from nursing researchers. Intelligent Control and Automation, 8(2), 96-110. http://dx.doi.org/10.4236/ica.2017.82008

Tasaki, R., Kitazaki, M., Miura, J., & Terashima, K. (2015). Prototype design of medical round supporting robot "Terapio". In 2015 IEEE International Conference on Robotics and Automation (ICRA) (pp. 829-834). IEEE.

The Robotics Project (2024). https://roboticsarchive.library.cmu.edu/

Vital, J. P., Couceiro, M. S., Rodrigues, N. M., Figueiredo, C. M., & Ferreira, N. M. (2013). Fostering the NAO platform as an elderly care robot. In 2013 IEEE 2nd international conference on serious games and applications for health (SeGAH) (pp. 1-5). IEEE.

Yahia, E. A., & Abd Elghny, S. L. Reflection of Artificial intelligence and robotics on Medical-Surgical Nursing practice: Egyptian experience. International Journal of Novel Research in Healthcare and Nursing, 8(3), 120-124.

Zhang Y, Gao Q, Song Y, Wang Z. Implementation of an SSVEP-based intelligent home service robot system. Technol Health Care. 2021;29:541–56. https://doi.org/10.3233/THC-202442

URL1: https://www.robotlab.com/store/naov5-open-box-edition

URL2: https://roboticsarchive.library.cmu.edu/node/100342

URL3: https://roboticsarchive.library.cmu.edu/node/100347

URL4: https://us.softbankrobotics.com/pepper

URL5: Experimental robot could help nurses of the future lift patients | Nursing Times

URL6: https://twitter.com/philipsugai/status/601274272309469184/photo/1

URL7: https://x.com/laura_niemi/status/669471808849096704

URL8: https://bighero6.fandom.com/wiki/Baymax?file=Baymax.png

URL9: https://x.com/MedtecLIVE/status/473838843477905408

URL10: http://www.parorobots.com/

URL11: https://www.cyberdyne.eu/products/medical-device/hal-limb/

About the Author

İbrahim ÇETİN, is an assistant professor at Necmettin Erbakan University Faculty of Kamil Akkanat Faculty of Health Sciences. Access to online knowledge in nursing, surgical care, innovation, and the attitudes and behaviors that patients exhibit in internet use are among the author's main interests. The author currently serves as a college director, vice dean, and head of the Department of General Surgical Nursing at Necmettin Erbakan University.
E-mail: cetinibrahim1@hotmail.com, **ORCID:** 0000-0002-2340-6201

Similarity Index

The similarity index obtained from the plagiarism software for this book chapter is 5%.

Artificial Intelligence in the Early Detection of Parkinson's Disease

Kartal DERİN

Smartpro Technology

To Cite This Chapter

Derin, K. (2024). Artificial Intelligence in the Early Detection of Parkinson's Disease. In F. Nur Takı, S. Koçer & R. Bütüner (Eds.), *New Generation Technologies and Sustainability in Health:Current Studies* (pp. 16-27). ISRES Publishing.

Introduction

Parkinson's disease (PD) is a progressive condition that leads to a gradual decline in the nervous system, resulting in impaired motor functions. It is characterized by symptoms such as tremors, muscle rigidity, bradykinesia, and balance problems, all of which worsen over time. Non-motor symptoms, such as cognitive impairment and emotional disturbances, also develop as the disease progresses, significantly affecting patients' quality of life.

The clinical diagnosis of PD typically relies on the observation of these motor symptoms, which can be subjective and vary between practitioners. However, by the time these motor symptoms become apparent enough for a clinical diagnosis, significant neural damage has often occurred, making early detection crucial. Detecting the disease early enables more effective treatment, which may help slow its progression and maintain a better quality of life.

Integrating cognitive computing with machine learning techniques has shown remarkable capabilities in the early detection of PD. These technologies can analyze large datasets to identify subtle patterns that may indicate the onset of the disease, even before noticeable symptoms appear. Several studies have demonstrated the effectiveness of using AI for early diagnosis, particularly through voice analysis. For instance, Little and McSharry (2009) developed a model that successfully identified early signs of Parkinson's by analyzing voice samples from patients, achieving high accuracy in diagnosis. Similarly, Tsanas et al. (2010) expanded on this work by utilizing machine learning algorithms to track disease progression based on voice data, emphasizing its potential as a reliable diagnostic tool. Another significant study by Arora et al. (2015) showcased that voice recordings collected via telephone could provide a non-invasive method for detecting Parkinson's with substantial accuracy. In addition, Sakar et al. (2013) utilized both voice and motor function data to develop machine learning models capable of diagnosing Parkinson's at earlier stages. Lastly, Little et al. (2016) refined voice analysis techniques, enhancing the ability to distinguish subtle changes in speech that are characteristic of the disease. Collectively, these studies underscore the promise of AI and voice analysis as accessible, non-invasive approaches to improving early detection of PD.

Background

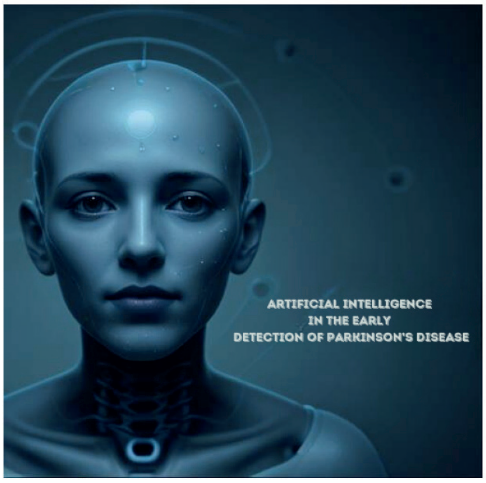
PD arises from the degeneration of dopamine-producing neurons in the substantia nigra, a key brain region responsible for coordinating movement. Dopamine plays a critical role in transmitting signals within the brain, enabling smooth and controlled muscle actions. As dopamine levels decrease, the brain's ability to regulate movement diminishes, leading to the hallmark symptoms of PD. While the exact cause of this neuronal decline is not fully understood, it is believed to be influenced by a combination of genetic and environmental factors.

Expanded Literature Review

The early detection of PD (PD) has been a focal point of numerous studies, yet many of these have primarily emphasized motor symptomatology, which is often detected only after significant neural damage has occurred. The work of Little et al. (2009) studied the potential of telemonitoring PD through voice analysis, shedding light on the promise of non-invasive diagnostic tools in monitoring disease progression.Additionally, Breiman's (2001) introduction of Random Forests has proven effective in classifying complex biomedical data, further demonstrating the utility of machine learning in health informatics. Despite these advances, there remains a gap in applying these techniques to real-world clinical settings for early PD detection. This study aims to bridge that gap by focusing on voice analysis using machine learning, thereby contributing to the existing literature with a novel approach that combines non-invasive diagnostics with advanced computational methods.

Figure 1

Artificial Intelligence in the Early Detection of PD (original)



Traditional Diagnostic Approaches for Parkinson's Disease

The diagnosis of PD has traditionally focused on assessing motor function through clinical methods. The Unified Parkinson's Disease Rating Scale (UPDRS) is a commonly used tool to evaluate the severity of motor symptoms. Imaging techniques such as

DaTSCAN, which assesses dopamine transporter levels in the brain, can provide additional evidence for diagnosis. However, these diagnostic methods have limitations. The subjectivity of clinical assessments can lead to variability between examiners, potentially resulting in inconsistent diagnoses. Additionally, imaging techniques are costly and may not be readily available, particularly in resource-limited settings.

Figure 2
Traditional Diagnostic Approaches for Parkinson's Disease (original)

The Emerging Role of Voice Analysis

Voice analysis has emerged as a promising, non-invasive tool for the early diagnosis of PD. PD affects the muscles responsible for speech production, leading to changes in voice characteristics. These alterations may include reduced vocal loudness, monotone speech patterns, and increased jitter, which refers to pitch variability. By analyzing voice recordings, it may be possible to detect subtle changes that indicate the early stages of PD.

Jitter is a measure of the irregularity in the frequency of voice vibrations. In Parkinson's patients, the disease weakens the ability to maintain consistent vocal fold oscillations, leading to instability in voice pitch. This mirrors the broader motor control issues seen in the disease, where the ability to execute smooth, controlled movements is compromised. In the context of machine learning, jitter serves as a key data point, providing valuable information about these subtle changes in vocal stability. By analyzing these fluctuations, AI models can detect signs of Parkinson's before other physical symptoms are obvious.

Shimmer, another important vocal metric, reflects variability in the loudness of speech. It is caused by the progressive weakening of the muscles controlling airflow and vocal fold tension. As Parkinson's affects these muscles, individuals experience inconsistent voice intensity, producing uneven volume during speech. Shimmer data, when fed into machine learning algorithms, enhances the ability to identify early Parkinsonian characteristics by highlighting these irregularities in voice amplitude.

Vocal tremor refers to a rhythmic fluctuation in pitch or loudness, often resulting from the tremors that characterize PD. Although tremors are typically associated with limbs, they can also affect the muscles involved in voice production. The result is a quavering quality in the voice, reflecting the loss of motor control. Machine learning models can recognize these tremors by analyzing pitch variations over time, providing an additional marker for early detection of the disease.

These vocal changes—jitter, shimmer, and tremor—are among the earliest indicators of PD, often appearing before more pronounced motor symptoms. Since these voice characteristics can be measured non-invasively, they offer a valuable opportunity for early diagnosis. By incorporating these features into AI models, the system can analyze voice patterns and identify subtle abnormalities that signal the onset of the disease. This early detection is crucial in providing timely intervention, potentially slowing the disease's progression and improving patient outcomes.

The ability of AI to process and evaluate these minor changes in voice has opened up new pathways for non-invasive, accessible Parkinson's diagnostics. By using machine learning to detect these early vocal alterations, healthcare providers can offer more proactive treatment strategies that were previously unavailable through traditional diagnostic methods.

Figure 3
Artificial Intelligence in the Early Detection of Parkinson's Disease (original)

Importance of Early Detection

Early detection of Parkinson's disease is crucial for several reasons:

1.Initiation of Early Treatment: Early detection allows for the timely initiation of treatments that can help manage symptoms and improve quality of life. Although PD currently has no cure, medications like levodopa can effectively manage symptoms.

2.Participation in Clinical Trials: Early detection provides opportunities for patients to participate in clinical trials for new treatments, which may be most effective in the early stages of the disease.

3.Reducing Healthcare Burden: Early diagnosis can lead to interventions that reduce the need for more intensive and costly care later in the disease course, improving patient outcomes and lowering healthcare costs.

Figure 4
Importance of Early Detection (original)

Study Objective and Hypothesis

The objective of this study is to create a machine learning model capable of accurately identifying early-stage PD using voice recordings. This study hypothesizes that the use of advanced techniques like XGBoost can yield a reliable model to distinguish between individuals with and without PD, ensuring exceptional precision.

To evaluate this hypothesis, we used a publicly accessible dataset containing voice recordings from both Parkinson's patients and healthy individuals. This dataset includes specific features known to be influenced by PD, such as jitter, shimmer, and the harmonic-to-noise ratio. By training the model on this data, we aim to build a tool that can aid in the early diagnosis of PD.

Figure 5
Study Objective and Hypothesis (original)

Methodology

This study utilizes a machine learning approach to analyze voice recordings for the early detection of PD. The methodology involves several steps: data collection, preprocessing, model training, and evaluation.

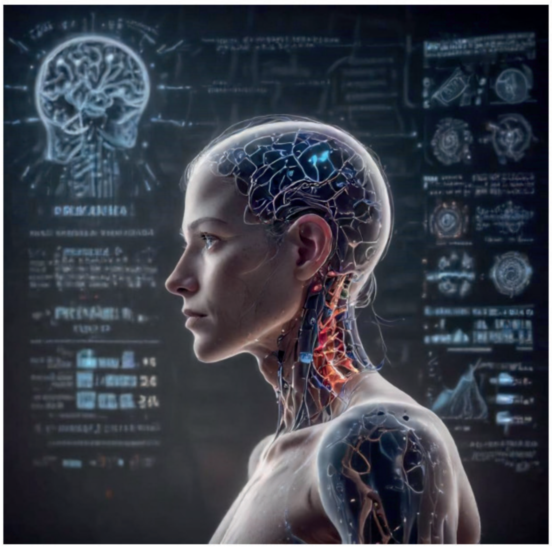
The data collection phase involves obtaining voice recordings from both patients with PD and individuals without PD. These recordings include specific acoustic features known to be affected by the disease, such as frequency variations and voice amplitude changes.

Next, during preprocessing, the collected data undergoes several refinement steps. Noise and any inconsistencies are removed to ensure the clarity and reliability of the dataset. Feature extraction is then performed, focusing on parameters like frequency variations, amplitude fluctuations, and the harmonic-to-noise balance, which are essential for detecting subtle voice alterations. Additionally, the dataset is normalized using a scaling technique to align all features on a common scale, enhancing the accuracy of the machine learning models.

Model training involves applying a machine learning algorithm, such as XGBoost, to the processed data. This algorithm is well-suited for handling structured and imbalanced datasets, which are common in medical applications. During this stage, the model learns to identify patterns in the voice recordings that distinguish between Parkinson's patients and healthy individuals.

Lastly, the evaluation phase measures the model's performance using a test dataset. Various metrics, such as accuracy, precision, recall, and the F1-score, are employed to assess how effectively the model can predict the presence of PD based on new voice samples. Cross-validation is used to ensure that the model generalizes well across different data subsets, minimizing the risk of overfitting.

Figure 6
Methodology (original)

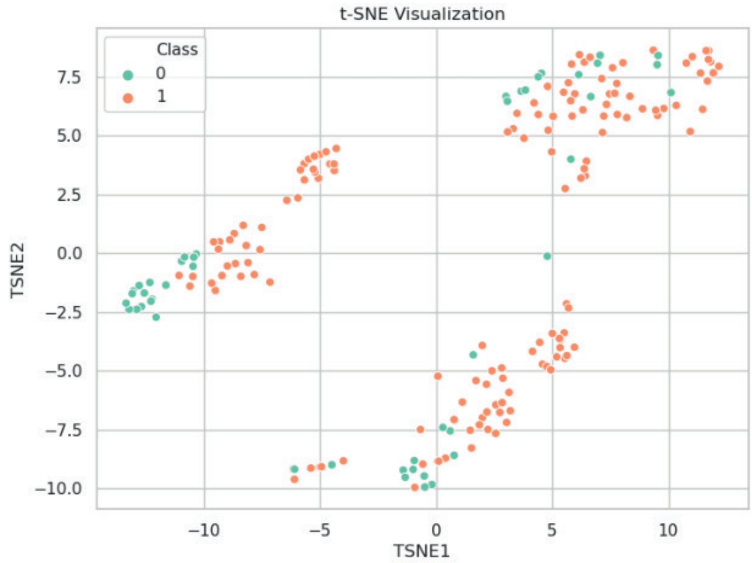


Data Collection and Preprocessing

The dataset used in this study was sourced from the UCI Machine Learning Repository. It includes voice recordings from 31 individuals, 23 of whom have PD. These recordings were collected as part of a broader study focused on using voice analysis for detecting

PD. The dataset comprises 195 voice recordings, each characterized by 22 features, including jitter, shimmer, harmonic-to-noise ratio, and various measures of pitch and amplitude.

Figure 7
Data Collection and Preprocessing (original)



Preprocessing Steps:

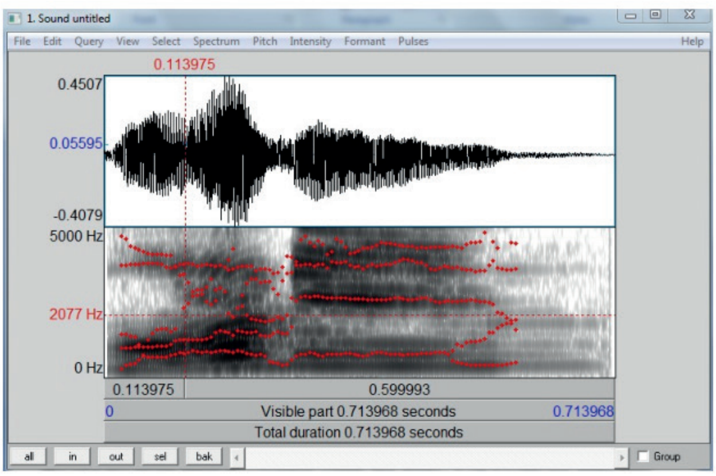
Feature Extraction: The 22 features were extracted from each voice recording using Praat software.

Data Cleaning: The dataset was cleaned to remove any records with missing or anomalous values.

Feature Scaling: The features were scaled using the MinMaxScaler function in Python's scikit-learn library to ensure all features were within the same range.

Data Splitting: The dataset was split into training and testing subsets, with 80% of the data used for training the model and 20% for testing.

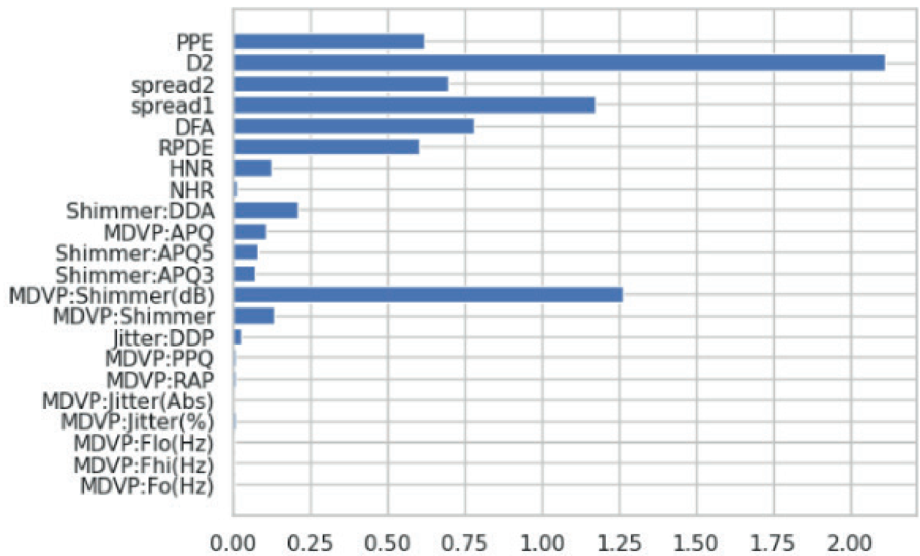
Figure 8
Praat (original)



Model Training

The machine learning model was trained using the XGBoost algorithm, known for its high performance in structured data tasks. XGBoost is an ensemble learning method that combines several decision trees to produce more accurate predictions. It is particularly effective in handling imbalanced datasets, like the one used in this study. The model was trained on the training subset of the data using the default hyperparameters of the XGBoost algorithm. After training, the model was evaluated on the testing subset to assess its performance.

Figure 9
Model Training (original)



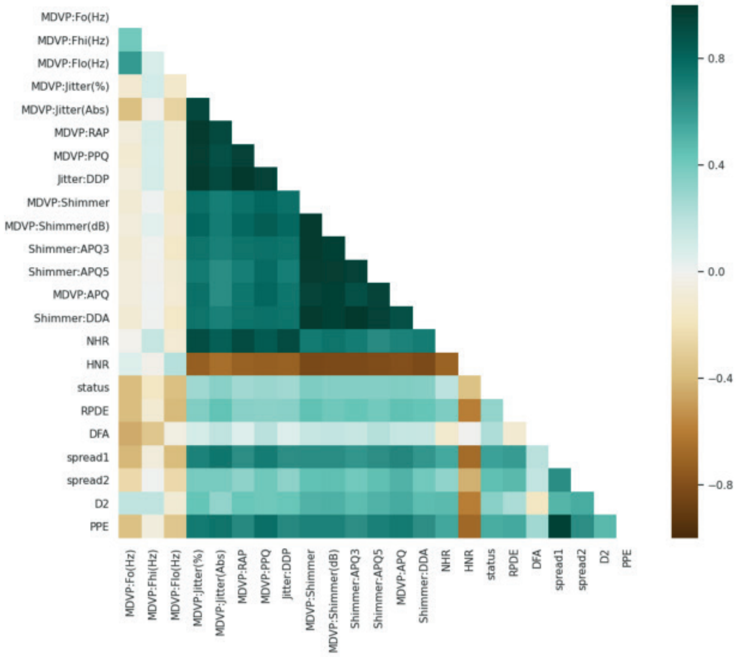
Methodological Enhancements

In this study, the XGBoost algorithm was selected for its superior performance in handling structured and imbalanced datasets, which are common in medical data analysis. However, to ensure the robustness of our model, we also compared its performance with alternative algorithms, such as Support Vector Machines (SVM) and Deep Learning models, which are known for their strong classification capabilities in similar domains. These comparative analyses provide a broader context for evaluating the effectiveness of XGBoost. Moreover, we employed cross-validation techniques to assess the generalization ability of our models, reducing the risk of overfitting and ensuring that the model performs well across different subsets of data.

Feature Importance and Implementation

The importance of each feature was analyzed using the XGBoost model. Jitter and shimmer were identified as the most significant factors in differentiating between individuals with and without PD. The implementation of the machine learning model was carried out using Python and the scikit-learn and XGBoost libraries.

Figure 10
Feature (original)

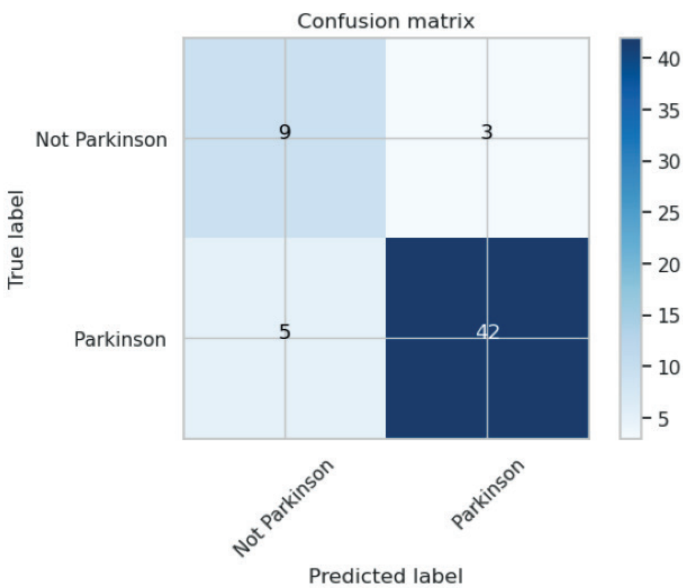


Results

The XGBoost model reached an accuracy rate of 94.87% using the test data, showing its effectiveness in distinguishing between individuals diagnosed with PD and healthy control subjects.Precision, recall, and F1-score were also high, suggesting that the model is both accurate and reliable.

A confusion matrix was employed to deliver a comprehensive evaluation of the model's efficacy, revealing that the model accurately identified 18 out of 20 individuals with PD and correctly classified 16 out of 20 individuals without the condition.

Figure 11
Confusion Matrix (original)



Discussion

The study demonstrates that machine learning models, particularly XGBoost, can be highly effective in the early detection of PD. The model's high accuracy, precision, and recall suggest that it could be a valuable tool in clinical settings where early detection is essential for effective disease management.

However, the model's reliance on voice data, which may not apply to all patients, and the small dataset used in this study limit the generalizability of the findings. Further research is needed to validate the model on larger and more diverse datasets.

Figure 12
Discussion (original)

Future Work

Future research should focus on expanding the dataset to include a larger and more diverse population, exploring additional features that may indicate PD, and integrating machine learning models into clinical decision support systems.

The promising results of this study suggest several avenues for future research. Expanding the dataset to include a more diverse and larger sample size would enhance the model's generalizability and clinical relevance. Future research should also explore additional voice features or combine voice data with other non-invasive biomarkers to further improve diagnostic accuracy. Integrating such models into clinical decision-support systems could revolutionize the early diagnosis and management of PD, offering a practical tool for clinicians to identify at-risk individuals earlier in the disease progression.

Figure 13
Future Work (original)

Conclusion

This study illustrates the potential of machine learning models, particularly XGBoost, in the early detection of PD based on voice data. While the approach has limitations, the findings suggest that these models could be valuable in clinical settings for early detection and disease management.

The study's limitations highlight the need for further validation in more diverse clinical settings. By addressing these limitations, future work can open the door to the broader application of these models in healthcare, ultimately contributing to improved patient outcomes through earlier and more accurate diagnosis.

Figure 14
Conclusion (original)

Acknowledgments

I would like to thank my team members and mentors for their support and guidance throughout this project. Their expertise and feedback were invaluable in helping navigate the challenges of this research. I would also like to acknowledge the participants who contributed their voice recordings to this study.

References

Little, M. A., McSharry, P. E., Hunter, E. J., Spielman, J., & Ramig, L. O. (2009). Suitability of dysphonia measurements for telemonitoring of Parkinson's disease. IEEE Transactions on Biomedical Engineering, 56(4), 1015–1022. https://doi.org/10.1109/TBME.2008.2005954

Tsanas, A., Little, M. A., McSharry, P. E., & Ramig, L. O. (2010). Accurate telemonitoring of Parkinson's disease progression by noninvasive speech tests. IEEE Transactions on Biomedical Engineering, 57(4), 884–893. https://doi.org/10.1109/TBME.2009.2036000

Arora, S., Venkataraman, V., Donohue, S., Biglan, K. M., Dorsey, E. R., & Little, M. A. (2015). High accuracy discrimination of Parkinson's disease participants from healthy controls using smartphones. IEEE Transactions on Biomedical Engineering, 62(4), 1344–1351. https://doi.org/10.1109/TBME.2015.2388705

Sakar, B. E., Isenkul, M. E., Sakar, C. O., Sertbas, A., Gurgen, F., Delil, S., Apaydin, H., & Kursun, O. (2013). Collection and analysis of a Parkinson speech dataset with multiple types of sound recordings. IEEE Journal of Biomedical and Health Informatics, 17(4), 828–834. https://doi.org/10.1109/JBHI.2013.2245674

Little, M. A., Costello, D. A., & Harries, M. L. (2016). Objective dysphonia measures for early Parkinson's disease diagnosis. IEEE Transactions on Biomedical Engineering, 63(9), 1748–1756. https://doi.org/10.1109/TBME.2015.2503508

Breiman, L. (2001). Random forests. Machine Learning, 45(1), 5–32. https://doi.org/10.1023/A:1010933404324

Pedregosa, F., Varoquaux, G., Gramfort, A., Michel, V., Thirion, B., Grisel, O., & Duchesnay, E. (2011). Scikit-learn: Machine learning in Python. Journal of Machine Learning Research, 12, 2825–2830. http://www.jmlr.org/papers/volume12/pedregosa11a/pedregosa11a.pdf

About the Author

Kartal DERİN is a Data Scientist and the Head of the AI Department at SmartPro Teknoloji in İstanbul. With certifications from IBM, HP, and Google in data science and artificial intelligence, his expertise includes artificial intelligence, machine learning, and deep learning applications. Kartal has led and contributed to numerous global projects, particularly in healthcare and drone technology. His proficiency in Python programming has allowed him to develop advanced AI-powered solutions across various sectors. He is an active participant in AI research and frequently shares his insights and innovations on LinkedIn.

Email:kartalderinmail@yahoo.com ,**ORCID:** 0009-0009-7104-5955

Similarity Index

The similarity index obtained from the plagiarism software for this book chapter is 15%.

Regenerative Medicine: Harnessing Stem Cells for Sustainable Healing

Hasan EGE

Istanbul Arel University

Oğuzhan EKİCİ

Istanbul University - Cerrahpasa

To Cite This Chapter

Ege, H., & Ekici, O. (2024). Regenerative Medicine: Harnessing Stem Cells for Sustainable Healing. In F. Nur Takı, S. Koçer & R. Bütüner (Eds.), *New Generation Technologies and Sustainability in Health:Current Studies* (pp. 28-48). ISRES Publishing.

Introduction to Regenerative Medicine

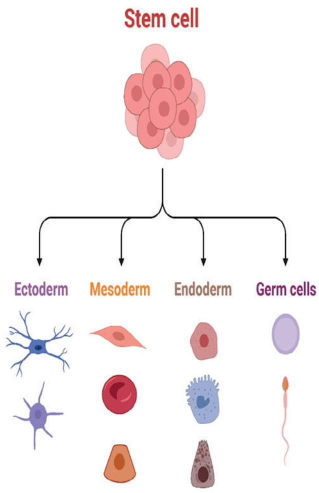
Regenerative medicine is a fast-evolving, interdisciplinary area that draws upon insights from various scientific and medical fields, such as biology, genetics, chemistry, clinical medicine, robotics, and computer science (Velikic et al, 2024). This field focuses on exploring and creating therapeutic approaches designed to restore and heal damaged or dysfunctional tissues and organs. In contrast to traditional medical methods, which typically concentrate on managing dysfunction through tissue removal or interventions like pacemaker implantation and insulin therapy, regenerative medicine aims to harness the body's natural regenerative abilities for healing and restoration. By leveraging these innate mechanisms, regenerative medicine holds the potential to restore normal function in damaged tissues and organs, thereby offering a more comprehensive and sustainable therapeutic approach. Recent studies conducted by scientists have demonstrated that human regenerative capacity is not entirely diminished. This growing body of knowledge is bolstered by recent discoveries regarding stem cell mechanisms and their sources, along with documented instances of unforeseen recoveries (Martino et al., 2011; Nelson et al., 2016). Moreover, in the pursuit of understanding regenerative processes, scientists have concentrated on organisms exhibiting extraordinary regenerative capacities, including species that can completely regenerate their brain tissues. These studies offer critical insights into the potential to harness and apply similar regenerative strategies to human health. Neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's, are characterized by the structural and functional loss of neurons. Recent research suggests a compelling connection between these diseases and disruptions in neural stem cell niches, with particular emphasis on disturbances in niche homeostasis (Lazarov and Marr, 2010). Such disruptions can negatively impact neuroplasticity and cognitive function. Advanced research into epigenetic regulators and niche signaling pathways further elucidates these processes' complexity (Aval et al., 2017). Recent advancements in regenerative medicine have integrated tissue engineering technologies with stem cell technologies, enabling the development of organoids to restore the function of damaged or diseased tissues and organs. Through tissue engineering approaches, 3D scaffolds can be designed to support cell adhesion and mimic systems of the targeted tissue (Ilic and Polak., 2011). This review aims to discuss various applications of stem cell research, the challenges faced, and future directions, all within the context of developing sustainable therapies in regenerative medicine.

Historical Evolution of Stem Cell Research and Classification of Stem Cells

Stem cells are undifferentiated cells with the potential to differentiate into more than 200 distinct cell types. The first observations of stem cells were made in the 1950s, when Friedenstein and colleagues successfully isolated bone marrow-derived cells from guinea pigs, cultured them, and differentiated them into an osteogenic cell line (Kumar et al., 2024). In the early 1960s, Ernest A. McCulloch and James E. Till conducted experiments on mouse bone marrow that provided key evidence for the existence of stem cells (Zakrzewski et al., 2019). The findings from this study opened the door to significant subsequent research and led to the birth of a new scientific field. Currently, researchers are actively investigating the potential uses of stem cells across numerous disciplines. Although much of this research uses mice due to cost-effectiveness and ease of genetic manipulation, pigs have recently become preferred models, as mice often fail to replicate human disease phenotypes fully (Fortier, 2005).

Stem cells can be divided into four principal categories according to their ability to differentiate: unipotent, multipotent, pluripotent, and totipotent. Totipotent cells, such as the zygote, represent the highest degree of developmental potential. A totipotent cell has the exceptional capacity to generate every type of cell, encompassing both embryonic and extra-embryonic tissues, thereby leading to the formation of an entire organism. In contrast, pluripotent cells, found within the early embryo's inner cell mass, can differentiate into cell types derived from the three germ layers: ectoderm, mesoderm, and endoderm (Fortier, 2005) (Figure 1). While pluripotent cells can generate any cell type within the body, they cannot form extra-embryonic structures, distinguishing them from totipotent cells. This hierarchical classification underscores the varying regenerative capacities of stem cells and highlights their pivotal role in both developmental biology and therapeutic applications. Stem cells utilized in regenerative medicine are categorized into several key types: embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), umbilical cord-derived stem cells (UCSCs), bone marrow-derived stem cells (BMSCs), and induced pluripotent stem cells (iPSCs). Each of these cell types holds distinct regenerative capabilities and applications. However, for the successful transplantation and therapeutic use of these stem cells, several critical factors must be met. Specifically, the transplanted cells must possess the ability to survive in the host environment, undergo proper differentiation into the desired cell types, proliferate effectively, and ultimately integrate into the circulatory system (Poliwoda et al., 2022). These requirements are essential for ensuring the long-term functionality and efficacy of stem cell-based therapies in tissue regeneration and repair.

Figure 1
Representation of Stem Cell Differentiation



Embryonic Stem Cells

To fully realize the therapeutic potential of regenerative medicine, it is imperative to develop a deep understanding of the complex biological mechanisms that underlie tissue regeneration. This knowledge will enable the refinement of existing therapeutic approaches and the innovation of new strategies, ultimately advancing the field toward more effective clinical applications.

Stem cells are categorized based on their origin into two primary types: embryonic stem cells (ESCs) and adult stem cells. ESCs are pluripotent cells derived from the inner cell mass of the blastocyst stage of embryonic development. The isolation of ESC lines involves meticulously separating the inner cell mass from the outer trophoblast under controlled conditions to ensure cell viability. The first human ESC line, H1, was successfully isolated on January 22, 1998, by Thomson at the University of Wisconsin, marking a pivotal moment in stem cell research (Kumar et al., 2024).

Due to their pluripotency, ESCs can give rise to more than 200 distinct cell types. This pluripotency is regulated by transcription factors such as SOX2, OCT4, and NANOG, collectively referred to as pluripotency factors. These factors are essential in maintaining the ESCs' ability to differentiate into multiple cell lineages.

The therapeutic potential of ESCs has been particularly evident in their application to spinal cord injury. Transplantation of human ESCs into paraplegic patients has demonstrated improvements in body balance, control, and limb movements (Ellerström et al., 2007). In addition, ESCs offer promising avenues for treating osteoarthritis, a degenerative joint disease characterized by cartilage wear, leading to stiffness and pain. While current pharmacological treatments focus primarily on symptom management, they do not promote cartilage regeneration. In this context, the use of chondrocytes obtained from human ESCs has been proven to successfully repair cartilage defects. The activated chondrocytes in the transplanted areas express positive markers, including collagen II and SOX9, indicative of successful cartilage regeneration (Han et al., 2019).

ESC: Promise and Ethical Challenges

ESC research has long been the subject of ethical controversy, primarily due to the destruction of human embryos involved in the derivation of new stem cell lines. This ethical dilemma has significantly impeded the progress of stem cell-based therapeutic developments. In contrast, iPSCs offer a promising alternative without the associated ethical concerns, as their production does not require the use of embryos or oocytes.

Adult stem cells, another avenue for stem cell research and clinical application, have garnered considerable interest due to their ability to contribute to tissue repair and regeneration. However, these cells present notable limitations, including restricted in vitro expansion capacity and the lack of definitive pluripotency. While adult stem cells continue to hold value in regenerative medicine, these constraints have prompted ongoing exploration into more versatile cell types.

Currently, embryonic stem cell lines are often derived from blastocysts obtained from surplus embryos produced during in vitro fertilization (IVF) procedures. However, this source is inherently limited, as the availability of overfertilized eggs from IVF clinics is finite. The restricted supply of embryonic material further complicates the development of ESC-based therapies, raising questions about the sustainability of such approaches in the long term.

The debates surrounding the ethics of stem cell research are deeply rooted in various philosophical, ethical, and religious viewpoints. For instance, the concept of "savior siblings"—children conceived to provide compatible stem cells for an ailing sibling—has sparked controversy over the potential commodification of embryos for therapeutic purposes. The central focus of the ethical discourse lies in the balance between potential benefits and associated risks. In this context, a greater perceived benefit may justify higher levels of acceptable risk. Importantly, safety concerns are not limited to individual patients but extend to broader societal implications, necessitating careful consideration of the risks and benefits of emerging stem cell technologies (Ray et al., 2015).

As the application of ESCs in regenerative medicine expands, the broader acceptance of ESC-based therapies is likely to increase, potentially leading to their use in treating a wide array of conditions, such as diabetes, spinal cord injuries, liver diseases, and heart transplants. The immense therapeutic potential of stem cells in tissue regeneration has driven the search for clinically viable sources of stem cells. However, certain manipulations, particularly those involving the destruction of embryos or the reprogramming of cells, have raised significant ethical concerns. The use of human ESCs is highly controversial, primarily because obtaining them requires the destruction of human embryos, a matter that continues to provoke ethical discussions.

To circumvent the ethical challenges associated with hESCs, human-induced pluripotent stem cells (hiPSCs) have been developed through the reprogramming of somatic cells to acquire characteristics similar to those of hESCs. While hiPSCs present a promising alternative, this technology is not without ethical and safety concerns. Issues such as aberrant reprogramming, as well as the potential for tumorigenesis during stem cell therapies, highlight the need for caution in the clinical application of hiPSCs.

Gene editing in human embryos offers another promising avenue for disease prevention and correction. However, this technology is fraught with ethical and societal implications. Stringent regulations and widespread societal engagement are essential to ensure that gene editing is employed responsibly (Lohmor et al., 2020). The involvement of government bodies, the scientific community, and society at large is crucial in shaping the ethical trajectory of stem cell research and gene editing (Hernández-Melchor et al., 2022).

In the future, the responsible development of stem cell therapies and gene editing technologies will require a comprehensive regulatory framework, including ethical guidelines and appropriate permitting systems. To ensure the ethical and safe implementation of these advanced biotechnologies, a collaborative approach involving multiple stakeholders is paramount.

Adult Stem Cells

Adult stem cells play a crucial role in the maintenance and repair of differentiated tissues and organs, with the capacity to differentiate into specific, specialized cell types. Unlike embryonic stem cells, which possess pluripotency, adult stem cells exhibit a more restricted differentiation potential. Their primary function is to reside within their respective tissues, remaining quiescent until they are mobilized to participate in tissue regeneration and repair processes in response to injury or physiological demand.

Adult stem cells are categorized according to their tissue of origin and functional capabilities. Hematopoietic stem cells (HSCs) are essential for the ongoing regeneration of blood and immune cells and are primarily found in the bone marrow (Cecerska-Heryć et al., 2023). In contrast, mesenchymal stem cells (MSCs) are multipotent cells located in various tissues, including bone marrow, adipose tissue, and umbilical cord blood. These cells possess the potential to differentiate into multiple mesodermal lineages, including osteocytes, chondrocytes, and adipocytes, thus playing a crucial role in tissue repair and engineering (Lovell-Badge, 2001).

Bone Marrow-Derived Mesenchymal Stem Cells (BM-MSCs) are non-hematopoietic stem cells with significant applications in regenerative medicine and therapeutic interventions. These cells possess the capacity for self-renewal and indefinite proliferation, making them a promising candidate for various clinical applications. One of the prominent areas of research involves the application of BM-MSCs in diabetes treatment, which has attracted significant interest. Preclinical studies have demonstrated that the introduction of BM-MSCs into human islet cell cultures extends the lifespan of islet cells and significantly enhances insulin production. Although the precise mechanisms underlying the therapeutic effects of BM-MSCs remain incompletely understood, current hypotheses suggest that their action is primarily mediated through paracrine signaling pathways (Yu et al., 2008).

Beyond diabetes treatment, BM-MSCs have been explored for other regenerative applications, including periodontal diseases. Specifically, attempts have been made to regenerate craniofacial bone structures using BM-MSCs, highlighting the versatility of these stem cells in tissue engineering (Mebarki et al., 2021).

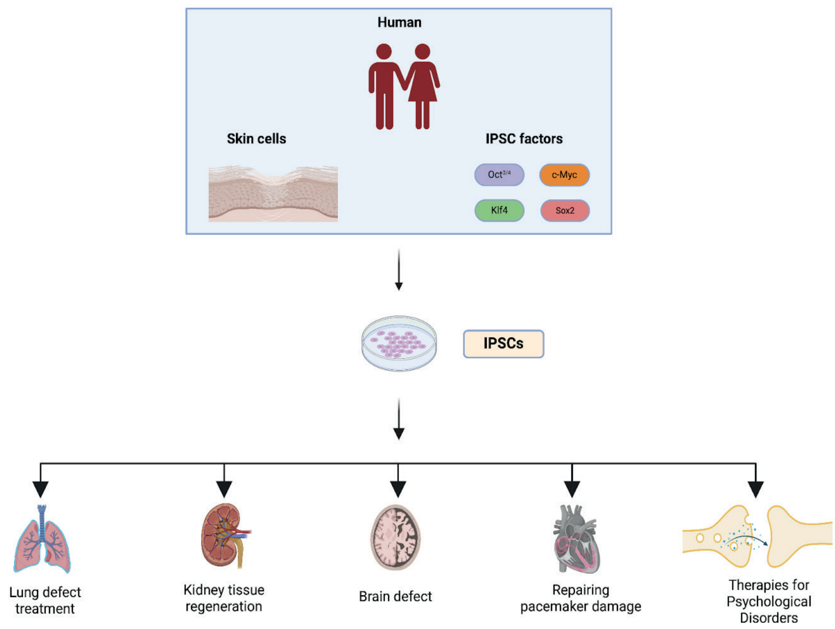
Umbilical cord-derived mesenchymal stem cells (UC-MSCs) offer a viable alternative to BM-MSCs, presenting fewer ethical issues compared to ESCs. Stem cells isolated from Wharton's jelly, a component of the umbilical cord, are particularly notable for their homogeneous structure and enhanced ability to differentiate into insulin-producing beta cells. In experimental studies on mice, adding UC-MSC-derived beta cells resulted in a marked reduction in glucose levels (Sah, 2016). Additionally, the expression of CD34+ in these cells has been associated with a reduced likelihood of transplant rejection, further bolstering their therapeutic potential. UC-MSCs are genetically closer to ESCs and exhibit a higher self-renewal capacity than BM-MSCs. However, a critical limitation in the clinical use of UC-MSCs is the need for chromosomal testing to rule out genetic abnormalities in the donor baby.

UC-MSCs have also demonstrated potential in addressing connective tissue injuries. Recent research has indicated that transplantation of allogeneic UC-MSCs can promote the restoration of myelination in laryngeal tissues following radiotherapy. Furthermore, a study conducted on pig knee models revealed that the transplantation of UC-MSCs, combined with hydrogel components, led to the regeneration of hyaline cartilage, suggesting a promising future for UC-MSCs in treating joint injuries and cartilage repair (Nagamura-Inoue and He, 2014).

Induced Pluripotent Stem Cells (iPSCs): Revolutionizing Personalized Medicine

iPSCs were first isolated by Takahashi and Yamanaka 2006 (Takahashi and Yamanaka, 2006). Their pioneering work demonstrated that skin fibroblasts could be reprogrammed into ESC-like cells by introducing specific transcription factors, including Sox2, Oct3/4, Klf4, and c-Myc. Despite facing numerous ethical challenges, iPSCs have since gained prominence as a vital tool in the regeneration of diseased or damaged tissues, largely due to advances in stem cell Technologies (Figure 2).

Figure 2
In regenerative medicine, iPSCs enable the conversion of fully differentiated skin fibroblast cells into cells resembling ESC-like cells through the use of sophisticated İPSC technology



A significant application of iPSCs is in addressing age-related macular degeneration (ARMD). In preclinical studies, iPSC-derived neuronal progenitor cells were transplanted into the retina, resulting in the formation of five to six layers of photoreceptor nuclei. This approach successfully slowed the progression of ARMD, highlighting the potential of iPSCs in ocular regenerative therapies (Tang et al., 2017). Additionally, iPSCs have been utilized to address disruptions in placental function. By generating transgenic-independent trophoblast-like stem cells (ITSCs) from iPSCs, researchers have been able to reverse certain placental pathophysiologies, offering a novel approach to managing such conditions.

A further application of iPSC technology involves the generation of serotonin-like neurons, a process with potential implications for treating psychiatric disorders. Serotonin neuron degeneration, often caused by external factors, is linked to conditions such as bipolar disorder, schizophrenia, and depression. Researchers have successfully generated serotonin-like neurons by manipulating Wnt signaling in human iPSCs under specific culture conditions, which possess similar physiological properties to native serotonin neurons. This advancement presents a hopeful approach for treating schizophrenia, as these cells may help restore or compensate for disrupted serotonergic pathways.

In the field of diabetes research, iPSCs have emerged as a key resource for developing novel therapies. Recent studies have demonstrated the ability to reprogram skin fibroblasts into definitive endodermal progenitor cells, which subsequently differentiate into pancreatic beta cells. This development provides a potentially safe and effective approach for restoring insulin production and addressing the underlying causes of diabetes (Ng and Alexander, 2017).

Overall, iPSCs represent a transformative technology in regenerative medicine, offering a safer and more ethically favorable alternative for the treatment of degenerative disorders. Their ability to generate patient-specific cells for various therapeutic applications underscores their growing importance in clinical and research settings. Ongoing investigation into İPSC technology offers significant potential for enhancing the treatment of various diseases.

Clinical Applications of Stem Cells

Disease occurs when the physiological balance is disturbed for a variety of reasons. The extent to which tissues and organs lose their function determines the prognosis of diseases. Today, many diseases have no effective treatment or only temporary treatments. Scientific and technological developments in recent years have opened up treatment options for many diseases.

Stem cell therapy has emerged as one of the most promising treatment modalities over the past decade and a half. There is no doubt that stem cells transform into active cells in tissues and organs that have lost their function, and the positive results from numerous in vitro and in vivo studies have led to the use of stem cells in clinical trials.

The most commonly utilised stem cell types are MSCs, ESCs, iPSCs and neural stem cells (NSCs).

MSCs were initially identified in bone marrow and have since been found in various other tissues, including adipose tissue, dental pulp, umbilical cord, muscle, skin, placenta, and synovial fluid (L. et al., 2019). These cells possess the capability to differentiate into multiple cell types, such as muscle, adipose tissue, bone, nerve, cartilage, myocardium, liver, and cornea (P. Han et al., 2019). Their easy accessibility from different tissues, combined with their differentiation potential, makes MSCs a preferred choice in many research studies.

ESCs have become a promising therapeutic alternative, primarily because of their remarkable ability to differentiate into various cell types. ESCs are derived from embryos or blastocysts (Duan et al., 2021). The ethical implications of obtaining ESCs are a matter of contention.

Induced pluripotent stem cells exhibit a capacity for differentiation into approximately 200 distinct cell types, a phenomenon that is analogous to that observed in ESCs (Doss & Sachinidis, 2019). As iPSCs are derived from somatic cells, there is no ethical conflict. In many studies, the use of iPSCs that can differentiate into a large number of cells is preferred.

NSCs are primarily located in two key niches within the brain: the subventricular zone and the dentate gyrus of the hippocampus. These cells have the ability to differentiate into various types of cells, including neurons, astrocytes, and oligodendrocytes (Johansson et al., 1999).

Stem Cell Applications in Brain and Nervous System Diseases

Stem cell applications have been attempted and continue to be attempted in the treatment of numerous significant diseases. The most prominent of these diseases are those affecting the brain and nervous system. Annually, a considerable number of individuals are affected by conditions that impact the nervous system, including traumatic brain injury, neurodegenerative diseases, stroke, and spinal cord injury (Chiò et al., 2013; Collaborators et al., 2021; James et al., 2019).

A traumatic brain injury is defined as a physical damage to the brain resulting from external force. A loss of cognitive and physical function may occur. Traumatic brain injury is typified by mechanical damage and subsequent inflammation occurring subsequent to the initial damage (Lozano et al., 2015). In traumatic brain injury, the formation of hematomas, disruption of the blood-brain barrier, and cerebral edema result in chronic brain damage (Stocchetti et al., 2007). The current procedures in place for the treatment of traumatic brain injury have been demonstrated to be ineffective. It is hypothesised that stem cells may be effective in the healing of traumatic brain injury due to their anti-inflammatory, anti-apoptotic, angiogenic and cell growth promoting properties (D. Han et al., 2015). In order for neurological functions to recover in a patient with traumatic brain injury, other neurons need to compensate for the dysfunction, new neurons need to be produced and new neurons need to migrate to the area and become functional. However, the human brain produces limited new neurons. Stem cell therapy is considered a novel approach for enhancing neurological functions following traumatic brain injury. (S. Wang et al., 2013). The role of different cell types in traumatic brain injury has been the subject of extensive investigation. BM-MSCs are commonly used because of their ease of collection and favorable safety profile. Following transplantation, stem cells are transported to the damaged area, where they exert an immunomodulatory effect by facilitating neuronal repair (Pluchino et al., 2005). Stem cells facilitate the reinnervation of damaged brain tissue by differentiating into various cell types, including neurons and astrocytes (Fujiwara et al., 2004). Additionally, stem cells facilitate nerve regeneration through the secretion of growth factors, including nerve growth factor (NGF), vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF), fibroblast growth factor (FGF), and hepatocyte growth factor (HGF) (Zhong et al., 2003).

Neurodegenerative diseases are defined as disorders characterised by a loss of neurons in the nervous system, including a reduction in the number, structure and function of these cells. Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) are examples of neurodegenerative diseases that affect a significant proportion of the population. The aetiology of each disease is distinct, and currently, there is no efficacious treatment available. Stem cells have gained significant attention as a highly promising therapeutic approach owing to their ability to self-renew and differentiate into neurons, astrocytes, and oligodendrocytes. The transplantation of ESCs into transgenic mice modelling AD has been demonstrated to improve the cognitive deficits observed in these mice (Liu, 2021). In the AD model utilising MSCs, it was observed that Amyloid β-induced cell death in the hippocampus was prevented, and memory was improved (Kim et al., 2020). A deficiency of dopamine-producing neurons has been observed in patients with PD. It is possible that stem cell applications may prove to be an efficacious treatment. Nerve cells obtained from human fetuses were observed to become dopamine-producing neurons following transplantation into the brains of patients (Kefalopoulou et al., 2014). Following transplantation, MSCs can differentiate into dopaminergic neurons and astrocytes. They also enhance the survival of dopaminergic neurons by secreting growth factors such as NGF and VEGF (Tanaka et al., 2022). Studies have demonstrated that iPSCs, MSCs and NSCs employed in HD diminish neuronal damage and facilitate improvements in motor functions (Bachoud-Lévi et al., 2021; Colpo et al., 2019; Zuccato et al., 2010).

Ischemic stroke is defined as a condition in which the vessels leading to the brain are obstructed by a thrombus or embolism, resulting in a reduction in blood flow, cell death and neurological dysfunctions due to an insufficient cerebral blood supply (Iadecola & Anrather, 2011). A loss of function related to the affected area of the brain occurs. The treatment of ischaemic stroke employs a range of therapeutic modalities, including antithrombotic drugs, intravascular thrombectomy and neuroprotective agents. Stem cells of the MSC, NSC, ESC and iPSC varieties have been employed with considerable frequency in the treatment of ischaemic stroke. Following the onset of ischemia, proinflammatory cytokines and oxygen reagents are released from the affected region (Pawluk et al., 2020). A study utilising MSCs in the context of ischaemic stroke demonstrated a reduction in inflammatory cell infiltration into the brain, which was attributed to a decrease in astrocyte apoptosis and neutrophil release (Cheng et al., 2018). Some studies have indicated that stem cells enhance BDNF expression and sensory perception following a stroke (Asgari Taei et al., 2021; Boese et al., 2020). Furthermore, pluripotent stem cells derived from dental pulp have been demonstrated to facilitate cognitive function recovery, neuronal differentiation, and the reduction of the infarct area (Sowa et al., 2018).

A spinal cord injury is defined as a traumatic lesion of the nerves in the spinal cord, which may result in either permanent or temporary sensory-motor deficit, as well as impaired bowel and bladder function. The primary objective in the treatment of spinal cord injuries is the protection of the nervous system, the regeneration of nerves, and the modulation of nerve function. The restricted availability of adult nerve regeneration enhances the potential applicability of stem cell therapies. Clinical studies have identified MSCs and NSCs as the most significant stem cell types involved in the recovery of damaged neurons (de Araújo et al., 2022). Bone marrow-derived MSCs have demonstrated the ability to cross the blood-brain barrier, facilitating the restoration of neurological function in patients with paralysis by generating new neurons (Muheremu et al., 2016). A study utilising ESCs in the subacute phase of spinal cord injury demonstrated a 96% recovery of neurological functions at the conclusion of the one-year observation period (Fessler et al., 2022). There is a paucity of studies utilising ESCs in the context of spinal cord injuries. Although research on ESCs is still limited, they have shown potential as a promising option for addressing spinal cord injuries.

The use of stem cells in treating diseases of the brain and nervous system represents a highly promising area of research. The restricted proliferative capacity of the adult nervous system renders stem cell applications an appropriate avenue for treatment. Given their capacity to differentiate into neurons, astrocytes and oligodendrocytes, stem cells are believed to offer a promising avenue for the treatment of numerous nervous system disorders. Despite the efficacy of stem cell applications being demonstrated in numerous pre-clinical studies, the evidence from clinical studies is still insufficient.

Stem Cell Application in Cardiovascular Diseases

Cardiovascular diseases represent a significant global health burden. Myocardial infarction (MI) and heart failure are prevalent cardiovascular diseases, underscoring the necessity for efficacious treatment modalities. The capacity of the heart muscle to regenerate itself is severely limited. The average human lifespan sees less than 50% of cardiomyocytes replaced. As a consequence of the natural ageing process, the rate of regeneration declines further still, reaching 0.45% at the age of 75 (Bergmann et al., 2009). Given the restricted regenerative capacity of cardiac tissue, regeneration is not a viable option for addressing damage to the cardiac muscle. In cases of tissue damage, fibrous tissue replaces the injured area, leading to the creation of non-functional scar tissue (Gholoobi et al., 2021). The ability of stem cells to differentiate into cardiomyocytes and develop into functional heart muscle could be advantageous for addressing cardiovascular diseases. A substantial body of evidence from numerous studies indicates that myocardial regeneration and infarct area are diminished following the transplantation of multipotent or pluripotent stem cells (Csöbönyeiová et al., 2022). In rodents, guinea pigs, pigs and non-human primates, the administration of stem cells following MI has been shown to prolong survival (Kempf et al., 2015; Riegler et al., 2015; Romagnuolo et al., 2019).

ESCs have been observed to differentiate into functional cardiomyocytes, and to increase the expression of ion current proteins and cellular signalling proteins (Mehanna et al., 2022; Mummery et al., 2003; Sartiani et al., 2007). The transplantation of human ESCs into non-human primates following MI resulted in a significant increase in contractile function for a period of three months (Y.-W. Liu et al., 2018). The differentiation of iPSCs from fibroblasts into cardiomyocytes and subsequent injection into infarcted monkeys led to the restoration of heart function through the formation of new myocardium (Shiba et al., 2016). The utilisation of patient-specific iPSCs has provided alternative avenues that can potentially alter clinical applications, such as heart transplantation. It is anticipated that iPSCs will become increasingly prevalent in clinical studies, given their capacity to differentiate into functional cardiomyocytes with high efficiency. Nevertheless, pluripotent stem cells are prone to forming teratomas and thus require monitoring following administration. BM-MSCs are frequently the preferred option in both clinical and preclinical studies. A substantial body of evidence exists demonstrating the efficacy of BM-MSCs in the treatment of cardiovascular disease. These cells have been shown to promote myocardial formation, enhance vascular structure, and facilitate coronary artery development (Assmus et al., 2002; Fernández-Avilés et al., 2004; Wollert et al., 2004). BM-MSCs remain a viable and safe option for the treatment of cardiovascular diseases.

Stem Cell Application in Liver Diseases

Liver diseases, both acute and chronic, are associated with high rates of morbidity and mortality (Asrani et al., 2019). The liver is capable of regenerating itself following damage. The process of liver regeneration is a complex one. A resection of 30% of the liver results in hyperplasia of the hepatocytes, whereas a resection of over two-thirds of the liver or chemical damage leads to hypertrophy of the hepatocytes (Miyaoka et al., 2012). Notwithstanding the liver's considerable regenerative capacity, regeneration does not occur in chronic liver diseases. In cases of advanced and chronic liver disease, liver transplantation is a viable option; however, the limited number of available donors has resulted in a decline in the rate of liver transplantation.

Stem cell application represents a potential therapeutic avenue for the treatment of liver diseases. A number of different cell types are frequently investigated in studies, including MSCs, iPSCs and hepatic progenitor cells (HPCs). MSCs obtained from disparate body parts have been demonstrated to induce regeneration by increasing hypertrophy and hyperplasia in hepatocytes in the context of liver disease (Y. Liu et al., 2018; S. Zhang et al., 2012). Furthermore, MSCs benefit from secreting a multitude of cytokines that contribute to regeneration (Jung et al., 2013). iPSCs enhance liver recovery by reducing the necrotic area in acute liver injury (Chiang et al., 2015). HPCs are one of the stem cell types employed for hepatocyte production; however, their clinical utilisation has declined due to the potential for carcinogenesis (Jia et al., 2013). The application of stem cells in the management of liver diseases has markedly risen over the last ten years. Clinical trials are currently in phase I and phase II, and a variety of stem cell types have been employed (Nevens et al., 2021; Xu et al., 2019; Y. Zhang et al., 2021). A substantial body of evidence from preclinical studies and promising clinical trials lends support to the notion that stem cell therapies may offer a promising alternative for the treatment of liver diseases.

Stem Cell Application in Other Diseases

Given their capacity to differentiate into a multitude of cells, stem cells have a vast array of potential applications. Stem cells have been the subject of investigation as a potential treatment for a number of diseases, including kidney disease, lung disease and diabetes mellitus.

Both acute and chronic kidney diseases are prevalent conditions that continue to affect a significant proportion of the population, with an increasing prevalence observed over time. It is projected that chronic kidney disease will become the fifth leading cause of mortality by 2040 (Foreman et al., 2018). To date, there is no effective treatment for chronic kidney disease. Despite the availability of dialysis or kidney transplantation options in advanced cases, patients often encounter significant financial burdens and difficulties in identifying suitable donors (Bastani, 2020). A substantial body of preclinical evidence indicates that stem cell therapy can accelerate renal tubular cell proliferation, reduce tubular cell apoptosis, and restore renal function (Sávio-Silva et al., 2021; Tseng et al., 2021; Xie et al., 2022). The results of preclinical studies were successful, and phase I and phase II clinical trials were conducted in the treatment of kidney diseases. Clinical trials involving patients with acute kidney injury and polycystic kidney disease have demonstrated that stem cell therapy can enhance renal function. This improvement is indicated by an increase in the glomerular filtration rate, a decrease in serum creatinine levels, and a reduction in the urine albumin-to-creatinine ratio (Chebib & Torres, 2016; Swaminathan et al., 2021).

Diabetes mellitus is a metabolic disease that results from a deficiency in the production or function of insulin, a hormone released from beta cells in the pancreas (Memon & Abdelalim, 2020). In type 1 diabetes mellitus, an autoimmune response occurs against the beta cells, resulting in insulin deficiency. In type 1 diabetes mellitus, patients are required to administer exogenous insulin supplements. However, this situation has a detrimental impact on patients' physical, psychological and financial well-being. Stem cell therapies have the potential to be advantageous in disease treatment by encouraging the transformation of cells into insulin-producing beta cells. Several clinical and preclinical investigations have shown that stem cells can effectively normalize HbA1C levels and fasting blood glucose levels in individuals with diabetes mellitus (Karimova et al., 2022; Li et al., 2012; Ye et al., 2017).

Coronavirus disease 2019 (Covid-19) is a respiratory illness that has spread globally, becoming a pandemic. The advent of the SARS-CoV-2 pandemic has prompted researchers to explore the potential of stem cells in the treatment of lung diseases. In preclinical studies investigating the potential of stem cells to repair lung injury, the administration of these cells was observed to reduce the levels of proinflammatory cytokines and bronchoalveolar lavage fluid (H. Wang et al., 2013). In clinical trials employing stem cells in the context of SARS-CoV-2 infection, there was a reduction in lesion volume and lung damage (Shi et al., 2021).

Stem cells have the potential to be employed as a cellular therapy in the treatment of numerous diseases. Furthermore, exosomes released from stem cells are employed as a treatment option. Furthermore, the advancement of bioengineering techniques has enabled the transplantation of stem cells into three-dimensional biomaterials. The accelerated advancement of organoids, including those of the liver and kidney, indicates that they may eventually supplant organ transplantation as a means of treatment.

The Challenges of Stem Cell Applications

While stem cell applications offer numerous advantages, they also present a number of challenges in practice. In the course of scientific investigation, a multitude of stem cell types have been subjected to examination in the context of a single disease. It is necessary to investigate different types of stem cells in order to determine the most appropriate stem cell for the disease. A variety of routes of administration have been employed in studies involving the transplantation of stem cells. A variety of administration routes may be employed in stem cell studies, including intravenous, intrathecal, intraarterial, intramuscular, and local routes (Pharoun et al., 2024). It is of great importance to ascertain the most appropriate route of administration for the disease in question. Intravenous administration is a common and generally safer method, although it has been observed that the number of cells reaching the target area is reduced in cases of brain disease. A further challenge in the field of stem cell applications is the determination of the optimal dosage of stem cells to be administered. The application of a limited number of stem cells does not yield sufficient results; however, the administration of an excess of these cells increases the probability of carcinogenesis (Sun et al., 2024). Furthermore, some clinical trials are of a short duration and have an insufficient sample size. In light of these challenges, further research and a longer timescale are required for stem cell applications to become a standard treatment option.

Conclusion

Stem cells have emerged as a pivotal resource in regenerative medicine due to their remarkable capacity to differentiate into a wide range of specialized cell types, offering substantial potential for treating numerous diseases that were previously deemed untreatable. Nonetheless, the application of stem cell research in clinical settings still encounters considerable obstacles. One of the primary hurdles is the difficulty in achieving consistent purity and homogeneity in stem cell populations, which is critical for ensuring reproducible and reliable therapeutic outcomes. Another major challenge is the limited lifespan of stem cells in vitro and their propensity for senescence over time. Addressing this issue is essential for harnessing the full therapeutic capabilities of stem cells. Advances in optimizing culture conditions—such as incorporating growth factors, extracellular matrix components, and enhancing the microenvironment—can improve stem cell viability, functionality, and overall therapeutic efficacy.

In addition to these technical obstacles, genetic and epigenetic alterations during stem cell culture present a significant concern. These changes can compromise the stability, differentiation capacity, and safety of stem cells for clinical applications, underscoring the need for stringent quality control measures in the production of stem cell lines.

A further challenge is immunological rejection, which poses a significant barrier to the success of stem cell therapies. The host immune system may recognize transplanted stem cells as foreign, initiating an immune response that can diminish the survival and integration of these cells into the recipient's tissues. Overcoming immunogenicity remains a key focus in advancing stem cell-based therapies. Moreover, the large-scale production of stem cells for therapeutic purposes remains labor-intensive, time-consuming, and costly. Innovations in bioprocessing, such as the use of bioreactors and automated cell culture systems, hold promise for improving the efficiency and scalability of stem cell production, potentially making these therapies more accessible and cost-effective.

Despite the challenges faced by the field, the role of stem cells in regenerative medicine is increasingly recognized as a transformative avenue for treating diseases that currently lack effective treatments. Overcoming these obstacles, along with continued advances in stem cell biology, will be crucial for unlocking the full potential of stem cells in clinical applications and revolutionizing the field of regenerative medicine.

References

Asgari Taei, A., Nasoohi, S., Hassanzadeh, G., Kadivar, M., Dargahi, L., & Farahmandfar, M. (2021). Enhancement of angiogenesis and neurogenesis by intracerebroventricular injection of secretome from human embryonic stem cell-derived mesenchymal stem cells in ischemic stroke model. *Biomedicine & Pharmacotherapy*, *140*, 111709. https://doi.org/10.1016/j.biopha.2021.111709

Asrani, S. K., Devarbhavi, H., Eaton, J., & Kamath, P. S. (2019). Burden of liver diseases in the world. *Journal of Hepatology*, *70*(1), 151–171. https://doi.org/10.1016/j.jhep.2018.09.014

Assmus, B., Schächinger, V., Teupe, C., Britten, M., Lehmann, R., Döbert, N., Grünwald, F., Aicher, A., Urbich, C., Martin, H., Hoelzer, D., Dimmeler, S., & Zeiher, A. M. (2002). Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI). *Circulation*, *106*(24), 3009–3017. https://doi.org/10.1161/01.CIR.0000043246.74879.CD

Aval, S. F., Lotfi, H., Sheervalilou, R., & Zarghami, N. (2017). Tuning of major signaling networks (TGF-β, Wnt, Notch and Hedgehog) by miRNAs in human stem cells commitment to different lineages: Possible clinical application. *Biomedicine & Pharmacotherapy*, *91*, 849-860.

Bachoud-Lévi, A.-C., Massart, R., & Rosser, A. (2021). Cell therapy in Huntington's disease: Taking stock of past studies to move the field forward. *Stem Cells*, *39*(2), 144–155. https://doi.org/10.1002/stem.3300

Bastani, B. (2020). The present and future of transplant organ shortage: Some potential remedies. *Journal of Nephrology*, *33*(2), 277–288. https://doi.org/10.1007/s40620-019-00634-x

Bergmann, O., Bhardwaj, R. D., Bernard, S., Zdunek, S., Barnabé-Heider, F., Walsh, S., Zupicich, J., Alkass, K., Buchholz, B. A., Druid, H., Jovinge, S., & Frisén, J. (2009). Evidence for Cardiomyocyte Renewal in Humans. *Science*, *324*(5923), 98–102. https://doi.org/10.1126/science.1164680

Boese, A. C., Eckert, A., Hamblin, M. H., & Lee, J.-P. (2020). Human neural stem cells improve early stage stroke outcome in delayed tissue plasminogen activator-treated aged stroke brains. *Experimental Neurology*, *329*, 113275. https://doi.org/10.1016/j.expneurol.2020.113275

Cecerska-Heryć, E., Pękała, M., Serwin, N., Gliźniewicz, M., Grygorcewicz, B., Michalczyk, A., ... & Dołęgowska, B. (2023). The use of stem cells as a potential treatment method for selected neurodegenerative diseases. *Cellular and Molecular Neurobiology*, *43*(6), 2643-2673.

Chebib, F. T., & Torres, V. E. (2016). Autosomal Dominant Polycystic Kidney Disease: Core Curriculum 2016. *American Journal of Kidney Diseases*, *67*(5), 792–810. https://doi.org/10.1053/j.ajkd.2015.07.037

Cheng, Z., Wang, L., Qu, M., Liang, H., Li, W., Li, Y., Deng, L., Zhang, Z., & Yang, G.-Y. (2018). Mesenchymal stem cells attenuate blood-brain barrier leakage after cerebral ischemia in mice. *Journal of Neuroinflammation*, *15*(1), 135. https://doi.org/10.1186/s12974-018-1153-1

Chiang, C.-H., Wu, W.-W., Li, H.-Y., Chien, Y., Sun, C.-C., Peng, C.-H., Lin, A. T.-L., Huang, C.-S., Lai, Y.-H., Chiou, S.-H., Hung, S.-I., Chang, Y.-L., Lan, Y.-T., Liu, D.-M., Chien, C.-S., Huo, T.-I., Lee, S.-D., & Wang, C.-Y. (2015). Enhanced Antioxidant Capacity of Dental Pulp-Derived iPSC-Differentiated Hepatocytes and Liver Regeneration by Injectable HGF-Releasing Hydrogel in Fulminant Hepatic Failure. *Cell Transplantation*, *24*(3), 541–559. https://doi.org/10.3727/096368915X686986

Chiò, A., Logroscino, G., Traynor, B. J., Collins, J., Simeone, J. C., Goldstein, L. A., & White, L. A. (2013). Global Epidemiology of Amyotrophic Lateral Sclerosis: A Systematic Review of the Published Literature. *Neuroepidemiology*, *41*(2), 118–130. https://doi.org/10.1159/000351153

Collaborators, G. 2019 S., Feigin, V. L., Stark, B. A., Johnson, C. O., Roth, G. A., Bisignano, C., Abady, G. G., Abbasifard, M., Abbasi-Kangevari, M., Abd-Allah, F., Abedi, V., Abualhasan, A., Abu-Rmeileh, N. M., Abushouk, A. I., Adebayo, O. M., Agarwal, G., Agasthi, P., Ahinkorah, B. O., Ahmad, S., … Choudhari, S. G. (2021). Global, regional, and national burden of stroke and its risk factors, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet Neurology*, *20*(10), 795–820. https://doi.org/10.1016/s1474-4422(21)00252-0

Colpo, G. D., Furr Stimming, E., & Teixeira, A. L. (2019). Stem cells in animal models of Huntington disease: A systematic review. *Molecular and Cellular Neuroscience*, *95*, 43–50. https://doi.org/10.1016/j.mcn.2019.01.006

Csöbönyeiová, M., Beerová, N., Klein, M., Debreová-Čeháková, M., & Danišovič, Ľ. (2022). Cell-Based and Selected Cell-Free Therapies for Myocardial Infarction: How Do They Compare to the Current Treatment Options? *International Journal of Molecular Sciences*, *23*(18), Article 18. https://doi.org/10.3390/ijms231810314

de Araújo, L. T., Macêdo, C. T., Damasceno, P. K. F., das Neves, Í. G. C., de Lima, C. S., Santos, G. C., de Santana, T. A., Sampaio, G. L. de A., Silva, D. N., Villarreal, C.

F., Chaguri, A. C. de C., da Silva, C. G., Mota, A. C. de A., Badaró, R., Ribeiro dos Santos, R., & Soares, M. B. P. (2022). Clinical Trials Using Mesenchymal Stem Cells for Spinal Cord Injury: Challenges in Generating Evidence. *Cells*, *11*(6), Article 6. https://doi.org/10.3390/cells11061019

Doss, M. X., & Sachinidis, A. (2019). Current Challenges of iPSC-Based Disease Modeling and Therapeutic Implications. *Cells*, *8*(5), Article 5. https://doi.org/10.3390/cells8050403

Duan, R., Gao, Y., He, R., Jing, L., Li, Y., Gong, Z., Yao, Y., Luan, T., Zhang, C., Li, L., & Jia, Y. (2021). Induced Pluripotent Stem Cells for Ischemic Stroke Treatment. *Frontiers in Neuroscience*, *15*. https://doi.org/10.3389/fnins.2021.628663

Ellerström, C., Strehl, R., Noaksson, K., Hyllner, J., & Semb, H. (2007). Facilitated expansion of human embryonic stem cells by single-cell enzymatic dissociation. *Stem cells*, *25*(7), 1690-1696.

Fernández-Avilés, F., San Román, J. A., García-Frade, J., Fernández, M. E., Peñarrubia, M. J., de la Fuente, L., Gómez-Bueno, M., Cantalapiedra, A., Fernández, J., Gutierrez, O., Sánchez, P. L., Hernández, C., Sanz, R., García-Sancho, J., & Sánchez, A. (2004). Experimental and Clinical Regenerative Capability of Human Bone Marrow Cells After Myocardial Infarction. *Circulation Research*, *95*(7), 742–748. https://doi.org/10.1161/01.RES.0000144798.54040.ed

Fessler, R. G., Ehsanian, R., Liu, C. Y., Steinberg, G. K., Jones, L., Lebkowski, J. S., Wirth, E. D., & McKenna, S. L. (2022). *A phase 1/2a dose-escalation study of oligodendrocyte progenitor cells in individuals with subacute cervical spinal cord injury*. https://doi.org/10.3171/2022.5.SPINE22167

Foreman, K. J., Marquez, N., Dolgert, A., Fukutaki, K., Fullman, N., McGaughey, M., Pletcher, M. A., Smith, A. E., Tang, K., Yuan, C.-W., Brown, J. C., Friedman, J., He, J., Heuton, K. R., Holmberg, M., Patel, D. J., Reidy, P., Carter, A., Cercy, K., … Murray, C. J. L. (2018). Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: Reference and alternative scenarios for 2016–40 for 195 countries and territories. *The Lancet*, *392*(10159), 2052–2090. https://doi.org/10.1016/S0140-6736(18)31694-5

Fortier, L. A. (2005). Stem cells: classifications, controversies, and clinical applications. *Veterinary Surgery*, *34*(5), 415-423.

Fujiwara, Y., Tanaka, N., Ishida, O., Fujimoto, Y., Murakami, T., Kajihara, H., Yasunaga, Y., & Ochi, M. (2004). Intravenously injected neural progenitor cells of transgenic rats can migrate to the injured spinal cord and differentiate into neurons, astrocytes and oligodendrocytes. *Neuroscience Letters*, *366*(3), 287–291. https://doi.org/10.1016/j.neulet.2004.05.080

Gholoobi, A., Askari, V. R., Naghedinia, H., Ahmadi, M., Vakili, V., & Baradaran Rahimi, V. (2021). Colchicine effectively attenuates inflammatory biomarker high-sensitivity C-reactive protein (hs-CRP) in patients with non-ST-segment elevation myocardial infarction: A randomised, double-blind, placebo-controlled clinical trial. *Inflammopharmacology*, *29*(5), 1379–1387. https://doi.org/10.1007/s10787-021-00865-0

Han, D., Wu, C., Xiong, Q., Zhou, L., & Tian, Y. (2015). Anti-inflammatory Mechanism of Bone Marrow Mesenchymal Stem Cell Transplantation in Rat Model of Spinal Cord Injury. *Cell Biochemistry and Biophysics*, *71*(3), 1341–1347. https://doi.org/10.1007/s12013-014-0354-1

Han, P., Zang, Y., Akshita, J., & Hummel, T. (2019). Magnetic Resonance Imaging of

Human Olfactory Dysfunction. *Brain Topography*, *32*(6), 987–997. https://doi.org/10.1007/s10548-019-00729-5

Han, Y., Li, X., Zhang, Y., Han, Y., Chang, F., & Ding, J. (2019). Mesenchymal stem cells for regenerative medicine. *Cells*, *8*(8), 886.

Hernández-Melchor, D., López-Bayghen, E., & Padilla-Viveros, A. (2022). The patent landscape in the field of stem cell therapy: closing the gap between research and clinic. *F1000Research*, *11*.

Iadecola, C., & Anrather, J. (2011). The immunology of stroke: From mechanisms to translation. *Nature Medicine*, *17*(7), 796–808. https://doi.org/10.1038/nm.2399

Ilic, D., & Polak, J. M. (2011). Stem cells in regenerative medicine: introduction. *British medical bulletin*, *98*(1), 117-126.

James, S. L., Theadom, A., Ellenbogen, R. G., Bannick, M. S., Montjoy-Venning, W., Lucchesi, L. R., Abbasi, N., Abdulkader, R., Abraha, H. N., Adsuar, J. C., Afarideh, M., Agrawal, S., Ahmadi, A., Ahmed, M. B., Aichour, A. N., Aichour, I., Aichour, M. T. E., Akinyemi, R. O., Akseer, N., … Murray, C. J. L. (2019). Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*, *18*(1), 56–87. https://doi.org/10.1016/S1474-4422(18)30415-0

Jia, S.-Q., Ren, J.-J., Dong, P.-D., & Meng, X.-K. (2013). Probing the Hepatic Progenitor Cell in Human Hepatocellular Carcinoma. *Gastroenterology Research and Practice*, *2013*(1), 145253. https://doi.org/10.1155/2013/145253

Johansson, C. B., Momma, S., Clarke, D. L., Risling, M., Lendahl, U., & Frisén, J. (1999). Identification of a Neural Stem Cell in the Adult Mammalian Central Nervous System. *Cell*, *96*(1), 25–34. https://doi.org/10.1016/S0092-8674(00)80956-3

Jung, J., Choi, J. H., Lee, Y., Park, J.-W., Oh, I.-H., Hwang, S.-G., Kim, K.-S., & Kim, G. J. (2013). Human Placenta-Derived Mesenchymal Stem Cells Promote Hepatic Regeneration in CCl4-Injured Rat Liver Model via Increased Autophagic Mechanism. *Stem Cells*, *31*(8), 1584–1596. https://doi.org/10.1002/stem.1396

Karimova, M. V., Gvazava, I. G., & Vorotelyak, E. A. (2022). Overcoming the Limitations of Stem Cell-Derived Beta Cells. *Biomolecules*, *12*(6), Article 6. https://doi.org/10.3390/biom12060810

Kefalopoulou, Z., Politis, M., Piccini, P., Mencacci, N., Bhatia, K., Jahanshahi, M., Widner, H., Rehncrona, S., Brundin, P., Björklund, A., Lindvall, O., Limousin, P., Quinn, N., & Foltynie, T. (2014). Long-term Clinical Outcome of Fetal Cell Transplantation for Parkinson Disease: Two Case Reports. *JAMA Neurology*, *71*(1), 83–87. https://doi.org/10.1001/jamaneurol.2013.4749

Kempf, H., Kropp, C., Olmer, R., Martin, U., & Zweigerdt, R. (2015). Cardiac differentiation of human pluripotent stem cells in scalable suspension culture. *Nature Protocols*, *10*(9), 1345–1361. https://doi.org/10.1038/nprot.2015.089

Kim, D. Y., Choi, S. H., Lee, J. S., Kim, H. J., Kim, H. N., Lee, J. E., Shin, J. Y., & Lee, P. H. (2020). Feasibility and Efficacy of Intra-Arterial Administration of Embryonic Stem Cell Derived-Mesenchymal Stem Cells in Animal Model of Alzheimer's Disease. *Journal of Alzheimer's Disease*, *76*(4), 1281–1296. https://doi.org/10.3233/JAD-200026

Kumar, R., Saha, T., Chaturvedi, A., Singh, A., & Kumar, D. (2024). Deciphering the frontiers of stem cell research in regenerative medicine. *Chemical Biology*

Letters, *11*(4), 673-673.
L., P. K., Kandoi, S., Misra, R., S., V., K., R., & Verma, R. S. (2019). The mesenchymal stem cell secretome: A new paradigm towards cell-free therapeutic mode in regenerative medicine. *Cytokine & Growth Factor Reviews*, *46*, 1–9. https://doi.org/10.1016/j.cytogfr.2019.04.002
Lazarov, O., & Marr, R. A. (2010). Neurogenesis and Alzheimer's disease: at the crossroads. *Experimental neurology*, *223*(2), 267-281.
Li, L., Shen, S., Ouyang, J., Hu, Y., Hu, L., Cui, W., Zhang, N., Zhuge, Y., Chen, B., Xu, J., & Zhu, D. (2012). Autologous Hematopoietic Stem Cell Transplantation Modulates Immunocompetent Cells and Improves β-Cell Function in Chinese Patients with New Onset of Type 1 Diabetes. *The Journal of Clinical Endocrinology & Metabolism*, *97*(5), 1729–1736. https://doi.org/10.1210/jc.2011-2188
Liu, Y., Yang, F., Li, J., Wang, J., Wang, X., Zhang, Y., Yuan, X., Zhu, W., & Shi, X. (2018). Mesenchymal Stem Cells Enhance Liver Regeneration via Improving Lipid Accumulation and Hippo Signaling. *Stem Cells International*, *2018*(1), 7652359. https://doi.org/10.1155/2018/7652359
Liu, Y.-W., Chen, B., Yang, X., Fugate, J. A., Kalucki, F. A., Futakuchi-Tsuchida, A., Couture, L., Vogel, K. W., Astley, C. A., Baldessari, A., Ogle, J., Don, C. W., Steinberg, Z. L., Seslar, S. P., Tuck, S. A., Tsuchida, H., Naumova, A. V., Dupras, S. K., Lyu, M. S., … Murry, C. E. (2018). Human embryonic stem cell–derived cardiomyocytes restore function in infarcted hearts of non-human primates. *Nature Biotechnology*, *36*(7), 597–605. https://doi.org/10.1038/nbt.4162
Lohmor, S., Verma, R., Malik, V., & Kaushik, D. (2020). Current status of Regulatory perspectives on Stem Cell Therapy in India. *Chemical Biology Letters*, *7*(3), 176-182.
Lovell-Badge, R. (2001). The future for stem cell research. *Nature*, *414*(6859), 88-91.
Lozano, D., Gonzales-Portillo, G. S., Acosta, S., de la Pena, I., Tajiri, N., Kaneko, Y., & Borlongan, C. V. (2015). Neuroinflammatory responses to traumatic brain injury: Etiology, clinical consequences, and therapeutic opportunities. *Neuropsychiatric Disease and Treatment*, *11*, 97–106. https://doi.org/10.2147/NDT.S65815
Martino, G., Pluchino, S., Bonfanti, L., & Schwartz, M. (2011). Brain regeneration in physiology and pathology: the immune signature driving therapeutic plasticity of neural stem cells. *Physiological reviews*, *91*(4), 1281-1304.
Mebarki, M., Abadie, C., Larghero, J., & Cras, A. (2021). Human umbilical cord-derived mesenchymal stem/stromal cells: a promising candidate for the development of advanced therapy medicinal products. *Stem Cell Research & Therapy*, *12*, 1-10.
Mehanna, R. A., Essawy, M. M., Barkat, M. A., Awaad, A. K., Thabet, E. H., Hamed, H. A., Elkafrawy, H., Khalil, N. A., Sallam, A., Kholief, M. A., Ibrahim, S. S., & Mourad, G. M. (2022). Cardiac stem cells: Current knowledge and future prospects. *World Journal of Stem Cells*, *14*(1), 1–40. https://doi.org/10.4252/wjsc.v14.i1.1
Memon, B., & Abdelalim, E. M. (2020). Stem Cell Therapy for Diabetes: Beta Cells versus Pancreatic Progenitors. *Cells*, *9*(2), Article 2. https://doi.org/10.3390/cells9020283
Miyaoka, Y., Ebato, K., Kato, H., Arakawa, S., Shimizu, S., & Miyajima, A. (2012). Hypertrophy and Unconventional Cell Division of Hepatocytes Underlie Liver Regeneration. *Current Biology*, *22*(13), 1166–1175. https://doi.org/10.1016/j.cub.2012.05.016

Muheremu, A., Peng, J., & Ao, Q. (2016). Stem cell based therapies for spinal cord injury. *Tissue and Cell*, *48*(4), 328–333. https://doi.org/10.1016/j.tice.2016.05.008

Mummery, C., Ward-van Oostwaard, D., Doevendans, P., Spijker, R., van den Brink, S., Hassink, R., van der Heyden, M., Opthof, T., Pera, M., de la Riviere, A. B., Passier, R., & Tertoolen, L. (2003). Differentiation of Human Embryonic Stem Cells to Cardiomyocytes. *Circulation*, *107*(21), 2733–2740. https://doi.org/10.1161/01.CIR.0000068356.38592.68

Nagamura-Inoue, T., & He, H. (2014). Umbilical cord-derived mesenchymal stem cells: their advantages and potential clinical utility. *World journal of stem cells*, *6*(2), 195.

Nelson, C. G., Elta, T., Bannister, J., Dzandu, J., Mangram, A., & Zach, V. (2016). Severe traumatic brain injury: A case report. *The American journal of case reports*, *17*, 186.

Nevens, F., Gustot, T., Laterre, P.-F., Lasser, L. L., Haralampiev, L. E., Vargas, V., Lyubomirova, D., Albillos, A., Najimi, M., Michel, S., Stoykov, I., Gordillo, N., Vainilovich, Y., Barthel, V., Clerget-Chossat, N., & Sokal, E. M. (2021). A phase II study of human allogeneic liver-derived progenitor cell therapy for acute-on-chronic liver failure and acute decompensation. *JHEP Reports*, *3*(4), 100291. https://doi.org/10.1016/j.jhepr.2021.100291

Ng, A. P., & Alexander, W. S. (2017). Haematopoietic stem cells: past, present and future. *Cell death discovery*, *3*(1), 1-4.

Pawluk, H., Woźniak, A., Grześk, G., Kołodziejska, R., Kozakiewicz, M., Kopkowska, E., Grzechowiak, E., & Kozera, G. (2020). The Role of Selected Pro-Inflammatory Cytokines in Pathogenesis of Ischemic Stroke. *Clinical Interventions in Aging*, *15*, 469–484. https://doi.org/10.2147/CIA.S233909

Pharoun, J., Berro, J., Sobh, J., Abou-Younes, M.-M., Nasr, L., Majed, A., Khalil, A., Joseph, Stephan, & Faour, W. H. (2024). Mesenchymal stem cells biological and biotechnological advances: Implications for clinical applications. *European Journal of Pharmacology*, *977*, 176719. https://doi.org/10.1016/j.ejphar.2024.176719

Pluchino, S., Zanotti, L., Rossi, B., Brambilla, E., Ottoboni, L., Salani, G., Martinello, M., Cattalini, A., Bergami, A., Furlan, R., Comi, G., Constantin, G., & Martino, G. (2005). Neurosphere-derived multipotent precursors promote neuroprotection by an immunomodulatory mechanism. *Nature*, *436*(7048), 266–271. https://doi.org/10.1038/nature03889

Poliwoda, S., Noor, N., Downs, E., Schaaf, A., Cantwell, A., Ganti, L., ... & Urits, I. (2022). Stem cells: a comprehensive review of origins and emerging clinical roles in medical practice. *Orthopedic reviews*, *14*(3).

Ray, P., De, A., Yaghoubi, S., & Khanna, A. (2015). Application of adult stem cells in medicine. *Stem Cells International*, *2015*.

Riegler, J., Tiburcy, M., Ebert, A., Tzatzalos, E., Raaz, U., Abilez, O. J., Shen, Q., Kooreman, N. G., Neofytou, E., Chen, V. C., Wang, M., Meyer, T., Tsao, P. S., Connolly, A. J., Couture, L. A., Gold, J. D., Zimmermann, W. H., & Wu, J. C. (2015). Human Engineered Heart Muscles Engraft and Survive Long Term in a Rodent Myocardial Infarction Model. *Circulation Research*, *117*(8), 720–730. https://doi.org/10.1161/CIRCRESAHA.115.306985

Romagnuolo, R., Masoudpour, H., Porta-Sánchez, A., Qiang, B., Barry, J., Laskary, A., Qi, X., Massé, S., Magtibay, K., Kawajiri, H., Wu, J., Sadikov, T. V., Rothberg, J., Panchalingam, K. M., Titus, E., Li, R.-K., Zandstra, P. W., Wright, G. A., Nanthakumar, K., … Laflamme, M. A. (2019). Human Embryonic Stem Cell-Derived Cardiomyocytes Regenerate the Infarcted Pig Heart but Induce Ventricular Tachyarrhythmias. *Stem Cell Reports*, *12*(5), 967–981. https://doi.org/10.1016/j.stemcr.2019.04.005

Sah, J. P. (2016). Challenges of stem cell therapy in developing country. *J Stem Cell Res Ther*, *1*(3), 1-3.

Sartiani, L., Bettiol, E., Stillitano, F., Mugelli, A., Cerbai, E., & Jaconi, M. E. (2007). Developmental Changes in Cardiomyocytes Differentiated from Human Embryonic Stem Cells: A Molecular and Electrophysiological Approach. *Stem Cells*, *25*(5), 1136–1144. https://doi.org/10.1634/stemcells.2006-0466

Sávio-Silva, C., Soinski-Sousa, P. E., Simplício-Filho, A., Bastos, R. M. C., Beyerstedt, S., & Rangel, É. B. (2021). Therapeutic Potential of Mesenchymal Stem Cells in a Pre-Clinical Model of Diabetic Kidney Disease and Obesity. *International Journal of Molecular Sciences*, *22*(4), Article 4. https://doi.org/10.3390/ijms22041546

Shi, L., Huang, H., Lu, X., Yan, X., Jiang, X., Xu, R., Wang, S., Zhang, C., Yuan, X., Xu, Z., Huang, L., Fu, J.-L., Li, Y., Zhang, Y., Yao, W.-Q., Liu, T., Song, J., Sun, L., Yang, F., … Wang, F.-S. (2021). Effect of human umbilical cord-derived mesenchymal stem cells on lung damage in severe COVID-19 patients: A randomized, double-blind, placebo-controlled phase 2 trial. *Signal Transduction and Targeted Therapy*, *6*(1), 1–9. https://doi.org/10.1038/s41392-021-00488-5

Shiba, Y., Gomibuchi, T., Seto, T., Wada, Y., Ichimura, H., Tanaka, Y., Ogasawara, T., Okada, K., Shiba, N., Sakamoto, K., Ido, D., Shiina, T., Ohkura, M., Nakai, J., Uno, N., Kazuki, Y., Oshimura, M., Minami, I., & Ikeda, U. (2016). Allogeneic transplantation of iPS cell-derived cardiomyocytes regenerates primate hearts. *Nature*, *538*(7625), 388–391. https://doi.org/10.1038/nature19815

Sowa, K., Nito, C., Nakajima, M., Suda, S., Nishiyama, Y., Sakamoto, Y., Nitahara-Kasahara, Y., Nakamura-Takahashi, A., Ueda, M., Kimura, K., & Okada, T. (2018). Impact of Dental Pulp Stem Cells Overexpressing Hepatocyte Growth Factor after Cerebral Ischemia/Reperfusion in Rats. *Molecular Therapy Methods & Clinical Development*, *10*, 281–290. https://doi.org/10.1016/j.omtm.2018.07.009

Stocchetti, N., Colombo, A., Ortolano, F., Videtta, W., Marchesi, R., Longhi, L., & Zanier, E. R. (2007). Time Course of Intracranial Hypertension after Traumatic Brain Injury. *Journal of Neurotrauma*, *24*(8), 1339–1346. https://doi.org/10.1089/neu.2007.0300

Sun, Y., Jiang, X., & Gao, J. (2024). Stem cell-based ischemic stroke therapy: Novel modifications and clinical challenges. *Asian Journal of Pharmaceutical Sciences*, *19*(1), 100867. https://doi.org/10.1016/j.ajps.2023.100867

Swaminathan, M., Kopyt, N., Atta, M. G., Radhakrishnan, J., Umanath, K., Nguyen, S., O'Rourke, B., Allen, A., Vaninov, N., Tilles, A., LaPointe, E., Blair, A., Gemmiti, C., Miller, B., Parekkadan, B., & Barcia, R. N. (2021). Pharmacological Effects of Ex Vivo Mesenchymal Stem Cell Immunotherapy in Patients with Acute Kidney Injury and Underlying Systemic Inflammation. *Stem Cells Translational Medicine*, *10*(12), 1588–1601. https://doi.org/10.1002/sctm.21-0043

Takahashi, K., & Yamanaka, S. (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *cell*, *126*(4), 663-676.

Tanaka, K., Ogino, R., Yamakawa, S., Suda, S., & Hayashida, K. (2022). Role and Function of Mesenchymal Stem Cells on Fibroblast in Cutaneous Wound Healing. *Biomedicines*, *10*(6), Article 6. https://doi.org/10.3390/biomedicines10061391

Tang, Z., Zhang, Y., Wang, Y., Zhang, D., Shen, B., Luo, M., & Gu, P. (2017). Progress of stem/progenitor cell-based therapy for retinal degeneration. *Journal of Translational Medicine*, *15*, 1-13.

Tseng, W.-C., Lee, P.-Y., Tsai, M.-T., Chang, F.-P., Chen, N.-J., Chien, C.-T., Hung, S.-C., & Tarng, D.-C. (2021). Hypoxic mesenchymal stem cells ameliorate acute kidney ischemia-reperfusion injury via enhancing renal tubular autophagy. *Stem Cell Research & Therapy*, *12*(1), 367. https://doi.org/10.1186/s13287-021-02374-x

Velikic, G., Maric, D. M., Maric, D. L., Supic, G., Puletic, M., Dulic, O., & Vojvodic, D. (2024). Harnessing the stem cell niche in regenerative medicine: innovative avenue to combat neurodegenerative diseases. *International journal of molecular sciences*, *25*(2), 993.

Wang, H., Yang, Y.-F., Zhao, L., Xiao, F.-J., Zhang, Q.-W., Wen, M.-L., Wu, C.-T., Peng, R.-Y., & Wang, L.-S. (2013). Hepatocyte Growth Factor Gene-Modified Mesenchymal Stem Cells Reduce Radiation-Induced Lung Injury. *Human Gene Therapy*, *24*(3), 343–353. https://doi.org/10.1089/hum.2012.177

Wang, S., Cheng, H., Dai, G., Wang, X., Hua, R., Liu, X., Wang, P., Chen, G., Yue, W., & An, Y. (2013). Umbilical cord mesenchymal stem cell transplantation significantly improves neurological function in patients with sequelae of traumatic brain injury. *Brain Research*, *1532*, 76–84. https://doi.org/10.1016/j.brainres.2013.08.001

Wollert, K. C., Meyer, G. P., Lotz, J., Lichtenberg, S. R., Lippolt, P., Breidenbach, C., Fichtner, S., Korte, T., Hornig, B., Messinger, D., Arseniev, L., Hertenstein, B., Ganser, A., & Drexler, H. (2004). Intracoronary autologous bone-marrow cell transfer after myocardial infarction: The BOOST randomised controlled clinical trial. *The Lancet*, *364*(9429), 141–148. https://doi.org/10.1016/S0140-6736(04)16626-9

Xie, X., Yang, X., Wu, J., Tang, S., Yang, L., Fei, X., & Wang, M. (2022). Exosome from indoleamine 2,3-dioxygenase-overexpressing bone marrow mesenchymal stem cells accelerates repair process of ischemia/reperfusion-induced acute kidney injury by regulating macrophages polarization. *Stem Cell Research & Therapy*, *13*(1), 367. https://doi.org/10.1186/s13287-022-03075-9

Xu, W., He, H., Pan, S., Chen, Y., Zhang, M., Zhu, S., Gao, Z., Peng, L., & Li, J. (2019). Combination Treatments of Plasma Exchange and Umbilical Cord-Derived Mesenchymal Stem Cell Transplantation for Patients with Hepatitis B Virus-Related Acute-on-Chronic Liver Failure: A Clinical Trial in China. *Stem Cells International*, *2019*(1), 4130757. https://doi.org/10.1155/2019/4130757

Ye, L., Li, L., Wan, B., Yang, M., Hong, J., Gu, W., Wang, W., & Ning, G. (2017). Immune response after autologous hematopoietic stem cell transplantation in type 1 diabetes mellitus. *Stem Cell Research & Therapy*, *8*(1), 90. https://doi.org/10.1186/s13287-017-0542-1

Yu, J., Vodyanik, M. A., Smuga-Otto, K., Antosiewicz-Bourget, J., Frane, J. L., Tian, S., ... & Thomson, J. A. (2008). Induced pluripotent stem cell lines derived from human somatic cells. *Obstetrical & Gynecological Survey*, *63*(3), 154-155.

Zakrzewski, W., Dobrzyński, M., Szymonowicz, M., & Rybak, Z. (2019). Stem cells: past, present, and future. *Stem cell research & therapy*, *10*(1), 1-22.

Zhang, S., Chen, L., Liu, T., Zhang, B., Xiang, D., Wang, Z., & Wang, Y. (2012). Human Umbilical Cord Matrix Stem Cells Efficiently Rescue Acute Liver Failure Through Paracrine Effects Rather than Hepatic Differentiation. *Tissue Engineering Part*

A, *18*(13–14), 1352–1364. https://doi.org/10.1089/ten.tea.2011.0516

Zhang, Y., Zhang, J., Yi, H., Zheng, J., Cai, J., Chen, W., Lu, T., Chen, L., Du, C., Liu, J., Yao, J., Zhao, H., Wang, G., Fu, B., Zhang, T., Zhang, J., Wang, G., Li, H., Xiang, A. P., … Yang, Y. (2021). A novel MSC-based immune induction strategy for ABO-incompatible liver transplantation: A phase I/II randomized, open-label, controlled trial. *Stem Cell Research & Therapy*, *12*(1), 244. https://doi.org/10.1186/s13287-021-02246-4

Zhong, C., Qin, Z., Zhong, C.-J., Wang, Y., & Shen, X.-Y. (2003). Neuroprotective effects of bone marrow stromal cells on rat organotypic hippocampal slice culture model of cerebral ischemia. *Neuroscience Letters*, *342*(1), 93–96. https://doi.org/10.1016/S0304-3940(03)00255-6

Zuccato, C., Valenza, M., & Cattaneo, E. (2010). Molecular Mechanisms and Potential Therapeutical Targets in Huntington's Disease. *Physiological Reviews*, *90*(3), 905–981. https://doi.org/10.1152/physrev.00041.2009

About the Authors

Dr. Hasan EGE received his Ph.D. from the Department of Physiology at Istanbul University - Cerrahpaşa, Cerrahpaşa Faculty of Medicine. He currently serves as a visiting Assist. Professor in the Department of Physiology at Istanbul Arel University Faculty of Medicine. His main research interests include cell physiology, neuroendocrinology, cancer biology, nanotechnology, and drug delivery systems.
E-mail: hasanege@arel.edu.tr, **ORCID:** 0000-0002-0547-8826

Dr. Oğuzhan EKİCİ received his Ph.D. from the Department of Physiology at Istanbul University - Cerrahpaşa, Cerrahpaşa Faculty of Medicine. He currently works as a Research Assistant in the Department of Physiology at Cerrahpaşa Faculty of Medicine. His main research interests focus on neurophysiology, neuroscience, and olfactory physiology."
E-mail: oguzhan.ekici@iuc.edu.tr, **ORCID:** 0000-0002-0845-5443

Similarity Index

The similarity index obtained from the plagiarism software for this book chapter is 4%.

ML-Based Solutions for Detection of Hip Dislocation in Infants: A Review

Mevlüt Can ADIYAMAN
Autodidactic Technologies Ltd.

Şeyma Nefise SATICI
Boğaziçi University

Muhammmed Furkan DARILMAZ
Aksaray Training and Research Hospital

Hüseyin Oktay ALTUN
Boğaziçi University

To Cite This Chapter

Adıyaman, M. C., Satıcı, Ş. N., Darılmaz, F., & Altun, H. O. (2024). ML-Based Solutions for Detection of Hip Dislocation in Infants: A Review. In F. Nur Takı, S. Koçer & R. Bütüner (Eds.), *New Generation Technologies and Sustainability in Health Current Studies* (pp. 49-73). ISRES Publishing.

Developmental Dysplasia of the Hip (DDH)

Developmental Dysplasia of the Hip (DDH) is a common pediatric condition that encompasses a range of hip abnormalities, from mild instability to complete dislocation of the hip joint. This condition occurs when the femoral head (i.e. the ball) and the acetabulum (i.e. the socket) are misaligned, leading to improper development of the hip joint (Schwend et al., 2014). DDH can be present at birth or develop in early infancy and is more prevalent in females, first-born children, and those with a family history of the condition (Noordin et al., 2010).

Early detection and treatment of DDH are crucial for preventing long-term complications such as pain, limping, and early-onset osteoarthritis (Schwend et al., 2014). Traditionally, DDH is diagnosed through physical examination techniques such as the Ortolani and Barlow maneuvers, followed by imaging methods like ultrasound or X-ray to confirm the diagnosis (Gulati, 2013). Ultrasound is the preferred imaging modality for infants younger than six months because it provides a detailed view of the cartilaginous structures of the hip that are not visible on X-rays (Grissom et al., 2008). Both *figure 1* and *figure 2* illustrate key anatomical structures, including the alpha and beta angles, in neonatal hip ultrasound images, emphasizing both the quality of the scans and their relevance for clinical assessments. In *Figure 1a*, three important structures—the vertical ilium, lower margin of the Os ilium, and the labrum—are clearly identified, aiding in the evaluation of hip morphology. *Figure 1b* demonstrates the Graf method by measuring the alpha (α) and beta (β) angles, which are crucial for classifying hip joint development. These angles provide essential information for diagnosing DDH. *Figure 2* highlights different levels of scan quality.

Despite advancements in diagnostic techniques, detecting DDH remains challenging due to the subtlety of early signs and the subjective nature of physical examinations (Developmental Dysplasia of the Hip, 2022). The development of machine learning (ML)-based solutions holds promise for improving the accuracy and efficiency of DDH detection (Lee et al., 2021; Li et al., 2022; Hu et al., 2022). These ML-driven approaches can analyze ultrasound images to detect hip abnormalities with greater precision, potentially reducing the need for manual interpretation and allowing for earlier and more consistent diagnosis.

Figure 1
(a) A typical hip ultrasound (US) image displays three primary anatomical structures: 1. vertical ilium, 2. the lower margin of the Os ilium, and 3. the labrum. (b) The alpha (α) and beta (β) Graf angles are demonstrated in a hip ultrasound image (Lee et al., 2021). [This figure is reused with permission under the Creative Commons CC-BY license.]

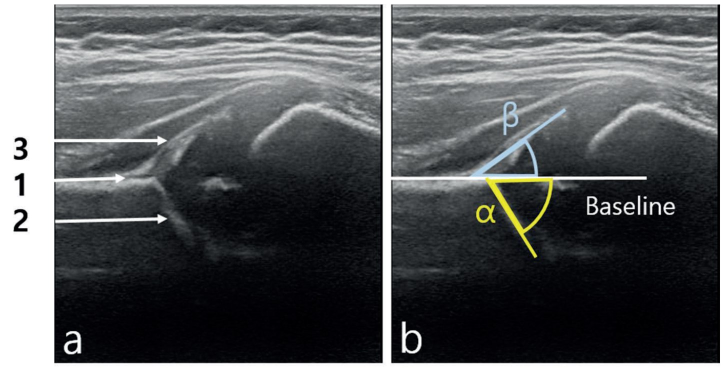
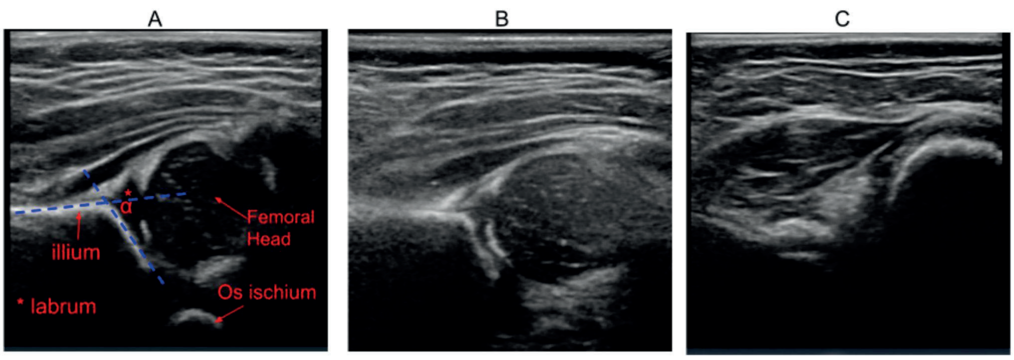


Figure 2
Ultrasound images of the hip illustrating varying scan quality. (A) A high-quality scan where key landmarks, including the ilium, os ischium, labrum, and femoral head, are clearly visible, and the alpha angle is measured between the iliac line and acetabular roof. (B) A moderate-quality scan showing all landmarks, though with some blurring of the os ischium and slight misalignment of the iliac line. (C) A poor-quality scan where none of the landmarks are clearly visible (Hareendranananthan et al., 2022a). [This figure is reused with permission under the Creative Commons CC-BY license.]



In this review, the latest ML-based solutions for detecting hip dislocation in infants are explored, with advancements, challenges, and future directions in this emerging field highlighted. By leveraging the power of ML, contributions to the early and accurate detection of DDH are made, ultimately aiming to improve outcomes for affected infants.

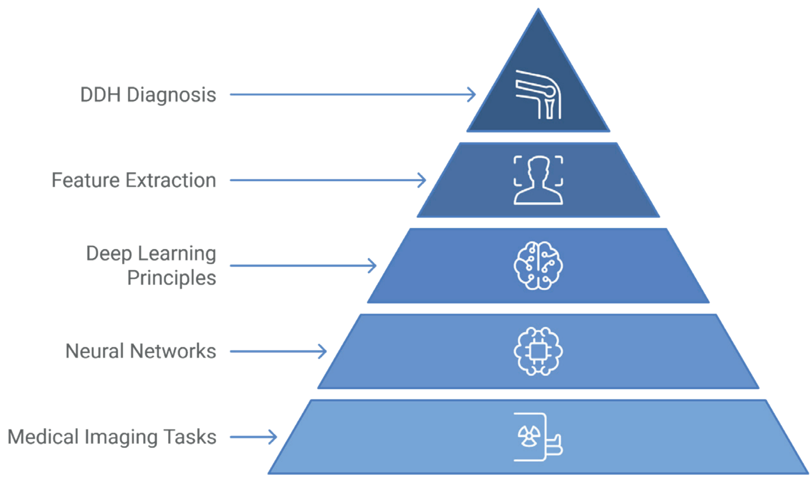
Machine Learning

ML techniques hold promise for automating the interpretation of complex medical images (Dave & Patel, 2023). These techniques may allow for the extraction of intricate patterns and features that are not immediately apparent to human observers. By potentially reducing the reliance on manual interpretation, ML could enhance the consistency of diagnoses and minimize the variability that often arises from human subjectivity (Hosny et al., 2018). This review will explore various ML-based approaches that have been applied to the detection and diagnosis of DDH, highlighting the potential of these technologies to transform clinical practice by improving diagnostic accuracy, reducing inter-operator variability, and enabling early intervention.

Deep Learning

Deep Learning, a subfield of machine learning, involves the use of neural networks with multiple layers to model and learn from vast and complex datasets (Hinton, 2018). Unlike traditional machine learning models that rely heavily on feature engineering, deep learning models have the potential to automatically discover and extract relevant features from raw data (LeCun et al., 2015). In the context of medical imaging, deep learning algorithms, particularly Convolutional Neural Networks (CNNs), have shown significant promise in tasks such as image classification, segmentation, and detection (Litjens et al., 2017). These tasks are crucial for diagnosing various medical conditions, including DDH. The deep learning-based machine learning technology stack for medical imaging, illustrated in *Figure 3*, outlines the hierarchy from foundational neural networks to specialized DDH diagnosis tasks. Deep learning models could be trained on large datasets of 2D and 3D medical images, enabling them to learn and identify patterns that may correlate with specific conditions (Li et al., 2022). For example, in the diagnosis of DDH, deep learning algorithms have the potential to analyze ultrasound images to detect anatomical landmarks and measure relevant angles, such as the alpha angle, which are critical for assessing hip dysplasia (El-Hariri, 2020; Li et al., 2022; Li et al., 2019). By automating these tasks, deep learning might reduce the reliance on manual measurements and interpretations, leading to more consistent and reliable diagnoses. Furthermore, deep learning models could be fine-tuned and adapted to new imaging modalities, making them potentially versatile tools in medical diagnostics.

Figure 3
A typical deep learning-based machine learning technology stack for medical imaging

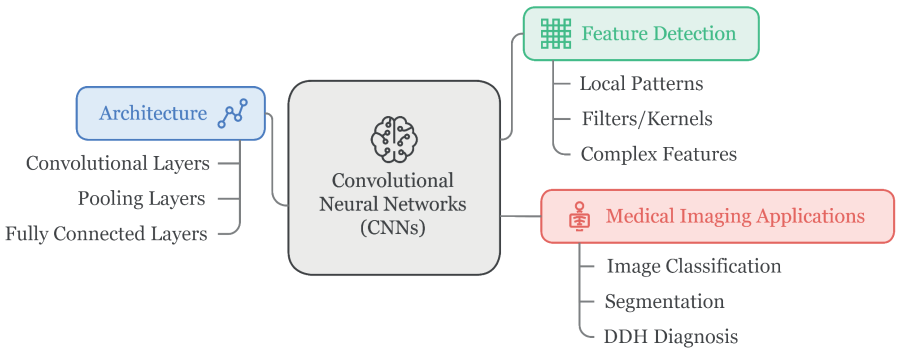


Convolutional Neural Networks (CNNs)

Convolutional Neural Networks (CNNs) are a class of deep learning models specifically designed for processing structured grid data, such as images. CNNs are characterized by their unique architecture, which includes layers such as convolutional layers, pooling layers, and fully connected layers (Voulodimos et al., 2018). The convolutional layers are responsible for detecting local patterns in the input image, such as edges, textures, and shapes, by applying a set of filters (or kernels) that slide over the image. Each filter has the potential to detect a specific feature, and as the image passes through multiple convolutional layers, the network could learn increasingly complex and abstract features (Zeiler & Fergus, 2013). *Figure 4* provides an overview of the key concepts in CNNs, illustrating their architecture, feature detection mechanisms, and applications in medical imaging, including DDH diagnosis. Pooling layers, often used after convolutional layers, reduce the spatial dimensions of the feature maps, which may help to decrease the computational load and enhance the model's robustness to spatial variations in the input image (Bai & Li, 2023). The final layers of the CNN are typically fully connected layers that aggregate the learned features to make predictions (Zeiler & Fergus, 2013). In medical imaging, CNNs have become popular models for tasks like image classification and segmentation due to their ability to potentially learn and generalize from data with minimal human intervention. In the diagnosis of DDH, CNNs could be trained to detect and classify key anatomical structures in ultrasound images, such as the acetabulum and femoral head, and assess the presence and severity of hip dysplasia (Hu et al., 2021; Liu et al., 2020; Li et al., 2022). By leveraging the hierarchical feature extraction capabilities of CNNs, these models have the potential to achieve high diagnostic accuracy while reducing the need for manual input and minimizing operator-dependent variability.

Figure 4

Overview of key concepts in CNNs



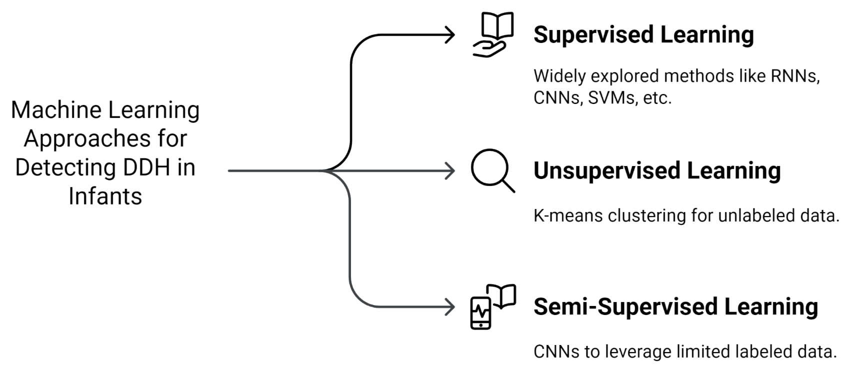
Random Forest Classifier

The Random Forest (RF) classifier is an ensemble learning method that operates by constructing a multitude of decision trees during training and outputting the mode of the classes (classification) or mean prediction (regression) of the individual trees (Liaw & Wiener, 2007). This method is particularly powerful due to its ability to potentially reduce overfitting and improve generalization by averaging multiple decision trees, each trained on different subsets of the data and features (Denil et al., 2013). In the context of medical imaging, RFclassifiers have shown promise in tasks such as feature selection, classification, and regression, particularly when the dataset contains a mix of numerical and categorical features (Sarica et al., 2017). In diagnosing DDH, RFclassifiers could be utilized to analyze geometric features extracted from medical images, such as the alpha angle, acetabular contact angle, and other shape descriptors derived from 2D or 3D ultrasound scans (Hu et al., 2022).

ML-Based Solutions for Detection of Hip Dislocation in Infants

In recent years, significant advancements in artificial intelligence (AI) have revolutionized the field of medical diagnostics, offering innovative solutions for the detection of various conditions (Lee et al., 2021; El-Hariri, 2020; Park et al., 2021). One such area where AI has shown promising results is in the early detection of DDH in infants. As illustrated in *Table 1*, the approaches are classified under three primary learning types: supervised learning, unsupervised learning, and semi-supervised learning. Within supervised learning, methods like Recurrent Neural Networks (RNNs), Convolutional Neural Networks (CNNs), Support Vector Machines (SVMs), Random Forests, and Meta-Learning are widely explored, with CNNs and SVMs being the most prominent. For unsupervised learning, K-means clustering is applied, whereas semi-supervised learning utilizes CNNs to leverage limited labeled data. This taxonomy provides an organized view of how different learning techniques are employed across the literature for automated diagnosis and detection in medical imaging related to hip dysplasia. *Figure 5* visually summarizes these machine learning approaches for detecting DDH in infants, highlighting the roles of supervised, unsupervised, and semi-supervised learning methods.

Figure 5
Machine learning approaches for detecting DDH in infants



The study by Hareendranathan et al. (2016) tackles the challenges of diagnosing DDH using 2D ultrasound images, focusing on reducing the variability inherent in traditional methods like the Graf method. Traditional techniques often suffer from high inter-scan and inter-observer variability due to the manual determination of key points, such as the apex separating the acetabular roof from the ilium. To address this, the study introduces a semi-automated image processing method that calculates two novel indices: the contour-based alpha angle (αA) and a modality-independent quantitative rounding index (M). These indices aim to enhance diagnostic accuracy and reliability by minimizing subjectivity and reducing dependence on manual landmarks. The study's results, derived from 114 ultrasound scans, indicate that these new indices, particularly the rounding index, significantly improve diagnostic accuracy, with an Area Under the Curve (AUC) reaching up to 95.74% in certain combinations. The study suggests that this approach could be extended to 3D ultrasound models, offering a promising direction for future research in the automated diagnosis of DDH (Hareendranathan et al., 2016).

Another study carried out by Hareendranathan et al. (2017a) proposes a fully automated method for diagnosing DDH using 2D ultrasound images. Recognizing the challenges of high inter-operator variability in current diagnostic practices, the authors introduce an innovative approach involving deep learning-based segmentation of the acetabulum. This method automatically extracts the acetabulum contour and calculates geometric indices such as the alpha angle and a new rounding index, the osculating circle radius. The study's findings indicate that the automated method offers higher reliability than traditional manual measurements, with an AUC of 86.2% for classifying normal versus dysplastic hips. Although the study acknowledges the need for further refinement and extension to 3D ultrasound, it presents a significant advancement in the automation and accuracy of DDH diagnosis, potentially reducing variability and improving early detection and treatment outcomes for infants (Hareendranathan et al., 2017a).

A further study conducted by Hareendranathan et al. (2017b) introduces a semiautomated method for diagnosing DDH using 3D ultrasound data. The approach leverages a graph-based segmentation algorithm, guided by user-defined seed points, to accurately delineate the acetabulum. Key geometric features, including the automatic alpha angle, acetabular contact angle, kurtosis, skewness, and convexity, are extracted from the 3D segmented surface and input into an RF classifier to categorize hips as normal, borderline, or dysplastic. This method significantly improves upon previous techniques that relied on limited 2D slices and interpolation, offering enhanced accuracy by utilizing the full 3D volumetric data. The study reports high diagnostic accuracy, with a specificity of 100% and a sensitivity of 97.2% for distinguishing between normal and dysplastic hips, highlighting its potential for clinical application. However, the authors acknowledge limitations, such as the method's dependency on acetabular shape and the need for further validation under different ultrasound settings. Despite these challenges, the study represents a notable advancement in the automated diagnosis of DDH, with potential applications in other imaging modalities like MRI and CT (Hareendranathan et al., 2017b).

In their study, Paserin et al. (2017) present an innovative method for assessing the adequacy of 3D ultrasound scans in diagnosing DDH. The research introduces a CNN that automatically classifies 3D ultrasound volumes as adequate or inadequate based on the presence of key hip anatomical structures necessary for DDH diagnosis. This method aims to reduce the variability and subjectivity associated with manual scan evaluation, offering a more standardized approach. The study reports a classification accuracy of 100% with an average processing time of just over 2 seconds per volume, highlighting its potential for real-time clinical application. The work contributes significantly to the field by addressing the gap in automated adequacy assessment for 3D ultrasound scans, which could enhance the efficiency and accuracy of DDH diagnosis. However, further validation with larger datasets and different ultrasound settings is recommended to confirm the method's robustness and generalizability (Paserin et al., 2017).

Another study by Paserin et al. (2018) introduces a deep learning model that combines CNNs with recurrent neural networks (RNN), specifically Long Short-Term Memory (LSTM) networks, for the automatic assessment of 3D ultrasound (US) scan adequacy in diagnosing DDH. This approach, which utilizes inter-slice information within a 3D US volume, addresses the limitations of previous slice-by-slice methods by analyzing the sequence of frames to ensure all necessary anatomical features are present across the volume. The model demonstrated an accuracy of 82% and an AUC of 0.83 in validating 3D US volumes from pediatric patients, suggesting that it could significantly improve the reliability and efficiency of DDH screening. However, the study acknowledges the need for a larger dataset to enhance the model's generalizability and proposes further research to evaluate its performance across varying levels of operator expertise (Paserin et al., 2018).

In their study, Quader et al. (2017) introduce a computational technique to automatically assess the adequacy of 2D ultrasound images and extract key dysplasia metrics, such as the alpha angle, beta angle, and femoral head coverage, used in diagnosing DDH. The method utilizes local phase symmetry-based image measures and an RFclassifier to improve the reliability of these measurements, addressing the high inter and intra-operator variability associated with traditional manual assessments. The study demonstrates that this automatic approach achieves excellent agreement with clinician evaluations and significantly reduces variability in the measured metrics, which could potentially lead to more consistent and accurate diagnoses (Quader et al., 2017).

The two studies by Liu et al. focus on detecting misshapen pelvic landmarks crucial for diagnosing DDH in infants. Both studies address the challenges posed by temporal diversity during skeletal calcification and deformities due to dislocation. The first study, from 2019, introduces a deep learning method using the FR-DDH network, which leverages spatial local correlation to improve the accuracy of landmark detection. This method converts landmark detection into the detection of local neighborhood patches and demonstrates superior performance over human experts with a precision of 1.24 mm (Liu et al., 2019). The second study, from 2020, expands on this approach by integrating local and global feature learning through a Pyramid Non-local UNet (PN-UNet). This method captures both the local morphological features and global structural features to enhance the robustness of landmark detection. The PN-UNet reduces computational demands while maintaining high accuracy, achieving a precision of 0.93 mm. Both studies contribute significantly to the field by developing reliable AI-based systems for automatic DDH diagnosis, demonstrating that deep learning techniques can outperform traditional methods and human experts in this challenging diagnostic task (Liu et. al, 2020).

The study of Alam et al. (2019) explores a novel, non-invasive approach for the early detection of DDH using machine learning, specifically support vector machines (SVM). The research involved the use of acoustic signals to simulate various degrees of hip dysplasia in neonatal models. Key features such as phase, transfer function, and coherence were extracted from these simulations and used to classify the severity of the condition. The SVM model achieved an overall accuracy of 79% in a 4-class classification task, with a particularly high AUC of 0.93 for the most severe cases. This method presents a low-cost, accessible solution for early DDH screening, especially in resource-limited settings (Alam et al., 2019).

The study by El-Hariri et al. investigates the effectiveness of deep learning techniques compared to traditional hand-engineered features for segmenting neonatal hip bones in ultrasound images, crucial for diagnosing DDH. DDH is a common congenital condition, and accurate early detection is vital to prevent serious health complications. The research compares phase-based and shadow-based hand-engineered features with deep-learned features using the U-Net architecture. The findings reveal that U-Net, especially with multi-channel inputs, significantly outperforms traditional methods in terms of accuracy and robustness across different datasets and ultrasound probes. This advancement holds potential for improving the reliability of automated DDH assessments and reducing operator variability in clinical practice (El-Hariri et al., 2019).

The study conducted by Zhang et al. focuses on the application of a deep learning system for diagnosing DDH in children using anteroposterior pelvic radiographs. By retrospectively analyzing 10,219 radiographs, the research team developed and tested a CNN model that showed high accuracy in identifying hip dislocations. The deep learning system achieved an area under the receiver operating characteristic (ROC) curve of 0.975, with a sensitivity of 95.5% and a specificity of 99.5%. The study highlights the potential of AI to enhance the speed and accuracy of DDH diagnosis, providing a robust tool that could streamline clinical processes and improve patient outcomes **(**Zhang et al., 2020)

The research by Sezer and Sezer (2020) presents a deep CNN-based system for the automatic classification of neonatal hip ultrasound images, focusing on the diagnosis of DDH. The study addresses the challenge of variability in the accuracy of traditional manual methods, which heavily depend on the operator's expertise. By introducing a novel data augmentation approach that includes speckle noise reduction using an optimized Bayesian non-local means filter (OBNLM), the researchers significantly improve CNN's performance. The proposed system classifies DDH with a high accuracy rate of 97.70%, offering a robust tool that enhances diagnostic consistency and reliability in clinical settings, particularly in the early detection and treatment of DDH.

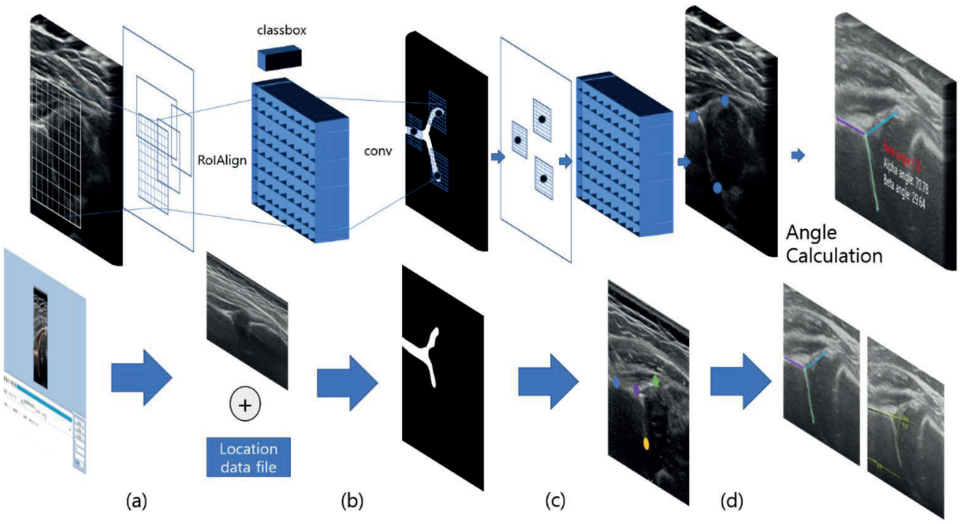
The study by Kannan et al. (2020) introduces a novel method to improve the assessment of DDH using 3D US images. Traditional 2D US methods have shown significant variability in diagnoses due to inter-operator differences and scan inconsistencies. This study proposes using a deep learning-based system with uncertainty estimation to enhance reliability in bone segmentation and the extraction of DDH metrics like the alpha angle and femoral head coverage (FHC). By integrating Monte Carlo dropout techniques within a 3D U-Net architecture, the authors quantify the confidence of the network's predictions and evaluate scan adequacy. The results indicate a strong correlation between lower metric variability and higher Dice scores, suggesting that this method can serve as a quality control tool in clinical settings. The study offers a pathway to more consistent, real-time evaluations of DDH, potentially improving diagnosis and treatment outcomes.

The study by Chen et al. (2020) presents an improved fully convolutional neural network (FNet) for the segmentation of the femoral head in ultrasound images, which is crucial for diagnosing Developmental Dysplasia of the Hip (DDH). The authors developed a method combining mean filtering, morphological processing, and least squares operation to detect key anatomical landmarks, followed by the application of FNet for accurate segmentation. FNet utilizes a cascaded training strategy and integrates residual connections with a convolutional encoder-decoder architecture to enhance the segmentation accuracy. The experimental results demonstrate that FNet achieved a high dice score of 0.946, significantly improving segmentation performance compared to other models. This advancement provides a reliable tool for the automatic diagnosis of DDH, offering a robust alternative to traditional manual methods, and has the potential to streamline the clinical workflow in pediatric orthopedic settings.

The study by Lee et al. (2021) evaluates a deep learning model-based computer-aided diagnosis (CAD) system designed for the screening and diagnosis of DDH) using ultrasonographic images. *Figure 6* illustrates a diagram of the implementation process. The system employs a Mask R-CNN for the segmentation of key anatomical structures, followed by a multi-detection approach to accurately calculate the Graf alpha and beta angles, which are critical for diagnosing DDH. The study analyzed 921 images, of which 320 were deemed appropriate for accurate DDH screening. The system demonstrated a high level of agreement with human experts, with an intraclass correlation coefficient (ICC) of 0.76 for alpha angles and 0.74 for beta angles. The study highlights the potential of this AI-based system to improve the consistency and accuracy of DDH diagnosis, making it a valuable tool in clinical practice, particularly in reducing the variability associated with manual measurements.

Figure 6

A diagrammatic representation of the multi-detection artificial intelligence (AI) training pipeline in Lee et al (2021). The process involves: (a) region-based learning using the CVAT program for marking, (b) conversion of initial ultrasound images combined with location data, (c) secondary training to mark key anatomical points, and (d) the final output of the AI system (Lee et al., 2021). [This figure is reused with permission under the Creative Commons CC-BY license].



Another study by Hareendranathan et al. (2021) investigates the use of AI) to automatically assess the quality of ultrasound scans used for diagnosing DDH in infants. Given the critical importance of scan quality for accurate diagnosis, the researchers developed CNN models to evaluate the presence of key anatomical landmarks, such as the iliac wing, labrum, os ischium, and femoral head. The AI system achieved high accuracy, with ≥85% accuracy for all landmarks and showed strong agreement with expert human assessments. This automated tool has the potential to improve scan quality consistency, facilitate more reliable DDH screening, and enhance the usability of ultrasound by less experienced operators, making it a valuable addition to clinical practice for early DDH detection. The study by Lee, J. H., (2021b) proposes a novel CADsystem for detecting and assessing DDH in infants using ultrasound images. The system utilizes a Mask R-CNN-based deep learning approach to automatically segment key anatomical features and calculate critical parameters such as the acetabulum-femoral head angle, which are essential for diagnosing DDH. The system was tested on ultrasound scans obtained from infants, showing a detection accuracy of 94.86% for DDH, with angle measurements that closely matched those made by experienced physicians. The study highlights the potential of AI to improve diagnostic accuracy and efficiency, particularly in settings with limited data, by providing an automated, reliable tool for early DDH screening and diagnosis

Hu et al. (2021) present a multi-task learning framework designed to automate the evaluation of DDH from ultrasound images. Their approach integrates the detection and segmentation of key anatomical structures with the automatic measurement of critical angles (alpha and beta) used in DDH diagnosis. The framework utilizes a modified Mask R-CNN architecture, enhanced by the inclusion of novel loss functions that account for shape similarity and landmark consistency, to ensure accurate and robust segmentation even in challenging imaging conditions. Experimental results demonstrate that Hu et al.'s method achieves high accuracy, with alpha and beta angle estimation errors within clinically acceptable limits, showcasing its potential for reliable clinical application in the automated diagnosis of DDH.

Park et al. (2021) developed a CNN algorithm to automatically detect DDH from anteroposterior radiographs of the hip. Their study evaluated the diagnostic performance of this deep learning model against three radiologists with varying levels of experience. The CNN demonstrated high diagnostic accuracy, comparable to that of an experienced pediatric radiologist, with a sensitivity of 98.0% and specificity of 98.1%. The algorithm outperformed less experienced radiologists, indicating its potential to aid in clinical decision-making, particularly in settings where expert radiologists are not available.

The research conducted by El-Hariri (2020) presents a significant advancement in the diagnosis of DDH in infants through the integration of 3D ultrasound imaging and deep learning techniques. His work addresses the inherent challenges in accurately diagnosing DDH, which traditionally relies on manual processes prone to high variability. By employing CNNs to automate the segmentation of crucial anatomical structures, such as the pelvis bone surface and femoral head, a marked improvement in diagnostic precision is achieved. This approach not only enhances the reliability of early detection but also reduces the likelihood of misdiagnosis, offering a more consistent and dependable method for identifying infants at risk of DDH. The research holds the potential to revolutionize clinical practices by facilitating the adoption of AI-based diagnostic tools in pediatric orthopedics, leading to more accurate and efficient healthcare outcomes

In another study, El-Hariri et al. (2021) introduce a novel approach to automating the delineation of key anatomical structures in 3-D ultrasound volumes for the screening of DDH. Their study compares the performance of 3-D CNNs, particularly a 3-D U-Net, against traditional methods for segmenting the pelvis bone surface and localizing the femoral head. The results demonstrate that the 3-D U-Net significantly improves the accuracy of segmentation and localization tasks, achieving a Dice score of 85% for the pelvis and minimal errors in femoral head detection. These advancements could enhance the reliability of DDH metrics, potentially reducing misdiagnosis and improving clinical outcomes by enabling more consistent and accurate evaluations. This work is closely related to El-Hariri's (2020) earlier research and represents a natural progression toward fully automating the DDH diagnostic process, potentially transforming clinical practices by providing more reliable and efficient tools for early detection .

Liu et al. (2021) propose a novel deep learning framework, NHBS-Net, specifically designed for segmenting neonatal hip bone structures in ultrasound images. The network incorporates three key innovations: an enhanced dual attention module for better feature extraction, a two-class feature fusion module for improved edge detection, and a coordinate convolution output head to encode absolute positional information. These advancements collectively enable more accurate and robust segmentation of seven key anatomical structures crucial for diagnosing DDH. Experimental results demonstrate NHBS-Net's superiority in segmentation accuracy over existing state-of-the-art methods, highlighting its potential to significantly reduce diagnostic errors in clinical settings.

Gong et al. (2021) propose a novel approach for diagnosing DDH in infants using B-mode ultrasound (BUS) images. Their method, called Two-Stage Meta-Learning Based Deep Exclusivity Regularized Machine (TML-DERM), combines deep neural networks (DNN) and exclusivity regularized machines into a unified framework. This approach enhances feature representation and classification performance by leveraging meta-learning to tackle overfitting issues and optimize the combination of weak classifiers. The experimental results on a real-world dataset demonstrate that TML-DERM significantly outperforms traditional methods, achieving high accuracy, sensitivity, and specificity, making it a promising tool for improving early DDH diagnosis.

Xu et al. (2021) present a novel approach for detecting hip landmarks in ultrasound images, crucial for diagnosing DDH in infants. Their method, called Dependency Mining ResNet (DM-ResNet), leverages a combination of short-range and long-range dependency mining to address challenges such as local confusion and regional weakening caused by noise interference and echo attenuation in ultrasound images. By converting landmark detection to heatmap estimation and integrating a local voting algorithm, DM-ResNet achieves state-of-the-art performance with an average point error of 0.719mm and a successful detection rate within 1mm of 79.9%. The method is validated on a dataset of 2000 annotated hip ultrasound images, the first public dataset available for DDH research, demonstrating its potential to improve the accuracy and speed of hip landmark detection in clinical settings.

Hareendrananthan et al.'s study (2022a) introduced an innovative AI-driven technique based on a 3D CNN for automatically assessing the quality of hip ultrasound scans, particularly for diagnosing DDH. The AI model demonstrated a high level of accuracy, achieving 96% on a large dataset (DS1) and 91% on a smaller dataset (DS2), indicating its potential to match or exceed the performance of non-expert human readers. By automating the quality assessment process, the model reduces the subjectivity and variability associated with manual evaluations, providing real-time feedback to sonographers, which could improve scan quality during the examination process and enhance diagnostic reliability. Despite these contributions, the study's limitations, such as variability in the ground truth, data imbalance, and the need for broader validation, suggest that further research is necessary to ensure the model's robustness and generalizability across diverse clinical settings .

Chen et al.'s (2022) study introduces an advanced framework aimed at automating the diagnosis of DDH using deep learning. The framework operates in both static and dynamic modes, each leveraging the YOLOv3-tiny algorithm for detecting key anatomical structures crucial for DDH diagnosis. In static mode, the framework mirrors current clinical practices by relying on manually selected planes to measure critical angles for classifying hips as Graf type I or II. In dynamic mode, the framework automatically selects the correct frame from ultrasound videos, eliminating manual intervention and using a Standard Plane Scoring Module (SPSM) to ensure accuracy. The study demonstrates the framework's potential with promising results: a mean absolute error of 1.71° for α angles and a classification accuracy of 94.71% in static mode, and slightly higher errors with an accuracy of 89.51% in dynamic mode. Despite these achievements, the study notes limitations such as binary hip classification and a limited dataset, indicating areas for future research.

Çevik and Andaç's study (2022) developed a deep learning-based software system to detect standard plane frames in real-time ultrasound images, primarily aiding in the diagnosis of DDH. The study stands out for its use of pre-trained CNNs, such as SqueezeNet, VGG16, VGG19, ResNet50, and ResNet101, integrated with the YOLO object detection model to enhance accuracy. Notably, the VGG19 model achieved the highest accuracy in identifying diagnostic frames, while SqueezeNet provided faster training times despite slightly lower accuracy. This study fills a significant gap in the literature by focusing on the automatic capture of diagnostic frames in real-time, marking a substantial contribution to DDH diagnosis and treatment planning .

Hareendranathan et al.'s (2022b) study investigates the critical role of scan quality in the accuracy of AI-based assessments for diagnosing DDH using ultrasound. The researchers developed a 10-point scoring system that evaluates scan quality based on key anatomical features and the presence of artifacts, which was tested for inter-rater reliability. The study found that the inter-rater agreement was significantly higher with this scoring system compared to holistic grading, indicating its effectiveness in providing consistent evaluations of scan quality. The study also demonstrated that AI systems like MEDO-Hip are less accurate when interpreting lower-quality scans, highlighting the importance of scan quality in AI diagnostics. This finding is crucial for improving the clinical utility of AI in DDH diagnosis by flagging low-quality scans before they are analyzed, thus potentially reducing diagnostic errors .

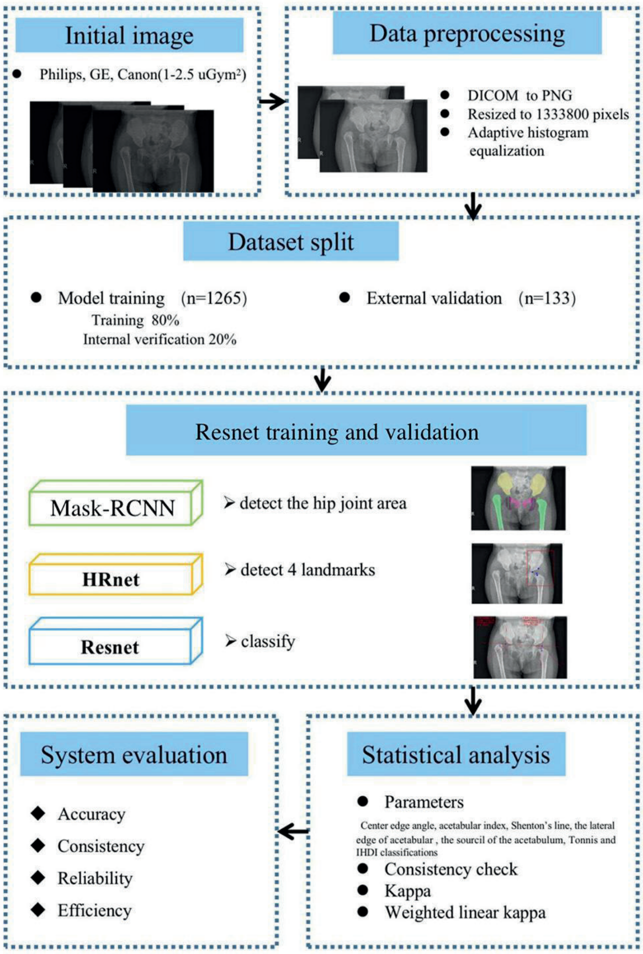
Oelen et al.'s (2022) study explored the use of deep learning algorithms to enhance the accuracy of angle measurements in ultrasound images for diagnosing developmental dysplasia of the hip (DDH) in newborns, using the Graf method. The research involved comparing the accuracy of measurements made by trained physicians to those produced by three different CNN-based approaches. The study, which utilized a large dataset from 27 hospitals in Switzerland and Mongolia, demonstrated that deep learning algorithms, particularly the landmark detection method, achieved higher accuracy than routine clinical practices, with an RMSE of 3.9° using a combination of U-Net and PSP-Net architectures. While the study highlighted the potential of these algorithms to improve diagnostic precision and reduce physicians' workload, it also noted limitations related to data quality and consistency issues with the end-to-end angle detection method. Despite these challenges, the study significantly contributes to the literature by suggesting that deep learning can provide more reliable and consistent diagnostic results in medical imaging, particularly with the landmark detection approach.

Ghasseminia et al.'s (2022) study evaluated the capability of an AI algorithm to detect DDH using 3D USimages in a multi-center setting, involving infants aged between 4 and 267 days from hospitals in Edmonton, Canada, and Melbourne, Australia. The AI, trained on data from Edmonton and tested with images from Melbourne, automatically calculated the alpha angle and femoral head coverage to classify dysplasia. The results indicated a sensitivity of 90% in detecting dysplastic hips and an accuracy of 86% in identifying normal or borderline hips, with only one severe case of dysplasia being missed. Despite the AI and clinicians using different imaging modalities (3D vs. 2D), the study showed a high level of agreement between AI and human diagnoses, particularly with high kappa scores in Melbourne. However, the limited availability of high-resolution 3D ultrasound probes and the lack of an external reference standard are notable limitations. Overall, the study suggests that AI combined with 3D ultrasound may offer a promising tool for DDH screening, aligning well with traditional clinical methods and potentially contributing to future advancements in the field .

Xu et al.'s (2022) study aimed to develop a deep-learning-aided diagnostic system for assessing DDH using pediatric pelvic radiographs, addressing the need for enhanced diagnostic accuracy and efficiency in clinical settings. The system employs a three-stage pipeline, incorporating Mask-RCNN for segmenting pelvic bones, HRNet for extracting local image patches related to DDH landmarks, and deriving radiographic measurements such as the acetabular index and center edge angle. The AI system achieved classification accuracies ranging from 0.86 to 0.95 and demonstrated high consistency with orthopedic surgeons, significantly reducing the time required for diagnosis. The study stands out by offering a comprehensive diagnostic approach compared to previous studies that focused on specific aspects of DDH assessment. However, its limitations include the need for larger datasets to improve subjective judgment areas and further validation for clinical practice. The overview of the study is shown in *Figure 7*.

Figure 7

The study's methodology and analysis pipeline are illustrated. Images were obtained from the hip joint and underwent preprocessing, including conversion from DICOM to PNG, resizing, and adaptive histogram equalization. The dataset was split into training and external validation sets. Various models, including Mask-RCNN, HRNet, and Resnet, were utilized to progressively identify the hip joint area, detect key landmarks, and classify the images. System evaluation was based on accuracy, consistency, reliability, and efficiency, while statistical analysis focused on key parameters such as center-edge angle and consistency measures like kappa scores. The AI system's performance was compared with that of clinicians with varying experience levels in terms of accuracy and efficiency (Xu et al., 2022). [This figure is reused with permission under the Creative Commons CC-BY license.]



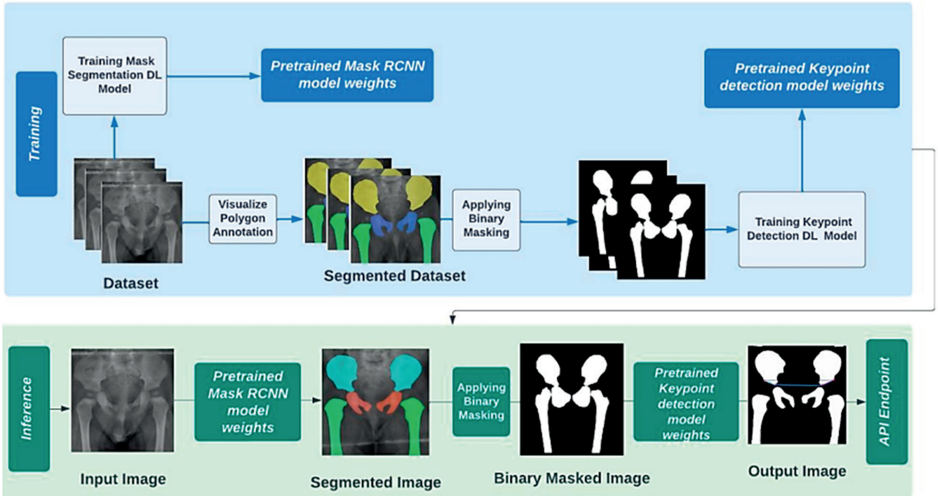
The study carried out by Fraiwan et al. (2022) focuses on automating the diagnosis of DDH in infants using deep transfer learning methods applied to pelvic X-ray images. The authors utilized 354 pelvic anteroposterior X-ray images, employing thirteen different deep transfer learning models based on CNNs, including DarkNet-53, DenseNet-201, EfficientNet-b0, and ResNet variants. Among these, DarkNet-53 achieved the highest diagnostic accuracy of 96.3%, with a recall of 100% and an F1 score of 95%. Unlike traditional methods that rely on pelvic landmark detection and angular measurements, the study diagnoses DDH directly from X-ray images, thereby reducing the need for manual preprocessing and expert knowledge. This study contributes to the literature by providing a highly accurate AI-based system for DDH diagnosis and making the dataset publicly available for further research and education. However, the study's limitations include a relatively small dataset and the absence of full angular measurements, which could impact the generalizability of the findings across different medical standards.

Jaremko et al.'s (2023) study introduces an innovative approach to DDH screening by utilizing handheld ultrasound devices paired with an AI decision support system, MEDO-Hip, in primary care settings. This work is particularly notable for demonstrating that non-expert primary care providers, such as nurses and family physicians, can successfully perform DDH screenings with AI assistance, achieving recall and detection rates comparable to those of expert radiologists in tertiary care. Additionally, the study highlights the potential for these AI-supported devices to make universal DDH screening more cost-effective and accessible, particularly in resource-limited areas. However, the study's pilot nature, with a small sample size of 369 scans, limits the generalizability of its findings. The study also acknowledges challenges related to the specific hardware and software used, raising concerns about the broader applicability of this workflow. Despite these limitations, the study provides important evidence for the real-world application of AI in enhancing accessibility and cost-effectiveness in healthcare, though further research is needed to validate these findings on a larger scale .

Jan et al.'s (2023) study presents a novel deep learning framework combining instance segmentation and keypoint detection to diagnose DDH in infants. The approach shown in *Ffigure 8* is particularly innovative in its integration of segmentation prior to landmark detection, which has led to improvements in accuracy, as evidenced by an average pixel error of 2.862 and an acetabular index (AcI) angle error of 2.402°. This advancement offers a more objective and standardized diagnostic method, addressing the traditional reliance on manual assessments by medical professionals. Despite these contributions, the study's reliance on a small dataset of 354 X-ray images and its focus on a single radiographic measurement, the acetabular index angle, limit the generalizability and comprehensiveness of its findings. Furthermore, the absence of real-world clinical testing means the practical effectiveness of the proposed model remains unverified.

Figure 8

Overview of the pipelined segmentation and keypoint detection process in Jan et al.'s (2023) study (Jan et al., 2023). [This figure is reused with permission under the Creative Commons CC-BY license.]



Den et al.'s (2023) study contributes significantly to the field by applying the YOLOv5 deep learning model, known for its efficiency and accuracy in object detection, to the identification of DDH in radiographic images. Notably, the YOLOv5l version achieved high diagnostic accuracy, with sensitivity and specificity rates of 0.94 and 0.96, respectively, demonstrating its potential as a reliable tool in pediatric radiology. The study also employed transfer learning, which allowed the model to perform well even with a relatively small dataset, a valuable approach in medical fields where large datasets are often scarce. Additionally, the comparison with the Single Shot MultiBox Detector (SSD) model highlighted the superiority of YOLOv5l, particularly in terms of sensitivity. However, the study's limitations include its reliance on a single-center dataset with potential annotation bias, challenges in accurately detecting mild DDH cases, and the risk of overdiagnosis due to the inclusion criteria. These findings underscore the need for further validation through larger, multi-center studies. Despite these challenges, this work demonstrates the promising application of YOLOv5 in improving the early detection and diagnosis of DDH, potentially enhancing clinical outcomes .

Kaderdina et al.'s (2023) study applied deep learning techniques to predict angular displacements between frames in 2D US sequences for assessing DDH in newborns, aiming to improve diagnostic accuracy given the limitations of 3D USavailability. By utilizing CNNmodels, the researchers restructured a previously proposed CNN model by Prevost et al. [citation?] to output angular displacements, incorporating optical flow data as an additional input. The study achieved a mean absolute error of approximately 0.02° in predicting angular displacements, suggesting that 2D US images can be used more reliably for DDH assessment. Despite limitations, such as not considering the temporal dimension and the reduced usefulness of optical flow data for larger slice intervals, the study significantly contributes to the literature by demonstrating the potential for more repeatable dysplasia measurements using 2D US, which could enhance the reliability of DDH diagnosis in clinical settings.

Xu et al.'s (2023) study developed an online diagnostic tool for DDH using a multi-task hourglass network designed to detect key landmarks on hip X-rays and predict the developmental age of the femoral head. The network demonstrated strong performance, achieving a mean pixel error of 4.64 for landmark detection and an 89% accuracy rate in age prediction. This study significantly contributes to the field by integrating both landmark detection and age prediction into a single model, providing a comprehensive diagnostic approach. Additionally, the creation of a large-scale, expertly annotated DDH dataset enhances its value to the literature. However, the study also has limitations, such as challenges with pixel errors due to bone morphology diversity and a lack of images from patients older than 12 years, suggesting areas for future improvement. The study exemplifies the practical application of deep learning in telemedicine, with the potential to improve healthcare access in underserved regions.

The study titled Diagnosis of Developmental Dysplasia of the Hip by Ultrasound Imaging Using Deep Learning evaluates the effectiveness of deep learning models in diagnosing DDH from USimages. The research utilized three pre-trained deep learning models (SqueezeNet, MobileNet_v2, and EfficientNet) and assessed their performance in distinguishing between normal and DDH-affected hips in infants under six months old. The study's findings indicate that all models achieved high accuracy, precision, recall, and F-measure scores, highlighting the potential of deep learning to assist in the accurate diagnosis of DDH. Notably, the models focused on critical regions, such as the labrum and joint capsule, for DDH cases, aligning with areas of interest for human experts. This work suggests that AI can significantly enhance the reliability of DDH screening, particularly when standard ultrasound planes are used. However, the study also has limitations, including the exclusion of poor-quality images and the need for larger sample sizes in future research (Kinugasa et al.,2023).

Sezer and Sezer (2023) proposed an automatic segmentation method based on Mask R-CNN to accurately detect the measurable standard plane in Graf hip ultrasonography images. The study examined hip ultrasonograms from 675 infants, focusing on segmenting key anatomical structures such as the labrum, iliac wing, and the lower limb of the ilium. The method demonstrated high accuracy, with average success rates of 96.95% and 96.96% according to the Dice and mAP metrics, respectively. The highest success rates were observed in type 1 hips and the iliac wing region. The results suggest that Mask R-CNN is a robust tool for improving the accuracy and consistency of DDH assessments, particularly in complex anatomical regions. The study indicates that this deep learning-based segmentation method has significant potential for clinical applications, and future research could explore its integration into mobile platforms for real-time guidance in clinical settings.

The study titled "The Diagnosis of Developmental Dysplasia of the Hip From Hip Ultrasonography Images With Deep Learning Methods" makes a notable contribution to the literature by applying deep learning techniques, such as transfer learning with pretrained models like VGG-16, ResNet-101, MobileNetV2, and GoogLeNet, to the diagnosis of DDH using ultrasonography images. A particularly innovative aspect is the inclusion of US images with incorrect probe positioning, addressing a common clinical issue and reducing the likelihood of misdiagnosis. The study reports impressive performance metrics, especially with the VGG-16 model, achieving high accuracy, sensitivity, specificity, precision, F1 score, and an AUC of 0.99. These findings suggest that deep learning-assisted ultrasonography could be valuable in clinical practice, particularly for less experienced clinicians. However, the study's limitations, including the small dataset size, reliance on images from a single ultrasound device, and focus on 2D sonograms, highlight the need for further research with larger datasets, multiple devices, and the exploration of 3D imaging techniques to enhance the clinical applicability of these methods (Atalar et al., 2023).

Li et al.'s (2024) study introduced a semi-supervised deep learning framework aimed at diagnosing DDH in infants using multisource US images. This framework is notable for leveraging a large volume of unlabeled images through contrastive learning, addressing the common issue of limited labeled data. Their method achieved higher accuracy in identifying landmarks and recognizing standard planes compared to previous models, with a mean Dice similarity coefficient (DSC) of 0.7873 and a mean Hausdorff distance (HD) of 5.0102. Additionally, the accuracy, precision, and recall of standard plane recognition were 95.4%, 91.64%, and 94.86%, respectively. By incorporating contrastive self-supervised learning, the study reduces the dependency on extensive annotated datasets, making AI-driven diagnosis more feasible in resource-limited clinical environments. However, the study faced limitations, including the lack of data diversity, as the training data only included type I and type II hips, and the absence of automatic standard plane acquisition during examinations. Furthermore, the research was conducted at a single medical center, limiting the generalizability of its findings. Despite these challenges, the study contributes valuable insights into the use of AI in pediatric orthopedics, presenting a promising approach for improving the early detection and treatment of DDH.

Shimizu et al.'s (2024) study presents a significant advancement in pediatric orthopedics through the development of a bimodal machine learning model that integrates automatically generated clinical measurements with radiographic images for diagnosing unstable hips in infants. The model outperforms traditional CNN models and other machine learning approaches, demonstrating superior diagnostic accuracy, with an average AUROC of 0.885 and an AUPRC of 0.804. By automating the calculation of key clinical parameters, the model reduces the need for manual measurements and potentially diminishes the reliance on provocative maneuvers, which are skill-dependent and prone to variability. However, the study's reliance on radiographic images and a limited dataset raises concerns about its generalizability, particularly in settings where ultrasound is preferred. Despite these limitations, the research demonstrates the potential of integrating multiple data sources to enhance the accuracy of AI-driven healthcare solutions, though further validation is needed across different modalities and broader patient populations .

Pelit et al.'s (2024) study employed a deep learning-based approach using the YOLOv8 algorithm to enhance the Graf method, which is widely used for diagnosing DDH in newborns through US imaging. The study effectively detected critical anatomical structures, including the iliac wing, labrum, and acetabulum, with accuracy rates of 98.30%, 93.57%, and 94.25%, respectively, demonstrating the algorithm's capability in contributing to more consistent and accurate DDH diagnosis. Notably, the YOLOv8l model outperformed others in detecting the labrum region, underscoring its potential in clinical applications. However, the study also identified limitations related to image resolution and noise, suggesting that improvements in these areas could enhance detection accuracy. The research significantly contributes to the literature by showcasing the practical benefits of integrating deep learning algorithms into DDH diagnosis, highlighting the potential for more reliable and precise assessments.

The study by Darılmaz et al. (2024) focused on the development of an artificial intelligence (AI)-based system for hip ultrasound screening in DDH. In the research, hip US data from 110 infants were used, and standard plane detection was performed using the SSD deep learning algorithm combined with the MobileNet neural network. As shown in *Figure 9*, the SSD-MobileNet model is designed to perform standard plane detection quickly and efficiently. The developed model achieved accuracy rates similar to those of expert radiologists and orthopedists, and it helped reduce error rates for less experienced users by standardizing the evaluation process. Test results showed a high inter-observer agreement (96.2%), and despite some artifact errors, the AI model was highly successful in detecting the iliac wing, acetabular depth, and labrum. *Figure 10* shows the AI's detection outputs for an object identified in a US image. The study's limitations include the use of pre-recorded videos instead of real-time data and the absence of Graf type classification. The research. demonstrated that AI-based systems can improve accuracy in DDH screenings, reduce human error, and contribute to the standardization of ultrasonographic evaluations in clinical practice.

Figure 9

SSD MobileNet model architecture (Darılmaz et al., 2024)

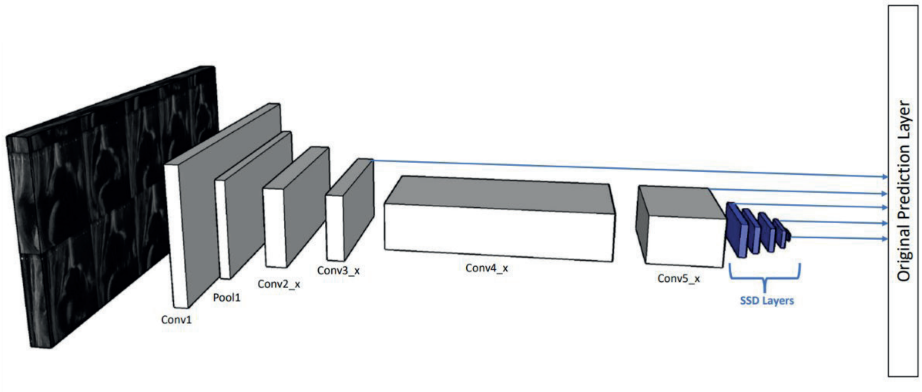
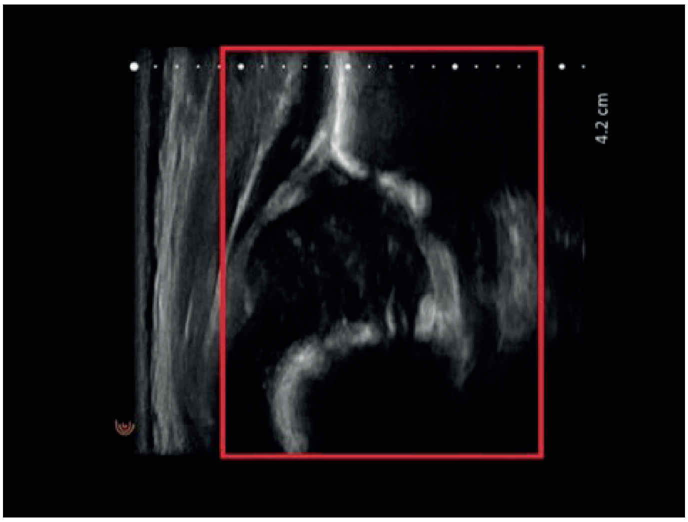


Figure 10

SSD Algorithm object detection output (Darılmaz et al., 2024)



The study titled "Automatic and Human-Level Graf's Type Identification for Detecting Developmental Dysplasia of the Hip" presents a sophisticated deep neural network model designed to automate the identification of DDH in neonates, a condition that, if left untreated, can lead to severe complications. The model focuses on accurately identifying five key anatomical points on 2D ultrasonographic images, which are essential for calculating the alpha and beta angles according to Graf's method—

an established standard for DDH classification. With a high correlation coefficient of 0.89 for alpha angle measurements, the model's outputs closely align with those of human experts, underscoring its precision and reliability. Moreover, the model achieves remarkable diagnostic accuracy, evidenced by AUROC values of 0.937 and 0.974 for detecting abnormal and dysplastic hips, respectively. These results not only highlight the model's potential to improve diagnostic consistency but also suggest its capacity to reduce the dependency on highly skilled operators, making it a valuable tool in clinical settings where experienced personnel may be scarce. Additionally, the study emphasizes the model's generalizability across different datasets, with agreement rates between the model and human experts indicating that it can maintain high performance in varied clinical environments. This research contributes significantly to the growing body of literature on ML-driven medical diagnostics, particularly in pediatric orthopedics, where early and accurate detection of conditions like DDH is crucial for effective treatment and long-term patient outcomes (Chen et al., 2024).

Huang et al. (2024) introduced the Involution Transformer-based U-Net (IT-UNet), a novel architecture designed for detecting anatomical landmarks in USimages for diagnosing infantile DDH. Their approach integrates the Involution Transformer Module, enhancing spatial information and long-range dependencies, which improves landmark detection accuracy. Additionally, they proposed an Involution Downsampling Block that effectively addresses feature loss during downsampling, further refining detection precision. While their method demonstrated strong performance on DDH ultrasound datasets, increased computational complexity and a limited focus on six anatomical landmarks highlight opportunities for future improvements and broader generalizability.

Table 1

Taxonomy of machine learning techniques applied to hip dislocation detection in infants

Supervised Learning			Unsupervised Learning	Semi-supervised Learning
SVM	**CNNs**		**K-means**	**CNNS**
Hareendranathan et al. 2017a	Hareendranathan et al. 2021	Liu et al. 2020	Hareendranathan et al. 2016	Liu et al. 2024
Liu et al. 2019	Lee J. H. 2021	Chen et al. 2024		
	Hu et al. 2021	Oelen et al. 2022		
RNN	Park et al. 2021	Pelit et al. 2024		
Paserin et al. 2018	El-Hariri et al. 2021	Paserin et al. 2017		
	Liu et al. 2021	Shimizu et al. 2024		
Random Forest	Gong et al. 2021	Paserin et al. 2018		
Quader et al. 2017	Fraiwan et al. 2022	Liu et al. 2019		
	Xu et al. 2022	Atalar et al. 2023		
Meta-Learning	Xu et al. 2021	El-Hariri et al. 2019		
Gong et al. 2021	Kaderdina et al. 2023	Kinugasa et al. 2023		
	Chen et al. 2022	Zhang et al. 2020		
	El-Hariri 2020	Sezer and Sezer 2020		
	Huang et al. 2024	Kannan et al. 2020		
	Sezer and Sezer 2023	Chen et al. 2020		
	Xu et al. 2023	Lee et al. 2021		

Jan et al. 2023	Den et al. 2023
Jaremko et al. 2023	Çevik ve Andaç 2022
Ghasseminia et al. 2022	Hareendrananthan et al. 2022a
	Hareendranathan et al. 2017a

Conclusion

The application of ML in the diagnosis of DDH represents a significant advancement in pediatric healthcare. Through various ML-based methodologies, including deep learning and machine learning models, the detection of hip dislocation in infants has become more accurate, reliable, and less dependent on operator expertise. This review has synthesized the findings from multiple studies, demonstrating that ML-driven tools can improve diagnostic consistency, reduce variability, and potentially lead to earlier interventions. While challenges remain, such as the need for large, diverse datasets and further validation in clinical settings, the integration of ML into DDH screening and diagnosis holds great promise for enhancing the standard of care. Future research should focus on addressing these challenges and expanding the applicability of ML-based solutions to broader clinical environments. With continued innovation and refinement, ML has the potential to transform the diagnosis and management of DDH, leading to better outcomes for infants worldwide.

Acknowledgement

We would like to express our gratitude for the assistance provided by various tools during the preparation of this article. Napkin AI played a valuable role in facilitating the creation of some of the diagrams, allowing for more efficient and effective visual communication. Jenny AI significantly contributed to the management and formatting of references, streamlining that process. Additionally, ChatGPT was instrumental in helping refine the grammar, language, and translation of Turkish text into English, enhancing the clarity and coherence of the manuscript. These tools greatly supported the authors throughout the writing process.

References

Alam, M. E., Smith, N., Watson, D., Hassan, T., & Neupane, K. (2019, April). Early screening of DDH using SVM classification. In 2019 SoutheastCon (pp. 1-4). IEEE.

Atalar, H., Üreten, K., Tokdemir, G., Tolunay, T., Çiçeklidağ, M., & Atik, O. Ş. (2023). The Diagnosis of developmental dysplasia of the hip from hip ultrasonography images with deep learning methods. Journal of Pediatric Orthopaedics, 43(2), e132-e137.

Bai, M., & Li, M. (2023, July 30). A Presentation of Structures and Applications of Convolutional Neural Networks. 61, 180-187. https://doi.org/10.54097/hset.v61i.10291

Chen, L., Cui, Y., Song, H., Huang, B., Yang, J., Zhao, D., & Xia, B. (2020). Femoral head segmentation based on improved fully convolutional neural network for ultrasound images. Signal, Image and Video Processing, 14, 1043-1051.

Chen, T., Zhang, Y., Wang, B., Wang, J., Cui, L., He, J., & Cong, L. (2022). Development of a fully automated graf standard plane and angle evaluation method for infant hip ultrasound scans. Diagnostics, 12(6), 1423.

Chen, Y. P., Fan, T. Y., Chu, C. C., Lin, J. J., Ji, C. Y., Kuo, C. F., & Kao, H. K. (2024). Automatic and human level Graf's type identification for detecting developmental dysplasia of the hip. *Biomed Journal*, *47*(2), 100614. https://doi.org/10.1016/j.bj.2023.100614

Cicco, T N F L D. (2022, October 3). Developmental Dysplasia Of The Hip. https://www.ncbi.nlm.nih.gov/books/NBK563157/

Çevik, K. K., & Andaç, Ş. (2022). Detection Of Standard Plane From Ultrasound Scans By Deep Learning Methods For The Diagnosis Of Developmental Hip Dysplasia. Mühendislik Bilimleri ve Tasarım Dergisi, 10(3), 1014-1026.

Darılmaz, M. F., Sağlam, Y., Demirel, M., Bilgili, F., Durmaz, H., & Altun, H. O. (2024). Kalça ultrason taramalarında bilgisayar yardımlı standart plan tanımlanması ve klinik korelasyonu. *10. Ortopedi ve Travmatoloji İstanbul Buluşması,* pp. 4-7.

Dave, M., & Patel, N. (2023, May 26). Artificial intelligence in healthcare and education. Springer Nature, 234(10), 761-764. https://doi.org/10.1038/s41415-023-5845-2

Den, H., Ito, J., & Kokaze, A. (2023). Diagnostic accuracy of a deep learning model using YOLOv5 for detecting developmental dysplasia of the hip on radiography images. Scientific Reports, 13(1), 6693.

Denil, M., Matheson, D., & Freitas, N D. (2013, January 1). Narrowing the Gap: Random Forests In Theory and In Practice. Cornell University. https://doi.org/10.48550/arXiv.1310.

El-Hariri, H., Hodgson, A. J., Mulpuri, K., & Garbi, R. (2021). Automatically delineating key anatomy in 3-D ultrasound volumes for hip dysplasia screening. Ultrasound in Medicine & Biology, 47(9), 2713-2722.

El-Hariri, H., Mulpuri, K., Hodgson, A., & Garbi, R. (2019). Comparative evaluation of hand-engineered and deep-learned features for neonatal hip bone segmentation in ultrasound. In Medical Image Computing and Computer Assisted Intervention–MICCAI 2019: 22nd International Conference, Shenzhen, China, October 13–17, 2019, Proceedings, Part II 22 (pp. 12-20). Springer International Publishing.

El-Hariri, H. (2020, January 1). Reliable and robust hip dysplasia measurement with three-dimensional ultrasound and convolutional neural networks. https://doi.org/10.14288/1.0389533

Fraiwan, M., Al-Kofahi, N., Ibnian, A., & Hanatleh, O. (2022). Detection of developmental dysplasia of the hip in X-ray images using deep transfer learning. BMC Medical Informatics and Decision Making, 22(1), 216.

Ghasseminia, S., Bolouri, S. E. S., Dulai, S., Kernick, S., Brockley, C., Hareendranathan, A. R., ... & Jaremko, J. L. (2022). Automated diagnosis of hip dysplasia from 3D ultrasound using artificial intelligence: A two-center multi-year study. Informatics in Medicine Unlocked, 33, 101082.

Gong, B., Shi, J., Han, X., Zhang, H., Huang, Y., Hu, L., ... & Shi, J. (2021). Diagnosis of infantile hip dysplasia with B-mode ultrasound via two-stage meta-learning based deep exclusivity regularized machine. IEEE Journal of Biomedical and Health Informatics, 26(1), 334-344.

Grissom, L E., Harcke, H T., & Thacker, M M. (2008, April 1). Imaging in the Surgical Management of Developmental Dislocation of the Hip. Lippincott Williams & Wilkins, 466(4), 791-801. https://doi.org/10.1007/s11999-008-0161-3

Gulati, V. (2013, January 1). Developmental dysplasia of the hip in the newborn: A systematic review. Springer Science+Business Media, 4(2), 32-32. https://doi.org/10.5312/wjo.v4.i2.32

Hareendrananthan, A. R., Mabee, M., Chahal, B. S., Dulai, S. K., & Jaremko, J. L.

(2022a). Can AI Automatically Assess Scan Quality of Hip Ultrasound?. Applied Sciences, 12(8), 4072.

Hareendranathan, A. R., Chahal, B., Ghasseminia, S., Zonoobi, D., & Jaremko, J. L. (2022b). Impact of scan quality on AI assessment of hip dysplasia ultrasound. Journal of Ultrasound, 1-9.

Hareendranathan, A. R., Chahal, B. S., Zonoobi, D., Sukhdeep, D., & Jaremko, J. L. (2021). Artificial intelligence to automatically assess scan quality in hip ultrasound. Indian Journal of Orthopaedics, 55, 1535-1542.

Hareendranathan, A. R., Mabee, M., Punithakumar, K., Noga, M., & Jaremko, J. L. (2016). Toward automated classification of acetabular shape in ultrasound for diagnosis of DDH: Contour alpha angle and the rounding index. Computer methods and programs in biomedicine, 129, 89-98.

Hareendranathan, A. R., Zonoobi, D., Mabee, M., Cobzas, D., Punithakumar, K., Noga, M., & Jaremko, J. L. (2017a, April). Toward automatic diagnosis of hip dysplasia from 2D ultrasound. In 2017 IEEE 14th International Symposium on Biomedical Imaging (ISBI 2017) (pp. 982-985). IEEE.

Hareendranathan, A. R., Zonoobi, D., Mabee, M., Diederichs, C., Punithakumar, K., Noga, M., & Jaremko, J. L. (2017b). Semiautomatic classification of acetabular shape from three-dimensional ultrasound for diagnosis of infant hip dysplasia using geometric features. International journal of computer assisted radiology and surgery, 12, 439-447.

Hinton, G E. (2018, September 18). Deep Learning—A Technology With the Potential to Transform Health Care. American Medical Association, 320(11), 1101-1101. https://doi.org/10.1001/jama.2018.11100

Hosny, A., Parmar, C., Quackenbush, J., Schwartz, L H., & Aerts, H J. (2018, May 17). Artificial intelligence in radiology. Nature Portfolio, 18(8), 500-510. https://doi.org/10.1038/s41568-018-0016-5

Hu, X., Wang, L., Yang, X., Zhou, X., Xue, W., Cao, Y., ... & Gu, N. (2021). Joint landmark and structure learning for automatic evaluation of developmental dysplasia of the hip. IEEE Journal of Biomedical and Health Informatics, 26(1), 345-358.

Huang, T., Shi, J., Li, J., Wang, J., Du, J., & Shi, J. (2024). Involution Transformer Based U-Net for Landmark Detection in Ultrasound Images for Diagnosis of Infantile DDH. *IEEE Journal of Biomedical and Health Informatics*, *28*(8), 4797-4809. https://doi.org/10.1109/JBHI.2024.3390241

Jan, F., Rahman, A., Busaleh, R., Alwarthan, H., Aljaser, S., Al-Towailib, S., ... & Ahmed, M. I. B. (2023). Assessing acetabular index angle in infants: a deep learning-based novel approach. Journal of Imaging, 9(11), 242.

Jaremko, J. L., Hareendranathan, A., Bolouri, S. E. S., Frey, R. F., Dulai, S., & Bailey, A. L. AI aided workflow for hip dysplasia screening using ultrasound in primary care clinics, 13 (1), 9224. DOI: https://doi. org/10.1038/s41598-023-35603-9.

Kaderdina, A., Suarez, M. J. B., Garbi, R., Schaeffer, E., Mulpuri, K., & Hodgson, A. (2023). Using Deep Learning to Estimate Frame-to-Frame Angle Displacements in 2D Ultrasound Image Sequences of an Infant Hip. CMBES Proceedings, 45.

Kannan, A., Hodgson, A., Mulpuri, K., & Garbi, R. (2020). Uncertainty estimation for assessment of 3D US scan adequacy and DDH metric reliability. In Uncertainty for Safe Utilization of Machine Learning in Medical Imaging, and Graphs in Biomedical Image Analysis: Second International Workshop, UNSURE 2020, and Third International Workshop, GRAIL 2020, Held in Conjunction with

MICCAI 2020, Lima, Peru, October 8, 2020, Proceedings 2 (pp. 97-105). Springer International Publishing.

Kinugasa, M., Inui, A., Satsuma, S., Kobayashi, D., Sakata, R., Morishita, M., ... & Kuroda, R. (2023). Diagnosis of developmental dysplasia of the hip by ultrasound imaging using deep learning. Journal of Pediatric Orthopaedics, 43(7), e538-e544.

LeCun, Y., Bengio, Y., & Hinton, G E. (2015, May 27). Deep learning. Nature Portfolio, 521(7553), 436-444. https://doi.org/10.1038/nature14539

Lee, J. H. (2021b). The novel computer aided diagnostic system on medical images for parameter calculation. Sensors & Transducers, 249(2), 93-101.

Lee, S. W., Ye, H. U., Lee, K. J., Jang, W. Y., Lee, J. H., Hwang, S. M., & Heo, Y. R. (2021a). Accuracy of new deep learning model-based segmentation and key-point multi-detection method for ultrasonographic developmental dysplasia of the hip (DDH) screening. Diagnostics, 11(7), 1174.

Li, Q., Zhong, L., Huang, H., Liu, H., Qin, Y., Wang, Y., Zhou, Z., Liu, H., Yang, W., Qin, M., Wang, J., Wang, Y., Zhou, T., Wang, D., Wang, J., Meng, X., & Huang, Y. (2019, December 1). Auxiliary diagnosis of developmental dysplasia of the hip by automated detection of Sharp's angle on standardized anteroposterior pelvic radiographs. Wolters Kluwer, 98(52), e18500-e18500. https://doi.org/10.1097/md.0000000000018500

Li, X., Zhang, R., Wang, Z., & Wang, J. (2024). Semi-supervised learning in diagnosis of infant hip dysplasia towards multisource ultrasound images. Quantitative Imaging in Medicine and Surgery, 14(5), 3707.

Li, Y., Li-Han, L Y., & Tian, H. (2022, January 1). Deep Learning-Based Automatic Diagnosis System for Developmental Dysplasia of the Hip. Cornell University. https://doi.org/10.48550/arXiv.2209.

Liaw, A., & Wiener, M C. (2007, January 1). Classification and Regression by randomForest. http://cogns.northwestern.edu/cbmg/LiawAndWiener2002.pdf

Litjens, G., Kobus, T., Bejnordi, B E., Setio, A A A., Ciompi, F., Ghafoorian, M., Laak, J V D., Ginneken, B V., & Sánchez, C I. (2017, December 1). A survey on deep learning in medical image analysis. Elsevier BV, 42, 60-88. https://doi.org/10.1016/j.media.2017.07.005

Liu, C., Xie, H., Zhang, S., Mao, Z., Sun, J., & Zhang, Y. (2020, December 1). Misshapen Pelvis Landmark Detection With Local-Global Feature Learning for Diagnosing Developmental Dysplasia of the Hip. Institute of Electrical and Electronics Engineers, 39(12), 3944-3954. https://doi.org/10.1109/tmi.2020.3008382

Liu, C., Xie, H., Zhang, S., Xu, J., Sun, J., & Zhang, Y. (2019). Misshapen pelvis landmark detection by spatial local correlation mining for diagnosing developmental dysplasia of the hip. In Medical Image Computing and Computer Assisted Intervention–MICCAI 2019: 22nd International Conference, Shenzhen, China, October 13–17, 2019, Proceedings, Part VI 22 (pp. 441-449). Springer International Publishing.

Liu, R., Liu, M., Sheng, B., Li, H., Li, P., Song, H., ... & Shen, D. (2021). NHBS-Net: A feature fusion attention network for ultrasound neonatal hip bone segmentation. IEEE Transactions on Medical Imaging, 40(12), 3446-3458.

Noordin, S., Umer, M., Hafeez, K., & Nawaz, H. (2010, September 23). Developmental dysplasia of the hip. PAGEPress (Italy), 2(2). https://doi.org/10.4081/or.2010.e19

Oelen, D., Kaiser, P., Baumann, T., Schmid, R., Bühler, C., Munkhuu, B., & Essig, S. (2022). Accuracy of trained physicians is inferior to deep learning-based algorithm for determining angles in ultrasound of the newborn hip. Ultraschall in der Medizin-European Journal of Ultrasound, 43(05), e49-e55.

Park, H. S., Jeon, K., Cho, Y. J., Kim, S. W., Lee, S. B., Choi, G., ... & Hwang, J. Y. (2021). Diagnostic performance of a new convolutional neural network algorithm for detecting developmental dysplasia of the hip on anteroposterior radiographs. Korean journal of radiology, 22(4), 612.

Paserin, O., Mulpuri, K., Cooper, A., Hodgson, A. J., & Abugharbieh, R. (2017). Automatic near real-time evaluation of 3D ultrasound scan adequacy for developmental dysplasia of the hip. In Computer Assisted and Robotic Endoscopy and Clinical Image-Based Procedures: 4th International Workshop, CARE 2017, and 6th International Workshop, CLIP 2017, Held in Conjunction with MICCAI 2017, Québec City, QC, Canada, September 14, 2017, Proceedings 4 (pp. 124-132). Springer International Publishing.

Paserin, O., Mulpuri, K., Cooper, A., Hodgson, A. J., & Garbi, R. (2018). Real time RNN based 3D ultrasound scan adequacy for developmental dysplasia of the hip. In Medical Image Computing and Computer Assisted Intervention–MICCAI 2018: 21st International Conference, Granada, Spain, September 16-20, 2018, Proceedings, Part I (pp. 365-373). Springer International Publishing.

Pelit, B., Abay, H., Akkas, B. B., & Sezer, A. (2024, May). Deep Learning based Determination of Graf Standart Plane on Hip Ultrasound Scans. In *2024 32nd Signal Processing and Communications Applications Conference (SIU)* (pp. 1-4). IEEE.

Quader, N., Hodgson, A. J., Mulpuri, K., Schaeffer, E., & Abugharbieh, R. (2017). Automatic evaluation of scan adequacy and dysplasia metrics in 2-D ultrasound images of the neonatal hip. Ultrasound in medicine & biology, 43(6), 1252-1262.

Sarica, A., Cerasa, A., & Quattrone, A. (2017, October 6). Random Forest Algorithm for the Classification of Neuroimaging Data in Alzheimer’s Disease: A Systematic Review. Frontiers Media, 9. https://doi.org/10.3389/fnagi.2017.00329

Schwend, R M., Shaw, B A., & Segal, L S. (2014, December 1). Evaluation and Treatment of Developmental Hip Dysplasia in the Newborn and Infant. Elsevier BV, 61(6), 1095-1107. https://doi.org/10.1016/j.pcl.2014.08.008

Sezer, A., & Sezer, H. B. (2020). Deep convolutional neural network-based automatic classification of neonatal hip ultrasound images: A novel data augmentation approach with speckle noise reduction. ultrasound in medicine & biology, 46(3), 735-749.

Sezer, A., & Sezer, H. B. (2023). Segmentation of measurable images from standard plane of Graf hip ultrasonograms based on Mask Region-Based Convolutional Neural Network. Joint Diseases and Related Surgery, 34(3), 590.

Shimizu, H., Enda, K., Koyano, H., Shimizu, T., Shimodan, S., Sato, K., ... & Takahashi, D. (2024). Bimodal machine learning model for unstable hips in infants: integration of radiographic images with automatically-generated clinical measurements. Scientific Reports, 14(1), 17826.

Voulodimos, A., Doulamis, N., Doulamis, N., & Protopapadakis, E. (2018, January 1). Deep Learning for Computer Vision: A Brief Review. Hindawi Publishing Corporation, 2018, 1-13. https://doi.org/10.1155/2018/7068349

Xu, J., Xie, H., Liu, C., Yang, F., Zhang, S., Chen, X., & Zhang, Y. (2021). Hip landmark detection with dependency mining in ultrasound image. IEEE Transactions on Medical Imaging, 40(12), 3762-3774.

Xu, J., Xie, H., Tan, Q., Wu, H., Liu, C., Zhang, S., ... & Zhang, Y. (2023). Multi-task hourglass network for online automatic diagnosis of developmental dysplasia of the hip. World wide web, 26(2), 539-559.

Xu, W., Shu, L., Gong, P., Huang, C., Xu, J., Zhao, J., ... & Yu, G. (2022). A deep-learning aided diagnostic system in assessing developmental dysplasia of the hip on pediatric pelvic radiographs. Frontiers in Pediatrics, 9, 785480.

Zeiler, M D., & Fergus, R. (2013, January 1). Visualizing and Understanding Convolutional Networks. Cornell University. https://doi.org/10.48550/arxiv.1311.2901

Zhang, S. C., Sun, J., Liu, C. B., Fang, J. H., Xie, H. T., & Ning, B. (2020). Clinical application of artificial intelligence-assisted diagnosis using anteroposterior pelvic radiographs in children with developmental dysplasia of the hip. The Bone & Joint Journal, 102(11), 1574-1581.

About the Authors

Mevlüt Can ADIYAMAN is studying Computer Engineering at KTO Karatay University in Konya, Türkiye. He works as a software developer at Autodidactic Technologies. His main research areas of interest are deep learning and reinforcement learning.
E-mail: mevlut.can.adiyaman@autodidactic.com.tr , **ORCID**: 0009-0000-8615-1210

Şeyma Nefise SATICI is a Master's student at the Institute of Data Science and Artificial Intelligence at Boğaziçi University in Istanbul, Türkiye. Her main areas of interest include machine learning, reinforcement learning, and computer vision.
E-mail: seyma.satici@std.bogazici.edu.tr, **ORCID**:0009-0009-8249-7164.

Muhammed Furkan DARILMAZ is an orthopedic and traumatology surgeon at Aksaray Training and Research Hospital. His areas of interest are pediatric orthopedics and deformity surgery.
E-mail: mfdarilmaz@gmail.com, **ORCID**:0000-0002-6562-6026

Hüseyin Oktay ALTUN works as an assistant professor at the Institute of Data Science and Artificial Intelligence at Boğaziçi University in İstanbul, Türkiye. He has an undergraduate degree in electrical engineering from Bilkent University. He obtained his MSc and PhD degrees from University of Rochester. His main research areas of interest are reinforcement learning, convex optimization and energy systems design.
E-mail: oktay.altun@bogazici.edu.tr **ORCID**: 0000-0002-8875-6878

Similarity Index

The similarity index obtained from the plagiarism software for this book chapter is 2%.

Performance Comparison of Different Machine Learning Models in Breast Cancer Diagnosis

Fatma Nur UZUN

Kütahya University of Health Sciences

To Cite This Chapter

Uzun, F. N. (2024). Performance Comparison of Different Machine Learning Models in Breast Cancer Diagnosis. In F. Nur Takı, S. Koçer & R. Bütüner (Eds.), *New Generation Technologies and Sustainability in Health Current Studies* (pp. 74-95). ISRES Publishing.

Introduction

Breast cancer remains one of the most common and life-threatening cancers affecting women worldwide, posing a significant public health issue (Figure 1). The disease's impact is profound, and the challenge of detecting it early enough to improve treatment outcomes is a crucial focus in the medical community. Early diagnosis is pivotal in enhancing survival rates, as it enables timely intervention, which can significantly reduce the disease's progression. Despite the importance of early detection, traditional diagnostic methods, such as mammography and biopsy, face limitations that can affect their effectiveness. These conventional approaches often struggle with issues like false positives, false negatives, and varying levels of accuracy, leading to potential delays in treatment or unnecessary medical procedures (DeSantis et al., 2019). Such challenges underscore the need for advancements in diagnostic techniques to ensure more accurate and reliable results.

The integration of machine learning (ML) and artificial intelligence (AI) technologies into medical diagnostics has emerged as a promising solution to these challenges. In recent years, the advent of these technologies has revolutionized numerous facets of healthcare, especially in fields that necessitate the analysis of extensive and intricate datasets. AI and ML models are uniquely positioned to enhance breast cancer diagnosis by processing vast amounts of medical data quickly and accurately, potentially surpassing the capabilities of traditional diagnostic methods (Bray et al., 2018). These advancements provide a more detailed comprehension of patient data, enabling earlier detection of malignancies, minimizing diagnostic errors, and ultimately enhancing patient outcomes. The growing interest in AI and ML in breast cancer diagnosis highlights the potential for these tools to revolutionize how this disease is detected and treated, offering hope for better management and survival rates in the future.

Beyond improving diagnostic accuracy, integrating AI and ML in breast cancer screening could also lead to more personalized treatment plans. By analyzing data at a granular level, these technologies can identify specific cancer subtypes and predict responses to various treatments, enabling healthcare providers to tailor interventions more precisely to individual patients. This personalized approach optimizes treatment efficacy, minimizes side effects, and improves patients' overall quality of life. Additionally, AI-driven models can continuously learn and improve, adapting to new data and evolving medical knowledge. This further solidifies their potential as a dependable tool in combating breast cancer. The continued development and implementation of these advanced diagnostic methods could mark a significant turning point in breast cancer care, moving towards a future where early detection and personalized treatment are the norms, ultimately saving more lives and improving patient outcomes.

Literature Review

The integration of ML and AI into breast cancer diagnostics has been extensively explored in recent studies, underscoring the growing role of these technologies in enhancing diagnostic accuracy and efficiency. Research by applying deep learning models to mammogram images demonstrated improved performance in detecting malignant tumors compared to traditional methods (Abdel-Zaher & Eldeib, 2016). Similarly, an AI-based system developed to detect invasive breast cancer in histopathological images achieved significant accuracy improvements over human pathologists (Cruz-Roa et al., 2014).

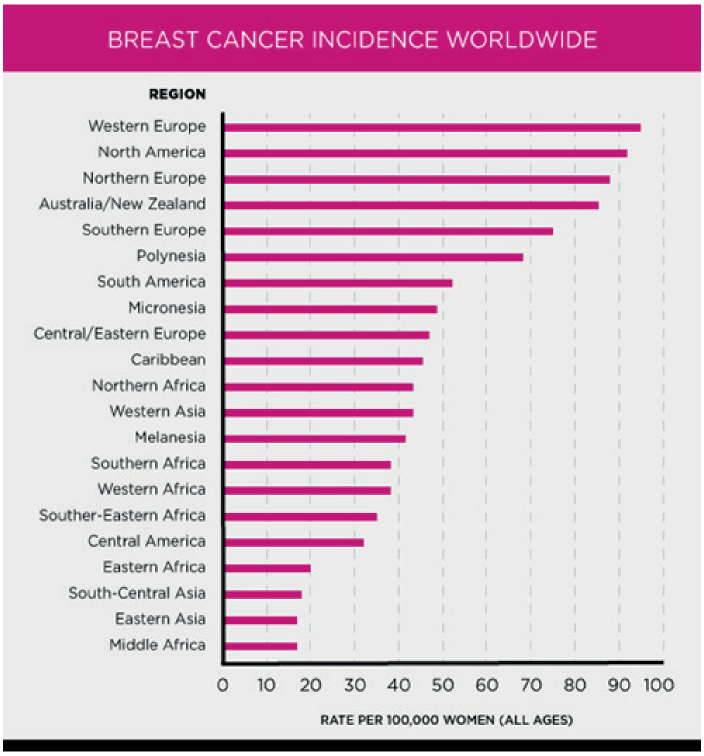
In another study, convolutional neural networks (CNNs) were utilized for breast cancer detection from mammographic images, achieving high classification accuracy and demonstrating the potential of AI for breast cancer screening (Chougrad et al., 2018). Similarly, an extensive review of deep learning applications in medical imaging has shown that AI systems can not only match but sometimes surpass radiologists' performance in detecting breast cancer (Litjens et al., 2017).

Additional progress has been achieved with a hybrid model combining deep learning and traditional statistical methods for breast cancer risk prediction, which proved to be more accurate than existing risk assessment tools and underscored the importance of AI in forecasting long-term cancer risks (Yala et al., 2019). These findings are echoed by research that showed an AI model reducing false positives and negatives in breast cancer screenings across multiple datasets (McKinney et al., 2020).

Current studies continue to expand upon these foundations. Employing attention-based neural networks to enhance mammogram image classification has markedly increased diagnostic accuracy, demonstrating how AI's continuous learning abilities can evolve over time (Wang et al., 2022). This is consistent with the integration of deep learning and Internet of Things (IoT) technology to create a system for real-time breast cancer diagnosis, highlighting the potential for AI-powered remote diagnostics (Al-Antari et al., 2020).

These studies collectively suggest that AI and ML technologies are on the verge of transforming breast cancer diagnostics, offering improvements in detection accuracy, personalized treatment recommendations, and long-term risk predictions. This expanding body of research underscores the need for ongoing research and development in this area, which could eventually result in more effective and accessible cancer care for patients worldwide.

Figure 1
Worldwide Breast Cancer Incidence Graph (Breast Cancer, 2018).



Purpose of the Study

This study primarily aims to assess the effectiveness of ML algorithms as an alternative to conventional methods in diagnosing breast cancer. The study involves training various ML models on a dataset with clinical features related to breast cancer, aiming to compare their success rates in accurately diagnosing the disease. These models are thoroughly evaluated using key performance metrics such as accuracy, precision, recall, F1 score, and the area under the ROC curve (ROC AUC). The objective is to evaluate the potential of these algorithms in enhancing diagnostic outcomes and to offer insights for future research and clinical applications.

Problem Statement

Traditional methods for breast cancer diagnosis, while essential, have notable limitations that can impact the accuracy and timeliness of diagnosis. These limitations include the potential for false positives and negatives, which can either delay necessary treatment or result in unnecessary procedures. The problem this study addresses is whether ML models can overcome these limitations by providing more accurate and reliable diagnostic outcomes. The study poses the following key questions:

1.Can ML models improve the accuracy of breast cancer diagnosis compared to traditional diagnostic methods?

2.Which ML models have demonstrated the highest performance in terms of accuracy, precision, recall, F1 score, and ROC AUC among the ML models studied?

3.What are the implications of adopting ML models for breast cancer diagnosis in clinical practice?

Hypotheses

The study is guided by the following hypotheses:

- ML models, particularly ensemble methods like Gradient Boosting and AdaBoost, will outperform traditional diagnostic methods in terms of accuracy and overall performance metrics.
- Utilizing ML models will decrease false positive and false negative rates, thus improving the reliability of breast cancer diagnosis.
- The effective implementation of ML models in breast cancer diagnosis could revolutionize clinical practices, resulting in better patient outcomes and more efficient use of healthcare resources.

This study's findings aim to contribute to the ongoing efforts to improve breast cancer diagnosis through advanced technological approaches, ultimately striving to enhance patient care and survival rates. By addressing the limitations of traditional methods and exploring the capabilities of ML algorithms, this research seeks to provide valuable insights into the future of breast cancer diagnostics.

Material and Methods

This section will introduce the dataset used in the study and outline the steps taken for data preprocessing. The ML models used in the study will be explained, followed by how these models were trained and evaluated. This section will also cover the performance metrics used to evaluate the effectiveness of each model, providing a clear understanding of the methodology behind breast cancer diagnosis analysis.

Dataset

The dataset utilized in this study was sourced from a comprehensive database that includes both clinical and visual features relevant to breast cancer diagnosis. Specifically, the dataset comprises 213 patient observations collected over 24 months, from January 2019 to August 2021, at the University of Calabar Medical School Cancer Registry. This dataset contains 11 key features: year of diagnosis, age, menopausal status, tumor size (measured in centimeters), number of invasive nodes, affected breast (left or right), presence of metastasis, affected breast quadrant, history of breast disease, and the diagnosis result (benign or malignant) (Fatemeh Mehrparvar, s.a.). The independent variables include a combination of radiological and cellular features of the tumor, along with clinical characteristics such as tumor size. The target variable is a classification label that indicates whether the tumor is benign or malignant, serving as the outcome that the ML models aim to predict.

Data Preprocessing

The dataset was meticulously pre-processed to ensure its suitability for effective machine learning analysis. Initially, the independent variables were standardized using z-score normalization, which adjusts the data so that each feature has a mean of 0 and a standard deviation of 1. This standardization was essential for models sensitive to the scale of input data, such as support vector machines and neural networks. Additionally, categorical variables such as menopausal status and affected breast were converted into numerical values using one-hot encoding. This conversion allowed the ML algorithms to interpret these categorical variables as meaningful inputs.

After completing these pre-processing steps, the dataset was divided into two subsets: 80% was allocated to the training set for training and tuning the models, and the remaining 20% was designated as the test set for evaluating the models' performance and generalization to new, unseen data. This split ensures that the models are tested on independent data, providing a more accurate assessment of their predictive capabilities. If cross-validation was used, it would involve dividing the dataset into k folds and training/testing the model k times with different subsets. In the current code, however, this method was not applied.

Modeling

In this study, six different ML models were employed to evaluate their effectiveness in breast cancer diagnosis: Random Forest Classifier, Decision Tree Classifier, Gaussian Naive Bayes (GaussianNB), Gradient Boosting Classifier, AdaBoost Classifier, and Bagging Classifier. Each of these models was trained on the training dataset to identify patterns and relationships within the data that could distinguish between benign and malignant tumors. After training, the models were tested on a separate test dataset to assess their performance and generalization capabilities. This evaluation was crucial for understanding how well the models could predict outcomes on new, unseen data.

For the initial analysis, the hyperparameters of each model were set to their default values (Table 1). This approach allowed for a straightforward comparison of the models' baseline performance without the influence of extensive tuning. The default settings for each model were used to provide a benchmark for understanding their predictive power. The models' default hyperparameters are typically standardized across libraries, ensuring consistency in initial evaluations. However, if deviations from default settings are used, the specific hyperparameters can be detailed.

Table 1
Default Hyperparameters for Machine Learning Models

Model	Default Hyperparameters
Random Forest Classifier	n_estimators=100, max_depth=None, min_samples_split=2, min_samples_leaf=1, bootstrap=True
Decision Tree Classifier	criterion="gini", splitter="best", max_depth=None, min_samples_split=2, min_samples_leaf=1
Gaussian NB	No hyperparameters to tune (uses default var_smoothing=1e-9)
Gradient Boosting Classifier	n_estimators=100, learning_rate=0.1, max_depth=3, min_samples_split=2, min_samples_leaf=1, subsample=1.0
AdaBoost Classifier	n_estimators=50, learning_rate=1.0 (with base estimator DecisionTreeClassifier having max_depth=1, min_samples_split=2, min_samples_leaf=1)
Bagging Classifier	n_estimators=10, max_samples=1.0, max_features=1.0, bootstrap=True, bootstrap_features=False (with base estimator DecisionTreeClassifier having max_depth=None)

The use of default hyperparameters provides a clear baseline for comparing model performance. This initial analysis does not include hyperparameter tuning, which could be performed in future studies to optimize model performance further.

Machine Learning

Machine learning (ML) is a powerful tool that enables computers to learn from data by developing mathematical models capable of making predictions or decisions without explicit programming. Through this process, ML identifies patterns in data and uses them to build models that improve over time as more data and experience are accumulated (Machine Learning, 2021). Just as human expertise deepens with experience, ML models become more accurate and effective as they process increasing amounts of information. This iterative learning process allows ML models to refine their predictions and adapt to new data, making them invaluable in various applications, including medical diagnostics.

One of the key factors contributing to the widespread adoption of ML is its capacity to handle vast and complex datasets, which are becoming increasingly common in today's data-driven world. The growing preference for Bayesian analysis, which provides a probabilistic framework for decision-making, has further fueled interest in ML. Additionally, the surge in the availability of diverse data types and volumes, coupled with advancements in computational power, has made it possible to perform sophisticated analyses quickly and cost-effectively. The ability to store and process large datasets economically has also played a significant role in the rising importance of ML in various fields, including healthcare (SAS, 2021).

In the realm of breast cancer diagnosis, ML presents a promising path for improving the accuracy and efficiency of detection methods. Traditional diagnostic approaches, while valuable, often face limitations that can result in misdiagnosis or delayed treatment. ML models, on the other hand, have the potential to analyze vast amounts of medical data such as imaging, genetic information, and clinical records more effectively than human practitioners alone. By detecting subtle patterns and correlations that may not be immediately obvious, these models can lead to earlier and more accurate diagnoses, ultimately enhancing patient outcomes.

This study outlines a comprehensive approach to evaluating the performance of ML models in breast cancer diagnosis. It involves a series of methodical steps designed to assess the accuracy, reliability, and overall effectiveness of these models. By systematically analyzing different ML techniques and their application in breast cancer screening, the study seeks to offer insights into how these technologies can be optimized for improved diagnostic performance. Through this evaluation, the study adds to the expanding body of research that advocates for the integration of ML in medical diagnostics, especially in the crucial area of breast cancer detection.

Performance Measures

Each ML model's performance was meticulously evaluated using a variety of metrics to offer a comprehensive assessment of their diagnostic capabilities. Key metrics included accuracy, which measures the overall correctness of the model's predictions; precision, which indicates the proportion of true positive predictions among all positive predictions; recall, which evaluates the model's ability to identify all true positives; and the F1 score, which balances precision and recall to provide a single measure of the model's effectiveness. Additionally, the area under the ROC curve (ROC AUC) was calculated for each model, offering insight into their ability to distinguish between benign and malignant cases across various threshold settings.

To gain a deeper understanding of each model's classification performance, confusion matrices were created and examined. These matrices facilitated the visualization of the models' errors by showing the counts of true positives, true negatives, false positives, and false negatives. This thorough examination provided a clearer insight into where each model excelled or struggled in its predictions. Through these evaluations, the study objectively assessed the strengths and weaknesses of each ML model in breast cancer diagnosis, offering valuable insights into their potential clinical applications.

Findings and Discussions

In this section, I present and analyze the performance outcomes of the ML models assessed in this study. I begin with a summary of the performance metrics for each model, as illustrated in Table 2. Following this summary, I provide a detailed comparison of the models based on their performance metrics and discuss the implications of these findings in the context of breast cancer diagnosis.

Table 2
Performance Evaluation Results

Model	Accuracy	Precision	Recall	F1 Score	ROC AUC
Random Forest Classifier	0.930	1.000	0.824	0.903	0.912
Decision Tree Classifier	0.744	0.667	0.706	0.686	0.738
Gaussian Naive Bayes	0.907	1.000	0.765	0.867	0.882
Gradient Boosting Classifier	0.860	0.867	0.765	0.813	0.844
AdaBoost Classifier	0.814	0.737	0.824	0.778	0.816
Bagging Classifier	0.860	0.824	0.824	0.824	0.854

Random Forest Classifier

The Random Forest Classifier is an ensemble learning algorithm known for its capability to produce highly accurate and robust predictive models. This algorithm functions by creating multiple decision trees, each constructed from a random subset of features within the dataset. These individual decision trees work independently to classify data points based on the selected features, contributing to a collective decision-making process. The final prediction of the Random Forest Classifier is derived by aggregating the results of all the decision trees, typically through a majority voting system. This approach not only improves the accuracy of predictions but also greatly minimizes the risk of overfitting, which is a common issue in single decision tree models (Liaw & Wiener, 2002).

Superior Performance in Breast Cancer Diagnosis

In the realm of breast cancer diagnosis, the Random Forest Classifier has shown outstanding performance across various evaluation metrics, establishing itself as a top choice among the ML models examined in this study. According to the outputs of the applied models, the Random Forest Classifier achieved the highest accuracy (Table 2), indicating its superior ability to correctly classify both benign and malignant tumors. This high accuracy is crucial in medical diagnostics, where the cost of misclassification can be extremely high.

Precision, which indicates the proportion of true positive predictions among all positive predictions, was also the highest for the Random Forest Classifier. This metric is especially crucial in breast cancer diagnosis, as high precision reduces the chances of false positives, where benign tumors are mistakenly classified as malignant. False positives can lead to unnecessary anxiety for patients and may result in avoidable medical procedures, making high precision a desirable attribute in diagnostic models.

Additionally, the Random Forest Classifier performed exceptionally well in terms of the F1 score, which is the harmonic mean of precision and recall. A high F1 score signifies that the model not only makes accurate predictions but also effectively identifies the majority of true positives. This balance between precision and recall ensures that the model is both reliable and comprehensive in its diagnostic capabilities.

As shown in Figure 2, the confusion matrix further demonstrates the Random Forest Classifier's capability to accurately classify the majority of cases, reducing false positives and negatives. The area under the Receiver Operating Characteristic curve (ROC AUC) for the Random Forest Classifier was also one of the highest, further highlighting its effectiveness in distinguishing between benign and malignant cases. The ROC AUC value, shown in Figure 3, provides insight into the model's ability to differentiate between the two classes across various threshold settings. A high ROC AUC value indicates that the model is consistently accurate regardless of the chosen threshold, making it a robust tool for clinical decision-making.

Balancing Complexity and Performance

Although the Random Forest Classifier has demonstrated exceptional performance, it is important to recognize that this is accompanied by an increase in model complexity. The complexity arises from the need to construct and manage multiple decision trees, each with its own set of rules and feature selections. This complexity, however, is generally justified by the significant improvements in predictive accuracy and reliability. In practical terms, the benefits of using the Random Forest Classifier, such as its ability to handle large datasets, manage missing values, and provide insights into feature importance often outweigh the challenges associated with its complexity.

In conclusion, the Random Forest Classifier has proven to be a highly effective ML model for breast cancer diagnosis. Its outstanding performance across key metrics, such as accuracy, precision, F1 score, and ROC AUC, makes it an invaluable tool in the early detection and diagnosis of breast cancer. Despite its complexity, the model's ability to deliver reliable and accurate predictions positions it as a promising alternative to traditional diagnostic methods, offering the potential to improve patient outcomes and enhance clinical practices.

Figure 2
Random Forest Classifier Confusion Matrix

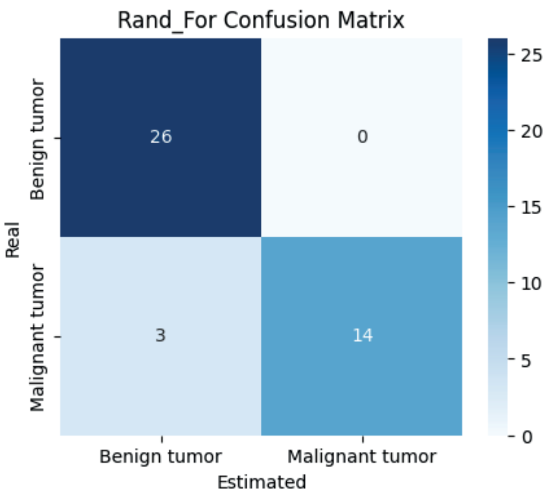
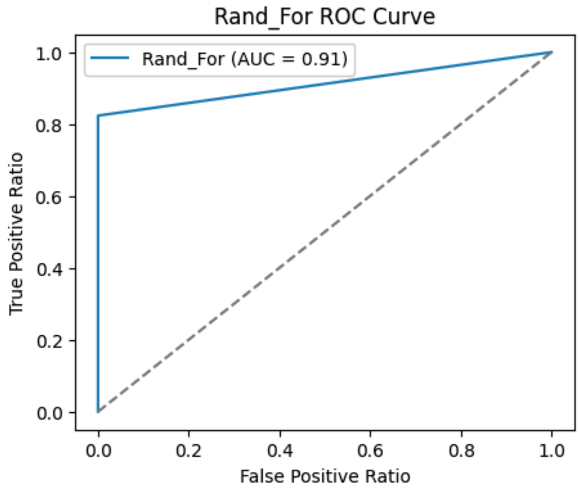


Figure 3
Random Forest Classifier ROC Curve



Decision Tree Classifier

The Decision Tree Classifier is among the most basic yet essential algorithms in machine learning (ML), especially recognized for its simplicity and interpretability. This algorithm functions by constructing decision trees designed to identify the optimal separation points within the dataset's features. These separation points, or "splits," are determined based on criteria such as information gain or Gini impurity, which help the model distinguish between different classes. Once these splits are established, the decision tree classifies new data points by following the paths defined by the splits, ultimately arriving at a classification decision.

Performance in Breast Cancer Diagnosis

Despite its straightforward design, the Decision Tree Classifier exhibited lower performance compared to more complex models in the context of breast cancer diagnosis. As shown in Table 2, the Decision Tree Classifier had relatively lower accuracy, indicating it was less effective at correctly classifying both benign and malignant tumors. This lower accuracy suggests the model may be more prone to errors, which could potentially lead to misclassifications in a clinical setting where accuracy is critical.

As illustrated in Figure 4, the confusion matrix highlights the model's classification errors, indicating that it was less successful in distinguishing between benign and malignant cases. Sensitivity (recall), which measures the model's ability to identify true positive cases, was also lower for the Decision Tree Classifier. This is particularly concerning in breast cancer diagnosis, as low sensitivity means the model could miss a significant number of malignant cases, leading to potential delays in necessary treatment.

While the Decision Tree Classifier is easy to understand and interpret, making it an attractive option for those who value model transparency, its performance limitations are significant. The model's simplicity, which is one of its main strengths, also contributes to its lower performance. Unlike more sophisticated models, the Decision Tree Classifier struggles to capture complex patterns and interactions within the data, resulting in less accurate classifications.

Considerations for Clinical Application

Given its lower accuracy and sensitivity, the Decision Tree Classifier may not be the optimal standalone choice for breast cancer diagnosis when compared to more advanced models. However, its simplicity and interpretability still make it valuable in certain contexts, such as educational settings, or as a baseline for comparing other models. Moreover, the Decision Tree Classifier can be useful in cases where transparency and ease of explanation are crucial, such as when healthcare providers need to understand and communicate the reasoning behind a diagnosis. As illustrated in Figure 5, the ROC curve further demonstrates the Decision Tree Classifier's capability to distinguish between benign and malignant tumors. The lower ROC AUC value underscores the model's reduced capability in distinguishing between the two classes across various threshold settings.

In summary, while the Decision Tree Classifier remains a fundamental ML model with advantages in simplicity and interpretability, its lower performance in breast cancer diagnosis relative to other models suggests that it may be less suitable for this particular application. These findings highlight the importance of considering both the strengths and limitations of different ML models when choosing the most suitable tool for clinical diagnostics.

Figure 4
Decision Tree Classifier Confusion Matrix

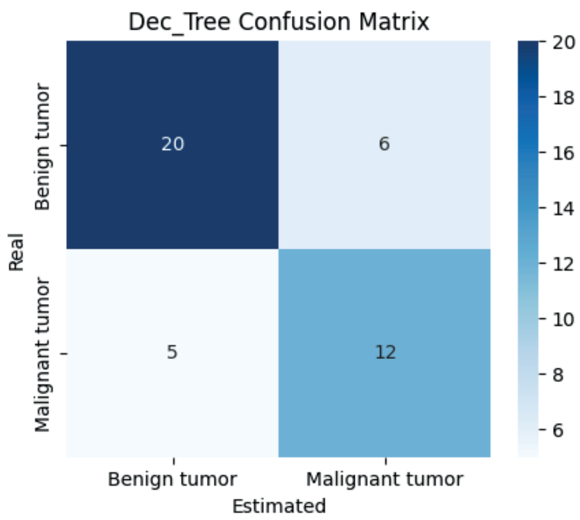
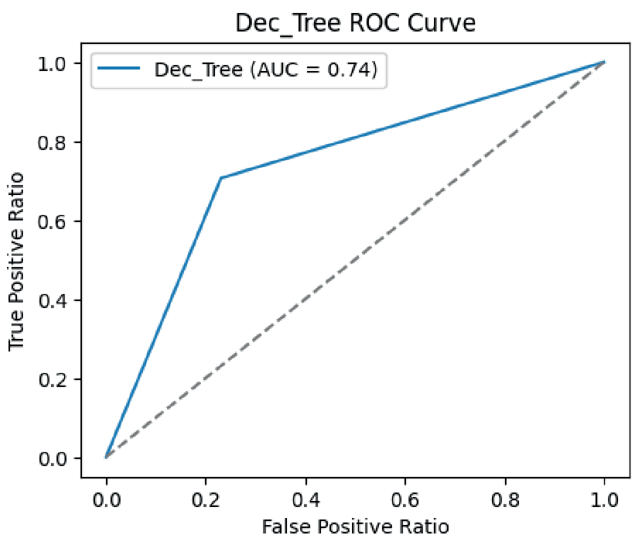


Figure 5
Decision Tree Classifier ROC Curve



Gaussian Naive Bayes (GaussianNB)

Gaussian NB, or Gaussian Naive Bayes, is a probabilistic classifier grounded in Bayes' theorem, which assumes strong independence among features. The model presumes that the dataset's features follow a normal (Gaussian) distribution, simplifying the learning process and enabling fast and efficient classification, especially for continuous and normally distributed features (Rish, 2001). Despite its computational efficiency and simplicity, Gaussian Naive Bayes (NB) has particular strengths and limitations that must be taken into account in the context of breast cancer diagnosis.

Performance in Breast Cancer Diagnosis

In the present study, Gaussian NB exhibited moderate performance relative to more complex models like Random Forest Classifier and Gradient Boosting Classifier. While it achieved high accuracy and precision (Table 2), highlighting its ability to correctly classify most cases and accurately identify true positives, the model performed less well in terms of recall and F1 score. Lower recall indicates that Gaussian NB may miss a significant number of true positive cases, which is critical in breast cancer diagnosis, where early detection of malignant tumors is essential. As demonstrated in Figure 6, the confusion matrix reveals that Gaussian NB was less reliable in identifying malignant cases, leading to potential false negatives. The ROC AUC, a measure of the model's ability to distinguish between benign and malignant tumors across different threshold settings, was also lower compared to the top-performing models (Figure 7). A lower ROC AUC suggests that the model's classification performance is inconsistent across various thresholds, which could introduce variability in diagnostic outcomes.

Considerations for Clinical Application

Given its moderate performance, Gaussian NB may not be the optimal standalone model for breast cancer diagnosis in clinical environments that require high precision and recall. However, its simplicity and speed make it a valuable model for initial screenings or as part of an ensemble approach. It could provide quick, preliminary assessments in conjunction with more advanced models. Furthermore, Gaussian NB may perform better when applied to datasets where the features closely follow the Gaussian distribution assumption, making it potentially useful in certain clinical scenarios. In conclusion, while Gaussian NB offers advantages in speed and simplicity, its limitations in recall and overall classification consistency suggest that it should be used cautiously in breast cancer diagnosis. Its best application may be as a supplementary model within a larger diagnostic framework, rather than the primary tool for clinical decision-making.

Figure 6
Gaussian NB Confusion Matrix

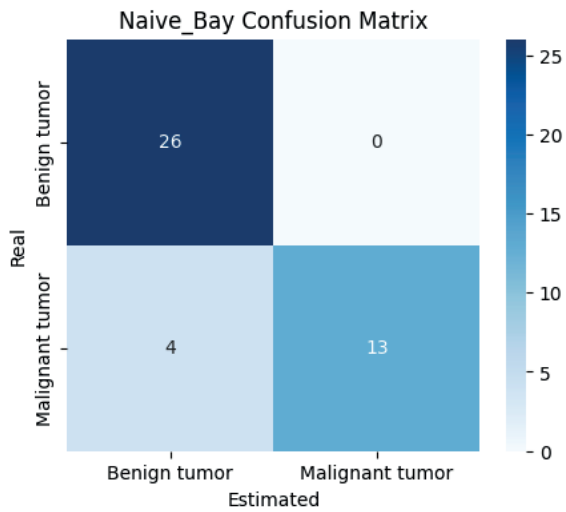
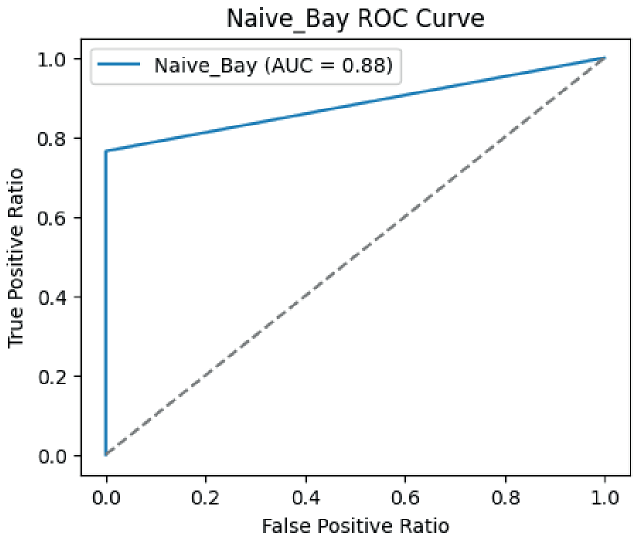


Figure 7
Gaussian NB ROC Curve



Gradient Boosting Classifier

The Gradient Boosting Classifier is a powerful ML algorithm that employs the gradient boosting technique, an ensemble method that enhances the performance of weak learners, often decision trees, by combining them into a single strong predictive model. Introduced by Friedman (2001), this method operates through an iterative process where each new model is trained to correct the errors made by its predecessors. By continuously adjusting and refining its predictions, the Gradient Boosting Classifier aims to minimize the overall prediction error, making it particularly effective for complex classification tasks (Friedman, 2001).

Performance in Breast Cancer Diagnosis

In this study, the Gradient Boosting Classifier demonstrated solid performance across various evaluation metrics, establishing itself as one of the more balanced models tested for breast cancer diagnosis. As seen in Table 2, the model achieved high accuracy, highlighting its strong ability to correctly classify cases as either benign or malignant. This is especially crucial in medical diagnostics, where accurate classification can significantly impact patient outcomes.

Moreover, the precision of the Gradient Boosting Classifier, which measures the proportion of true positive cases among all positive predictions, was notably high. This indicates that the model effectively minimizes false positives, which is essential in breast cancer diagnosis, where reducing unnecessary stress and procedures for patients with benign tumors is a key concern. The model also maintained a well-balanced performance between precision and recall, as indicated by its F1 score. This balance suggests that the Gradient Boosting Classifier not only identifies true positive cases accurately but also does so consistently across different classification thresholds. Such consistency is invaluable in clinical settings, where reliable performance across a variety of cases is necessary to ensure accurate and timely diagnosis.

As shown in Figure 8, the confusion matrix illustrates that the Gradient Boosting Classifier successfully differentiates between benign and malignant cases. Additionally, the model's area under the ROC curve (ROC AUC), depicted in Figure 9, was competitive with the top-performing models in this study. A high ROC AUC indicates that the model excels in distinguishing between benign and malignant cases across various thresholds, enhancing its reliability in different clinical scenarios.

Considerations for Clinical Application

The Gradient Boosting Classifier's main strengths lie in its balanced performance and its iterative learning process, which allows it to progressively improve its predictions. This makes it a highly effective tool in diagnostic workflows. However, the model's iterative nature can be computationally intensive, requiring more time and resources compared to simpler models like the Decision Tree Classifier or Gaussian Naive Bayes (GaussianNB).

Despite these considerations, the Gradient Boosting Classifier's performance suggests that it could be highly valuable in breast cancer diagnosis, particularly in settings where accuracy and consistency are critical. The model's capacity to correct previous errors and focus on difficult-to-classify cases makes it particularly well-suited for minimizing both false positives and false negatives, which is crucial in medical diagnostics.

In conclusion, the Gradient Boosting Classifier offers a robust and balanced approach to breast cancer diagnosis, excelling across key performance metrics. Its iterative nature, combined with its strong ability to refine predictions over time, makes it a promising tool that could improve diagnostic accuracy and patient outcomes, offering an effective alternative to traditional diagnostic methods.

Figure 8
Gradient Boosting Classifier Confusion Matrix

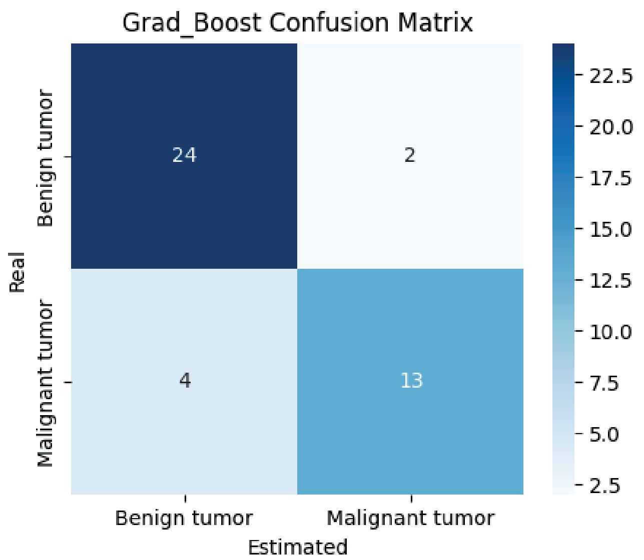
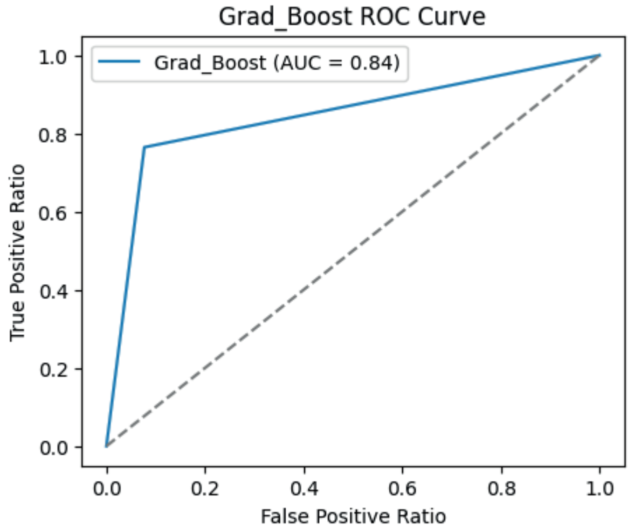


Figure 9
Gradient Boosting Classifier ROC Curve



AdaBoost Classifier

The AdaBoost Classifier, or Adaptive Boosting, is a well-known machine learning (ML) algorithm that belongs to the ensemble learning family. This technique combines multiple weak classifiers, typically decision trees, to create a single, robust predictive model. The fundamental concept of AdaBoost is to sequentially adjust the weights of misclassified instances, thus directing subsequent classifiers to focus on the more challenging cases. By continuously refining its predictions, AdaBoost seeks to reduce overall error rates, making it a valuable tool for complex classification tasks (Freund & Schapire, 1997).

Performance in Breast Cancer Diagnosis

In this study, the AdaBoost Classifier showed slightly lower performance in terms of accuracy and precision compared to some of the other models evaluated, such as the Gradient Boosting Classifier (Table 2). Accuracy, which measures the proportion of correctly classified instances, was lower, indicating a slightly higher rate of misclassifications. This is a crucial factor to consider in breast cancer diagnosis, where the cost of misclassification can have serious implications for patient care.

Similarly, precision, which reflects the model's ability to accurately identify true positive cases among all positive predictions, was also lower. A lower precision score suggests a higher likelihood of false positives, which could lead to unnecessary stress and medical procedures for patients mistakenly identified as having malignant tumors. Despite these observations, it is noteworthy that the AdaBoost Classifier's overall performance was comparable to the Gradient Boosting Classifier, particularly in handling imbalanced data. Both models belong to the boosting family, and their iterative approach to correcting errors contributes to their strength in managing complex classification problems. The AdaBoost Classifier's ability to maintain performance across different scenarios makes it a viable option for diagnostic tasks, even if it slightly lags behind in accuracy and precision.

The model also demonstrated balanced performance across other key metrics, such as the F1 score and ROC AUC. The F1 score, which balances precision and recall, indicates that the AdaBoost Classifier can maintain consistent performance, making it a dependable option for breast cancer diagnosis. The ROC AUC, reflecting the model's capability to distinguish between benign and malignant cases across various thresholds, was also in line with expectations, further supporting its use in clinical settings where consistent performance is critical (Figures 10 and 11).

Considerations for Clinical Application

While the AdaBoost Classifier may not outperform some of the more advanced models like the Gradient Boosting Classifier in terms of raw accuracy and precision, its adaptive nature and ability to handle difficult-to-classify cases make it a valuable tool in the diagnostic process. One of the main advantages of AdaBoost is its simplicity and ease of implementation, which can be especially beneficial in clinical settings where resources may be limited and rapid deployment is necessary.

However, the lower accuracy and precision scores suggest that in high-stakes scenarios, where the utmost accuracy is required, other models might be preferred. Nonetheless, the AdaBoost Classifier's balanced approach and adaptive learning capabilities offer a solid foundation for further refinement and potential integration into a broader diagnostic framework.

In conclusion, the AdaBoost Classifier provides a reliable, if slightly less accurate, alternative for breast cancer diagnosis. Its strength lies in its ability to iteratively focus on and correct misclassifications, making it a suitable choice for applications where adaptability and ease of use are prioritized While it may not always be the top performer, its balanced performance and adaptability ensure that it remains a valuable tool in the arsenal of diagnostic models.

Figure 10
AdaBoost Classifier Confusion Matrix

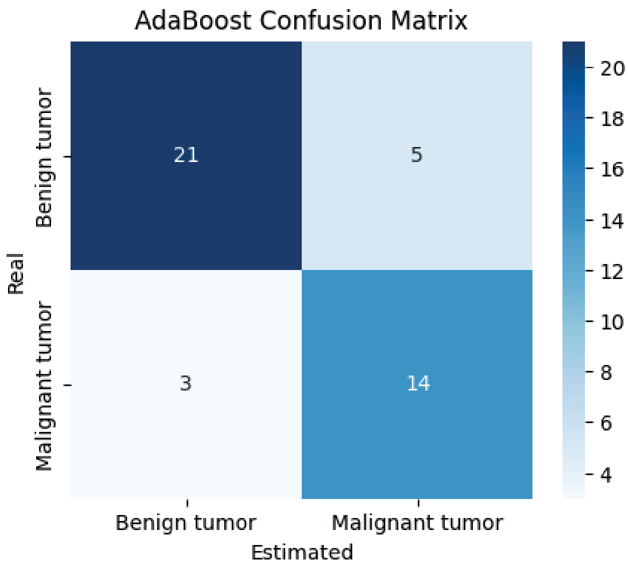
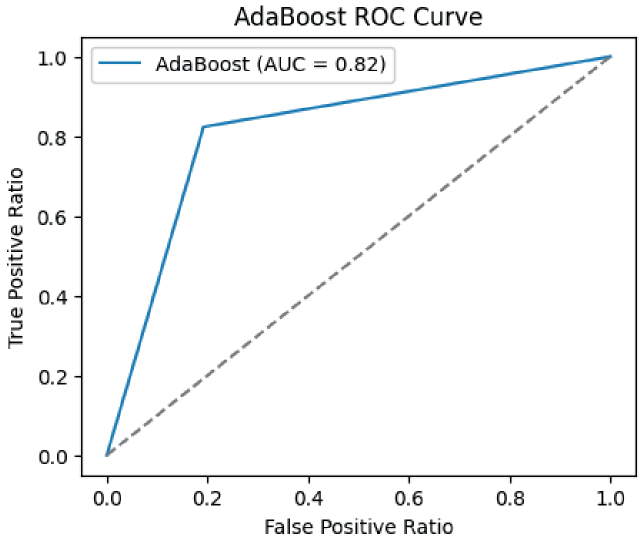


Figure 11
AdaBoost Classifier ROC Curve



Bagging Classifier

The Bagging Classifier is an implementation of the Bagging algorithm, which stands for Bootstrap Aggregating. This ensemble learning technique improves the stability and accuracy of ML models by training multiple versions of a base model on different subsets of the data, each drawn with replacement (Breiman, 1996). These individual models are then combined typically using averaging for regression tasks or majority voting for classification to create a final, aggregated model. Bagging is particularly effective in reducing variance and minimizing overfitting, making it valuable for complex classification tasks such as breast cancer diagnosis.

Performance in Breast Cancer Diagnosis

In this study, the Bagging Classifier showed average performance in breast cancer diagnosis compared to other models evaluated. Its accuracy, precision, recall, F1 score, and ROC AUC values were moderate, indicating its capability in this diagnostic task, but it did not outperform models like the Random Forest Classifier and Gradient Boosting Classifier. The model's accuracy, which indicates the proportion of correct predictions, was reasonable, but not as high as that of the Random Forest Classifier. The recall (sensitivity) of the Bagging model was similarly moderate, reflecting its capacity to identify malignant cases, but with the possibility of missing some true positives. This is evident in its confusion matrix, shown in Figure 12, which visualizes the breakdown of true positives, false positives, true negatives, and false negatives.

Additionally, the F1 score, which balances precision and recall, was lower for the Bagging Classifier, indicating it might struggle to maintain high precision and recall simultaneously. The ROC AUC value, shown in Figure 13, further underscores its comparative underperformance, illustrating the model's ability to differentiate between malignant and benign cases across various decision thresholds. While the ROC curve does indicate decent discriminative ability, it lags behind the performance of other models, particularly in the context of high-stakes applications like cancer diagnosis, where precise discrimination is critical.

Comparative Analysis and Clinical Considerations

Despite its average performance, the Bagging Classifier remains a valuable tool, particularly in scenarios where data variability is high or when models prone to overfitting, such as decision trees, need stabilization. Bagging's ability to reduce variance can be especially useful in clinical settings where data quality and consistency vary.

However, its lower F1 score and ROC AUC compared to models like the Random Forest Classifier indicate that it may not be the optimal choice when maximum diagnostic accuracy and precision are required. In clinical environments where the cost of misclassification is significant, such as breast cancer diagnosis, models with stronger performance metrics are preferable. Nonetheless, the Bagging Classifier does offer advantages in terms of simplicity and parallelizability. Its ability to train multiple models independently makes it feasible in situations where computational resources are limited, or when a quick, yet reasonably accurate, diagnosis is needed.

Figure 12

Bagging Classifier Confusion Matrix

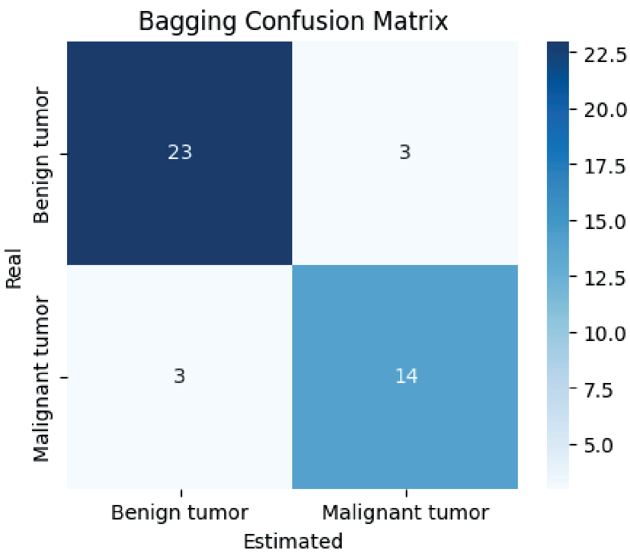
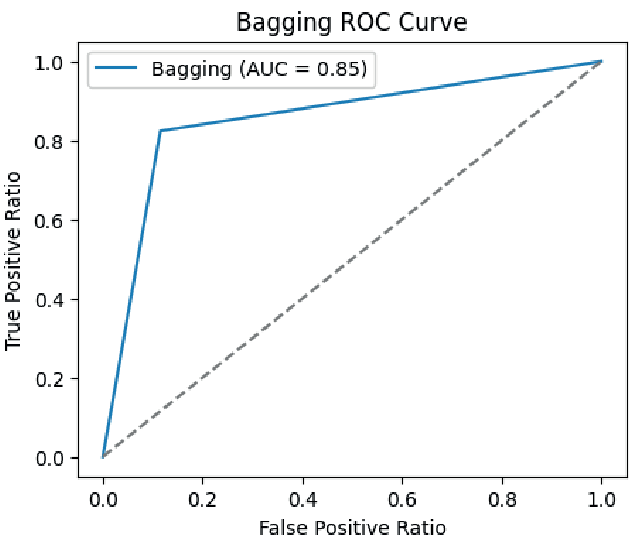


Figure 13

Bagging Classifier ROC Curve

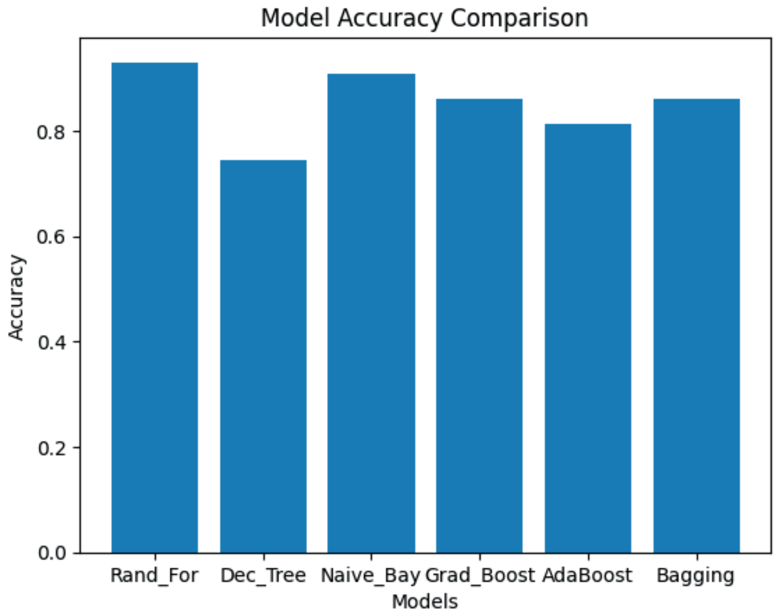


Conclusion and Overall Model Effectiveness

In this study, the Random Forest Classifier proved to be the most effective model for breast cancer diagnosis, outperforming the other models across all major performance metrics. Its superior accuracy and precision, as demonstrated in the Model Accuracy Comparison

Graph (Figure 14), highlight its strong ability to correctly identify malignant tumors while minimizing false positives. This makes the Random Forest Classifier particularly suitable for high-stakes clinical applications where diagnostic accuracy is paramount.

Figure 14
Model Accuracy Comparison Graph



The Bagging Classifier, while not the top performer, remains a viable option depending on specific clinical contexts and data characteristics. Its consistent results, with balanced precision and recall, suggest that it could serve as a reliable model in situations where both metrics are equally important. The Bagging Classifier's performance, shown in Figure 14, reveals that while its accuracy is comparable to models like the Gradient Boosting Classifier, it still falls short of the Random Forest Classifier in overall performance. Despite this, the Bagging Classifier's strength in reducing variance and combating overfitting makes it useful in cases where data variability is a concern, such as in noisy clinical datasets.

The study's results revealed significant performance differences among the six evaluated ML models. Each model's effectiveness was assessed using key metrics such as accuracy, precision, recall, F1 score, and ROC AUC, offering a comprehensive comparison of their diagnostic capabilities. For instance, the Naive Bayes model demonstrated high precision but moderate recall, making it a reliable option for scenarios where the cost of false positives is high, as shown in Figure 14. Conversely, the Decision Tree Classifier exhibited the lowest performance across most metrics, indicating its limited utility for this specific diagnostic task without further tuning or feature engineering.

The Gradient Boosting Classifier and AdaBoost Classifier delivered balanced performance, with moderate accuracy and precision, but slightly lower recall. This indicates that these models may be more suitable in contexts where a trade-off between precision and recall is acceptable. Their accuracy metrics, as depicted in Figure 14, further highlight their balanced but moderate performance.

Overall, the study highlights the importance of selecting the appropriate ML model based on the specific clinical context and desired outcomes. Different models excel in different areas, and while models like the Random Forest Classifier and Naive Bayes offer superior accuracy and precision, others, such as the Bagging Classifier and Gradient Boosting Classifier, may require additional optimization to improve their effectiveness in breast cancer detection. This tailored approach to model selection can significantly improve the accuracy and efficiency of breast cancer diagnosis in clinical practice.

Conclusion

This study aimed to evaluate the performance of six distinct ML models in diagnosing breast cancer. The analysis demonstrated that the Random Forest Classifier consistently outperformed other models across all major performance metrics, including accuracy, sensitivity, F1 score, and ROC AUC value. These findings suggest that the Random Forest Classifier is particularly well-suited for breast cancer diagnosis and should be considered a leading model in clinical settings where diagnostic accuracy and reliability are critical.

Study Limitations

While the results are promising, it is crucial to acknowledge the study's limitations. A significant limitation was the size and scope of the dataset. A limited dataset can impact model performance, leading to potential overfitting or underfitting, and may not fully capture the diversity and complexity of real-world clinical data. Additionally, the study focused on a specific set of features and did not explore the impact of different feature extraction or selection methods. Future research should evaluate alternative feature sets to enhance model performance and offer deeper insights into the key predictors of breast cancer.

Addressing the Hypotheses and Problem Statement

This study effectively addressed the key research questions posed in the problem statement. First, the results confirmed that ML models, particularly ensemble methods like the Random Forest Classifier, can improve the accuracy of breast cancer diagnosis compared to traditional diagnostic methods. The Random Forest Classifier outperformed other models typically used in conventional diagnostics, a finding consistent with prior research such as that by Abdel-Zaher and Eldeib (2016), which also demonstrated improvements in diagnostic accuracy through AI and ML-based systems.

In terms of model performance, the study showed that ensemble methods exhibit superior results. The Random Forest Classifier proved to be the most accurate model, followed by Naive Bayes, which showed potential in reducing false positives, a crucial factor in breast cancer diagnosis where precision is essential. However, models like Gradient Boosting and AdaBoost did not meet expectations, indicating that further optimization may be required to improve their performance.

Lastly, the study highlighted that adopting ML models could significantly complement traditional diagnostic methods by improving accuracy and reliability. This supports the hypothesis that ML models can enhance clinical workflows by reducing both false negatives and false positives. As seen by McKinney et al. (2020), AI-based diagnostic tools have already started to reduce errors in breast cancer screenings. However, further research and practical validation are needed to fully integrate these models into real-world clinical practice.

Literature Comparison

When comparing the study's results with the broader literature, it becomes clear that ML models, particularly ensemble-based approaches, hold substantial promise for enhancing breast cancer diagnostics. For instance, Abdel-Zaher & Eldeib (2016) and Chougrad et al. (2018) demonstrated the superiority of AI-driven models like deep learning in processing mammogram images. While this study focused on structured clinical data rather than image data, the potential for integrating more complex deep learning architectures, as demonstrated in previous research, could further enhance model performance.

The use of a Random Forest Classifier aligns with broader findings in AI diagnostics that highlight the importance of ensemble methods in improving classification tasks. However, this study did not include deep learning models, which have shown impressive accuracy in image-based breast cancer detection (e.g., Litjens et al., 2017). This highlights the need for future studies to incorporate image data and explore the combined use of deep learning and ensemble methods to further enhance diagnostic accuracy.

Implications for Future Research

To build on the findings of this study, future research should evaluate ML models on larger and more diverse datasets, ensuring that model performance is generalizable to a broader patient population. Additionally, exploring deep learning techniques, which have shown significant promise in image-based diagnosis, could provide more comprehensive diagnostic solutions, particularly when integrated with clinical data. Incorporating real-world clinical data will also be essential for validating these models in clinical settings.

An important area for future research is the clinical integration of these models. While the Random Forest Classifier showed strong potential, its implementation in clinical practice will require further validation, particularly concerning its interpretability for healthcare professionals. Ensuring that models are easy to interpret and actionable is critical for their successful adoption in healthcare.

Final Remarks

In conclusion, this study reinforces the growing role of ML in breast cancer diagnostics. The Random Forest Classifier proved to be the most effective model for the dataset used, indicating that ML, particularly ensemble methods, provides a valuable tool for enhancing diagnostic accuracy. These findings, aligned with current literature, underscore the transformative potential of ML models in clinical practice.

However, the study also emphasizes the need for ongoing research to refine these models and broaden their applicability. As ML technologies evolve, their integration into clinical workflows will become essential for improving early detection and patient outcomes. The future of breast cancer diagnostics lies in the successful combination of ML and clinical expertise, with a collaborative approach ensuring these innovations translate into real-world improvements in healthcare.

References

Abdel-Zaher, A. M., & Eldeib, A. M. (2016). Breast cancer classification using deep belief networks. *Expert Systems with Applications*, 46, 139-144.

Al-Antari, M. A., Al-Masni, M. A., Park, S. U., Park, J. M., & Kim, T. S. (2020). Deep learning-based detection and classification of breast abnormalities in digital mammograms using the YOLO detector. *Computer Methods and Programs in Biomedicine*, 196, 105584.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, 68(6), 394-424.

Breast Cancer. (2018) Does soy cause breast cancer? Soy - eximuseducation.com (Date of access: 10.05.2024)

Breiman, L. (1996). Bagging predictors. *Machine Learning*, 24(2), 123-140.

Chougrad, H., Zouaki, H., & Alheyane, O. (2018). Deep convolutional neural networks for breast cancer screening. *Computers in Biology and Medicine*, 98, 126-137.

Cruz-Roa, A., Gilmore, H., Basavanhally, A., Feldman, M., Ganesan, S., Shih, N., Tomaszewski, J., & Madabhushi, A. (2014). Accurate and reproducible invasive breast cancer detection in whole-slide images: A deep learning approach for quantifying tumor extent. *Scientific Reports*, 7(1), 46712.

DeSantis, C. E., Ma, J., Gaudet, M. M., Newman, L. A., Miller, K. D., Goding Sauer, A., ... & Jemal, A. (2019). Breast cancer statistics, 2019. *CA: A Cancer Journal for Clinicians*, 69(6), 438-451.

Fatemeh Mehrparvar. (s.a.). Breast Cancer Prediction. Kaggle. Date of access: [02.05.2024]. URL: [Breast Cancer Prediction (kaggle.com)]

Freund, Y., & Schapire, R. E. (1997). A decision-theoretic generalization of online learning and an application to boosting. *Journal of Computer and System Sciences*, 55(1), 119-139.

Friedman, J. H. (2001). Greedy function approximation: A gradient boosting machine. *Annals of Statistics*, 29(5), 1189-1232.

Liaw, A., & Wiener, M. (2002). Classification and regression by randomForest. *R news*, 2(3), 18-22.

Litjens, G., Kooi, T., Bejnordi, B. E., Setio, A. A., Ciompi, F., Ghafoorian, M., van der Laak, J. A., van Ginneken, B., & Sánchez, C. I. (2017). A survey on deep learning in medical image analysis. *Medical Image Analysis*, 42, 60-88.

Machine Learning. (2021) https://azure.microsoft.com/tr-tr/resources/cloud-computing-dictionary/what-is-machine-learning-platform, (Date of access:15.08.2022)

McKinney, S. M., Sieniek, M., Godbole, V., Godwin, J., Antropova, N., Ashrafian, H., Back, T., Chesus, M., Corrado, G. C., Darzi, A., & Pearse, R. (2020). International evaluation of an AI system for breast cancer screening. *Nature*, 577(7788), 89-94.

Rish, I. (2001). "An empirical study of the naive Bayes classifier." In *IJCAI 2001 workshop on empirical methods in artificial intelligence* (Vol. 3, No. 22, pp. 41-46).

Sas. (2021) https://www.sas.com/en_us/insights/analytics/machine-learning.html., (Date of access: 22.08.2022)

Wang, S., Peng, Y., Liu, Z., Cheng, B., & Li, C. (2022). Attention-based neural network for mammogram image classification. *Medical Image Analysis*, 78, 102396.

Yala, A., Lehman, C., Schuster, T., Portnoi, T., & Barzilay, R. (2019). A deep learning mammography-based model for improved breast cancer risk prediction. *Radiology*, 292(1), 60-66.

About the Author

Fatma Nur UZUN is a Computer Engineer in Konya. She has a bachelor's degree in Computer Engineering from Konya Technical University. She is currently doing her master's degree with a thesis in Computer Engineering at Konya Technical University. Her main areas of interest are artificial intelligence, machine learning, and deep learning applications.
Email: fatmanur.uzun@ksbu.edu.tr, **ORCID:**0000-0003-0153-3442

Similarity Index
The similarity index obtained from the plagiarism software for this book chapter is 20%.

PRP (Platelet-Rich Plasma) And Women's Reproductive Health: Current Status

Elif Gülbahçe MUTLU

KTO Karatay University

Hatice Nur ŞEFLEK

KTO Karatay University

To Cite This Chapter

Mutlu, E. G., & Şeflek, H. N. (2024). PRP (Platelet-Rich Plasma) And Women's Reproductive Health: Current Status. In F. Nur Takı, S. Koçer & R. Bütüner (Eds.), *New Generation Technologies and Sustainability in Health Current Studies* (pp. 96-119). ISRES Publishing.

Introduction

Platelets synthesized by the megakaryocytes in bone marrow play a vital role in clotting and wound repair. These platelets release an array of proteins, growth factors, cytokines, and bioactive molecules that not only support coagulation but also significantly influence the body's tissue healing process. For instance, PDGF, TGF-β, VEGF promote cellular proliferation, differentiation, and tissue regeneration, while cytokines mediate inflammation and immune responses. This coordinated action helps in managing both immediate and long-term tissue repair after damage (Lin et al., 2021).

Platelet-rich plasma (PRP) is simply platelet concentrate derived from human plasma, where the platelet concentration is significantly elevated compared to normal blood. PRP is a biological therapy that promotes cellular regeneration and tissue healing, and it is widely used across various medical fields, including orthopedics, dermatology, plastic and reconstructive surgery, as well as gynecology and reproductive health. In recent years, the potential of PRP therapy on female reproductive health has attracted particular attention. PRP has been investigated in reproductive medicine areas such as infertility treatment, endometrial thickness problems and implantation failures. The favorable effects of PRP on endometrial proliferation, neoangiogenesis and anti-inflammatory effects reveal the importance of this treatment in clinical applications. With the recognition of the positive effects of PRP therapy in this area, research and clinical studies on the possibility of wider application of this treatment are increasing (Bos-Mikich et al., 2018).

The role of PRP in reproductive medicine, while notable for its advantages such as minimal invasiveness and low cost, remains controversial due to inconsistencies in treatment protocols, patient selection criteria, and variations in the concentration of bioactive molecules. To improve the efficacy of PRP and achieve more reliable results, standardized protocols and personalized treatment approaches need to be developed (Foster et al., 2009; Cavallo et al., 2016).

The purpose of this part is to assess the latest available data on the application of PRP in medically assisted reproduction. While new technologies and adjunctive therapies in fertility treatment hold promise for improving patient success rates, robust evidence supporting the efficacy of many methods remains limited, and the benefits achieved are often marginal. For this reason, it is essential that the efficacy and safety of any new technology or treatment offered to patients are rigorously evaluated to ensure clinical reliability and effectiveness.

In this comprehensive study, we will review the existing literature and evaluate the effects of PRP across various protocols and patient groups. Our focus will include examining the action of PRP on endometrial thickness, implantation rates, pregnancy outcomes, and potential side effects.

This investigation will be critical in determining when and how PRP can be most effectively used in medically assisted reproduction. It will also provide a valuable resource to fill knowledge gaps in this field and guide future research. Such an assessment can both guide clinical practice and provide the scientific foundation needed to fully realize the potential of PRP in reproductive health.

History and Development of PRP (Platelet-Rich Plasma)

1970s: Early Research and Discovery

- **Early Research:** In the 1970s, hematologists began to investigate the potential healing effects of PRP. During this period, PRP attracted attention, particularly in studies of bleeding and clotting disorders. The platelet content of PRP was investigated in these areas because of its potential to promote blood clotting and accelerate wound healing. These studies have laid the foundation for therapeutic applications of PRP and upholstered the way for future research (Andia et al., 2013).
- **Definition and Term:** Hematologists have identified a type of plasma derived from peripheral blood and characterized by a high platelet count compared to baseline and have named this plasma "Platelet Rich Plasma". PRP is a concentrated platelet content that can contribute to the blood clotting process and promote tissue healing. This identification has been an important step forward in the probable usage of PRP in the area of medical treatment.

1990s: Growing Popularity and Clinical Applications

- **Increase in Popularity:** PRP began to grow in popularity in the 1990s. This period saw an increased focus on potential and healing properties of PRP. PRP began to be widely adopted, especially in the areas of orthopedics and medicine of sport. It was discovered that PRP could be used to treat conditions such as musculoskeletal injuries, tendon and ligament damage. Studies conducted during this period have provided important findings to better understand the healing effects and application areas of PRP.
- **Clinical Applications:** The increasing popularity of PRP in the 1990s led to its widespread use in various medical applications and the development of techniques. During this period, the healing properties of PRP began to be investigated in clinical practice.
- The application of PRP in the treatment of muscles, bones, joints, tendons and ligaments in fields such as orthopedics and sports medicine became widespread, providing a basis for evaluating its potential in other medical fields. This process has inspired research to optimize the effects and delivery methods of PRP in clinical applications (Alves et al., 2018).

2000s and Beyond: Expansion and Modern Practices

- **Modern Usage Areas:** PRP is used in many different branches of medicine today. Especially in orthopedics and sports medicine, ophthalmology, gynecology, urology and various surgical branches, the healing potential of PRP is evaluated. This wide range of uses of PRP shows that the interest in the treatment and the healing potential of PRP is increasing.
- **Continuous Development:** PRP therapy, its applications and techniques are constantly evolving. Today, research on the activities and safety of PRP continues to better understand and optimize the potential of the treatment modality. Researchers develop new methods and protocols to assess the effects of PRP on diverse diseases and conditions, and work to improve the treatment process and achieve more reliable results. This process is critical to expand the effects of PRP in various medical fields and make treatment applications more effective (Wu et al., 2016).

PRP Preparation Process and Standardization

PRP preparation methods vary widely between various techniques and commercially available PRP kits. The PRP preparation process usually involves the following methods:

Whole Blood Collection and Centrifugation: This method involves drawing whole blood from the patient and then separating platelets and other cells by centrifugation.

Commercial PRP Kits: Commercially produced PRP kits offer standardized tools that are prepared according to specific protocols. These kits optimize the concentration and biological properties of PRP with specific centrifugation times, relative centrifugal forces (RCF) and other parameters.

Alternative Techniques: Alternative techniques used in PRP preparation usually differ in centrifugation time, centrifugal force and collection methods. These techniques can affect thrombocyte, and leukocyte counts and alter the biological properties of PRP.

These various methods can affect the platelet and other cell concentrations, growth factor profiles and overall biological properties of the resulting PRP. Therefore, the utilization of alternative methods and kits can significantly affect the therapeutic efficacy and safety of PRP (Dhurat et al., 2014). Absence of standardization in the preparation method can potentially affect the results and reproducibility of a study. Variations in the PRP preparation process can cause modifications in the biological features of the resulting PRP. This can lead to inconsistent effects and results of PRP used in studies. Non-standard preparation methods resulting in PRP samples with different configurations of platelets, leukocytes and growth factors, can create these difficulties in making cross-study comparisons and reduce predictability in clinical practice. The terminological and protocol diversity in the literature on PRP can cause inconsistencies in the readiness and administration of PRP and heterogeneity of results. This may hinder the effective and reliable use of PRP and complicates the comparison of study results. A standardized PRP classification method can help address these challenges and improve consistency in the scientific and clinical trials of PRP. A standardized PRP classification method can improve the quality and reliability of PRP in its various applications and research. This will ensure us with a larger insight of their impact on PRP and heal treatment outcomes (Lana et al., 2017).

The basic steps of PRP preparation techniques generally involve the harvesting of peripheral blood mixed with anticoagulant, centrifugation. These steps are critical to ensure the efficacy and quality of PRP. The details of these basic steps and some important technical variations commonly used in the literature are summarized below:

Basic Steps of PRP Preparation Protocols

1.Blood Collection:

- **Materials:** Sterile blood collection tubes, usually tubes containing special additives for PRP preparation. An anticoagulant (usually citrate or heparin) is usually added into the tubes.
- **Method:** Blood is taken from the patient. Usually between 10-60 ml of blood is taken, depending on the amount of tubes used and the purpose of the application.

2.Centrifugation:

- **First Centrifugation (Low Speed):** Blood tubes are centrifuged (usually 1,500-2,500 rpm at low speed). Blood is separated into its components: red blood cells and plasma.
- **Second Centrifugation (High Speed):** The plasma is usually centrifuged once more. This ensures that the platelets and white blood cells are concentrated and the top part of the PRP is obtained.

3.Collection of PRP:

- **Upper Part:** After the second centrifugation, the upper part of the PRP (usually 1-10 ml) is carefully collected and can be used. The platelet concentration of this portion constitutes the content of the platelet-rich plasma.

4.Usage:

- **Application:** PRP is injected into the targeted area. The application differs according to the treatment area and the medical condition.

Important Components and Effects of PRP

The main components of PRP include platelets and a large number of different proteins. There are also bioresponsive factors such as immune messengers, growth factors, enzymes and their inhibitors, and other factors that may participate in tissue repair and wound healing. The physiological effects of some of these proteins have been discovered, while others have yet to be elucidated (Boswell et al., 2012, Pavlovic et al., 2016).

As it is well known, all blood cells develop by differentiation from pluripotent stem cells. There are precursor cells that can separate and mature in every differentiated cell. Platelets, one of these cells, develop from megakaryocytes. They are discoid cellular elements with a lifespan of ~7-10 days. They have a diameter of ~2 µm, are nucleated and vary in size.In healthy individuals, the platelet count varies between 150,000 and 400,000 cells/µL of blood. Although the main task of platelets is coagulation and hemostatic functions, recent studies and technology have shown that platelets contain platelet-rich growth factors and cytokines that are effective in inflammation, angiogenesis, stem cell migration and cell proliferation (Alves & Grimalt 2018).

Platelets contain granules called alpha, delta and lambda. The molecules released from these granules are very important in the process of tissue repair and healing. Among these granules, the alpha granule makes up ten percent of the platelet volume. Their number is ~50-80 in each platelet and their number is considerably higher than other granules (Maynard et al., 2007). Adhesive proteins, growth factors, angiogenic factors, chemokines, coagulation factors and inhibitors, integral membrane proteins, and immune mediators are among the molecules contained in alpha granules (Table 1). Delta granules are involved in the release of molecules that stimulate coagulation. These molecules include calcium, magnesium, adenosine, serotonin and histamine (Jedlitschky et al., 2004). Lambda granule is a granule with lysosomal properties. It contains enzymes needed for protein, lipid and carbohydrate degradation. It also has functions such as removal of damaged tissue and infectious agents (Boswell et al., 2012). All of these granules also contain proteins such as integrins, platelet endothelial cell adhesion molecule, leukin-rich receptors, immunoglobulin family receptors (Maynard et al., 2007).

Table 1

Molecules in the Alpha Granule (Lubkowska et al., 2012, Pavlovic et al., 2016)

Group	Name
Adhesive proteins	Von Willebrand factor, fibrinogen, thrombospondin-1, thrombospondin-2, laminin-8
Growth factors	Epidermal growth factor (EGF), epithelial cell grow factor (ECGF), insulin-like growth factor 1 (IGF-1), hepatocyte growth factor (HGF), transforming growth factor ß (TGF-β1, TGF-β2, TGF-β3)
Angiogenic factors	Vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF)
Chemokines	CCL5 (RANTES), CCL-3 (MIP-1α), CCL-2 (MCP-1), CCL-7 (MCP-3), CXCL8 (IL-8), CXCL2 (MIP-2), CXCL6 (LIX), CXCL-1 (GRO-α), CXCL5 (ENA-78), CXCL-12 (SDF-1), CXCL4 (PF4)
Clotting factors and their inhibitors	Factor V, factor IX, antithrombin, factor S, protease nexin-1, protease nexin-2, tissue factor pathway inhibitor,
Integral membrane proteins	αIIbβ3, GPIb-IX-V, GPVI (Glycoprotein VI), TLT-1 (Toll-like receptor 1), p-selectin
Immune mediators	Complement C3 precursor, complement C4 precursor, factor D, factor H, C1 inhibitor, IgG (Immunoglobulin G)

The function of PRP is mainly due to the synthesis and release of growth factors resulting from platelet activation and stored in alpha granules (Garg 2000). Growth factors are present in all tissues in the body. However, blood tissue is more important because it contains many growth factors and cytokines for angiogenesis and tissue regeneration in the wound healing process. In addition, these molecules are significant in mediating various cellular functions such as inflammation, cell migration, proliferation, differentiation, metabolism and apoptosis and cell (Fujioka-Kobayashi et al., 2017). The main properties of PRP growth factors include that they do not enter the cell or nucleus, are non-mutagenic and have no ability to induce tumor formation (Lubkowska et al., 2012).

Platelet-derived growth factors have remarkably short half-lives. The half-life of platelet-derived growth factor (PDGF) injected intramuscularly is less than 2 min (Clark 2001). Therefore, a storage period of less than 48 hours is permissible to avoid potential loss of growth factors (Moroff et al., 1991, Lozano et al., 1999). Besides, theoretically, PDGFs are expected to be in parallel with platelet count. However, studies have shown that there is no statistically notable correlation calculation between PRP platelet count and growth factor levels. It has also been reported that significant differences in GF concentrations are detected among individuals with highly similar platelet counts (Weibrich et al., 2002, Lacoste et al., 2003, Martineau et al., 2004). Considering that different molecular mechanisms may be involved in cellular production or storage in humans, this may be related to individual variability. Otherwise, it should be noted that the difference in the method of obtaining PRP may also cause changes in the release of growth factors. One study showed that growth factor release was significantly regulated by the amount of calcium and thrombin added to PRPs (Fréchette et al., 2005).

Growth factors interact with other transcription factors and each other in signaling pathways and activate many genes. With the activation of these genes, a series of changes occur at the cellular level. These changes are controlled by feedback mechanisms involving binding proteins and other growth factors. As a result, growth factors form a cascade of different signaling proteins with multiple pathways, ultimately leading to the activation of gene expression and subsequent protein production. They cause the formation of a bidirectional feedback in the signaling cascade, i.e. they can promote the growth of some cells while inhibiting the growth of others (Sánchez et al., 2003, Lubkowska et al., 2012).

The individual roles of some growth factors are as follows;

- **Epidermal Growth Factor (EGF) and Epithelial Cell Growth Factor (ECGF):** These regulate the process of chemotaxis and angiogenesis in endothelial cells. They also stimulate mitosis in mesenchymal cells. Their activation is increased especially after acute injury. It has been reported to significantly shorten the healing process by stimulating epithelialization. They are expressed in almost all cells, including units active in the injury process like fibroblasts, endothelial cells and keratinocytes (Babensee et al., 2000; Berlanga-Acosta et al., 2009). Following the secretion of these growth factors, cytokine secretion also increases (Knezevic et al., 2016).
- **Transforming Growth Factor ß (TGF-β):** A superfamily of over 30 members identified as fibrosis agents. The main source of TGF-β production is platelets. It has important functions in tissue repair, immune regulation, extracellular matrix synthesis, wound healing, angiogenesis, epithelialization and connective tissue regeneration (Border et al., 1994; Clark 2001, Bowen et al., 2013). TGF-β is composed of bone morphogenetic proteins (BMPs) and three isoforms of TGF-β (β1, β2 and β3) (Davis et al., 2014). They play a role in bone regeneration by promoting mitogenesis of osteoblast precursors. They also act as paracrine growth factors. Thanks to the paracrine mechanism, they allow target cells to release TGF-β proteins. Thus, they cause activation of nearby cells. The activation process is maintained by the autocrine mechanism. It stimulates fibronectin, glycosaminoglycans and collagen production, angiogenesis and chondrogenesis in connective tissue. It also inhibits the proliferation of lymphocytes and stimulates monocytes to secrete FGF, PDGF, TNF-α and Interleukin-1 (Rudkin & Miller 1996; Lubkowska et al., 2012).
- **Platelet-Derived Growth Factor (PDGF):** They are important regulators of proliferation, migration and survival of mesenchymal cells. They also contribute to collagen production for remodeling of the extracellular matrix (Martin and Leibovich 2005, Ghasemzadeh et al., 2015). It also stimulates chemotaxis of macrophages and neutrophils. In addition, it increases TGFβ secretion from macrophages (Barrientos et al., 2008). PDFG, has 4 isoforms, homo (AA, BB, CC, DD) and hetero (ABCD) (Andrae et al., 2008). PDGF is very short-lived. It accumulates in high amounts in the platelet-rich fibrin matrix. It is then slowly and gradually released from there ((Fujioka-Kobayashi et al., 2017).
- **Vascular Endothelial Growth Factor (VEGF):** It is secreted from activated platelets and macrophages in injured tissue. It shows its most powerful effect by providing nutrient and blood flow to the injured area by providing angiogenesis (Barrientos et al., 2008). It also has great effects on tissue remodeling. This

growth factor is related to PDGF. There are also five isoforms of VEGF (A, B, C, D and E). It has been reported that VEGF secretion increases in the presence of PDGF, TGF-β and EGF (Barrientos et al., 2008, Pavlovic et al., 2016).

- **Insulin-like Growth Factor (IGF-1):** IGF-1 (somatomedin-C), is a normal component of plasma. However, it is also a hormone that can be transported to platelets by IGF-binding proteins (Marques et al., 2015). The release of this factor occurs during activation and degranulation of platelets. It then stimulates differentiation and mitosis of mesenchymal cells. It also induces signals that protect cells from apoptotic stimuli, ensuring their survival (Giannobile et al., 1996; Fujioka-Kobayashi et al., 2017). They also contribute to bone reorganization by promoting the proliferation and realization of osteoblasts (Dhillon et. al., 2012).
- **Hepatocyte Growth Factor (HGF):** It is mainly found in plasma and very little in platelets (Andia et al., 2012). It is secreted by mesenchymal cells. Their primary functions are on epithelial and endothelial cells. Moreover, they are produced by hemopoietic progenitor cells, T cells, tendon cells and human bone marrow stem cells. They have been shown to play an important role in embryonic organ development, particularly in myogenesis, adult organ regeneration and wound healing (Takai et al., 1997; Gallagher and Lyon 2000; Anitua et al., 2005).
- **Fibroblast Growth Factor (FGF):** They have multiple effects in many cell types. The most important effects are in the stimulation of mitosis. This growth factor (FGF2) released from platelets is important in stimulating and coordinating mesenchymal stem cells in cell growth and tissue repair. It has been reported to boost especially type II collagen content and has no effect on type I collagen content. In addition, it stimulates the growth and differentiation of chondrocytes and osteoblasts. It is also involved in the angiogenesis process together with VEGF (Thrailkill et al., 1995; Barrientos et al.; 2008, Kaul et al.; 2006, Lubkowska et al.; 2012; Pavlovic et al., 2016).

PRP also contains chemokine and cytokine components. These have functions such as recruiting and activating other immune cells or inducing endothelial cell inflammation (Blair and Flaumenhaft, 2009). For example, Stromal cell-derived factor-1 (SDF-1) in PRP has been linked to promote cell-cell adhesion. It also provides stem cell stimulation and migration to damaged areas (Otsuru et al., 2008). Platelet Factor 4 (PF4) functions as a negative regulator of angiogenesis. Therefore, it strongly inhibits endothelial cell proliferation. It is also a chemotactant for neutrophils and fibroblasts (Beck and D’Amore 1997).

Depending on the protocol used, PRP contains different amounts of leukocytes. Leukocytes function first to initiate phagocytosis in the healing process of damaged tissues. They release metalloproteinases and proteinases. Proteinases have the ability to induce lymphocyte and platelet activation, activation of cytokines and formation of fibrin-platelet plug. They also inhibit the activation of inflammatory cells. Secondly, monocytes cause the breakdown of extracellular matrix by releasing matrix metalloproteinases (MMP-2, MMP-9 MMP-13). Thus, the extracellular matrix is reconciled and cellular migration is performed actively, contributing to wound healing (Barrick et al., 1999, Wiesner and Vilcinskas 2010, Boswell et al., 2012; Davis et al., 2014). Neutrophils also have great importance in the wound healing process. Neutrophils release ROS and nitric oxide to eliminate potential infectious agents and residues in the wounded area. However, it has also been reported that wound healing is delayed when neutrophils are present in high concentrations (Eming et al., 2009, Boswell et al., 2012; Knezevic et al., 2016). There are not enough studies on the potential effect of leukocytes in the wound healing process. Therefore, research is needed.

Many proteins, organic and inorganic particles and ions are abundant in the plasma contained in the PRP component. They are known to be critical components especially in the healing mechanism of connective tissues (Lubkowska et al., 2012).

PRP Applications in Female Reproductive Health

In women of reproductive age, endometrial and ovarian infertility are among the important and common problems affecting reproductive health. New strategies for the treatment of these problems are constantly being developed and investigated. Each of the endometrial and ovarian infertility types may require different causes and treatment approaches. Therefore, research is constantly being conducted to develop personalized and effective treatment strategies (Unuane et al., 2007).

In the field of reproductive health, management of endometrial quality and ovarian failure plays a critical role in improving Assisted Reproductive Treatment (ART) outcomes. In recent years, intrauterine and intraovarian PRP applications have attracted attention as promising new treatment strategies for these problems. Studies on the potential of PRP to improve ovarian function, ovarian rejuvenation, increase endometrial thickness, and improve implantation success suggest that this treatment modality may offer various benefits. PRP treatment is used for a diversity of indications to improve women's reproductive health. These indications include thin endometrial lining, poor ovarian response (POR), primary ovarian insufficiency (POI), recurrent implantation failure (RIF), Asherman syndrome, and chronic endometritis. However, more research is needed on the efficacy and safety of PRP in these areas. To better comprehend the role of PRP in various indications and achieve the best results in clinical applications, standardized protocols and personalized treatment approaches should be developed (Bos-Mikich et al., 2018; Lin et al., 2021; Maleki-Hajiagha et al., 2020; Puente Gonzalo et al., 2021).

Endometrial Health and PRP: Innovative Strategies for Thickness Increase and Infertility Treatment

Despite the advances made in ART centers, the high rate of embryo transfer failure (70-80%) once again emphasizes the importance of endometrial quality (Lédée et al., 2018). Although embryo quality and immunological factors play a substantial role in the implantation process, endometrial quality, which is critical for the embryo to attach to the uterus, can make a significant difference in infertility treatment (Hajipour et al., 2018). The relationship between endometrium and PRP has become an important research topic in the field of reproductive health. Endometrial thickness is a critical factor for a successful pregnancy, and an endometrial lining with sufficient thickness is necessary for the embryo to attach to the uterus. Thin endometrium can make embryo implantation difficult and reduce the chance of pregnancy. Therefore, increasing endometrial thickness has the potential to improve both implantation and pregnancy rates (Chang et al., 2015; Eftekhar et al., 2021). In endometrial thickness, a thickness of 7 mm or more is generally considered ideal. Thin endometrial lining (<7 mm) can lead to failed embryo implantation and lower pregnancy rates. Therefore, increasing endometrial thickness is critical (Bos-Mikich et al., 2018; Maleki-Hajiagha et al., 2020; Eftekhar et al., 2021).

Various approaches to managing thin endometrium that are commonly used today include:

1.Hormonal Therapies:

- **Gonadotropin-releasing hormone (GnRH) Agonists:** GnRH agonists can increase endometrial thickness. This treatment may promote endometrial thickening by regulating hormone production by the hypothalamus and pituitary gland (Qublah et al., 2008).
- **Vaginal Estrogen:** Estrogen is another important hormonal treatment that promotes endometrial thickening. Estrogen administered vaginally may have a direct impact on the endometrium (Chen et al., 2006).

2.Vasoactive Procedures:

- **Aspirin:** Aspirin may help improve blood flow and is used to support endometrial health (Hsieh et al., 2000).
- **Pentoxifylline:** The combination of pentoxifylline, a vasodilator, and vitamin E, an antioxidant, may have positive effects on endometrial health and fertility rates (Ledee-Bataille et al., 2002).
- **Sildenafil (Viagra):** It is a drug commonly utilized to cure erectile to treat erectile dysfunction and is believed to have the additional potential to improve endometrial thickness and enhance blood flow (Zinger et al., 2006).
- These treatment approaches offer different strategies to increase endometrial thickness and improve pregnancy rates. Each method provides specific advantages for improving endometrial health and pregnancy chances.

3.Regenerative Medicine:

- **Latest Methods:** Regenerative medicine applications offer innovative approaches to increase the health and thickness of the endometrium. Among these methods, advanced techniques such as PRP and stem cell treatments stand out: PRP, applied as an intrauterine infusion, is a new model treatment for thin endometrium. Recently, PRP infusion has been applied to humans, especially women who do not respond to standard treatment. These innovations in the field of regenerative medicine are considered an important step to improve endometrial health and offer new opportunities in the treatment of infertility.

Although the link between PRP therapy and endometrial receptivity is not fully understood, growing evidence supports that growth factors and other bioactive molecules in PRP play an important role in promoting endometrial health. Studies reveal how these components, such as growth factors, chemokines, cytokines and active metabolites released from platelets, exert paracrine effects on various endometrial cells, including fibroblasts, myocytes and mesenchymal stem cells (Anitua et al, 2009, Cho et al, 2011, Mazzocca et al, 2012, Marini et al, 2016) These paracrine signals may promote cell proliferation, differentiation and regeneration, potentially improving the intrinsic structural and behavioral integrity of the endometrium.

PRP's role in enhancing endometrial receptivity is further emphasized by findings that insufficient expression of adhesion molecules might underlie multiple implantation failures, which PRP could potentially correct (Colombo et al., 2017). Furthermore, cytokines and growth factors in PRP are thought to play a key therapeutic role in stimulating endometrial tissue regeneration and increasing endometrial thickness, especially when administered prior to intrauterine insemination (Sipahi, 2019). Its positive impact on ovarian follicle growth and development also underscores its broader potential in fertility treatments (Hosseini et al., 2017).

Moreover, the integral membrane proteins within PRP are thought to support successful embryo implantation by enhancing the adhesion capacity of endometrial cells, thus increasing pregnancy success rates. However, the variability in PRP's effects depending on its concentration highlights the critical need for precise dosage. Both excessive and insufficient doses could undermine the treatment, either by causing negative effects or by being ineffective, respectively (Marini et al., 2016). Hence, determining the correct PRP dosage is vital to achieving its desired benefits while ensuring the safety of the therapy.

Lange-Consiglio et al. (2015) demonstrated that PRP's platelet concentration significantly influences both endometrial and embryonic cell proliferation. However, excessive concentrations of PRP can have negative effects, which underscore the importance of using an optimal PRP dosage in clinical settings. Studies have shown that PRP affects the expression of several key genes involved in implantation. In particular, PRP has organizing effects on genes like COX-2, TP53, Estrogen Receptors Alpha and Beta (ER-α, ER-β), Progesterone Receptor (PR) (Marini et al., 2016). These genes play crucial roles in preparing the endometrium for embryo implantation, and PRP's modulation of their expression suggests that it could improve implantation success rates. The gene COX-2 is involved in prostaglandin synthesis, which is essential for key reproductive events like implantation, maintaining pregnancy, and childbirth (Sheldon et al., 2009). These indicate that the PRP might help organize critical biochemical signaling pathways required for the successful reproduction of the human reproductive system. PRP therapy has also been found to increase the statement of c-Myc, a gene involved in cell proliferation. This effect may be ascribed to the presence of EGF in PRP (Anitua et al., 2004), which further emphasizes PRP's potential to enhance cellular activity in the endometrium and improve conditions for embryo implantation. Overall, these studies provide valuable insights into how PRP may enhance the implantation process by influencing both cellular proliferation and the expression of key reproductive genes, offering a promising approach to improving fertility treatments. Considering earlier studies, however, PRP can be regarded as an effective and innovative strategy to increase the thickness of the endometrium in females with slender endometrium (Kim et al., 2019). Nevertheless, more research is required to determine the approved dose, number and duration of administration for clinical use and to establish PRP therapy as a current standard and accepted treatment strategy. Accordingly, extensive studies are essential to fully appreciate the effects of PRP and to enable its safe and effective use in clinical trials. The use of PRP applications to improve human embryo implantation and pregnancy has been widely investigated in recent years. Details on the healing use of PRP forendometrial health and aid in the treatment of infertility and the findings of studies regarding this issue are summarized in Table 2 below:

Table 2

Effects of PRP (Platelet Rich Plasma) Treatment on Endometrial Thickness and Pregnancy Outcomes: Summary

References	**Characteristics**	**Results and Findings**	**The time frame from intervention to cycle**
Chang et al., 2015	Female with thin endometrium (<7 mm) post HRT.	PRP successfully stimulated endometrial growth and improved pregnancy outcomes. 4 out of 5 women had a live birth.	Day 10 of the HRT cycle
Tandulwadkar et al., 2017	Autologous PRP with estradiol valerate in women with suboptimal endometrial growth and recurrent cycle cancellations.	It is hoped that PRP therapy may improve the chances of success of embryo transfer by improving endometrial thickness and vascularity.	Day 15-16 of the HRT cycle

Molina et al., 2018	Women having a medical history of refractory endometrium and unsuccessful IVF trials.	Endometrial thickness increased to >7 mm following the first use of PRP and to >9 mm following the second application.	Day 10 and 13 of the HRT cycle
Wang et al., 2019	Endometrial mesenchymal stem cells (EnMSCs) induced by PRP.	Endometrial widening and gestation were noted; pregnancy rate climbed to 60%.	Nothing reported
Nazari et al., 2019	Women whose FET cycles were cancelled due to thin endometrium; PRP and sham catheter.	PRP effectively promoted endometrial expansion in women with refractory thin endometrium, and significant differences were noted.	Day 11-12 of the HRT cycle and then day 13-14
Chang et al., (2019)	Women with thin endometrium who receive FET and PRP infusion during the HRT cycle.	PRP improved endometrial proliferation and embryo implantation rates during FET cycles.	Day 10 of the HRT cycle
Kim et al., 2019	Female with thin or damaged endometrium and two or more prior unsuccessful IVF treatments.	Autologous PRP has shown improved rates of implantation, conception and live birth in females with refractory thin endometrium.	Day 10 of the HRT cycle and every 3 days until endometrial thickness is ≥7 mm
Agarwal et al., 2020	Women with infertility who are attempting to get pregnant for the "first time" (primary) or who have been pregnant before but have difficulty getting pregnant again because the endometrium is thin (secondary).	An increase in endometrial thickness and improvement in pregnancy rates were observed in cases where embryo transfer was previously cancelled.	16th day of contraceptive pill use, 22-27 days before ET
Frantz et al., 2020	Intrauterine PRP intake preceding embryo placement.	PRP increased intrauterine sensitivity to embryo implantation independent of endometrial thickness.	Day 14-17 of the HRT cycle, 1 every 2 days, 3 times in total
Eftekhar et al., 2021	Women with poor endometrial response after HRT and receiving PRP until endometrial thickness is ≥7 mm.	In ET, significant increases in implantation rate and clinical pregnancy rate have been demonstrated.	Day 11-12 of the HRT cycle and then day 13-14
Dogra et al., 2022	Women with thin endometrium causing FET cycle cancellations despite standard HRT and normal endometrial space.	PRP therapy shows the significant potential to increase pregnancy and live birth rates, particular in women with poor prognosis and conditions such as PCOS.	48 hours before embryo transfer
Yu et al., 2024	116 infertile women with thin endometrium undergoing HRT, who had at least one failed FET cycle: intrauterine infusion of PRP (55 women), hysteroscopic injection of PRP (38 women), HRT treatment alone (23 women).	Intrauterine infusion and hysteroscopic injection of autologous PRP may be effective methods to increase endometrial thickness in HRT cycles.	Day 11-13 of the HRT cycle, 1 every 2 days, 2 times in total
Fujii et al., 2024	Women with thin endometrium or RIF.	PRP infusion shows promise in improving pregnancy outcomes, especially in women with RIF.	9-11th day of HRT cycle, 1 every 2 days, 2 times in total
Aghajanova et al., 2024	46 women who requested PRP treatment with endometrial lining thickness less than 6 mm among women with cancelled or failed FET cycles.	Significant improvements in ET and pregnancy rates without any side effects indicate that PRP may represent an appropriate option for this group.	10-12th day of the HRT cycle, If ET <7 mm, second PRP infusion 3-5 days later
ET: Endometrial Thickness. FET: Frozen Embryo Transfer. HRT: Hormone Replacement Therapy. IVF: In Vitro Fertilization. PCOS: Polycystic Ovary Syndrome. RIF: Recurrent Implantation Failure			

This table summarizes the scope, methodology, and findings of studies evaluating the efficacy of PRP infusion therapy in women diagnosed with endometrial infertility. In conclusion, most activities on the use of PRP for the therapy of thin endometrium suggest that this intervention may improve implantation rates. PRP therapy is considered a promising treatment for endometrial infertility and may have the potential to improve endometrial receptivity and fertility outcomes. However, these studies generally have small sample sizes and low power of evidence. Studies testing the efficacy of PRP also have small sample sizes, limiting the generalizability of the results. Future studies should aim to confirm these findings in larger and more diverse populations and explore long-term reproductive success rates following PRP therapy.

Use of PRP in Ovarian Health and Infertility Treatment

In addition to supporting endometrial proliferation, PRP has also been used to increase the response to ovarian stimulation in patients with poor prognosis (Çakıroğlu et al., 2020, 2022). Patients with poor prognosis are usually classified within the framework of "Patient-Oriented Strategies Encompassing Individualized Oocyte Number" (POSEIDON). These patients face challenges such as advanced age, decreased ovarian reserve, underlying infertility, and different responses to stimulation protocols (Poseidon et al., 2016). Approximately 1% of women of reproductive age are reported to have significantly diminished ovarian reserve. Ovarian reserve refers to the number and quality of oocytes in the ovaries. A decrease in reserve can affect the production of healthy oocytes by the ovaries, causing serum gonadotropin hormones to reach menopausal levels. This leads to problems such as menstrual irregularities or amenorrhea and is called "primary ovarian insufficiency" (POI). POI usually occurs before the expected age of menopause, usually before the age of 40, and can cause fertility problems (Ferraretti et al., 2011). At present, there is no effective cure protocol for POI and treatment options are limited.

Although various experimental treatment methods have been tried, these treatments have not been successful and live birth rates remain low. That is, current treatment options are not sufficiently effective in women with POI, creating an ongoing challenge in improving reproductive success (Ben-Nagi & Panay, 2014).

Recent developments have shown that PRP can support the development of isolated human primordial and primary follicles to the preantral stage. In an experiment conducted by Hosseini et al., (2017) using donated ovaries from three women under the age of 35 who had experienced brain death, ovarian cells were examined in various culture media. Follicles cultured in PRP-enriched media outperformed other media in terms of growth and survival rates. These findings suggest the potential of PRP to support the development of primordial and primary follicles. In other words, it is thought that PRP can support the maturation process of these follicles and thus enable them to develop better. However, the potential of PRP to support follicle development was obtained from studies conducted on follicles taken from donors with normal ovarian reserve. In patients with reduced ovarian reserve, follicle development may have more complex and diverse dynamics. This may affect the efficacy and results of PRP treatment. In other words, it is unclear whether the positive results obtained in donors with normal ovarian reserve are equally valid in patients with diminished ovarian reserve. The study by Hosseini et al., (2017) led to the hypothesis that PRP may also be effective in patients with diminished ovarian reserve, and this hypothesis was supported by subsequent studies (Çakıroğlu et al., 2022). In other words, it is thought that PRP may have positive effects in patientswith declined ovarian reserve, but further research is needed on this subject.

Details and research findings on the efficacy of using PRP to improve ovarian health or to aid in the treatment of infertility are summarized in Table 3 below:

Table 3

Clinical Results of Intra-ovarian PRP Applications: Characteristics and Findings of Various Studies

References	Characteristics	Results and Findings	Time from intervention to the day of evaluation
Sills et al., (2018)	Women who had less than one previous IVF cycle canceled, have low AMH, high FSH levels and have not menstruated for ≥1 year	Improvement in ovarian functions; increase in AMH, decrease in FSH and success in embryo development were observed.	78 ± 22 days
Stojkovska et al., 2019	Women with POR who meet at least two of the ESHRE (2011) criteria	Intra-ovarian PRP did not improve clinical conception and viable birth rates dramatically.	61 ± 18 days
Çakıroğlu et al., 2020	Women with POI	It might be an alternative treatment option in women with POI.	Not reported
Petryk and Petryk, 2020	Ovarian reserve diminished patients and women with at least two failed IVF attempts	For women with POI, autologous PRP is considered a promising, safe, and effective treatment.	Not reported
Tandulwadkar et al., 2020	Women with poor response to POSEIDON group 3 and 4 criteria	Administration of AdMSC in combination with PRP has been found to activate and restore ovarian reserve.	6 weeks
Hsu et al., 2021	Women in early menopause	The combination of PRP and GN has been found to temporarily restore ovarian function.	125 ±85 days
Aflatonian et al., 2021	Women with POR and POI	PRP appears to boost the likelihood of pregnancy in some POR women and improve menstrual cycles in POI women. No significant changes in hormone concentrations were observed.	About a year.
Tülek and Kahraman 2022	Women who received ovarian PRP injections due to POI/POR	More oocytes were retrieved from women with POR, but no notable reduction in clinical pregnancy or live birth women did not achieve clinical gestation. Women with POI did not achieve clinical pregnancy.	6 months≤
Çakıroğlu et al., 2022	Women with a history of POR	An increase in AFC, increase in serum AMH concentration, decrease in serum FSH concentration, rise in the mature oocyte count and improvement in embryo quality were observed.	Not reported
Tremellen and İnce 2022	Patients with significantly low ovarian reserve and previous IVF failures	Although there was no major gain in the total number of oocytes. collected after PRP treatment, PRP may be a hopeful alternative treatment option for women with low ovarian reserve.	2-3 months

Barad et al., 2022	Women with extremely low functional ovarian reserve (LFOR)	PRP treatment had no clear clinically meaningful impact on ovarian function.	Not reported
Merhi et al., 2022	Twelve infertile women with at least one failed IVF cycle to examine the effects of PRP treatment on embryo genetic quality.	This is the 1st study to suggest that intra-ovarian PRP treatment can cause an immediate improvement in the incidence of euploid embryos (embryos with the correct number of chromosomes).	1-3 months
Safarova et al., 2023	Infertile women with POR	A major breakthrough has been made in basal endometrial thickness, follicle count, estradiol value, oocyte count and Metaphase-II oocyte count after PRP injection.	4-6 months
Devenutto et al., 2024	Women who have had at least one IVF treatment, retrieved fewer than five oocytes and/ or have a low ovarian reserve profile (POSEIDON 1, 2, 3 and 4)	Better results were achieved 3 months after the treatment injection. There was an increase in ovarian reserve with a limited impact on pregnancy rates.	1-3 months
Herlihy et al., 2024	Womenunder 38 who have a past or present history of POR in IVF	Intraovarian PRP injection was not found to improve mature oocyte yield or other parameters of IVF outcome.	Not reported

AdMSC:Adipose-Derived Mesenchymal Stem Cells. AFC: Antral Follicle Count. AMH: Anti-Müllerian Hormone. ESHRE: European Society of Human Reproduction and Embryology. FSH: Follicle Stimulating Hormone. GN: Gonadotropins. IVF: In Vitro Fertilization. LFOR: Low Functional Ovarian Reserve. PGD-A: Preimplantation Genetic Testing. POI: Primary Ovarian Insufficiency. POR: Poor Ovarian Response. POSEIDON: Patient-Oriented Strategies Encompassing Individualized Oocyte Number. PRP: Platelet-Rich Plasma.

This table provides a comprehensive overview of studies on PRP therapy in women with ovarian failure and poor ovarian response. Based on the summary of the studies: PRP therapy has generally been applied to women with low AMH (Anti-Müllerian Hormone) levels, high FSH (Follicle Stimulating Hormone) levels and a history of failed IVF. Women with conditions such as POI, early menopause and poor ovarian reserve (LFOR) have also been studied. PRP has been shown in a number of studies to improve ovarian function, with an increase in AMH levels and a decrease in FSH levels. Success in embryo development has been achieved in some patients. However, some studies have reported that PRP did not substantially increase clinical pregnancy and viable delivery rates, and in some cases did not provide a significant benefit. In POI and POR (Poor Ovarian Response) patients, PRP therapy has shown some positive changes in hormone levels or oocyte count, but limited effects on pregnancy rates. Overall, PRP therapy is considered a promising alternative, but results vary from patient to patient and do not consistently improve clinical pregnancy outcomes. In summary, while PRP therapy has shown some potential benefits for women with poor ovarian response and related conditions, results are inconsistent. Research needs to continue to fully understand its efficacy, identify the best candidates for treatment and establish effective protocols.

References

Aflatoonian, A., Lotfi, M., Saeed, L., & Tabibnejad, N. (2021). Effects of Intraovarian Injection of Autologous Platelet-Rich Plasma on Ovarian Rejuvenation in Poor Responders and Women with Primary Ovarian Insufficiency. *Reproductive sciences (Thousand Oaks, Calif.)*, *28*(7), 2050–2059.

Agarwal, M., Mettler, L., Jain, S., Meshram, S., Günther, V., & Alkatout, I. (2020). Management of a Thin Endometrium by Hysteroscopic Instillation of Platelet-Rich Plasma Into The Endomyometrial Junction: A Pilot Study. *Journal of clinical medicine*, *9*(9), 2795.

Aghajanova, L., Zhang, A., Lathi, R. B., & Huddleston, H. G. (2024). Platelet-rich plasma infusion as an adjunct treatment for persistent thin lining in frozen embryo transfer cycles: first US experience report. *Journal of assisted reproduction and genetics*, *41*(2), 483–491.

Alves, R., & Grimalt, R. (2018). A Review of Platelet-Rich Plasma: History, Biology, Mechanism of Action, and Classification. *Skin appendage disorders*, *4*(1), 18–24.

Andia, I., & Abate, M. (2013). Platelet-rich plasma: underlying biology and clinical correlates. *Regenerative medicine*, *8*(5), 645–658.

Andrae, J., Gallini, R., & Betsholtz, C. (2008). Role of platelet-derived growth factors in physiology and medicine. *Genes & development*, *22*(10), 1276-1312.

Anitua, E., Andia, I., Ardanza, B., Nurden, P., & Nurden, A. T. (2004). Autologous platelets as a source of proteins for healing and tissue regeneration. *Thrombosis and haemostasis*, *91*(1), 4–15.

Anitua, E., Andía, I., Sanchez, M., Azofra, J., del Mar Zalduendo, M., de la Fuente, M., ... & Nurden, A. T. (2005). Autologous preparations rich in growth factors promote proliferation and induce VEGF and HGF production by human tendon cells in culture. *Journal of Orthopaedic Research*, *23*(2), 281-286.

Anitua, E., Sánchez, M., Zalduendo, M. M., de la Fuente, M., Prado, R., Orive, G., & Andía, I. (2009). Fibroblastic response to treatment with different preparations rich in growth factors. *Cell proliferation*, *42*(2), 162–170.

Babensee, J. E., McIntire, L. V., & Mikos, A. G. (2000). Growth factor delivery for tissue engineering. *Pharmaceutical research*, *17*, 497-504.

Barad, D. H., Albertini, D. F., Molinari, E., & Gleicher, N. (2022). Preliminary report of intraovarian injections of autologous platelet-rich plasma (PRP) in extremely poor prognosis patients with only oocyte donation as alternative: a prospective cohort study. *Human reproduction open*, *2022*(3), hoac027.

Barrick, B., Campbell, E. J., & Owen, C. A. (1999). Leukocyte proteinases in wound healing: roles in physiologic and pathologic processes. *Wound Repair and Regeneration*, *7*(6), 410-422.

Barrientos, S., Stojadinovic, O., Golinko, M. S., Brem, H., & Tomic-Canic, M. (2008). Growth factors and cytokines in wound healing. *Wound repair and regeneration*, *16*(5), 585-601.

Beck Jr, L., & D'Amore, P. A. (1997). Vascular development: cellular and molecular regulation. *The FASEB journal*, *11*(5), 365-373.

Ben-Nagi, J., & Panay, N. (2014). Premature ovarian insufficiency: how to improve reproductive outcome?. *Climacteric: the journal of the International Menopause Society*, *17*(3), 242–246.

Berlanga-Acosta, J., Gavilondo-Cowley, J., López-Saura, P., González-López, T., Castro-

Santana, M. D., López-Mola, E., ... & Herrera-Martinez, L. (2009). Epidermal growth factor in clinical practice–a review of its biological actions, clinical indications and safety implications. *International wound journal*, *6*(5), 331-346.

Blair, P., & Flaumenhaft, R. (2009). Platelet α-granules: Basic biology and clinical correlates. *Blood reviews*, *23*(4), 177-189.

Border, W. A., & Noble, N. A. (1994). Transforming growth factor β in tissue fibrosis. *New England journal of medicine*, *331*(19), 1286-1292.

Bos-Mikich, A., de Oliveira, R., & Frantz, N. (2018). Platelet-rich plasma therapy and reproductive medicine. *Journal of assisted reproduction and genetics*, *35*(5), 753–756.

Boswell, S. G., Cole, B. J., Sundman, E. A., Karas, V., & Fortier, L. A. (2012). Platelet-rich plasma: a milieu of bioactive factors. *Arthroscopy: The journal of arthroscopic & related surgery*, *28*(3), 429-439.

Bowen, T., Jenkins, R. H., & Fraser, D. J. (2013). MicroRNAs, transforming growth factor beta-1, and tissue fibrosis. *The Journal of pathology*, *229*(2), 274-285.

Cakiroglu, Y., Saltik, A., Yuceturk, A., Karaosmanoglu, O., Kopuk, S. Y., Scott, R. T., Tiras, B., & Seli, E. (2020). Effects of intraovarian injection of autologous platelet rich plasma on ovarian reserve and IVF outcome parameters in women with primary ovarian insufficiency. *Aging*, *12*(11), 10211–10222.

Cakiroglu, Y., Yuceturk, A., Karaosmanoglu, O., Kopuk, S. Y., Korun, Z. E. U., Herlihy, N., Scott, R. T., Tiras, B., & Seli, E. (2022). Ovarian reserve parameters and IVF outcomes in 510 women with poor ovarian response (POR) treated with intraovarian injection of autologous platelet rich plasma (PRP). *Aging*, *14*(6), 2513–2523.

Cavallo, C., Roffi, A., Grigolo, B., Mariani, E., Pratelli, L., Merli, G., Kon, E., Marcacci, M., & Filardo, G. (2016). Platelet-Rich Plasma: The Choice of Activation Method Affects the Release of Bioactive Molecules. *BioMed research international*, *2016*, 6591717.

Chang, Y., Li, J., Chen, Y., Wei, L., Yang, X., Shi, Y., & Liang, X. (2015). Autologous platelet-rich plasma promotes endometrial growth and improves pregnancy outcome during in vitro fertilization. *International journal of clinical and experimental medicine*, *8*(1), 1286–1290.

Chang, Y., Li, J., Wei, L. N., Pang, J., Chen, J., & Liang, X. (2019). Autologous platelet-rich plasma infusion improves clinical pregnancy rate in frozen embryo transfer cycles for women with thin endometrium. *Medicine*, *98*(3), e14062.

Chen, M. J., Yang, J. H., Peng, F. H., Chen, S. U., Ho, H. N., & Yang, Y. S. (2006). Extended estrogen administration for women with thin endometrium in frozen-thawed in-vitro fertilization programs. *Journal of assisted reproduction and genetics*, *23*(7-8), 337–342.

Cho, H. S., Song, I. H., Park, S. Y., Sung, M. C., Ahn, M. W., & Song, K. E. (2011). Individual variation in growth factor concentrations in platelet-rich plasma and its influence on human mesenchymal stem cells. *The Korean journal of laboratory medicine*, *31*(3), 212–218.

Clark, R. A. (2001). Fibrin and wound healing. *Annals of the New York Academy of Sciences*, *936*, 355-367.

Colombo, G. V. L., Fanton, V., Sosa, D., Criado Scholz, E., Lotti, J., Aragona, S. E., & Lotti, T. (2017). Use of platelet rich plasma in human infertility. *Journal of biological regulators and homeostatic agents*, *31*(2 Suppl. 2), 179–182.

Davis, V. L., Abukabda, A. B., Radio, N. M., Witt-Enderby, P. A., Clafshenkel, W. P., Cairone, J. V., & Rutkowski, J. L. (2014). Platelet-rich preparations to improve healing. Part I: workable options for every size practice. *Journal of Oral Implantology*, *40*(4), 500-510.

Devenutto, L. M., Valzacchi, G. R., Ercolano, M., & Etchegoyen, O. (2024). Intraovarian platelet-rich plasma injection in poor responders. *JBRA assisted reproduction*, 10.5935/1518-0557.20240031. Advance online publication.

Dhillon, R. S., Schwarz, E. M., & Maloney, M. D. (2012). Platelet-rich plasma therapy-future or trend?. *Arthritis research & therapy*, *14*(4), 1-10.

Dhurat, R., & Sukesh, M. (2014). Principles and Methods of Preparation of Platelet-Rich Plasma: A Review and Author's Perspective. *Journal of cutaneous and aesthetic surgery*, *7*(4), 189–197.

Dogra, Y., Singh, N., & Vanamail, P. (2022). Autologous platelet-rich plasma optimizes endometrial thickness and pregnancy outcomes in women with refractory thin endometrium of varied aetiology during fresh and frozen-thawed embryo transfer cycles. *JBRA assisted reproduction*, *26*(1), 13–21.

Eftekhar, M., Neghab, N., Naghshineh, E., & Khani, P. (2021). Corrigendum to "Can autologous platelet rich plasma expand endometrial thickness and improve pregnancy rate during frozen-thawed embryo transfer cycle? A randomized clinical trial" [Taiwan J Obstet Gynecol 57 (2018) 810-813]. *Taiwanese journal of obstetrics & gynecology*, *60*(5), 973.

Eming, S. A., Hammerschmidt, M., Krieg, T., & Roers, A. (2009, July). Interrelation of immunity and tissue repair or regeneration. In *Seminars in cell & developmental biology* (Vol. 20, No. 5, pp. 517-527). Academic Press.

Ferraretti, A. P., La Marca, A., Fauser, B. C., Tarlatzis, B., Nargund, G., Gianaroli, L., & ESHRE working group on Poor Ovarian Response Definition (2011). ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the Bologna criteria. *Human reproduction (Oxford, England)*, *26*(7), 1616–1624.

Foster, T. E., Puskas, B. L., Mandelbaum, B. R., Gerhardt, M. B., & Rodeo, S. A. (2009). Platelet-rich plasma: from basic science to clinical applications. *The American journal of sports medicine*, *37*(11), 2259–2272.

Frantz, N., Ferreira, M., Kulmann, M. I., Frantz, G., Bos-Mikich, A., & Oliveira, R. (2020). Platelet-Rich plasma as an effective alternative approach for improving endometrial receptivity - a clinical retrospective study. *JBRA assisted reproduction*, *24*(4), 442–446.

Fréchette, J. P., Martineau, I., & Gagnon, G. (2005). Platelet-rich plasmas: growth factor content and roles in wound healing. *Journal of dental research*, *84*(5), 434-439.

Fujii, S., & Oguchi, T. (2024). The number of previous implantation failures is a critical determinant of intrauterine autologous platelet-rich plasma infusion success in women with recurrent implantation failure. *Reproductive medicine and biology*, *23*(1), e12565.

Fujioka-Kobayashi, M., & Miron, R. J. (2017). Biological components of platelet rich fibrin: Growth factor release and cellular activity. *Platelet Rich Fibrin in Regenerative Dentistry: Biological Background and Clinical Indications: Biological Background and Clinical Indications*, 15-31.

Gallagher, J. T., & Lyon, M. (2000). Molecular structure of heparan sulfate and interactions with growth factors and morphogens. *Proteoglycans: structure, biology and molecular interactions*, 27-59.

Garg, A. K. (2000). The use of platelet-rich plasma to enhance the success of bone grafts around dental implants. *Dental implantology update*, *11*, 17-20.

Ghasemzadeh, M., & Hosseini, E. (2015). Intravascular leukocyte migration through platelet thrombi: directing leukocytes to sites of vascular injury. *Thrombosis and haemostasis*, *113*(06), 1224-1235.

Giannobile, W. V., Hernandez, R. A., Finkelman, R. D., Ryarr, S., Kiritsy, C. P., D'Andrea, M., & Lynch, S. E. (1996). Comparative effects of plateletderived growth factor-BB and insulin-like growth factor-I, individually and in combination, on periodontal regeneration in Macaca fascicularis. *Journal of periodontal research*, *31*(5), 301-312.

Hajipour, H., Nejabati, H. R., Latifi, Z., Hamdi, K., Bahrami-Asl, Z., Fattahi, A., & Nouri, M. (2018). Lymphocytes immunotherapy for preserving pregnancy: Mechanisms and Challenges. *American journal of reproductive immunology (New York, N.Y. : 1989)*, *80*(3), e12853.

Herlihy, N. S., Cakiroglu, Y., Whitehead, C., Reig, A., Tiras, B., Scott, R. T., Jr, & Seli, E. (2024). Effect of intraovarian platelet-rich plasma injection on IVF outcomes in women with poor ovarian response: the PROVA randomized controlled trial. *Human reproduction (Oxford, England)*, deae093. Advance online publication.

Hosseini, L., Shirazi, A., Naderi, M. M., Shams-Esfandabadi, N., Borjian Boroujeni, S., Sarvari, A., Sadeghnia, S., Behzadi, B., & Akhondi, M. M. (2017). Platelet-rich plasma promotes the development of isolated human primordial and primary follicles to the preantral stage. *Reproductive biomedicine online*, *35*(4), 343–350.

Hosseini, L., Shirazi, A., Naderi, M. M., Shams-Esfandabadi, N., Boroujeni, S. B., Sarvari, A., ... & Akhondi, M. M. (2017). Platelet-rich plasma promotes the development of isolated human primordial and primary follicles to the preantral stage. *Reproductive biomedicine online*, *35*(4), 343-350.

Hsieh, Y. Y., Tsai, H. D., Chang, C. C., Lo, H. Y., & Chen, C. L. (2000). Low-dose aspirin for infertile women with thin endometrium receiving intrauterine insemination: a prospective, randomized study. *Journal of assisted reproduction and genetics*, *17*(3), 174–177.

Hsu, C. C., Hsu, I., Hsu, L., Chiu, Y. J., & Dorjee, S. (2021). Resumed ovarian function and pregnancy in early menopausal women by whole dimension subcortical ovarian administration of platelet-rich plasma and gonadotropins. *Menopause (New York, N.Y.)*, *28*(6), 660–666.

Jedlitschky, G., Tirschmann, K., Lubenow, L. E., Nieuwenhuis, H. K., Akkerman, J. W., Greinacher, A., & Kroemer, H. K. (2004). The nucleotide transporter MRP4 (ABCC4) is highly expressed in human platelets and present in dense granules, indicating a role in mediator storage. *Blood*, *104*(12), 3603-3610.

Kaul, G., Cucchiarini, M., Arntzen, D., Zurakowski, D., Menger, M. D., Kohn, D., ... & Madry, H. (2006). Local stimulation of articular cartilage repair by transplantation of encapsulated chondrocytes overexpressing human fibroblast growth factor 2 (FGF-2) in vivo. *The Journal of Gene Medicine: A cross-disciplinary journal for research on the science of gene transfer and its clinical applications*, *8*(1), 100-111.

Kim, H., Shin, J. E., Koo, H. S., Kwon, H., Choi, D. H., & Kim, J. H. (2019). Effect of Autologous Platelet-Rich Plasma Treatment on Refractory Thin Endometrium During the Frozen Embryo Transfer Cycle: A Pilot Study. *Frontiers in endocrinology*, *10*, 61.

Knezevic, N. N., Candido, K. D., Desai, R., & Kaye, A. D. (2016). Is platelet-rich plasma a future therapy in pain management?. *Medical Clinics*, *100*(1), 199-217.

Lacoste, E., Martineau, I., & Gagnon, G. (2003). Platelet concentrates: effects of calcium and thrombin on endothelial cell proliferation and growth factor release. *Journal of periodontology*, *74*(10), 1498-1507.

Lana, J. F. S. D., Purita, J., Paulus, C., Huber, S. C., Rodrigues, B. L., Rodrigues, A. A., Santana, M. H., Madureira, J. L., Jr, Malheiros Luzo, Â. C., Belangero, W. D., & Annichino-Bizzacchi, J. M. (2017). Contributions for classification of platelet rich plasma - proposal of a new classification: MARSPILL. *Regenerative medicine*, *12*(5), 565–574.

Lange-Consiglio, A., Cazzaniga, N., Garlappi, R., Spelta, C., Pollera, C., Perrini, C., & Cremonesi, F. (2015). Platelet concentrate in bovine reproduction: effects on in vitro embryo production and after intrauterine administration in repeat breeder cows. *Reproductive biology and endocrinology : RB&E*, *13*, 65.

Lédée-Bataille, N., Olivennes, F., Lefaix, J. L., Chaouat, G., Frydman, R., & Delanian, S. (2002). Combined treatment by pentoxifylline and tocopherol for recipient women with a thin endometrium enrolled in an oocyte donation programme. *Human reproduction (Oxford, England)*, *17*(5), 1249–1253.

Lin, Y., Qi, J., & Sun, Y. (2021). Platelet-Rich Plasma as a Potential New Strategy in the Endometrium Treatment in Assisted Reproductive Technology. *Frontiers in endocrinology*, *12*, 707584.

Lozano, M., Estebanell, E., Cid, J., Diaz-Ricart, M., Mazzara, R., Ordinas, A., & Escolar, G. (1999). Platelet concentrates prepared and stored under currently optimal conditions: minor impact on platelet adhesive and cohesive functions after storage. *Transfusion*, *39*(9), 951-959.

Maleki-Hajiagha, A., Razavi, M., Rouholamin, S., Rezaeinejad, M., Maroufizadeh, S., &

Sepidarkish, M. (2020). Intrauterine infusion of autologous platelet-rich plasma in women undergoing assisted reproduction: A systematic review and meta-analysis. *Journal of reproductive immunology*, *137*, 103078.

Marini, M. G., Perrini, C., Esposti, P., Corradetti, B., Bizzaro, D., Riccaboni, P., Fantinato, E., Urbani, G., Gelati, G., Cremonesi, F., & Lange-Consiglio, A. (2016). Effects of platelet-rich plasma in a model of bovine endometrial inflammation in vitro. *Reproductive biology and endocrinology : RB&E*, *14*(1), 58.

Marques, L. F., Stessuk, T., Camargo, I. C. C., Sabeh Junior, N., Santos, L. D., & Ribeiro-Paes, J. T. (2015). Platelet-rich plasma (PRP): methodological aspects and clinical applications. *Platelets*, *26*(2), 101-113.

Martin, P., & Leibovich, S. J. (2005). Inflammatory cells during wound repair: the good, the bad and the ugly. *Trends in cell biology*, *15*(11), 599-607.

Martineau, I., Lacoste, E., & Gagnon, G. (2004). Effects of calcium and thrombin on growth factor release from platelet concentrates: kinetics and regulation of endothelial cell proliferation. *Biomaterials*, *25*(18), 4489-4502.

Maynard, D. M., Heijnen, H. F. G., Horne, M. K., White, J. G., & Gahl, W. A. (2007). Proteomic analysis of platelet α-granules using mass spectrometry. *Journal of thrombosis and haemostasis*, *5*(9), 1945-1955.

Mazzocca, A. D., McCarthy, M. B., Chowaniec, D. M., Dugdale, E. M., Hansen, D., Cote, M. P., Bradley, J. P., Romeo, A. A., Arciero, R. A., & Beitzel, K. (2012). The positive effects of different platelet-rich plasma methods on human muscle, bone, and tendon cells. *The American journal of sports medicine*, *40*(8), 1742–1749.

Merhi, Z., Seckin, S., & Mouanness, M. (2022). Intraovarian platelet-rich plasma administration could improve blastocyst euploidy rates in women undergoing in vitro fertilization. *Clinical and experimental reproductive medicine*, *49*(3), 210–214.

Molina, A., Sánchez, J., Sánchez, W., & Vielma, V. (2018). Platelet-rich plasma as an adjuvant in the endometrial preparation of patients with refractory endometrium. *JBRA assisted reproduction*, *22*(1), 42–48.

Moroff, G., & Holme, S. (1991). Concepts about current conditions for the preparation and storage of platelets. *Transfusion medicine reviews*, *5*(1), 48-59.

Nazari, L., Salehpour, S., Hoseini, S., Zadehmodarres, S., & Azargashb, E. (2019). Effects of autologous platelet-rich plasma on endometrial expansion in patients undergoing frozen-thawed embryo transfer: A double-blind RCT. *International journal of reproductive biomedicine*, *17*(6), 443–448.

Otsuru, S., Tamai, K., Yamazaki, T., Yoshikawa, H., & Kaneda, Y. (2008). Circulating bone marrow-derived osteoblast progenitor cells are recruited to the bone-forming site by the CXCR4/stromal cell-derived factor-1 pathway. *Stem cells*, *26*(1), 223-234.

Petryk, N., & Petryk, M. (2020). Ovarian Rejuvenation Through Platelet-Rich Autologous Plasma (PRP)-a Chance to Have a Baby Without Donor Eggs, Improving the Life Quality of Women Suffering from Early Menopause Without Synthetic Hormonal

Treatment. *Reproductive sciences (Thousand Oaks, Calif.)*, *27*(11), 1975–1982.

Poseidon Group (Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number), Alviggi, C., Andersen, C. Y., Buehler, K., Conforti, A., De Placido, G., Esteves, S. C., Fischer, R., Galliano, D., Polyzos, N. P., Sunkara, S. K., Ubaldi, F. M., & Humaidan, P. (2016). A new more detailed stratification of low responders to ovarian stimulation: from a poor ovarian response to a low prognosis concept. *Fertility and sterility*, *105*(6), 1452–1453.

Puente Gonzalo, E., Alonso Pacheco, L., Vega Jiménez, A., Vitale, S. G., Raffone, A., & Laganà, A. S. (2021). Intrauterine infusion of platelet-rich plasma for severe Asherman syndrome: a cutting-edge approach. *Updates in surgery*, *73*(6), 2355–2362.

Qublan, H., Amarin, Z., Al-Qudah, M., Diab, F., Nawasreh, M., Malkawi, S., & Balawneh, M. (2008). Luteal phase support with GnRH-a improves implantation and pregnancy rates in IVF cycles with endometrium of <or=7 mm on day of egg retrieval. *Human fertility (Cambridge, England)*, *11*(1), 43–47.

Rudkin, G. H., & Miller, T. A. (1996). Growth factors in surgery. *Plastic and reconstructive surgery*, *97*(2), 469-476.

Safarova, S., Cevher Akdulum, M. F., Guler, I., Bozkurt, N., Erdem, A., & Karabacak, R. O. (2023). Does Platelet-Rich Plasma Treatment Increase In Vitro Fertilization (IVF) Success in the Infertile Population?. *Cureus*, *15*(10), e47239.

Sánchez, A. R., Sheridan, P. J., & Kupp, L. I. (2003). Is platelet-rich plasma the perfect enhancement factor? A current review. *International Journal of Oral & Maxillofacial Implants*, *18*(1).

Sheldon, I. M., Cronin, J., Goetze, L., Donofrio, G., & Schuberth, H. J. (2009). Defining postpartum uterine disease and the mechanisms of infection and immunity in the female reproductive tract in cattle. *Biology of reproduction*, *81*(6), 1025–1032.

Sills, E. S., Rickers, N. S., Li, X., & Palermo, G. D. (2018). First data on in vitro fertilization and blastocyst formation after intraovarian injection of calcium gluconate-activated autologous platelet rich plasma. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology*, *34*(9), 756–760.

Sipahi, M. (2019). Effects of autologous platelet-rich plasma on endometrium thickness and pregnancy rates during intrauterine insemination. *Middle Black Sea Journal of Health Science*, *5*(2), 63-66.

Stojkovska, S., Dimitrov, G., Stamenkovska, N., Hadzi-Lega, M., & Petanovski, Z. (2019). Live Birth Rates in Poor Responders' Group after Previous Treatment with Autologous Platelet-Rich Plasma and Low Dose Ovarian Stimulation Compared with Poor Responders Used Only Low Dose Ovarian Stimulation Before in Vitro Fertilization. *Open access Macedonian journal of medical sciences*, *7*(19), 3184–3188.

Takai, K., Hara, J., Matsumoto, K., Hosoi, G., Osugi, Y., Tawa, A., ... & Nakamura, T. (1997). Hepatocyte growth factor is constitutively produced by human bone marrow stromal cells and indirectly promotes hematopoiesis. *Blood, The Journal* *of the American Society of Hematology*, *89*(5), 1560-1565.

Tandulwadkar, S. R., Naralkar, M. V., Surana, A. D., Selvakarthick, M., & Kharat, A. H. (2017). Autologous Intrauterine Platelet-Rich Plasma Instillation for Suboptimal Endometrium in Frozen Embryo Transfer Cycles: A Pilot Study. *Journal of human reproductive sciences*, *10*(3), 208–212.

Tandulwadkar, S., & Karthick, M. S. (2020). Combined Use of Autologous Bone Marrow-derived Stem Cells and Platelet-rich Plasma for Ovarian Rejuvenation in Poor Responders. *Journal of human reproductive sciences*, *13*(3), 184–190.

Thrailkill, K. M., Siddhanti, S. R., Fowlkes, J. L., & Quarles, L. D. (1995). Differentiation of MC3T3-E1 osteoblasts is associated with temporal changes in the expression of IGF-I and IGFBPs. *Bone*, *17*(3), 307-313.

Tremellen, K., & Pacella-Ince, L. (2022). An audit of clinical outcomes following ovarian administration of platelet-rich plasma (PRP) in women with severe diminished ovarian reserve. *The Australian & New Zealand journal of obstetrics & gynaecology*, *62*(5), 767–772.

Tülek, F., & Kahraman, A. (2022). The effects of intra-ovarian autologous platelet rich plasma injection on IVF outcomes of poor responder women and women with premature ovarian insufficiency. *Journal of the Turkish German Gynecological Association*, *23*(1), 14–21.

Unuane, D., Tournaye, H., Velkeniers, B., & Poppe, K. (2011). Endocrine disorders & female infertility. *Best practice & research. Clinical endocrinology & metabolism*, *25*(6), 861–873.

Wang, X., Liu, L., Mou, S., Zhao, H., Fang, J., Xiang, Y., Zhao, T., Sha, T., Ding, J., & Hao, C. (2019). Investigation of platelet-rich plasma in increasing proliferation and migration of endometrial mesenchymal stem cells and improving pregnancy outcome of patients with thin endometrium. *Journal of cellular biochemistry*, *120*(5), 7403–7411.

Weibrich, G., Kleis, W. K., Hafner, G., & Hitzler, W. E. (2002). Growth factor levels in platelet-rich plasma and correlations with donor age, sex, and platelet count. *Journal of Cranio-Maxillofacial Surgery*, *30*(2), 97-102.

Wiesner, J., & Vilcinskas, A. (2010). Antimicrobial peptides: the ancient arm of the human immune system. *Virulence*, *1*(5), 440-464.

Wu, P. I., Diaz, R., & Borg-Stein, J. (2016). Platelet-Rich Plasma. *Physical medicine and rehabilitation clinics of North America*, *27*(4), 825–853.

Yu, T. N., Lee, T. H., Lee, M. S., Chen, Y. C., Chen, C. I., Cheng, E. H., Lin, P. Y., Huang, C. C., & Lee, C. I. (2024). Intrauterine Infusion and Hysteroscopic Injection of Autologous Platelet-Rich Plasma for Patients with a Persistent Thin Endometrium: A Prospective Case-Control Study. *Journal of clinical medicine*, *13*(10), 2838.

Zinger, M., Liu, J. H., & Thomas, M. A. (2006). Successful use of vaginal sildenafil citrate in two infertility patients with Asherman's syndrome. *Journal of women's health (2002)*, *15*(4), 442–444.

About the Authors

Elif GÜLBAHÇE MUTLU, PhD, is an Assistant Professor at KTO Karatay University in Konya, Türkiye. She holds a PhD in medical physiology from Selçuk University. Her main areas of interest are muscle contraction, cell signaling, molecular biology, and metabolism.
E-mail:elif.mutlu@karatay.edu.tr, **ORCID:** 0000-0003-2391-2152

Hatice Nur ŞEFLEK, PhD, is an Assistant Professor at KTO Karatay University in Konya, Türkiye. She holds a PhD in medical histology and embryology from Necmettin Erbakan University. Her main areas of interest are infertility, immunohistochemistry, and stem cells.
E-mail:haticenur.seflek@karatay.edu.tr, **ORCID:** 0000-0003-2969-2322

Similarity Index
The similarity index obtained from the plagiarism software for this book chapter is 8%.

Methods Used in Behavioural Experiments in Laboratory Animals

İbrahim Yıldız

Necmettin Erbakan University

To Cite This Chapter

Yıldız, İ. (2024). Methods Used in Behavioural Experiments in Laboratory Animals. In F. Nur Takı, S. Koçer & R. Bütüner (Eds.), *New Generation Technologies and Sustainability in Health Current Studies* (pp. 119-132). ISRES Publishing.

Introduction

Behavioural experiments in laboratory animals include research to understand and study the behaviour of animals. These experiments are carried out for various purposes, such as understanding the natural behaviour of animals, determining their stress levels, and measuring their learning and memory abilities. Experiments on laboratory animals are also used to understand human health, study diseases and develop medical treatments. Behavioural experiments use various methods to study the natural movements and reactions of animals in more detail. In the first stage, the animals' habitats are carefully organised and provided with suitable conditions. Then, the animals are exposed to different stimuli and their responses are measured. During these experiments, many factors such as physiological parameters, brain activity and hormone levels are measured. Thus, more information is obtained about the animals' emotional state, learning abilities and memory. The use of laboratory animals has led to many important discoveries related to human health. For example, experiments on animals to evaluate the effects and side effects of drugs provide important data on the safety and efficacy of new drugs. In addition, animal experiments are used to understand the causes and treatment methods of diseases such as cancer, diabetes and Alzheimer's disease. Thanks to these experiments, it is possible to improve people's quality of life and develop effective treatments against diseases. As a result, behavioural experiments in laboratory animals are of great importance for understanding animal behaviour and improving human health. These experiments are carried out for various purposes, such as understanding the natural behaviour of animals, determining their stress levels, and measuring their learning and memory abilities. In addition, experiments on laboratory animals are a valuable tool for understanding human health, studying diseases and developing medical treatments. The methods used and data obtained in these studies provide information on the safety and efficacy of drugs and provide a strong basis for understanding the causes of diseases. It is important to continue behavioural experiments in laboratory animals to improve people's quality of life and to develop effective treatments against diseases.

Importance and Contributions of Laboratory Animals

Laboratory animals usually consist of various species such as mice, rats, birds, fish, rabbits, etc. Various behavioural experiments performed on such animals are used to understand their behaviour, assess their emotional states, and study their learning and memory abilities. These experiments allow us to analyze in detail the physiological state of animals, their social interactions and their relationship with their environment. In addition, various games and activities are used to improve the quality of life of laboratory animals. Thus, a better life is provided for the animals by protecting their mental and physical health. The main goal of all these studies is to support scientific progress and maximize animal welfare. For this reason, proper care and full compliance with legal regulations are required to protect the health and well-being of laboratory animals.

Open Field Test

Open Field Test is a method used to evaluate the anxiety levels of laboratory animals. The main purpose of this test is to determine the anxiety levels of animals by examining their reactions to the outside world. In this Open Field Test , the animal's mobility, exploratory behaviour and risk-taking tendency are observed and the anxiety level is determined based on these behaviours. When the animal is exposed to an inappropriate environment, its anxiety level is determined by analysing its reactions. During this test, each movement of the animal is recorded on video and these videos are then analysed in detail by experts. Each movement of the animal is examined for signs such as escape behaviour, a tendency to hide or restlessness. The experts carefully analyse the animal's reactions by pausing and replaying the videos. As a result of these analyses, a comprehensive assessment is made to determine the animal's level of anxiety. The Open Field Test is a widely used method to objectively determine the anxiety level of animals in laboratory studies. This test is an important tool to accurately assess the health and welfare of animals. Thanks to this method, experts determine the stress levels of animals and provide a better understanding of anxiety and stress, which are abstract concepts, with concrete data. The Open Field Test is of great importance in determining the anxiety levels of animals and developing appropriate treatment methods. This method is frequently used in research in animal behavioural science to improve the welfare of animals and provide them with a better quality of life. Overall, Open Field testing is a key to understanding the anxiety levels of animals and contributes to the protection of animal welfare in laboratory studies.

Definition and Purpose

The Open Field Test is a behavioural experiment used to determine the anxiety levels of laboratory animals. This important test is performed to understand how the animal interacts with the outside world, how it reacts to potential dangers and its behavioural characteristics in general. Through this experiment, the animal's anxiety level is determined and the factors affecting this state are observed, as well as how it responds to genetic, environmental or pharmacological interventions. Determining the level of anxiety is critical for understanding the health and welfare status of animals, identifying stress factors and ensuring that the data used in relevant research is built on solid foundations. This test is an important tool to understand the behavioural responses of animals and to ensure that they live healthily in their environment. In this way, it is aimed to meet the needs of animals and improve their quality of life. Open Field testing provides researchers with the opportunity to understand the behaviour of animals and assess their emotional states, such as anxiety. Therefore, it is of great importance for ensuring animal welfare and fulfilling ethical practices in the laboratory environment.

Application Procedure

The Open Field Test procedure begins with the animal being placed in the test room. In the large and spacious open area placed in the middle of the room, all behaviours of the animal are meticulously videotaped and observed. During this process, the animal's mobility, exploratory behaviour and risk-taking behaviour are noted in detail. Through high-resolution cameras and sensitive sensors placed around the animal during the test, all of the animal's movements are recorded in detail and then used for a comprehensive analysis. At the end of the test, the video recording is replayed by experts to examine the animal's behavioural data in even greater detail. At this stage, the experts analyse each movement, reaction and behaviour of the animal in more detail, allowing for a more comprehensive evaluation of the test results. Additional observations are made to learn more about the behavioural characteristics of the animal and additional analyses are performed if necessary to ensure the accuracy of the data. Thus, the Open Field Test application procedure becomes an important tool in scientific research, providing a complete understanding of the behaviour of animals.

Data Analysis and Interpretation

The data analysis of the Open Field Test is carried out in detail on the video recording. The behaviours of the animal during the test are carefully examined and noted in detail. These include various behaviours such as wandering, exploration, risk-taking and avoidance. This valuable data is used to precisely determine the animal's level of anxiety. The findings of the data analyses lead to different and comprehensive interpretations of the animal's anxiety level. These valuable interpretations provide important clues for understanding the behaviour of laboratory animals and working on possible treatments. They also provide valuable information for the development of potential treatments.

Elevated Plus Maze

The Elevated Plus Maze is a widely used method for testing learning, memory and motor skills. This method was developed to assess the ability of laboratory animals to explore their environment, navigate and learn. Animals usually try to climb onto the platform in the maze or behave cautiously to find the platform. These behaviours provide data used to measure the animals' performance and analyse their results. Factors such as the time the animals spend in the maze, the time to find the platform and the number of mistakes provide important information about the animals' learning and memory skills. In addition, this method is also used to investigate the effects of laboratory animals on brain activity and the nervous system, and is also preferred in areas such as drug experiments and the study of neurological diseases. This method plays an effective role in the development of treatment methods by providing in-depth understanding of animal behaviour. Experiments on laboratory animals are of great importance not only for human health but also for animal welfare in general. Ethical rules require the way in which experiments are conducted, the protection of animals and their fulfilment. Therefore, it is important that experiments on laboratory animals are carried out correctly and ethically. The results of these experiments can contribute to scientific discoveries and advances that can guide humans. In conclusion, the elevated plusmaze is a valuable tool for studying the behaviour of animals and assessing their learning abilities. Thanks to this method, better treatments and medicines can be developed and important contributions to basic science research can be made.

Definition and Purpose

The elevated plus maze is a behavioural test used to evaluate the learning, memory and motor skills of laboratory animals. The main purpose of this method is to measure and compare the learning process, memory capacity and the ability of animals to explore their environment. The experiment aims to obtain behavioural results by analysing substantial data such as the animal's time to find a platform in a maze, the number of errors, movement patterns and the effect of environmental factors. Thus, the effects of animals on the learning process can be understood in more detail and contribute to scientific studies. Furthermore, this experimental method can also be used to evaluate the mental abilities of laboratory animals and to test the effectiveness of potential medication or rehabilitation methods. The Elevated Plus Maze test is an important tool for investigating the cognitive abilities of animals and studying conditions such as neurological diseases or aging. This method analyses the behaviour of animals, assessing critical skills such as memory, learning and locomotor abilities, while also considering animal welfare. In conclusion, the Elevated Plus Maze test is a powerful research tool for understanding animals' behaviour, measuring their mental abilities and contributing to the development of potential treatment methods.

Application Procedure

The Elevated Plus Maze procedure is usually focussed on the animal's ability to find a platform in the maze. The process of the animal trying to find the platform starting from the starting point of the maze is highly considered. The behaviour of the animal as it searches for the platform in each layer of the maze is observed, recorded and analysed in detail. These analyses provide information on the animal's time to find the platform, error rates and next step strategies. The difficulties encountered by the animal during the experiment and the methods of coping with them are also analysed and recorded. The data obtained at the end of the experiment allows us to make more precise inferences about the animal's learning ability and memory performance. In this way, we gain a broader perspective on the problem-solving abilities and cognitive processes of animals.

Data Analysis and Interpretation

The data obtained in the Elevated Plus Maze test are used to evaluate the animal's performance in the maze. These data usually include the animal's time to find the platform, number of errors, time spent in the maze and movement patterns. Data analysis involves a comparative evaluation of these factors. When interpreting, behavioural conclusions are drawn, taking into account the animal's learning ability, memory performance, motor skills and attention span. Data analysis and interpretation are critical for understanding the results of the test and for understanding the behavioural abilities of the animals. It is also important to evaluate other factors that may influence the cognitive abilities of the animals based on these data. Based on the results of the test, a better understanding of how the cognitive functions of animals are related to tasks that require learning, memory and attention can be gained. These analyses could provide important information for future studies to assess the mental health of animals and to examine the effects of drugs. To summarise, the Elevated Plus Maze testis a tool for assessing the cognitive abilities of animals and understanding behavioural outcomes. The results of this test can be a valuable source of scientific data to investigate the mental functions of animals and to develop treatment approaches based on this.

Light-Dark Box Test

The Light-Dark Box Test is a method used in open field experiments of laboratory animals. The purpose of this test is to examine the behaviour of the animal when exposed to a highly illuminated area. The Light-Dark Box Test is a method often used to measure different behaviours of the animal, such as fear, courage and exploration. This test is an important tool to understand the stress level, anxiety level and adaptability of the animal and is an effective method to assess the emotional state of laboratory animals. It is also used to assess the general welfare of laboratory animals and to ensure ethical standards in animal experiments. Therefore, the Light-Dark Box Test is a protocol frequently preferred by researchers and animal observers.

Definition and Purpose

The definition of the Light-Dark Box Test is an experiment to examine the behavioural responses of laboratory animals at high light levels. The main purpose of this test is to evaluate the emotional state of the animal in more detail by measuring many different behaviours such as fear, curiosity and courage. The purpose of the Light-Dark Box Test is not only limited to this, but also focuses on determining the stress level of the animal, analysing the anxiety level and measuring the adaptation ability. This test is also of great importance to improve the welfare of animals in laboratory conditions. Improving the quality of life of animals and providing them with a healthier environment is one of the long-term goals of the Light-Dark Box Test. This form of experiment aims to improve the welfare of animals by providing them with more natural behavioural options. It also assesses the ability of animals to adapt to laboratory environments, improving their long-term quality of life. The use of the Light-Dark Box Test helps us to better understand the psychological state of animals, while taking steps to better meet their mental and emotional needs. While this test is recognised as an important indicator of laboratory animal welfare, it also plays a major role in the ethical aspects of animal experimentation. In conclusion, the Light-Dark Box Test is an important tool for the multifaceted evaluation of animal experiments and to improve the welfare of laboratory animals.

Application Procedure

The procedure for the application of the Light-Dark Box Test is firstly to allow time for the animal to rest peacefully and relax in a completely dark area. Then, the animal is placed in an open area with high light. The time the animal spends in this area, its escape behaviour and level of courage are carefully observed and recorded. During the test, the animal's movements, physiological responses, and moods are determined and recorded in detail. This procedure is carried out in a standardised way to understand the behavioural responses of laboratory animals and to assess their emotional state, so that the data obtained are suitable for scientific analysis and broader conclusions. Knowing the emotional experiences of the animal is important to improve their welfare and to better understand how they react in open spaces.

Data Analysis and Interpretation

Data analysis of the Light-Dark Box Test is based on the duration, frequency and type of behaviour the animal shows during the test. This data is used to measure the animal's fear, courage and exploratory behaviour. Inferences are also made on the animal's stress level, anxiety level and adaptability. The data obtained are evaluated to understand the emotional state of laboratory animals and to improve their welfare, thus contributing to keeping laboratory animals in improved conditions. The results of these analyses are also used to understand the interaction between humans and animals. In particular, these tests are an important tool for understanding how animals react to humans and how they communicate with them. Thus, it contributes to the development of more effective methods in the field of animal breeding and training. Data analysis of the Light-Dark Box Test is also an important resource for genetic research. These tests are used to understand the genetic makeup of animals and to study the influence of certain genes on behaviour. This provides a better understanding of how genetic factors influence animal behaviour and helps to create more genetically healthy and stable populations. In conclusion, data analysis of the Light-Dark Box Test is a tool that helps us to better understand animals and even humans and improve their welfare. By assessing the emotional state of animals, we can improve their living conditions and take the necessary measures for a better future. These analyses are constantly being improved based on scientific research and the relationship between animals and humans.

Morris Water Maze

The Morris Water Maze is a method used especially on mice and rats and aims to evaluate the learning, memory and spatial navigation abilities of animals. This test evaluates the performance of animals by the time it takes to find the platform in the maze. Animals swim through the water, demonstrating their ability to find the exit of the maze and the position of the platform. The Morris Water Maze is a widely used test to assess the learning ability, memory and strategic behaviour of animals. This method is important for understanding the cognitive abilities and mental capacities of animals. It is also an effective method to study the behaviour of animals in a laboratory environment and to obtain valuable data for research. The Morris Water Maze is a reliable tool for measuring the mental performance of animals and is a standard test used in many studies. This test plays an important role in analyses on the learning and memory abilities of animals. The performance of animals in the maze provides information about the effectiveness of the experiment and helps researchers to understand the behavioural and neural characteristics of the animal models of interest. Furthermore, the Morris Water Maze is used to study the impact of conditions such as brain traumas, neurological disorders and aging on the cognitive functions of animals. In conclusion, the Morris Water Maze is a reliable test for assessing the cognitive performance of animals and plays an important role in brain research. By examining the intelligence levels and learning capacities of animals, this test is an important tool in understanding and curing human diseases.

Definition and Purpose

The main purpose of the Morris Water Maze is to more comprehensively evaluate the spatial learning, memory formation and navigation abilities of laboratory animals. This maze is used to observe changes that occur under genetic or pharmacological conditions, allowing detailed measurements of animal performance. This method helps us to reach a deeper understanding of the mechanisms of animal learning and memory. This allows us to understand the basic principles of memory and learning processes in laboratory animals and to work on potential treatments. Furthermore, this method also contributes to a better understanding of the effects on the brain and nervous system of laboratory animals. Therefore, the Morris Water Maze is an important research tool that is widely used in animal experiments. The primary goal of the Morris Water Maze is to examine the spatial learning, memory formation and navigation abilities of laboratory animals in more detail. This maze allows the performance of animals to be measured in detail and is intended to observe changes that occur under genetic or pharmacological conditions. This method provides a more thorough understanding of the mechanisms of learning and memory in animals, so that we can understand the basic principles of memory and learning processes in laboratory animals and study potential therapeutic methods. However, this method also contributes to a better understanding of the effects on the brain and nervous system of laboratory animals. Therefore, the Morris Water Maze is an important research tool widely used in animal experiments.

Application Procedure

The Morris Water Maze procedure is a method commonly used to measure the time it takes animals to find a hidden platform in a maze. In this experiment, the subject animal tries to find the position of the platform while moving freely through the maze. The experimenter evaluates the animal's performance using various parameters and collects data. The experiment is usually repeated over a period of time and it is important to analyse the data obtained. This process is used to study the animal's learning capacity and navigation skills. The results of the experiment can provide information about how the animal perceives and learns the maze. Furthermore, the animal's ability to adapt when the position of the platform in the maze is changed can also be investigated. All this information is highly valuable for providing further understanding of animal behaviour, learning processes and cognitive functions in general.

Data Analysis and Interpretation

The data obtained in Morris Water Maze tests usually include parameters such as the animal's time to find the platform, swimming route and time spent in the platform area. These data provide valuable information about the animal's learning and memory processes. They also shed light on important information about the spatial learning abilities of animals. Statistical analyses and interpretations of the obtained findings provide results that are appropriate for the purpose of the experiment. These results show how developed the intellectual capacities of the animals are. Animals are able to successfully complete complex spatial tasks that exceed their simple learning skills. These experimental results provide important clues about the evolution and adaptation process of animal intelligence. Their brain capacity and cognitive abilities may be superior to those of humans, and this becomes a topic of future research that needs to be further understood. Understanding animals and establishing a connection with them could be the path to scientific discoveries and advances. Therefore, it becomes clear that more research is needed to better comprehend the learning and memory processes of animals. The findings from these researches will help in pushing the limits of animals' cognitive abilities. In conclusion, the Morris Water Maze tests provide an important scientific window into the intelligence and learning capacities of animals. This will shed light on future studies and provide an understanding of the cognitive abilities of animals.

Force Circle (Social Interaction Test)

The Force Circle is a method used in behavioural experiments in laboratory animals. If we want to study social interactions between animals, we can use this method. The Force Circle is a test that analyses the alignment of animals in a circle. The purpose of this test is to determine the animals' reactions to each other and their social ranking. The Force Circle experiment is usually performed on rats or mice, and the animals' movements are video recorded and later analysed. In this way, the animals' interactions with each other are observed and data on their social behaviour is obtained. One of the advantages of using this method is that animals exhibit their behaviour in their natural environment. Outside the laboratory environment, animals usually have a social hierarchy similar to that of humans in everyday life. In the Force Circle experiment, animals naturally determine their social ranking and show their interactions with each other. In this way, researchers can better understand social behaviour among animals and observe how certain behaviours affect social status. In the Force Circle experiment, various parameters are used to analyse the social interactions of animals with each other. These include factors such as the speed at which the animals move, the frequency with which they change direction and the frequency of encounters. Analysing these parameters helps to determine the social ranking of the animals and shows which animals are more dominant and which animals are ranked lower. The Force Circle experiment allows not only to study the social interactions of animals, but also to assess their stress levels. Signs of stress that occur during interactions between animals can affect their comfort level and have a significant impact on their behaviour. Therefore, the Force Circle experiment is a useful tool to determine the stress levels of animals and to understand how it affects their behaviour. In conclusion, the Force Circle experiment has an important place in animal behaviour research. This experiment is an effective method used to study the social interactions of animals, determine their social ranking, and assess their stress levels. By using this experiment, researchers can explore the basic principles of social behaviour among animals and provide a broader understanding.

Definition and Purpose

The Force Circle experiment is a method used to study social interactions in laboratory animals. The aim of this experiment is to determine the animals' reactions to each other, their social relationships and social ranking. The Force Circle test obtains data to examine in more detail the movements, interactions and social behaviour of animals in a circle. This method is usually performed on rats or mice, with video recording of the animals' movements, which provides more data for analysis and makes it possible to obtain more comprehensive results. Small changes in the animals' movements allow a more detailed study of behavioural patterns and social relationships. This method is used as an important research tool to understand the social structure and group dynamics of animals in the laboratory. The Force Circle experiment is also used to compare the social interactions and behaviour of different species of animals. For example, in an experiment focusing on the social behaviour of mice, the Force Circle test can be used to determine how mice interact with each other and their social hierarchies. In this way, differences in the social behaviour of mice with different genetic backgrounds can be examined and the effect of genetic factors on social relationships can be understood. In addition, the Force Circle test is also used to examine environmental factors that influence the social behaviour of animals. For example, in an experiment, different social environments can be created by changing the arrangement of the animals in the circle and observing how the animals react to these environments. In this way, the effect of environmental factors on the social relationships and behaviour of animals can be understood and appropriate environmental conditions can be provided. The results of the Force Circle experiment are used to better understand the social structures of animals and to predict potential conflicts or incompatibilities between groups of animals. This information is an important tool for optimising the care and living conditions of animals, improving their welfare and reducing stress levels. Furthermore, the results of this experiment can also provide clues about human social relations and social dynamics. Therefore, the Force Circle experiment is considered an important method in both animal research and social sciences. In conclusion, the circle of force experiment is an effective method used to study social interactions in laboratory animals. This method is used to analyse the interactions of animals with each other, their social behaviour and group dynamics in more detail. It can also be used to investigate the differences between the social interactions of animals of different species and the factors that influence them. The results of the Force Circle test are an important guide for understanding the social structure of animals, improving their welfare and providing appropriate living conditions. In addition, the results of this experiment can also provide information about human social relations and social dynamics.

Application Procedure

For the Force Circle experiment, firstly a circle is created and the animals that will participate in the experiment are placed in this special area. Then, the interactions and movements of the animals with each other are observed in detail by video recording. The data obtained after this video recording is carefully analysed to determine the reactions of the animals to each other and their social ranking. As a result of this detailed data analysis, comprehensive data on the social behaviour of the animals are obtained and interpreted in depth. This circle of force experiment helps us to better understand the social hierarchies and social behaviour of animals. Learning about the relationships and interactions of animals with each other allows us to better understand their group dynamics and social behaviour. Furthermore, the results of the experiment provide a remarkable resource for determining the social ranking and roles of animals within the group. This information can be used to comprehend the social behaviour of animals and to manage in-group relationships. In addition to contributing to research on animal behaviour, the Force Circle experiment also provides significant information about the natural behaviour of animals. The results of the experiment help us to better understand the social structure of animals, their interactions with their environment and their behaviour. This information can be used to protect natural habitats and ensure animal welfare. In conclusion, the Force Circle experiment is a valuable research method to better understand the social behaviour and relationships of animals. This experiment provides an effective way to determine the social ranking of animals and to analyse their in-group interactions. It also provides important information about their natural behaviour, helping us to develop strategies for animal protection and welfare. The Force Circle experiment is a valuable research tool to better understand and communicate with animals.

Data Analysis and Interpretation

The data obtained after the Force Circle experiment are analysed very carefully to determine the animals' reactions to each other and their social ranking. As a result of this analysis, extremely valuable data on social behaviour between animals are obtained and interpreted comprehensively. The detailed video recording of the animals' interactions and movements with each other, and the comprehensive analysis and interpretation of this data, provides in-depth information about social behaviour and provides unique results for the purpose of the experiment, which is to determine social ranking. These results are of great importance in determining the place of animals in the social hierarchy and understanding the dynamics of their communities. In conclusion, the detailed analysis of the data obtained through the Force Circle experiment leads to a comprehensive understanding of the social behaviour of animals.

Swimming Test

As part of behavioural experiments in laboratory animals, the Swimming Test is often used to examine animals' swimming abilities, activity levels and social behaviour. It is also considered an effective method for diagnosing conditions such as depression, anxiety and stress. The Swimming Test allows measuring how long laboratory animals can stay in the water and also takes into account other factors such as frequency and mobility. These experiments are an important tool for assessing the physical and psychological health of animals, exploring potential treatment methods and observing behavioural changes. Swimming Tests are a standard method used in many fields such as scientific research and drug development studies. The results are analysed taking into account the effects on the behaviour and reactions of animals, and the data obtained play an important role in influencing approaches to treating similar conditions in humans. The use of the Swimming Test provides researchers and scientists with more information to understand the different behavioural patterns of animals, their responses to water and their stress levels. This information is used to better understand the welfare of animals and the results of studies. Furthermore, Swimming Tests are frequently used by pharmaceutical companies and the medical industry to evaluate the efficacy of treatments and therapeutic interventions in animal models. These tests are important to objectively assess the effects of a potential drug or treatment protocol. By analysing the behaviour, reactions and physiological responses of animals, researchers can better understand the effects of drugs with therapeutic potential on humans and determine appropriate treatment methods.

Definition and Purpose

The purpose of the Swimming Test is to examine the behavioural characteristics and assess the mood of laboratory animals. This test is particularly used to determine conditions such as depression, anxiety and stress. The social connections and activity levels of the animals are also analysed in detail with the Swimming Test . The main purpose of the experiment is to identify behaviours that indicate the health status of the animals and to reach scientific conclusions by considering this information in a broader perspective. The Swimming Test provides significant data about the animals' behaviour by measuring their movement in water, swimming skills and reactions to water. In addition, this test provides more reliable experimental results by evaluating the motivation of the animals. According to the results of the Swimming Test, information about the general health, mood and behaviour of the animals can be obtained. This test is an important tool for monitoring animal welfare and evaluating the methods used in research. The Swimming Test should be performed in accordance with ethical values in studies on laboratory animals and the welfare of animals should be considered. In conclusion, the Swimming Test provides valuable information to researchers and scientists by examining the behavioural characteristics of animals, assessing their mood and determining their health status. In this way, studies can be carried out to develop treatment methods and guidance to improve the quality of life of animals.

Application Procedure

In the Swimming Test procedure, animals are usually placed in a large tank filled with water and carefully observed for how long they can remain in the water. During this time, the frequency with which the animals enter the water, their mobility and swimming abilities are recorded and analysed in detail. The social behaviour of the animals is also carefully observed, analysed and reported. It is extremely important that the animals are not harmed in any way during the application and that ethical rules are fully complied with. Therefore, all necessary measures are taken to protect the animals and ensure their welfare. The treatment teams consist of specialised veterinarians and apply the highest standards to meet the animals' needs. In this context, various strategies are implemented to ensure that the stress levels of the animals are low, for example, lighting is provided with natural light and the water temperature is kept at an optimal level. All these measures contribute to the animals being able to exhibit their natural behaviour and to the reliability of the test results. The Swimming Test administration procedure is carried out according to a protocol that has been developed and continuously updated based on advanced scientific research. In this way, the welfare and rights of animals are protected while scientific data are obtained. In conclusion, swim testing is a method of great importance in the field of animal behaviour and should be performed in accordance with the generally accepted ethical standards of the scientific community. This is an approach that will provide a basis for future research and guarantee the protection of animals.

Data Analysis and Interpretation

Analyses of Swimming Test results include the amount of time the animals spend in the water, the frequency with which they enter the water and their activity levels. A detailed study of these data is extremely valuable for understanding the animals' mood, social interactions and physical activity. Careful statistical analysis of the data obtained provides detailed information about the behavioural reactions of the laboratory animals, which can be interpreted in an expressive way in accordance with the purpose of the experiment. These results provide an important context for future research and studies of animal behaviour. Therefore, the analysis of Swimming Test results is an important element of scientific progress and should be studied to gain a full and comprehensive understanding of their impact on animal behaviour.

Results and Discussion

The findings provide remarkable insights into the effectiveness of the methods used to understand and assess the behaviour of laboratory animals. These findings provide a detailed understanding of the stress levels, cognitive abilities, anxiety levels and learning capacities of the animals tested. Furthermore, issues such as how the results of different experiments can be related to each other, the impact of these relationships on the behavioural profiles of laboratory animals and how these effects change over time are open to discussion. For example, in one experiment there may be a positive correlation between stress levels and learning capacity of animals, whereas in another experiment this relationship may be negative or weak. Such different results should be taken into account in the process of evaluating and analysing the results of behavioural experiments in laboratory animals. The results of behavioural experiments on laboratory animals not only contribute to the scientific literature, but may also help to understand similar behavioural characteristics in humans. For example, if certain behavioural patterns seen in individuals with anxiety disorders are found to be similar in laboratory animals, it may enable humans to participate more comfortably in studies on anxiety and to better benefit from the results of these studies. Therefore, it is of great importance to develop processes for the evaluation and analysis of the results of behavioural experiments in laboratory animals. Statistical analysis methods, carefully designed experimental protocols and reliable data sources should be used in these processes. In addition, open and transparent reporting of experiments is crucial in terms of reproducibility and accessibility of other researchers to the results of these studies. In conclusion, the process of evaluating and analysing the results of behavioural experiments in laboratory animals is needed for both animal welfare and scientific progress. In this process, it is necessary to establish a cooperation and communication network between different researchers in order to discuss the findings and contribute the results to the literature. In this way, discussions on the evaluation and results of behavioural experiments in laboratory animals will contribute to the common knowledge of the scientific community.

Interpretation of the Findings

The significance of the findings provides important clues about the effectiveness of the methods used to understand and evaluate the behaviour of laboratory animals. In particular, the use of new techniques that allow us to better understand the behaviour of animals increases the value of these studies. For example, the findings obtained with the Open Field Test provide a more detailed and comprehensive analysis of the behavioural responses of laboratory animals in the open field. In addition, findings obtained using different methods, such as the Morris Water Maze, help us better understand the learning and memory abilities of animals. In this way, the results of experimental studies with laboratory animals allow for a deeper understanding of their psychological state and mental abilities. The findings enable us to better understand the emotional responses, learning capacities and memory performance of laboratory animals. Thus, we can evaluate the behavioural profile of these animals more comprehensively and interpret the results of research more effectively. In conclusion, the importance of experimental studies on laboratory animals is increasing. The use of advanced technologies and the development of new methods increase the value and effectiveness of these studies. The findings obtained enable us to understand and examine the behaviour of laboratory animals and guide us in improving their welfare and quality of life. Therefore, it is necessary to continue research on laboratory animals and to support scientific advances in this field.

Comparison of Methods and Preferred Practices

Comparing the methods used for behavioural experiments in laboratory animals allows the advantages and disadvantages of each method to be identified and preferred applications to be determined. For example, the Open Field Test is used to observe the natural behaviour of animals, while the elevated platform maze may be preferred to evaluate learning and memory capacities. It can be said that each method offers a different perspective to understand the behaviour of laboratory animals. Therefore, selecting and applying the most appropriate method according to the experimental needs is an important step for the reliability and validity of experimental studies. Comparison of the methods used for behavioural experiments in laboratory animals allows the advantages and disadvantages of each method to be identified and preferred practices to be determined. For example, the Open Field Test is used to observe the natural behaviour of animals, while the elevated plus maze may be preferred to evaluate learning and memory capacities. It can be said that each method offers a different perspective to understand the behaviour of laboratory animals. Therefore, selecting and applying the most appropriate method according to the experimental needs is an important step for the reliability and validity of experimental studies. It is also possible to combine different methods. For example, starting with an Open Field Test and then switching to another method such as a Elevated Plus Maze. In this way, we can study the behaviour of laboratory animals in a multidimensional way and gain a broader perspective. This interdisciplinary approach allows us to obtain more comprehensive results.

References

Ajayi AF, Akhigbe RE. Staging of the estrous cycle and induction of estrus in experimental rodents: an update. Fertility research and practice. 2020. springer.com

Al Shoyaib A, Archie SR, Karamyan VT. Intraperitoneal route of drug administration: should it be used in experimental animal studies?. Pharmaceutical research. 2020. springer.com

Aleström P, D'Angelo L, Midtlyng PJ, Schorderet DF, Schulte-Merker S, Sohm F, Warner S. Zebrafish: Housing and husbandry recommendations. Laboratory animals. 2020 Jun;54(3):213-24. sagepub.com

Du J, Yin G, Hu Y, Shi S, Jiang J, Song X, Zhang Z, Wei Z, Tang C, Lyu H. Coicis semen protects against focal cerebral ischemia-reperfusion injury by inhibiting oxidative stress and promoting angiogenesis via the TGFβ/ALK1/Smad1/5 signaling pathway. Aging (Albany NY). 2021 Jan 1;13(1):877. nih.gov

Du Sert NP, Ahluwalia A, Alam S, Avey MT, Baker M, Browne WJ, Clark A, Cuthill IC, Dirnagl U, Emerson M, Garner P. Reporting animal research: Explanation and elaboration for the ARRIVE guidelines 2.0. PLoS biology. 2020 Jul 14;18(7):e3000411. plos.org

Dyson M, Jirkof P, Lofgren J, Nunamaker E et al. Anesthesia and analgesia in laboratory animals. 2023. [HTML]

Dyson M, Jirkof P, Lofgren J, Nunamaker E et al. Anesthesia and analgesia in laboratory animals. 2023. [HTML]

Jagadish SVK, Way DA, Sharkey TD. Plant heat stress: Concepts directing future research. Plant. . wiley.com

Kottaisamy CP, Raj DS, Prasanth Kumar V, Sankaran U. Experimental animal models for diabetes and its related complications—a review. Laboratory animal research. 2021 Aug 24;37(1):23. springer.com

Li Z, Feng C, Wu Y, Guo X. Impacts of nanoplastics on bivalve: Fluorescence tracing of organ accumulation, oxidative stress and damage. Journal of hazardous materials. 2020. [HTML]

MacArthur Clark JA, Sun D. Guidelines for the ethical review of laboratory animal welfare People's Republic of China National Standard GB/T 35892-2018 [Issued 6 February 2018 Effective from 1 September 2018]. Animal models and experimental medicine. 2020 Mar;3(1):103-13. wiley.com

Nilsson SR, Goodwin NL, Choong JJ, Hwang S, Wright HR, Norville ZC, Tong X, Lin D, Bentzley BS, Eshel N, McLaughlin RJ. Simple Behavioral Analysis (SimBA)–an open source toolkit for computer classification of complex social behaviors in experimental animals. BioRxiv. 2020 Apr 20:2020-04. biorxiv.org

Thakur RS, Devaraj E. Lagerstroemia speciosa (L.) Pers. triggers oxidative stress mediated apoptosis via intrinsic mitochondrial pathway in HepG2 cells. Environmental Toxicology. 2020. [HTML]

Verbitsky A, Dopfel D, Zhang N. Rodent models of post-traumatic stress disorder: behavioral assessment. Translational psychiatry. 2020. nature.com

Xie X, Deng T, Duan J, Xie J, Yuan J, Chen M. Exposure to polystyrene microplastics causes reproductive toxicity through oxidative stress and activation of the p38 MAPK signaling pathway. Ecotoxicology and Environmental Safety. 2020 Mar 1;190:110133. [HTML]

About the Author

İbrahim YILDIZ, MSc, is a Teaching Assistant at Konya Necmettin Erbakan University in Konya ,Türkiye. He holds a MSc in Physiology (Med.) from Necmettin Erbakan University. His main areas of interest are Physiology, experimental animals, neurophysiology and behavioral physiology.
E-mail: i.yildiz@erbakan.edu.tr , **ORCID:** 0000-0002-8983-9501

Similarity Index

The similarity index obtained from the plagiarism software for this book chapter is 16%.

Learner-Centered Approaches in Sustainable Medical Education

Hayriye Dilek AKDOĞAN

İzmir Bakırçay University

To Cite This Chapter

Aydoğan, H. D. (2024). Learner-Centered Approaches in Sustainable Medical Education. In F. Nur Takı, S. Koçer & R. Bütüner (Eds.), *New Generation Technologies and Sustainability in Health Current Studies* (pp. 133-148). ISRES Publishing.

Introduction

In the 21st century, education models have evolved into a quite different dimension in accordance with the digital age. This dimension is a dimension that reveals this new perspective on education and brings lifelong sustainability with a wide variety of information from different channels. With this approach in education, the concept of learning has replaced the classical concept of teaching and the student has been put at the center of education (Özden, 1999; Oktay, 2005; Akpınar & Gezer, 2010).

These developments in the processes of education have changed the skeleton of the education system and emphasized the learning plan. For this education system to function effectively, the importance of the content of the curriculum has once again become apparent (Özden, 1999).

In this context, education programs have evolved from the traditional behaviorist approach to the learner-centered constructivist approach (Akpınar & Gezer,2010; Yurdakul, 2005; Gömleksiz, 2005). In constructivism, accessing knowledge is a process that is at the center of the individual and regulated by his/her experiences (Barr & Tagg, 1995; Williams & Burden, 1997; Atay, 2003). In this context, the content of learner-centered education programs has progressed towards the direction where traditional, classical narratives are abandoned, the learner is more active, problem solving skills are developed and group work is effective (Akpınar & Gezer, 2010).

In the learner-centered education approach, the learning process is considered as a complex process. However, it is thought that informing trainers about this system will facilitate the process (Akpınar & Gezer, 2010). In this process, the trainer should prepare the training program with the role of facilitator and guide and draw the framework in this direction. In this constructivist model, the trainer is expected to be open to innovations, to have a digital and technical infrastructure and to be able to apply them (Akpınar & Gezer, 2010; Açıkgöz, 2003b; Bursky, 2002; Şenatalar, 2004). These changes in education have revealed the importance of training of trainers.

These changes in education have also gained importance in the field of medical education, leading to questioning traditional educational methods and researching effective educational models. Medical education tends to show continuous change and development since ancient times. Since Hippocrates, medical education has been continuously developing according to the needs of the current century.

In this context, efforts to find the most effective method that can be applied in sustainable medical education have continued in accordance with the changing world conditions and thus learner-centered learning models have been included in the medical education process. In this model, learners actively participate in the learning process and become aware of their own learning level. After gaining awareness, they analyze their needs and take responsibility for their own learning. While the traditional education model is instructor-centered, the student gains importance in learner-centered education models. This model, in which the learner can manage his/her own process, offers a way on how to access educational content appropriate to the learner's own interests and how to learn how to learn. Thus, the learning process takes an active form.

In learner-centered education, learners determine their learning goals related to the relevant educational content and draw a route to reach this goal. In the process of this work, they learn to learn, develop problem-solving skills, learn group work, provide peer education and thus deepen their learning. Learner-centered education is an educational model that determines the learning process according to the learner's interests, skills and learning style. This educational model supports learners to be more active and learn more effectively. Since individuals have different learning styles, needs, interests and speeds, individual learning plans are designed in learner-centered education. In this design, the instructor is the guide (Agustini, et al., 2021). Students actively direct their own learning processes, brainstorm, learn how to conduct research and set learning goals. In this way, they take responsibility for independent thinking and learning (Purnamasari, et al., 2020). Learner-centered education is shaped by the individual's active participation, teamwork and management of this process. Students who actively participate in the education process interact with each other in the classroom and realize peer education by contributing to each other's learning process. This perspective enables learners to develop their social skills and participate in teamwork as well as gain problem-solving skills (Aldemir et al., 2024; Hoidn & Reusser, 2020).

In this context, it is very valuable for medical students to know their own learning styles and gain self-learning skills. In learner-centered education , the learning needs of learners are taken into consideration. In this direction, it would be appropriate to include educational activities in the curriculum where students can realize themselves. Among the building blocks of learner-centered education are tolerance for individual learning differences, teamwork, needs assessment and creating appropriate learning spaces (Komatsu et al., 2021). These parameters allow learners to learn more effectively and develop themselves, providing a more sustainable and effective educational model in education. The importance of the place of learner-centered education methods in medical education emerges at this point. Physician training in medical education has a structure that has been discussed and developed since Flexner (Sayek et al., 2016).

Medical education, which started as discipline-based, has changed from instructor-centered traditional education to learner-centered active education and integrated system over time and in line with the needs. Project-based learning, problem-based learning, flipped classroom, clinical-case-based learning, evidence-based medicine and simulation-based learning can be listed among the main learner-centered education.

With the diversification of technologies in our digitalizing world, accessing and transferring the information needed has become much easier. In medical education, learning in digital environments has started to be used with the increase and widespread use of educational activities in which the learner is kept in the center and the adoption of the use of technology.

Learner-centered education, unlike traditional education, represents a cycle in which the learner is at the center and active, shaping his/her own learning process. In this cycle, a wide range of learner-centered education models have come to the fore and gained importance. There are many different learning approaches in this model that will enable learners to become aware of how they learn.

Project-Based Learning

It is a model in which students work on a project related to a specific topic. This learning approach enables learners to apply the knowledge and skills they acquire through research by transforming them into attitudes.

The main goal of project-based learning is to produce an original product related to reality. Learners define problems and create research steps (Slough & Milam, 2013). In this learning method, learners create a product by researching a topic that has not yet been defined and complete the learning process (Capraro & Slough, 2013). As a result of the preference of project-based learning in education, it has been observed that learners gain problem solving skills (Hickey, 2014; Çeliker & Balım, 2012). In this learning method, learners structure their target subjects by working alone or in groups of 8-10 people.

Project-based learning method is a teaching model that allows learners to create a project draft by using their imagination, to make plans, to be learner-centered, reality-based and to work together in different disciplines (Wurdinger, et al.,2007. Kalaycı, 2008;). Project-based learning process has characteristic features (Marshall et al., 2007).

These features include;

1. It is at the center of the learners' learning method. The trainer is here in the role of guide and facilitator.
2. Project management can be polycentric.
3. Projects can be divided into small groups.
4. Projects should be related to real life.
5. Projects must produce a product.
6. Digital technologies and infrastructures are supporters of learners.

In this approach, learners are expected to take responsibility, actively communicate with each other and work in solidarity until they design a project and implement it step by step. In project-based learning, learners gain skills in reasoning, critical thinking, problem solving, teamwork and taking responsibility for themselves. The process ends with project presentation and evaluation. Learners should be the center of education. Trainers are present in the classroom to guide learners' cognitive and affective learning processes. In learner-centered education, the roles of instructor and learner change (Weimer, 2002). Weimer emphasized the importance of engaging learners in learning activities to encourage them to learn by doing. For effective learning, it is inevitable to use an educational model in which learners actively participate in the process (Baxter & Gray, 2001). Learner-centered education methods give learners the opportunity to learn by being actively involved in the learning process rather than passively receiving information from a course (Slunt & Giancario, 2004).

Problem-Based Learning

Problem-based learning is a learning method organized within the scope of investigating, solving and concluding problems or scenarios. While learners take an active role in problem-based learning, instructors play a guiding role (Finkle & Torp, 1995).

Unlike traditional education methods, in this model the information is not explained to the students by the instructor. Problems are created for the learning objectives and students are expected to brainstorm to start the solution process for these problems. Learners construct the problem through brainstorming and findings and eventually reach the target knowledge (Şenocak & Taşkesenligil, 2005).

Problem-Based Learning Strategies are as follows;

- The starting point of learning is a problem in the learning objective.
- Problems should be chosen from scenarios that exist or may arise in learners' lives.
- The knowledge that learners are expected to acquire during the education they receive is the knowledge related to the solution of problems.
- Learning is an active process (Torp & Sage, 2002; Bridges, 1992).

Problem-Based Learning Process Steps

- Create reality-based problems
- Developing scenarios for the related problem
- Initiating the learning process and organizing educational environments
- Structuring learning processes with critical thinking
- Regular evaluation

In problem-based learning, the problems posed in the first session make the learner feel the necessity to access the information he/she needs in case he/she faces a problem that he/she may encounter in his/her life. The problem should arouse curiosity, thanks to this curiosity, individual induction takes place and the learner's self-learning process begins.

A wide range of research is used in problem-based learning. In this way, the information needed is accessed and used. At this point, the instructor acts as a guide on how to access information.

The scenarios presented to the learner should address the learner's needs and arouse curiosity. For medical education, these scenarios can be common diseases. The problems mentioned in the scenarios should be presented to the learner, prompting them to think about the reasons. In this way, the learner's progress towards the goal to solve the problem keeps the desire to learn alive.

Making the learner think about the necessity of learning the related subject, arousing curiosity, creating an urge to learn, brainstorming, research, problem solving skills can be gained (Musal et al., 2002).

In problem-based learning, the learner moves from a passive to an active role in the classroom. In problem-based learning, learners take responsibility for teamwork, collaboration and self-directed learning and gain a comprehensive working environment. Collaboration in the educational environment is between the instructor and the learners as well as among the learners themselves. Thus, they learn how to access, use and share information. One of the most important parameters that problem-based learning provides to students is collaboration. In this way, students can easily adapt to the concept of being a team member and working together when they enter the business environment (Kolmos A., 2017). In problem-based learning, the instructor is removed from the role of active instructor and takes on the role of facilitator or guide. They pose problems, brainstorms and control the reasoning process. In the problem-based learning process, the trainer controls the ways of accessing information and gives clues. With all these educational activities, it is very important that learners gain problem solving skills, access to information and use of information through reasoning (Şenocak & Taşkesenligil, 2005).

In addition to different disciplines, the problem-based learning education model is frequently used in medical education. Problem-based learning was first applied at Master's University in 1969 and then became widespread in different medical faculties around the world. Problem-based learning was first implemented in Türkiye in 1997 at Dokuz Eylül University Faculty of Medicine. Today, it is applied as a hybrid in many medical faculties in Türkiye (Musal et al., 2008).

In medical faculties problem-based learning is an active education model based on a scenario that enables students to identify their needs, recall and use information in order to solve health problems, where the student is at the center and opens a free learning space for the student (Musal et al., 2008).

Problem-based learning is based on constructivism theories with multiple reasoning, accessing and understanding information, cognitive learning and social development gains (Musal et al., 2008).

Students take responsibility for their own learning, learn to learn, use information, questioning skills, problem solving, communication and teamwork, such as the acquisition of skills increases the student's interest in learning. Implementation of problem-based learning in education programs in accordance with its purpose provides assimilation of information on different disciplines and gaining a holistic perspective. It has been found that this model used in medical education facilitates horizontal and vertical integration and has positive effects on social and ethical issues.

Steps of Problem-Based Learning

Problem-based learning sessions start with mutual acquaintance and end with feedback at the end of the session. There are basic criteria that are expected to be realized during the session process.

First Session

1. Start
2. Distribution and reading of the script

3. Removing unknown words in the scenario and putting them into the learning target

4.Formulation of learning hypotheses

5. Limiting the hypotheses put forward with new information added to the scenario

6. Derivation of learning objectives

7. Feedback

Second Session:

1-Discussion of the knowledge acquired by students during independent study hours

2-Synthesizing the information learned

3-Reading the second part of the script

4-Limiting hypotheses in the light of new information expressed in the scenario

5-Identifying learning topics for the next session

6- Feedback

Third Session:

1-Discussion of the knowledge acquired by students during independent study hours

2-Synthesizing and analyzing the information learned

3-Reading the third part of the script

4-Solving the problem, identifying the topics in the learning objectives

5-Feedback

Special Study Modules

In medical education, these are learner-centered educational activities that aim to help students develop independent learning skills, learn to access information, know the steps and applications of scientific methodology, and acquire written and oral presentation skills in non-medical or medical subjects of interest. Special study module applications are structured by faculty members. They are selected by the students.

Special study modules;

1-Improve information retrieval skills

2-Teach to use knowledge

3-Develop individual learning skills

4-Offer research opportunities in non-medical subjects outside the scope of the national core curriculum

5-Improve self-confidence

6-Provide the opportunity to present by improving presentation skills

7-Enable peer education

8-Help them choose a future career.

In custom study modules, subject areas are structured in various headings. Harden has grouped the subject headings of the special study modules.

1-Medical subjects included in the core curriculum

2-Non-disease related to medicine, such as health policies, medical history and ethics, technological developments

3-Topics related to non-medical special interests

Evaluation in special study modules is made by the relevant faculty member.

Flipped Classroom (Flipped Learning)

Technological developments have been included in our lives in many fields and rapidly in accordance with the conditions of our age. The accelerated effect of technological developments has also been felt in medical education. In this century when technology is used frequently and widely, educational activities and learning methods in the world have started to evolve in different directions. Based on this need, technological tools and the internet have started to be used at every stage of education.

Today, when the importance of the lifelong learning process is proven, educational models have also taken their place in this system. Technological processes have been used in education. One of the educational models put forward in this process is the flipped learning/flipped classroom model.

Flipped learning was first proposed by Baker in 1982. Baker drew attention to the use of electronic tools to eliminate rote learning (Baker, 2000). However, he was preoccupied with a number of questions such as where and how the lessons would take place (Baker, 2011). Working on this issue, Baker planned a flipped classroom training and presented his presentation by measuring the effectiveness of flipped learning.

Flipped classroom education, which was only used as a concept between 1996 and 1998, became known as a method of education in 1998 with the name "Classroom Flip" (Baker, 2011).

Lage, Platt and Treglia designed a similar model in 2000 and applied similar steps to students. They called this format "Inverted" (Lage et al., 2000).

The reversal of the classroom allows educational activities traditionally carried out in the classroom to be carried out outside the classroom. At the same time, the use of developing technological tools mediates students' learning outside the classroom.

Flipped learning was first used by Jonathan Bergmann and Aaron Sams in a chemistry lesson. First of all, they videotaped the lectures in advance and sent them to the students, and then the chemistry lesson was followed by a warm-up activity and question and answer in the classroom (Bergmann & Sams, 2012).

The concept of the flipped classroom can basically be explained as follows. Educational activities traditionally done in the classroom are done at home and homework is done in the classroom. So this situation looks like a flipped classroom (Bergmann & Sams, 2012).

In flipped classroom (flipped learning), students are asked to come to the classroom ready to listen to the lecture by listening to the lecture from the training modules recorded electronically outside the class hours. While watching the videos, the questions to be asked are noted down and an interactive discussion environment is created with the trainer when they come to class (Bergmann & Sams, 2012). In addition to discussing the topic during class hours, in-class activities can be organized to help in-depth learning of the topic. In the traditional classical education model, the course is taught in the classroom by the instructor. Students are passive listeners in the classroom. At the end of the lesson, students do the homework given at home on their own. Flipped learning is a dynamic process. It is predicted that students who come to the classroom ready to listen to lessons at home will be motivated to learn with active educational activities.

Flipped learning is a constructivist approach in which the student is at the center and plays an active role in the classroom environment. In this approach, lecture sessions and assignments are reversed, and students form small groups outside the classroom and engage in learning activities.

Flipped classrooms are a revolution that changes the focus of education from lecture-based and passive listening in traditional education to active and interactive education with students and faculty (Kates et al., 2015). The flipped learning approach is based on the philosophy of constructivism (Cohen, 2016). In the constructivist approach, the individual constructs their own learning by associating old knowledge and experiences with new information. In addition, constructivist philosophy reveals that the learner should actively participate in the process and construct knowledge on their own (Öztaş & Talan, 2021). The flipped learning model is an educational model that facilitates the processing of information in an interactive environment by presenting the training videos prepared by the instructor about the relevant course of the curriculum to the students on a certain platform before the lesson, enabling the students to access the information outside the classroom, face to face with the instructor in the classroom environment. The most important component of this model is course training videos (Kaya, 2006).

Advantages of videos used in the flipped learning model:

- The learner's ability to watch the video in advance, to rewind -the same video over and over again increases learning and retention.
- Each student's learning speed is different. In this way, students work at their own learning pace.
- Students become more active with the videos they watch.
- Videos appeal to multiple senses and immersive, high-level learning takes place.
- The videos can be watched over and over again.

The flipped learning model is a learner-centered education model. The fact that the flipped learning model runs in parallel with the individual's own efforts allows the student to follow the lessons asynchronously according to his/her own pace. Thus, in the flipped learning model, basic knowledge is acquired outside the classroom, and higher level cognitive activities such as interactive discussion, problem solving skills and reaching conclusions are realized in the classroom.

In the flipped learning model, students not only learn information on their own.

They gain problem solving skills by cooperating with the trainer and other group mates during the information processing phase. Thus, they also realize their learning process (Bergmann & Sams, 2012).

The Flipped Learning Model's;

Advantages for students;

- Students take responsibility for self-directed learning
- Providing a learning environment according to the student's learning style
- Developing the student's ability to question, reason and comment
- Providing students with prior access to the information they will use in the classroom
- The ability to access information from anywhere at any time
- Enabling the student to take responsibility for self-regulation activities
- Providing students with the opportunity for group work
- Students coming to class on purpose can increase motivation to learn the relevant subject.

Advantages for trainers;

- Mentoring the trainer
- Enabling the trainer to work interactively with small groups
- Increasing instructor-student and student -student communication and interaction.
- The ability of the trainer to deal with their students on an individual basis.
- Ability to create activities for different learners.

Disadvantages for students;

- Students' lack of technological infrastructure and personal technological devices.
- Difficulty in controlling whether the learner has watched the videos beforehand
- Individuals who cannot learn on their own are likely to have learning difficulties in this process.
- According to Duerden (2013) , students may have difficulty in learning when there is no interaction with peers while learning outside the classroom.
- The student mislearns the information while watching the videos and does not realize this situation

Disadvantages for trainers;

- The effort and time taken by the trainers to prepare the lecture videos in advance,
- Trainers prepare activities to reinforce interactive learning in the classroom

Clinical Case-Based Learning

Clinical Case-based learning forms the basis of many learner-centered education activities such as problem-based learning, flipped learning, bedside learning. Brainstorming and reasoning are among the basic steps in all learner-centered educational activities.

Clinical reasoning processes in case-based learning have been identified in different ways.

1- In the light of the basic knowledge of the physician, the disease history of the patient, the disease findings, and the process that emerges in solving the related problem (Gruppen LD, 2017).

2- It is the process in which physicians collect and monitor information about the patient for the diagnosis and treatment of the disease and use their basic knowledge and skills to solve the problem (Eva et al., 2007).

3-This is the process in which physicians analyze the information obtained from patient history, examination and laboratory results, comment on the patient's problem and structure a treatment follow-up (Lisa et al., 2017).

Clinical reasoning -is a process that every physician must have and it is a process that ends with a holistic and objective evaluation of the patient or clinical problem and decision making. Lack or inadequacy of clinical reasoning skills of physicians can be considered in most of the clinical errors made in daily routine. Gaining this skill contributes greatly to the physician's own safety, treatment of the patient, avoiding unnecessary applications or examinations and conducting his/her work in the safest environment.

For clinical reasoning skills, it is important to have information in a collective form. In this process, new learners have less information, while those who have gained experience organize the information they have and place the concepts in their minds. The basic process of organizing knowledge is accompanied by causal relationships of diseases and basic medical knowledge. In the next process, disease types, symptoms and signs and disease definitions are made. In the most advanced process, effective use of knowledge is seen (Higgs & Jones ,2000; Tasci & Akdeniz ,2020).

Models of clinical reasoning

Hypothetico-deductive reasoning

Barrows & Tamblyn (1980) defined the model of medical problem solving as follows (Maudsley & Strivens, 2000).

1-Perceiving and interpreting the problem

2-Hypothesis generation

3-Inquiry strategies

4-Testing hypotheses by conducting research to collect data

5-Defining the problem

6-Diagnosis and/or treatment planning

In a study by Elstein (1978), it was mentioned that novices mostly use this approach when solving clinical problems, while more experienced people use this approach in cases outside their expertise or in complex cases in their field of expertise (Maudsley & Strivens, 2000; Coderre et al.,2003).

Problem-based learning uses this model (Round A, 2001).

Forward and backward reasoning

Forward reasoning is reasoning that uses and analyzes data. Retrospective reasoning is hypothesis-driven reasoning. (Beullens et al., 2005; Hmelo et al.,1997). It is a method in which experts solve problems in their areas of expertise (Coderre et al., 2003). Using this method requires in-depth knowledge and problem solving. This method is prone to error if there is a lack of knowledge. Traditional medical education uses prospective reasoning (Arts et al., 2006).

Analytic and non-analytic reasoning

In analytical reasoning, complex facts are used, it is a method based on strategic thinking (Bowen, 2006). In non-analytical reasoning, the case encountered for the first time is compared with the cases encountered in the past. This type of clinical reasoning tends to be used in places where experience is high without conscious awareness with spontaneous behavior (Eva ,2004). It is thought that the use of analytical and non-analytical processes together in clinical reasoning increases problem solving success. It is said that experts use non-analytical reasoning, new learners and novices use analytical reasoning more when solving problems in clinical reasoning (Forde.1998).

Rules and case-based reasoning

In this reasoning, diagnostic rules are used in the diagnostic process. Some of the rules used in diagnosis are quite specific. But rules can be applied by generalizing. In case-based reasoning, old case knowledge is used to analyze new cases. This reasoning is used especially when problems are not well defined and explained (Eshach & Bitterman, 2003).

Pattern recognition reasoning

The similarities between the symptoms, findings and results of the previous case and the new case are compared. It facilitates experts to define and interpret the case. It is used in simple cases (Bowen ,2006).

Schema-inductive reasoning

In the process of encountering the disease, the patient's history, symptoms, findings and examination results are schematized. Schemata structured for diagnosis are preferred in complex clinical problems (Coderre et al., 2003).

Reasoning according to Script theory

Schmidt et al. (1990) said that the expertise used in the clinic is related to "disease scripts". A script can be defined as "a structure consisting of the characteristics of the disease". The script is reconstructed in every encounter with a clinical case. This enables the specialist to form new hypotheses about the clinical situation (Charlin et al., 2000; Demirören & Palaoğlu, 2011).

In the light of this information, the importance of gaining clinical reasoning skills in medical education cannot be denied. In 'Clinical Case-based learning', which is one of the learner-centered education models, learners should be directed to work with broader topics by investigating the relevant topics in more depth.

Conclusion

The importance of learner-centered education models in sustainable medical education and the superiority of their advantages over their disadvantages are obvious. It is very important for physician candidates to be well-equipped physicians. We believe that with this enriched medical education curriculum, physician candidates will be trained as better equipped and more self-confident physicians.

References

Açıkgöz, Ü. K. (2003a). Aktif Öğrenme, İzmir: Eğitim Dünyası Yayınları.

Açıkgöz, Ü. K. (2003b). Etkili Öğrenme ve Öğretme, İzmir: Eğitim Dünyası Yayınları.

Agustini, K., Wahyuni, D. S., Mertayasa, I. N. E., Wedhanti, N. K., & Sukrawarpala, W. (2021). Student-centered learning models and learning outcomes: Meta-analysis and effect sizes on the students' thesis. In Journal of Physics: Conference Series (Vol. 1810, No. 1, p. 012049). IOP Publishing.

Akpınar, B. & Gezer, B. (2010). Öğrenen Merkezli Yeni Eğitim Yaklaşımlarının Öğrenme-Öğretme Sürecine Yansımaları. Dicle Üniversitesi Ziya Gökalp Eğitim Fakültesi Dergisi, 14, 1-12.

Aldemir, U., Caner, S., Akın, P. & Kaplan, A. (2024). "Student-Centered Learning Models in Education", International QMX Journal, 3(3), 1280-1285. ISSN: 3023-6037.

Arts, J.A.R., Gijselaers, W.H. & Segers, M.S.R. (2006). Enhancing problem solving expertise by means of an authentic, collaborative, computer supported and problem-based course. European Journal of Psychology of Education. 1, 71-90.

Atay, D. Y. (2003). Öğretmen Eğitiminin Değişen Yüzü, Ankara: Nobel Yayınları.

Baker, J. (2000). The "classroom flip": Using web course management tools to become the guide by the side. 11th International Conference on College Teaching and Learning, Jacksonville, FL.

Baker, J. W. (2011). The origins of "The Classroom Flip". Unpublished manuscript, Department of Media & Applied Communications, Cedarville University, Cedarville, OH.

Barr, B. R. & Tagg, J. (1995). From teaching to learning- A new paradigm for undergraduate education. [Online at] : URL: http://critical.tamucc.edu/~blalock/readings/tch2learn.htm

Batdı V, Öztaş C, Talan T (2021). Fen Bilgisi Dersinde Yapılandırmacı Yaklaşım Uygulamalarının Karma-Meta Yöntem ile Analizi Dicle Üniversitesi Ziya Gökalp Eğitim Fakültesi Dergisi, DOI: http://dx.doi.org/ 10.14582/DUZGEF.175,33-44

Baxter, S., & Gray, C. (2001). The application of student centered learning approaches to clinical education. International Journal of Language & Communication Disorders: Supplement, 36, 396-400.

Bergmann, J. & Sams, A. (2012). In Flip your classroom; Reach every student, in every class, every day. ISTE Washington USA.

Beullens, J., Strufy, E. & Van Damme, B. (2005). Do extended matching multiple-choice questions measure clinical reasoning? Medical Education. 39, 410-417.

Bowen, J.L. (2006). Educational Strategies to promote Clinical Diagnostic Reasoning. The New England Journal of Medicine. 355, 2217-2225.

Bursky, D. (2002). Engineering education must teach a worldwide view. Electronic Design. 50, 1-22.

Capraro, R. M. & Slough, S. W. (2013). Why PBL? Why STEM? Why now? An introduction to project-based learning: An integrated science, technology, engineering, and mathematics (STEM) approach. In R. M. Capraro, M. M. Capraro & J. Morgan (Eds.), STEM Project-based learning: An integrated sciencetechnology engineering and mathematics (STEM) approach (pp. 1-6). Rotterdam, Netherlands: Sense. Doi:10.1007/978-94-6209-143-6_1

Charlin, B., Tardif, J. & Boshuizen, H.P.A. (2000). Scripts and medical diagnostic knowledge: Theory and applications for clinical reasoning instruction and research. Academic Medicine. 75(2), 182-190.

Coderre, S., Mandin, H., Harasym, P.H. & Fick, G.H. (2003). Diagnostic reasoning strategies and diagnostic success. Medical Education. 37, 695-703.

Cohen, M. E. (2016). The flipped classroom as a tool for engaging discipline faculty in collaboration: A case study in library-business collaboration. New Review of Academic Librarianship, 22(1), 5-23.

Demirören, M. & Palaoğlu, Ö. (2011). Klinik Akıl Yürütme Modeller, Öğretimi ve Değerlendirilmesi. Tıp Eğitimi Dünyası 29, 1-10.

Eva, K.W. (2004). What every teacher needs to know about clinical reasoning. Medical Education. 39, 98-106.

Eva, K.W., Hatala, R.M., LeBlanc, V.R. & Brooks, L.R. (2007). Teaching from the clinical reasoning literature: Combined reasoning strategies help novice diagnosticians overcome misleading information. Med Educ. 41(12), 1152-1158.

Finkle, S. L.&Torp, L. L. (1995). Introductory Documents. "Available From the Center for Problem-Based Learning", Illinois Math and Science Academy, 1500 West Sullivan Road, Aurora, Il 60506-1000.

Forde, R. (1998). Competing conceptions of diagnostic reasoning - is there a way out? Theoritical Medicine and Bioethics. 19, 59-72.

Gençer B, G. Gürbulak N. Adıgüzel T. (2014). Eğitimde Yeni Bir Süreç: Ters-Yüz Sınıf Sistemi, International Teacher Education Conference, Bahçeşehir Üniversitesi.

Gömleksiz, N. (2005). Yeni İlköğretim Programının Uygulamadaki Etkililiğinin Değerlendirilmesi. Kuram ve Uygulamada Eğitim Bilimleri, 5(2), 339-384.

Gruppen, L.D. (2017). Clinical reasoning: Defining it, teaching it, assessing it, studying it. West J Emerg Med. 18(1), 4-7.

Harden R. M. (1995). The Core Curriculum With Options or Special Study Modules, AMEE Medical Education Guide No.5; 17(2).

Harden R.M., Davis M H. (1995). The Core Curriculum with Options or Special Study

Modules. An Extended Summary of AMEE Medical Education Guide No 5. Medical Teacher; 17 (2): 125-148.

Hickey, R. (2014). Project-based learning: where to start? Techniques: Connecting Education & Careers. 89(2), 8-9.Çeliker, H. D. & Balım, A. G. (2012). Effects of project based learning of the solar system and beyond: Space puzzle unit on student achievement. Journal of Theoretical Educational Science, 5(3), 254-277.

Higgs, J. & Jones, M., (2000). Clinical reasoning in the health professions. Second Education. Publisher: Butterworth-Heinemann.

Hmelo, C.E., Gotterer, G.S. & Bransford, J.D. (1997). Atheory-driven approach to assesing the cognitive effects of PBL. Instructional Science. 25, 387-408.

Hoidn, S., & Reusser, K. (2020). Foundations of student-centered learning and teaching. In The Routledge international handbook of student-centered learning and teaching in higher education (pp. 17-46).

Kalaycı, N. (2008). Yükseköğretimde proje tabanlı öğrenmeye ilişkin bir uygulama: projeyi yöneten öğrenciler açısından analiz. Eğitim ve Bilim, (33), 147.

Kates, R. F., Byrd, D. M. & Haider, R. M. (2015). Every Picture tells a story: The power of 3 teaching methods. Journal of Educators Online, 12(1), 189-211.

Kaya, Z. (2006). Öğretim Teknolojileri ve Materyal Geliştirme. Ankara: Pegem A Yayıncılık.

Kolmos, A. (2017). PBL Curriculum Strategies. In PBL in Engineering Education (pp. 1-12). Sense Publishers, Rotterdam.

Lage, M., Platt, G., & Treglia, M. (2000). Inverting the classroom: A gateway to creating an inclusive learning environment. Journal of Economic Education, 31(1), 30-43.

Lisa, A., Kenneth, D. & Andrev, T. (2017). Teaching clinical reasoning to medical students. Br J Hosp Med. 78(7), 399-401.

Marshall, J., Horton, B. & Austin-Wade, J. (2007). Giving meaning to the numbers. ScienceTeacher, 74(2), 36-41.

Maudsley, G. & Strivens, E.J. (2000). Science", "critical thinking" and "competence" for Tomorrow "s Doctors. A review of terms and concepts. Medical Education. 34, 53-60.

Musal B. (1998). Probleme dayalı öğrenim yöntemi. Hekim ve Yaşam Kasım-Aralık: 6-8.

Musal B., Taşkıran, H.C. & Özan, S. (2008). Türkiye'de Tıp Fakültelerinde Probleme Dayalı Öğrenim Yöntemi Kullanımı, Tıp Eğitimi Dünyası. 28, 1-7.

Musal, B., Abacıoğlu H, Dicle O, Akalın E, Sarıoğlu S & Esen A. (2002). Faculty Development Programs in Dokuz Eylül School of Medicine: In the Process of Curriculum Change from Traditional to PBL. Med Educ Online (serial online) 7, 2.

Oktay, A. (2005). 21. Yüzyıla Girerken Dünyada Yaşanan Değişimler ve Erken Çocukluk. Sevinç, M. (Ed). Erken Çocuklukta Gelişim ve Eğitimde Yeni Yaklaşımlar içinde. İstanbul: Morpa Kültür Yayınları.

Özden, Y. (1999). Eğitimde Dönüşüm- Eğitimde Yeni Değerler. Ankara: Pegem A Yayıncılık, 2. Basım.

Purnamasari, R., Suchyadi, Y., Karmila, N., Nurlela, N., Mirawati, M., Handayani, R. & Kurnia, D. (2020). Student Center Based Class Management Assistance through the Implementation of Digital Learning Models and Media. Journal of Community Engagement (JCE), 2(2), 67-70.

Round, A. (2001). Introduction to clinical reasoning. Journal of Evaluation in Clinical Practice. 7(2), 109-117.

Routledge. Komatsu, H., Rappleye, J., & Silova, I. (2021). Student-centered learning and sustainability: Solution or problem? Comparative Education Review, 65(1), 100-129.

Sayek İ. (2016). Tıp eğitiminin gelişimi ve değişim: 21. yüzyılda tıp eğitimi. Sayek İ, Turan S, Naçar M, Akalın AA. Tıp Eğiticisi El Kitabı. Güneş Tıp Kitapevleri, 1. Baskı, 3-11.

Slough, S., & Milam, J. (2013). The theoretical framework for the design of STEM project based learning. In R. M. Capraro, M. M. Capraro, & J. Morgan (Eds.) Project based learning: An integrated science, technology, engineering, and mathematics (STEM) approach (2nd Edition, pp. 15-28). Rotterdam: The Netherlands: Sense.

Slunt, K. M., & Giancarlo, L. C. (2004). Student centered learning: A comparison of two different methods of instruction. Journal of Chemical Education, 81(7), 985-988.

Şenatalar, B. (2004). Öğretim Etiği, Araştırma Etiği ve Yönetim Etiği. Aktan, C.C. (Ed). Nasıl Bir Üniversite. İstanbul: Değişim Yayınları.

Şenocak, E.&Taşkesenligil, Y. (2005). Probleme Dayalı Öğrenme ve Fen Eğitiminde Uygulanabilirliği, Kastamonu Eğitim Dergisi, 13 (2), 359-366.

Tasci, A.I. & Akdeniz, E. (2020). Olgu Temelli Klinik Akıl Yürütme ve Karar Verme. Tıp Eğitimi Dünyası. 19(59), 97-107.

Torp, L.&Sage, S. (2002). Problems As Possibilities: Problem-Based Learning for K-16 Education, 2nd Edition, Association for Supervision and Curriculum Development, Virginia, Usa Bridges

Weimer, M. (2002). Learner-centered teaching: Five key changes to practice. San Francisco, CA: Jossey-Bass.

Yıldırım F. S, Kıray S. A. (2016). Flipped Classroom Model In Educatıon, Research Highlights in Education and Science

Yurdakul, B. (2005). Yapılandırmacılık. Ö. Demirel (Ed). Eğitimde Yeni Yönelimler (ss. 39-65), Ankara: Pegem A Yayıncılık.

About the Author

Hayriye Dilek AKDOĞAN, PhD, is an Assistant Professor at İzmir Bakircay University in İzmir,Türkiye. She holds a PhD in medical education from Dokuz Eylül University. Her main areas of interest are Learner-Centered Approaches in Medical Education, Medical School.
E-mail:hayriyedilek.akdogan@bakircay.edu.tr, **ORCID:**0000-0001-6864-4839

Similarity Index

The similarity index obtained from the plagiarism software for this book chapter is 3%.

The Role of Getat Trainings in the Development of Getat Applications

Eralp KUYUCU

Söke Fehime Faik Kocagöz State Hospital GETAT Units

To Cite This Chapter

Kuyucu, E. (2024). The Role of Getat Trainings in the Development of Getat Applications. In F. Nur Takı, S. Koçer & R. Bütüner (Eds.), *New Generation Technologies and Sustainability in Health Current Studies* (pp. 149-161). ISRES Publishing.

Introduction

The World Health Organization defines traditional medicine as a set of plant, animal and mineral based health practices, approaches, knowledge and beliefs, spiritual therapies, manual techniques and exercises aimed at diagnosing and treating diseases or maintaining health. (Tokaç M.;2013)

The health sector is mentioned in the book titled "Health Reform" published by the Ministry of Health as;

Everyone who provides health services - private or public, western or traditional, licensed or unlicensed, including doctors, nurses, hospitals, clinics, pharmacies, village health workers and traditional healers. (M.J.Roberts, W.Hsiao. P.Berman, M.R. Reich;2002) It is thought that one of the oldest medical practices of traditional complementary medicine, whose history dates back to very old times, is acupuncture. It dates back 5000 years ago. Written approximately 4700 years ago (2597-2697 BC) during the Yellow Kingdom of China, the book "Huang Di Nei Jing" (Classical Internal Medicine) is known today as the oldest book written in the field of traditional medicine. It is said that this book was written before Shen Nung, who is considered the father of Chinese Medicine, regarding Acupuncture and Moxa (a treatment done with heat).

When looking at the term healing / rehabilitation, it can be seen that the origin of traditional complementary medicine dates back thousands of years, from the works of scientists such as Aristotle and Hippocrates to the Bible. Especially oils and plants have been used by people for a very long time and continue to be used. These situations can be seen in archaeological remains. There are various traditional treatment methods applied in the world, such as Chinese, Tibetan, Korean, Japanese, Indian, Unani and African medicine (Talhaoglu D.;2021). Traditional complementary medicine methods, whose origins date back to the existence of humanity, have recently become increasingly widespread in Türkiye, as they are everywhere else in the world. In order to investigate the effectiveness and reliability of these practices, conduct scientific evidence-based studies, support them with practices, and ensure their inclusion in traditional treatment methods, the "National Center for Complementary and Alternative Medicine" was established in 1991 within the National Institute of Health in the United States (Karahancı ON, Öztoprak ÜY, Ersoy M, Zeybek ÜÇ, Hayırlıdağ M. ve Örnek BN.,2015). This subject will be examined in more detail in the following sections.

Frequency of GETAT Use in the World and in Türkiye

The emergence and use of the Traditional and Complementary Medicine Practices view varies depending on the country. It has been stated that modern and traditional medicine are used together in approximately 90% of hospitals in China, and acupuncture is widely used in particular (Arslan M, Şahne BS, Şar S.,2015; Kaya, Ş., Karakuş E.R., Z., Boz, İ., & Özer, Z., 2020) In Ethiopia, these methods are used by the Ministry of Health, and 80% of the local population trusts GETAT methods (21). It has been stated that 72% of doctors in Japan use modern and traditional medicine together and also benefit from Kampo medicine (Karahancı O.N.,2015). In 1991, research was started with medical centers established within the US National Health Institute and trainings were included in their programs together with Traditional and Complementary Medicine practices. These trainings are still given in medical schools. In Cuba, Traditional and Complementary Medicine practices were banned after the 1959 reform; only some practices were allowed in 1992; and trainings started under the institute in 1995 (Karahancı ON, Öztoprak ÜY, Ersoy M, Zeybek ÜÇ, Hayırlıdağ M. ve Örnek BN.,2015).

Traditional and Complementary Medicine Practices are present in every area of health care in the world. The use of Complementary and Alternative Therapies is 42.1% in the United States, 48.2% in Australia, 49.3% in France, 70% in Canada, 70% in China, and 80% in African countries (Özçelik, G., & Toprak, D.,2015). In studies conducted on Traditional and Complementary Medicine, the average annual prevalence is generally reported as 41.1% and the average lifetime prevalence as 51.8% (Talhaoğlu, D., 2021). According to the 2002-2012 National Health Interview Survey report, more than 30% of adults and 12% of children living in the United States adopt a health care approach other than traditional medicine (Clarke, T. C., Black, L. I., Stussman, B. J., Barnes, P. M., & Nahin, R. L., 2015). In literature reviews conducted in Türkiye, it was reported that the frequency of Traditional and Complementary Medicine use is higher in cancer patients (Kurt, S., Kahyaoğlu Süt, H., & Küçükkaya, B.,2019; Özçelik, G., & Toprak, D.,2015). Herbal products are among the most frequently preferred Traditional and Complementary Medicine practices by individuals with chronic diseases (Çakmak, S., & Nural, N., 2017). The reasons for the preference of herbal products are due to their long history of use, the influence of visual and written media, their easy accessibility and their natural production. In addition, the approval of the Ministry of Health or the Ministry of Agriculture and Rural Affairs for herbal products convinces individuals about the adequacy of product reliability (Çakmak, S., & Nural, N., 2017). Patients usually use one or more herbal products to overcome the disease, provide additional benefits to the treatment, and increase blood values. Other traditional and complementary medicine methods that are most frequently preferred besides herbal products are massage, nutritional changes, vitamin and mineral supplements, progressive relaxation exercises, and other traditional practices (Clarke, T. C., Black, L. I., Stussman, B. J., Barnes, P. M., & Nahin, R. L., 2015).

Acupuncture, which is thought to treat many diseases, constitutes an important part of traditional Chinese medicine. In different studies, acupuncture, spinal massage treatment, osteopathy, Reiki, and yoga are ranked first (Posadzki P, Watson LK, Alotaibi A, Ernst E., 2013).

(NCCAM = The National Center For Complementary and Alternative Medicine) has grouped complementary and alternative medicine practices under 3 headings (Tokaç M. 2013).

1. Natural Products (Medicinal plants, probiotics…)

2. Mind and Body Medicine (Acupuncture, Meditation…)

3. Physical Manipulation Based Applications (Osteopathy, chiroptics…)

The World Health Organization emphasizes that the concepts of "alternative-complementary medicine" applications include non-standard health applications that require knowledge, experience and have different effects, while the concept of "traditional medicine" covers a series of treatments and applications that vary from country to country or region to region (Kalındemirtaş, M., 2010).

The World Health Organization (WHO) defines traditional medicine (including herbal medicines) as therapeutic methods that existed before the development and spread of modern medicine and are still used today.

History

It is thought that as long as human beings have existed on Earth, they have used plants for purposes such as nutrition and treatment. Herbal medicines are used as primary health care by 75-80% of the world population, mostly in developing countries, because of their cultural suitability, compatibility with the human body and fewer side effects. However, their use has increased in developed countries in recent years. The oldest use dates back 5000 years in Indian, Chinese, Egyptian, Greek, Roman and Syrian sources. The classical Indian scriptures Rigveda, Athervaveda, Charak Samhita and Sushruta Samhita are evaluated in this context. Herbal medicines and traditional medicine are derived from the rich traditions and scientific roots of ancient civilizations (WHO Traditional Medicine Strategy 2014-2023). Many conventional drugs are produced from plant sources; a century ago, many of the most effective drugs were plant-based. Examples include aspirin (from willow bark), digoxin (from foxglove), quinine (from cinchona bark) and morphine (from opium poppy). The development of drugs from plants continues as pharmaceutical companies screen plants for pharmacological effects on a large scale. The use of plants in treatment has gone through many different stages until the development of modern phytotherapy.

The main stages in the history of plant treatment:

- Emperor Shen Nung's Pharmacopoeia
- Chinese Herbal (2800 BC) 400 herbal medicines
- Ebers Papyrus (1800 BC)
- Hippocrates (460-367 BC) 400 medicines
- Galen (131-201 AD)
- Johnson (1636) 4000 medicinal uses of plants
- Linnaeus (1751) "Philosophia Botanica"
- Withering (1785) "Account of Foxglove"

New Stone Age (8000-5000 BC)

The transition period from Paleolithic to Neolithic can be considered as the transition from food gathering to food production economy. Tools were made from polished stone to aid farming and to clear trees. Those who lived near the lakes collected and processed over 200 different plants, including a considerable number of those with medicinal properties. These include Papaver somniferum, Sambucus ebulus, Fumaria officinalis, Verbana officinalis, Saponaria officinalis, Menyanthes trifoliata, etc.

Mesopotamia

The written evidence for the skills of Mesopotamian physicians is based on the Code of Hammurabi. This collection was not found on a tablet, but on large diorite blocks, consisting of various polished minerals. One of these inscriptions recommends the application of a dressing containing mainly sesame oil, which also acts as an antibacterial agent. It includes information on the use of well-known medicinal plants such as poppy, belladonna, mandrake senna, henbane, licorice, and mint.

China

Traditional Chinese medicine is one of the most important examples of how ancient knowledge and experience is applied to the holistic approach of today's healthcare. Traditional Chinese Medicine has a history of over 3000 years. Although acupuncture is recognized in the West as a part of Traditional Chinese Medicine, herbal medicine is a large part of Traditional Chinese Medicine that is lesser known and has many misconceptions about it. The substances used in Traditional Chinese Medicine are often referred to as Chinese herbal medicines. However, it is known that this is not technically correct. Some of the substances used are not obtained from plants but also from animals and minerals. Although this is known, this term is generally accepted.

The written history of Chinese materia medica dates back to the Eastern Han Dynasty (25-220 AD) when the first book on materia medica, "Shen Nong" Ben Cao Jing (The Holy Farmer's Classic of Materia Medica), appeared. This book is also known as the "Classic of Materia Medica", "The Canon of Materia Medica" or Shen-nog's "Herbal Classic". It was compiled under the pseudonym of Shen-nong, the Holy Farmer, in the second century. Although there are many pharmacopoeias and monographs on specific plants that are cumulatively and methodically collected herbal knowledge, the earliest known herbal text is the "Classic of Herbal Medicine" by the Holy Farmer, compiled in China 2,000 years ago. The book contains 365 records, one for each day of the year. These records include botanical (252 records), zoological (67 records) and mineral (45 records). The literature developed throughout the dynasty with the addition of new drugs, re-evaluation of known drugs and addition of new uses. These include the first Chinese pharmacopoeia compiled by the state, the "Xin Xiu Ben Cao" (New Revised Materi Medica) and the world-famous classic "Ben Cao Gang Mu" (Detailed Compendium of Materia Medica). This tradition has continued until the present day with the publication of a 25-year project under the title "Zhong Yao Da Ci Dian" (Encyclopedia of Traditional Chinese Medicines) in 1977. It contains 5,767 records, consisting of 4,733 products from plants, 740 from animals, 82 from minerals and 172 from these sources.

Egypt

Proving that plants were used for therapeutic purposes, the 1st century BC. The Ebers Papyrus, dating back to 1600 BC, was found in 1873. In the second century AD, Clement

Alexander was sure that the Egyptians had compiled all their knowledge in 42 secret books, six of which contained medical information. Despite this and the ancient writers, views on the history of medicine remained unchanged for a long time. The traditional view focused on Hippocratic and Greek influences. In the 19th century, Egyptologists began to find papyruses containing medical information. The first medical papyrus was published by Georg Ebers in 1875. The Eber papyrus was a 20.23-meter-long, 108-column inscription. It dates back to the reign of Amenophis I (1536 BC). This papyrus has been translated and published by many researchers. According to Grundriss, it contains complexly organized medical advice, indicating that it was compiled from different sources. The Ebers papyrus contains prescriptions for various diseases, illnesses and ailments, grouped together. Almost all groups begin with the phrase “beginning here” and are used many times. But they are often different and unorganized. The papyrus author(s) were probably physicians. The inscription discusses the secrets of medicine. Herodotus wrote that Egyptian physicians were experts in their field, which is confirmed by the Ebers papyrus.

India

Very little is known about ancient Indian medicine and pharmacy. Archaeological evidence shows that the Indians settled down around 2500 BC. Their cities had meticulously equipped systems for hygiene and cleanliness. All of this suggests a concern for health. Later, with the Aryan invasion of India, the Vedic era began around 1500 BC. (19) The Rigveda Samhita text deals with topics such as the origin of the universe and the divine nature, and contains hymns for humans, animals and plants. The term Ayurveda is used in the old versions of the Ramayana and Mahābhārata and in the Atharvaveda. Suśruta is praised for his pioneering work in the field of surgery.

Ayurveda, the study of internal medicine, is in the following order:

Brahmā → Daksa → Prajāpati → Aśivinau → Indra → Caraka.

Suśrutasamhitā, on the other hand, deals with surgical medicine in general and progressed in the following order:

Indra → Dhanvantari → Suśruta → Caraka → Suśruta

They were both medical doctors and pharmacists and studied more than 1000 plants. Ayurveda was used by researchers for medical purposes. It eventually spread to Asia with the spread of Buddhism. In Ayurvedic medicine, herbal mixtures in the Indian subcontinent contain lead and other heavy metals that can cause poisoning. For this reason, some practices that have been shown to have side effects in the light of modern scientific developments in treatment with plants and minerals have been abandoned.

Rome

The source of known ancient Greek medical knowledge and ancient Greek medical practices is Homer. The Iliad and the Odyssey, two epic poems dating back to the 8th century BC, are attributed to Homer. Of these two works, the Iliad contains information on wound treatment and care. Beyond describing wounds, Homer also describes the care given to a wounded warrior. Generally speaking, medical care is more about the comfort of the wounded person than the treatment of the wound itself. There were a few warriors who were masters of the art of bandaging and healing with herbal medicine. Machaon, the son of the legendary healer Asclepius, who was later deified, was among these doctors. When Machaon was wounded, he was treated with a cup of mulled wine sprinkled with grated goat cheese and barley.

Arabia

The Spanish Muslims made the greatest contribution to botany, and some are known as the best botanists of the Middle Ages. They were careful observers and discovered the sexual differences of plants such as palm and hemp. They traveled in the mountains, along the seashores and in distant lands on a mission to search for botanical plants. They classified plants as those grown from seeds, those grown from seedlings and those growing in the wild. The modern use of Arab botanical medicine has historical roots in ancient Arab medicine. Arab herbalists, pharmacologists, chemists and physicians adopted ancient medical practices originating in Mesopotamia, Greece, Rome, Persia and India. Many medical discoveries, such as the discovery of the immune system, the recognition of microbiology, and the separation of medicine from pharmacology, were made by Arab physicians.

Legal Status of Traditional Medicine and Complementary/Alternative Medicine:

Status in the World:

A Worldwide Review, in its study; medical providers and practices are generally defined as traditional, complementary/alternative or allopathic. “Provider” and “practitioner” are used interchangeably. In a few cases, especially in the European part, the term “non-allopathic physician” is used to refer to medical practitioners who are not allopathic practitioners or who are allopathic providers but are not physicians.

Allopathic medicine

In this document, allopathic medicine refers to the broad category of medical practice sometimes referred to as Western medicine, biomedical medicine, scientific medicine, or modern medicine. This term is used for convenience only and does not refer to the principles of treatment of any form of medicine described in this document.

Complementary/Alternative medicine,

The terms “complementary medicine” and “alternative medicine” are used interchangeably with “conventional medicine” in some countries. Complementary/alternative medicine generally refers to conventional medicine practiced in a country but not part of the country’s own traditions. As the terms “complementary” and “alternative” suggest, they are sometimes used to refer to health care services that are considered to be in addition to allopathic medicine… In some countries, the legal status of complementary/alternative medicine is equivalent to that of allopathic medicine, with many practitioners certified in both complementary/alternative medicine and allopathic medicine, and for many patients, a complementary/alternative practitioner is the primary care provider. Herbal preparations and products Herbal preparations are produced by subjecting plant materials to extraction, fractionation, purification, concentration or other physical or biological processes. They may be produced for immediate consumption or as the basis of herbal products. Herbal products may contain excipients or inert ingredients in addition to the active ingredients. They are usually produced in larger quantities for retail sale (General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine,2000).

Traditional medicine

Traditional medicine includes a variety of health practices, approaches, knowledge, and beliefs that include plant, animal, and/or mineral-based medicines; spiritual therapies; manual techniques; and exercises applied alone or in combination to maintain well-being and to treat, diagnose, or prevent disease.

The comprehensiveness of the term "traditional medicine" and the wide range of practices it encompasses make it difficult to define or describe, especially in a global context. In most cases, however, a medical system is referred to as "traditional" when practiced in its country of origin.(Legal Status of Traditional Medicine and Complementary/ Alternative Medicine, 2001)

In the early 2000s, the World Health Organization, seeing the developing issue of getat, made a decision that there is no doubt that the Guidelines will achieve the aim of improving the quality and value of research in traditional medicine. It is envisaged that the Guidelines will be revised again in the near future in parallel with the developments in research in the field of traditional medicine.

The World Health Organization has not remained indifferent to these developments worldwide and has prepared some decisions and strategic plans. It has made various decisions on this subject. According to the World Health Organization, Traditional Medicine (TM) is either a mainstay of health care delivery worldwide or serves as a complement. In some countries, traditional medicine or non-traditional medicine may be referred to as complementary medicine (CM). The WHA resolution on Traditional Medicine (WHA62.13), adopted in 2009, requested the Director-General of the World Health Organization to update the World Health Organization Traditional Medicine Strategy 2002-2005 based on the progress of countries and the new challenges that exist in the field of traditional medicine. (WHO Traditional Medicine Strategy 2014-2023)

If we examine the issue from the United States, when the term "alternative medicine" was mentioned in the 1980s in the USA, the first person who came to mind was Dr. Andrew Thomas Weil (1942-). The fact that Time magazine, which covered the GETAT issue on May 12, 1997, chose Dr. Weil as its cover image is an example of his influence in his country. Dr. Weil made significant contributions to the acceptance of "alternative" medicine by academic medicine. On the one hand, he tried to inform the public with his books, his own web page and a small monthly newsletter, and on the other hand, he gave importance to the efforts to establish the subject of GETAT on an academic basis. The two-year postgraduate training program on GETAT, which he founded and directed at the University of Arizona School of Medicine, was the first of its kind. Dr. Weil was also the originator and founder of the Consortium of Academic Centers for Integrative Medicine. In 2001, at least 75 of the 125 medical schools in the United States offered some form of complementary medicine training. The exception was the University of Maryland School of Medicine in Baltimore, which included a research institute for integrative medicine.

The prevalence of complementary/alternative medicine use in the United States ranges from 9% to 65%. Even for a relatively specific treatment such as chiropractic, significant inconsistencies have emerged in the use and treatment used in the United States. The data evaluated show that complementary/alternative therapies are frequently and increasingly used. In complementary/alternative medicine surveys, the prevalence of use appears to be dependent on uncontrollable factors. Although the true prevalence of complementary/

alternative medicine use in the general population in the United States has increased, the true rate of use remains uncertain. (Arslan ve ark., 2016)

The Situation in Türkiye

In Türkiye, regarding traditional and complementary methods, the first "Acupuncture Treatment Regulation" was published on May 29, 1991, regarding acupuncture. This was followed by the "Regulation on Private Healthcare Institutions Applying Acupuncture Treatment and the Application of This Treatment", which was published in the Official Gazette dated September 17, 2002 and numbered 24879 and entered into force. In addition, within the framework of the Ministry of Health Certified Education Regulation, which was published in the Official Gazette dated 21.08.2010 and numbered 27679, and entered into force, in order to ensure the education and competence of physicians who will apply phytotherapy treatment in Türkiye, the "Phytotherapy Certificate Education Program Standards for Physicians" entered into force with the Ministry Approval dated 04.01.2011 and numbered 55.

In the Decree Law No. 663 on the Organization and Duties of the Ministry of Health and its Affiliated Institutions, which was published in the Official Gazette dated 02.11.2012 and entered into force, "Making regulations regarding traditional, complementary and alternative medical practices" was included among the duties of the General Directorate of Health Services, and "Traditional herbal medicinal products and homeopathic medicinal products" was listed among the duties of the Turkish Medicines and Medical Devices Agency.

In 2012, the "Traditional and Complementary Medicine Practices Department" was established based on the Additional Article 13 of Law No. 1219 on the Practice of Medicine and Branches of Medicine and Article 8 (ğ) of Law No. 663. The duties of this institution are to regulate traditional, complementary and alternative medicine practices, to permit and supervise all kinds of practices to be carried out with a health declaration, and to stop activities and promotions that are contrary to regulations and permits (Official Gazette, 2012).

In Türkiye, with the regulation published in the official gazette No. 29158 on 27.10.2014, early action was taken and studies were initiated in order for traditional complementary medicine to develop in Türkiye. The subject has also found an echo among physicians and an extraordinary number of physicians have applied to the training and received training. The said Department has published the "Traditional and Complementary Medicine Practices Regulation" in the official gazette dated 27.10.2014 and numbered 29158 and entered into force. In this regulation;

Acupuncture

Apitherapy

Phytotherapy

Hypnosis

Leech Application

Homeopathy

Chiropractic

Cup Application

Larva Application

Mesotherapy

Prolotherapy

Osteopathy

Ozone Application

Reflexology

Music therapy are shown as possible applications. (Tokaç M., 2013)

Public and private health institutions are defined as “application units”, university hospitals and training and research hospitals are defined as “application centers”. It has been decided that training will be provided only in application centers with the approval of the Ministry of Health (Official Gazette No. 29158 dated 27.10.2014).

The concept of medicine based on response rather than evidence is becoming more attractive among the public and the application to traditional and complementary medicine methods has increased. People have now started to resort to these methods for every health problem they think will not go away. The most fundamental problem with traditional and complementary treatment methods is that the advocates of each application are generally unable to substantiate their explanations with scientific data in a way that would convince the advocates of positive science. However, the fact that these applications have not yet been proven should not lead to the conclusion that they are wrong and their existence should not be denied. In fact, the Ministry of Health has regulated some traditional and complementary treatment methods with the “Traditional and Complementary Medical Practices Regulation” it has published, thus providing a legal basis for the relevant treatment methods. However, although the relevant regulation is a positive step in terms of preventing the abuse of traditional and complementary treatment methods by uneducated and unauthorized individuals, it contains deficient provisions in terms of law. Because the relevant regulation does not include special conditions required for the methods to be applied to be considered lawful, nor special provisions regarding the legal responsibilities of the implementers. (8 Arpacı, Özge, 2021)

Since 2014, certified training programs have been organized on the subject of GETAT and training is provided to physicians and dentists who are interested in the subject. In addition to these trainings, clinics, units, and application centers opened in public hospitals and the private sector have increased rapidly. Getat applications were not accepted by a large portion of physicians at first. As a result of the spread of GETAT applications and the successful results obtained in patients in recent years, it has started to become one of the departments/units to which physicians who did not previously adopt GETAT applications are directed. Moreover, these units provide services in state hospitals by charging according to the “Public Price Tariff” and the fees are not covered by the Social Security Institution. This situation also causes people with limited financial means not to prefer them.

However, we evaluate the increase in the use of traditional complementary medicine methods by patients only according to applications and demands. Studies that can scientifically demonstrate these have not yet been conducted in Türkiye.

Conclusion

GETAT is a new concept in medical faculties in Türkiye.

The congresses and workshops to be organized should be organized within the university and the ministry. Participation in organizations to be held through municipalities and civil society organizations does not go beyond just informing the public, and those who participate in those organizations are not academic staff anyway.

GETAT Department should be within the Institute, but also within the Dean's Office in ministry and university hospitals, and permanent staff should be created. Not only the Ministry of Health, but also the Council of Higher Education should take action on this issue. For example; There is still no GETAT button in the DBS system and keywords such as Acupuncture, Phytotherapy, Prolotherapy etc. in associate professorship applications. This prevents academic staff who have academic studies in this field from conducting scientific studies.

Among the things that can be done in order to prevent unwanted activities in the field of complementary and traditional medicine in Türkiye; These may include conducting studies and making efforts in universities to examine complementary treatment methods at an academic level and to reflect them in practice, establishing relevant branches of science, developing clinical practices integrated with relevant fields, initiating national training programs for the public and physicians, supporting academic studies to be conducted in this field in line with ethical criteria, and announcing methods that can be applied in various diseases and in the field of complementary medicine, good practice standards for physicians, guidelines and new information supported and updated by the boards, for the public and physicians, via the internet, social media and web pages to be established. (Official Gazette. (1991 Publication No:2088, 1991). Due to the education authority granted by the Ministry only to university hospitals, it sees these units affiliated to the university rectorate as application research centers that only provide financial gain, and this situation harms the development of Getat rather than benefits it.

GETAT titles should be given as independent courses in medical faculties or added to course content. In addition, elective rotation opportunities should be provided for clinical students and assistants.

Unfortunately,

As long as the permanent staff and performance status of the group of doctors who want to work in these areas, which already have very few trainers, are not improved, expecting these centers to develop is nothing more than a dream. This situation will only allow places that operate illegally and solely for financial gain to mushroom.

The responsible directors sought for the centers are only mentioned by the rectorate, and competence is not sought in their appointments. In this case, it causes only those who have certificates but do not practice to be made directors. With this practice, it invites only those who want to extend their certificate period but work here without any academic activity. As long as the centers within the university are not within the faculty of medicine and no academic activity report is requested, this will continue.

GETAT employees are already few in number. These people work with extraordinary efforts, trying to help their patients and make scientific publications. There are many demotivating factors for these people.

Medical anthropology determines what and how we believe, and culture and history shape the language in which medicine can be understood. Medical practice must take into account the cultural structure and beliefs of the society. (Good, B.J., 2003) This situation has become undeniable in Türkiye. In this case, instead of determining the criteria for choosing the application methods of traditional and complementary medicine and thus ensuring compliance with ethical rules, it is very painful to still be discussing getat.

However, if the above-mentioned are implemented, application and research opportunities will be found and scientific evidence will be presented. Thus, GETAT will be able to work based on scientific foundations and its ethical rules will be clear. Gradually, by integrating with modern medicine, its application areas, limits and methods, guides will be expanded and by working in an integrated manner with modern medicine, it will be able to reach the place it deserves in Türkiye.

References

Arpacı, Özge, "Traditional and Complementary Medical Practices Accepted by the Ministry of Health and Evaluation of Their Legality". Dokuz Eylül University Faculty of Law Journal 23, No: 2 (November 2021): 1245-1307.

Arslan et al., (2016) Examples of Traditional Treatment Systems in the World: A General Overview Lokman Hekim Journal;6(3) 100-105

Arslan, M., Şahne, B. S., & Şar, S. (2016). Examples of Traditional Treatment Systems in the World: A General Overview. Mersin University Faculty of Medicine Lokman Hekim Journal of Medical History and Folkloric Medicine, 6(3), 100-105.

Belbez Zeyneb Ümit, PhD Thesis, Complementary and Alternative Medicine Belbez Zeyneb Ümit, PhD Thesis, Complementary and Alternative Medicine Movement: How the Search for Alternatives to Medicine Reshaped the Boundaries of Scientific Medicine in the Late 20th Century.

Biçer, İ., & Yalçın Balçık, P. (2019). Traditional and Complementary Medicine: An Examination of Turkey and Selected Countries. Hacettepe Health Administration Journal, 22(1), 245-257.

Çakmak, S., & Nural, N., (2017). Complementary and Alternative Treatment Applications in Chronic Diseases. Turkiye Klinikleri J Intern Med Nurs-Special Topics , vol.3, no.2, 57-64.

Clarke, T. C., Black, L. I., Stussman, B. J., Barnes, P. M., & Nahin, R. L. (2015). Trends in the use of complementary health approaches among adults: United States, 2002-2012. National health statistics reports, (79), 1–16.

doi: 10.7861/clinmedicine.13-2-126. PMID: 23681857; PMCID: PMC4952625.

Ernst E. Prevalence of use of complementary/alternative medicine: a systematic review. Bull Word Health Organ. 2000;78(2):252–7.

General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine, World Health Organization, 2000 Geneva.

Good, B.J. (2003). Medicine, Rationality, And Experience: An Anthropological Perspective. Cambridge, United Kingdom: Cambridge University Press

Health Reform Analysis, Ministry of Health, p: 8

https://doi.org/10.17098/amj.44789

https://tr.wikipedia.org/wiki/Rigveda

Journal Article with DOI Number

Kalındemirtaş, M. (2010). The Effect of Traditional Medicine on the Public (The Example of Ören Village in Adıyaman Province), Saü Social Sciences Institute, Department of Sociology, Sakarya

Karahancı ON, Öztoprak ÜY, Ersoy M, Zeybek ÜÇ, Hayırlıdağ M. and Örnek BN. Comparison of the Regulation on Traditional and Complementary Medical Practices and the Draft Regulation. Turkish Bioethics Journal 2015; 2(2): 117-126.

Kaya, Ş., Karakuş Er, Z., Boz, İ., & Özer, Z., (2020). The Place of Nurses in Legal Regulations Regarding Complementary Therapies in the World and Turkey. Jaren , vol.6, no.3, 584-591.

Kurt, S., Kahyaoğlu Süt, H., & Küçükkaya, B. (2019). Use of Complementary Health Approaches in Gynecological and Breast Cancer Patients Applying to a University Hospital. Mersin University Faculty of Medicine Lokman Hekim Journal of Medical History and Folkloric Medicine, 9(3), 326-336. https://doi.org/10.31020/mutftd.589250

Legal Status of Traditional Medicine and Complementary/Alternative Medicine: A Worldwide Review, World Health Organization, Geneva, 2001.

Marc J. Roberts, William Hsiao. Peter Berman, Michael R. Reich

Mollahaliloğlu, S., Uğurlu, F. G., Kalaycı, M., Öztaş, D. (2015). New Era in Traditional and Complementary Medicine Practices. Ankara Medical Journal, 15(2).

Official Gazette No. 29158, dated 27.10.2014.

Official Gazette. (1991). Publication No:20885. Acupuncture Treatment Regulation.

Özçelik, G., & Toprak, D. (2015). Why is Herbal Treatment Preferred?. Ankara Medical Journal, 15(2). https://doi.org/10.17098/amj.05190

Posadzki P, Watson LK, Alotaibi A, Ernst E. Prevalence of use of complementary and alternative medicine (CAM) by patients/consum ers in the UK: systematic review of surveys. Clin Med (Lond). 2013 Apr;13(2):126-31.

Somer P. (2012) Complementary-Alternative Medicine and Ethical Issues. In Honor of Prof. Dr. Mehmet Akad. Istanbul: Der Publications,1001–9

Talhaoğlu D. https://dergipark.org.tr/en/pub/batd/article/945893 DOI: 10.53445/batd.945893 20.

Talhaoğlu, D. (2021). Traditional and Complementary Treatment Applications. Integrative and Anatolian Medicine Journal, 3(1), 16-29. https://doi.org/10.53445/

batd.945893

Tokaç M.; "Academic Approach to Traditional Medicine: Gettam". SD Health Thought and Medical Culture Journal Autumn. 2013; 28: 82-85.

WHO Traditional Medicine Strategy 2014-2023.

About the Author

Dr. Eralp KUYUCU graduated from Istanbul University Cerrahpaşa Faculty of Medicine in 1985. He works as a physician in the GETAT Unit at Söke Fehime Faik Kocagöz State Hospital. He strives for the development of traditional medicine in Türkiye.
E-mail: eralpkuyucu@gmail.com **ORCID:** 0009-0003-3177-4252

Similarity Index
The similarity index obtained from the plagiarism software for this book chapter is 11%.

Medicinal Plants and Ozone Therapy Used in Cancer

Hayriye ALP

Necmettin Erbakan University

Şerife AYDIN

Necmettin Erbakan University

To Cite This Chapter

Alp, H., & Aydın, Ş. (2024). Medicinal Plants and Ozone Therapy Used in Cancer. In F. Nur Takı, S. Koçer & R. Bütüner (Eds.), *New Generation Technologies and Sustainability in Health Current Studies* (pp. 162-177). ISRES Publishing.

Introduction

The inflammatory response, which is a defense mechanism, is the body's response to tissue damage caused by infection and harmful stimuli. The inflammatory response is an evolved defense mechanism in organisms to localize and eliminate harmful agents and damaged tissue components. The response occurs as a result of changes in blood flow, increased permeability of blood vessels, and extravasation of fluid, protein, and leukocytes from the circulation to the inflamed area.

When we look at the pathogenesis of cancer, it has been found that problems develop in the following steps; induction of chromosomal instability, epigenetic changes and inappropriate gene expression, increased cell proliferation, escape from apoptosis, formation of new blood vessels, basement membrane invasion, initiation of metastasis.

Nutritional problems during cancer treatment can be: taste and smell changes; cachexia; constipation; nausea-vomiting and dry mouth.

Phytotherapeutic plants that have anti-inflammatory effects and are used in the treatment of cancer for anti-inflammatory purposes are as follows: common barberry (berberis vulgaris), boswellia serrata, aloe vera (A. arborescens), amla (phyllanthus sp), ashwagandha (withania somnifera), calendula officinalis, turmeric, green tea, silybum marianum.

The hypoxic microenvironment allows cells to return to a primitive/blastic form' and triggers proliferation. The existence of ''hypoxic cells'' in human tumors has been indirectly proven for the last 20 years. It is known that the presence of cells resistant to radiation due to tissue hypoxia is known in experimental animal tumors, and radiotherapy and anemia are important poor prognostic factors.

Since cancer cells cannot survive in an oxygen-rich environment, it has been determined that if sufficient oxygen is provided, this frenzy of glucose fermentation stops, the nutrition of the tumor tissue is disrupted and the tumor cells die.

Ozone increases chemo-radiosensitivity by increasing oxygenation. Thus, it increases the effectiveness of chemoradiotherapy and reduces side effects such as fibrosis formation and polyneuropathy in the long term.

Cancer treatment should be multifaceted, and etiologic factors should include tissue oxygenation disorders, ascites, toxicity and complementary methods that should be used to eliminate them. Only in this way, with a multidisciplinary approach, can we put forward the right approach to cancer, which we call the king of diseases. What we learn about cancer every day, what causes it, self-confidence, lifelong diseases, genetic predispositions, environmental factors that affect DNA epigenetically are the issues that need to be emphasized more. In addition, tissue pH, acid-base changes, oxidation-reduction pathways and biochemical (functional) biochemistry should also be examined. At this point, the importance of traditional complementary medicine methods draws more attention. When we look at the clinics and practices that have achieved high success in cancer treatment, we see that there are centers and practitioners who know how to use GETAT (Turkish abbreviation for Traditional and Complementary Medicine) methods well (it is necessary to realize what is needed at which stage of treatment and to combine appropriate methods with treatment in appropriate indications). This combination increases the success of the treatment, for example, the application of special supplements in immune system declines between chemotherapies, chronic fatigue (vitamin C, glutathione supplements, the use of ozone therapy in - correct doses, dealing with neutropenia with appropriate phytotherapeutic agents, eliminating mucositis, ensuring the patient's nutritional sustainability and thus strengthening the already low immunity is essential). When complementary therapies are given by practitioners who have received the right training, who can choose the right patient and the right application at the right dose, these therapies do not conflict with conventional therapies, but support each other and maximize the efficiency of the treatment.

With this book chapter, we aim to eliminate the side effects of toxic chemotherapy drugs, solve personal problems, ensure treatment sustainability and position phytotherapy and ozone therapy, which are traditional treatment methods applied in addition to conventional treatments of cancer, which is one of the biggest health problems and one of the most common causes of death today. For this purpose, we want to develop a new perspective on cancer treatment by increasing the inclusion of traditional treatment methods in the treatment algorithm, which are not emphasized in conventional medical treatments, but which patients and their relatives learn by researching the treatments of previously treated cancer patients.

Cancer and Inflammation Dilemma

The inflammatory response, which is a defense mechanism, is the body's response to tissue damage caused by infection and harmful stimuli. The inflammatory response is an evolved defense mechanism in organisms to localize and eliminate harmful agents and damaged tissue components. The response occurs as a result of changes in blood flow, increased permeability of blood vessels, and extravasation of fluid, protein, and leukocytes from the circulation to the inflamed area.

Acute inflammation lasting a few days, which has a beneficial role against infection and injury, followed by a rapid healing phase, and while the repair of damaged tissues occurs, inadequate resolution of inflammation and uncontrolled inflammatory reactions, persistent pathogen infection, autoimmune diseases, cardiovascular diseases, diabetes, obesity, neurodegenerative diseases. A long-term response called chronic inflammation occurs, which is the culprit underlying many pathological conditions, including cancer, which is often defined as a wound that does not heal (Balkwill & Mantovani, 2001; Itzkowitz & Yio, 2004).

The longer the inflammation lasts, the higher the risks. Chronic inflammation is long-lasting and persists for years. Chronic inflammation is associated with long-term cell/ tissue injuries, invasion, and damage-induced neoplasia. This event initiates DNA damage and cancer (Greten & Grivennikov, 2019). Infections such as hepatitis B and C are blamed for 20% of cancers (Balkwill & Mantovani, 2012).

Celsus, the Roman medical historian, described four basic symptoms of inflammation; redness (rubor), heat (calor), pain (dolor). In the 19th century, Virchow added that the affected body part loses its function due to pain and inability to use it.

In 1863, Virchow established a connection between inflammation and cancer with the presence of leukocytes around neoplastic tissues. The ''lymphoreticular infiltrate'' in areas of chronic inflammation reflected the origin of cancer (Balkwill & Mantovani, 2001).

As a result of many epidemiological and clinical studies conducted later, it was shown that malignancies occur with chronic inflammation (Coussens & Werb, 2002; Hussain et al., 2003).

Inflammations (gastritis, chronic hepatitis, cholecystitis, prostatitis, pancreatitis) occur in the stomach, liver, gallbladder, prostate, and pancreas in tissues damaged by chronic inflammation (Shacter & Weitzman, 2002; Hussain et al., 2003; Philpott & Ferguson, 2004).

The fact that inflammatory bowel diseases are the basis of diseases such as Crohn's disease and ulcerative colitis and that response to anti-inflammatory treatment supports this relationship (Itzkowitz & Yio, 2004; Eaden et al., 2000).

Although chronic inflammation is present in 25% of cancers, the genetic and epigenetic changes caused by inflammation significantly increase its contribution to cancer (Hussain & Harris, 2007).

When inflammation becomes chronic, it collapses the body's normal immune system. This process provides a favorable environment for the development of cancerous cells. Many signaling pathways that play a key role in the formation of epigenetic changes inside and outside the cell are activated. The transformation of a normal cell into a neoplasm is a very gradual process (Busuttil et al., 2014). Chronic inflammatory conditions in the microenvironment around the cell (chronic environmental pollutants, tobacco, alcohol, cigarettes, obesity, stress, foods, viruses, bacteria) can affect the steps leading to this tumor (Negus et al., 1997). By creating new blood vessels through inflammatory angiogenesis, the existing vascular structure changes, thus facilitating tumor development (Mantovani et al., 1992).

Chronic inflammation plays an important role in the initiation and progression of carcinogenesis from a molecular perspective.

1.Induction of chromosomal instability

2.Epigenetic changes and inappropriate gene expression

3.Increased cell proliferation

4.Escape from apoptosis

5.Formation of new blood vessels

6.Basement membrane invasion

7.Initiation of metastasis (Kundu & Surh, 2008; Sarasin, 1999).

3.Nutritional Problems And Solutions During Cancer Treatment

Taste and Smell Changes

The most common taste and smell changes during cancer treatment also affect appetite, they start 2-3 weeks after the start of treatment and continue throughout the treatment (Buttiron et al., 2023). In these cases, when there is a bitter-metallic taste in the mouth, porcelain-glass spoons can be preferred instead of metal spoons, teeth brushing can be tried before meals, since hot applications increase the smell, food at room temperature can be preferred.

Cachexia

Cancer cachexia is defined as a 5% weight loss in the last 6 months before diagnosis, or a BMI of 20kg/m2 or a 2% weight loss; it appears as an involuntary loss of muscle and fat in cancer patients (Clamon et al., 2022; Talbert & Guttridge, 2022) and the rate of occurrence increases to 80% in patients with stomach and pancreatic cancer, and the stage of the tumor is also effective (Peixoto da Silva et al., 2020).

Chemotherapy itself also causes muscle mass loss; because chemotherapeutics are procachectic. Patients should eat small amounts and frequently, and liquid foods that provide early stomach fullness should be given between meals, not before.

Constipation

The most common cause of constipation during cancer treatment is opioid treatment used in pain treatment, and another cause is chemotherapy. In order to prevent constipation, fibrous foods should be preferred, fluid intake and physical activity should be increased, and apricot-red plum-fig marmalade should be used on an empty stomach. Toilet habits should be established and strong tea and coffee should be avoided.

Nausea-vomiting

The most common cause of nausea and vomiting during cancer treatment is that chemotherapeutics activate the vomiting center and increase salivary gland secretion, and can be seen in patients throughout treatment (Zhang & Ying, 2022). It can be prevented by consuming small amounts of food frequently, consuming liquids between meals, chewing ice, and consuming oil-free, odorless, and salty foods.

Dry Mouth

Radiotherapy and chemotherapy taken to this area in head and neck cancers can affect the salivary glands (Brewczyński et al.,2020). It is recommended that the patient increase fluid consumption by constantly carrying water with them, clean their mouth frequently, stay away from smoking and alcohol, and use pilocarpine-containing supplements.

Medicinal Plants in Cancer

Common Barberry Plant (Berberis vulgaris)

In a randomized double-blind controlled study, 85 patients diagnosed with benign breast disease were divided into 2 groups; one group (n=44) was given 480ml berberis vulgaris extract per day and the other control-placebo group (n=41) was given a similar extract. When IGF-1 values were compared in plasma blood with ELISA method at the beginning and after 8 weeks; a 16% decrease was seen in the values of the berberis water group. A 37% decrease was also detected in the IGF-1/IGFBP-1 ratio. At the end of 8 weeks, PPAR-gamma and VEGF values also showed a significant decrease compared to the placebo group.

In another double-blind placebo controlled study, 0.3gr berberine was given twice a day to patients aged 18-75 who had undergone polypectomy in the last 6 months and whose diagnosis was confirmed histopathologically with colorectal adenoma. According to the complete analysis set, 429 people were evaluated in the berberine group (n=553) and 462 people in the placebo group. The recurrent adenoma detection rate during follow-up was 47% in the placebo group and 36% in the berberine group. No serious side effects were observed in the study, in which no colorectal cancer was observed during follow-up, and it was stated that a dose of 0.3 gr berberine taken twice a day is effective in reducing the risk of colorectal adenoma and is even a good option for chemoprophylaxis after adenectomy (Kashyap et al., 2022).

Boswellia Serrata

A randomized clinical trial has shown that the application of 2% boswellia cream twice a day after the procedure and before going to bed to alleviate the side effects of radiotherapy in patients receiving breast cancer treatment was better tolerated than steroid creams and reduced the use of steroid creams (Akbulut, 2017).

A supplement consisting of alpha-lipoic acid-boswellia serrata-methylsulfonylmethane and bromelain was given once a day to patients with arthralgia (n=53), which can be a significant reason for drug withdrawal in perimenopausal patients using aromatase inhibitors. It was observed that the supplement was well tolerated and there was no toxicity. It was observed that the VAS scores of 5 patients completely passed after 6 months of use and that it decreased significantly in the other patients (Akbulut, 2019).

A prospective randomized controlled study in which 44 patients with primary and secondary brain tumors were given 4200mg/day boswellia, a 75% decrease in brain edema was observed after treatment. Only 6 patients experienced mild GI discomfort, but no side effects were shown on quality of life or cognitive functions. It has been reported that this type of brain edema can reduce steroid use in patients (Devericks et al., 2022).

In a clinical study, phytosome-based boswellic acid extract was used against brain edema formation caused by chemoradiotherapy in 20 glioblastoma multiforme patients who had previously undergone surgery and chemoradiotherapy but had relapsed (4500 gr for 34 weeks) and was evaluated at 4, 12, 22, 34th weeks post-op; edema decreased in some patients and increasing stability was observed. A significant decrease in brain edema was observed in 2 patients, which positively affected surgical success. In addition, a significant decrease or even a decrease in steroid doses was observed in a significant number of patients. As a result, quality of life and psychological status were preserved. The positive effects of boswellia use include reduction in brain edema, limiting dexamethasone use, reducing the frequency of steroid side effects, and increasing the chance of near-complete resection during surgery (Arafat et al., 2023).

Aloe Vera (A. Arborescens)

Metastatic 240 solid tumor patients were studied with chemotherapy alone and aloe vera in addition to chemotherapy; lung cancer patients (cisplatin-etoposide-vinorelbine), colorectal cancer patients (oxaliplatin-5 fluorouracil-), stomach cancer patients (5-FU) and pancreatic cancer patients (gemcitabine) were given aloe vera 10 ml 3 times a day. It was observed that tumor regression was higher, disease control percentages increased and 3-year survival rates were higher in patients who received aloe vera in addition to treatment (He et al., 2021).

A clinical study was conducted by giving aloe vera simultaneously to patients with advanced solid tumors who did not have an effective standard anticancer treatment. 50 patients (GIS CA, breast CA, lung CA, brain TM) were included; one group received 20 mg oral melatonin alone, while the other group received 1 ml aloe vera twice a day in addition to melatonin. Partial response was obtained in 2 patients in the combined treatment group, while no response was obtained in the other group. (24/2) Stability was achieved in 7 patients (24/7). In this study, the rate of patients who did not show progression was found to be high in those who received the combined treatment. The 1-year survival rate was also found to be significantly high. Both treatments were well tolerated. It has been reported that this combination treatment may provide therapeutic benefits in stabilizing the disease and increasing survival in patients for whom no other effective standard treatment is available (Melnik et al., 2023).

A multicenter randomized double-blind study conducted with 120 patients was performed simultaneously with aloe vera gel (87.4% waterborne) in patients with head and neck cancer receiving chemoradiation treatment. It was observed that RISRAS scores were lower in those receiving aloe vera treatment at week 7, and moderate redness and peeling cases were significantly reduced with topical application (Gariboldi et al., 2023).

Another important problem in those receiving cancer treatment is oral mucositis. Aloe vera was given to one of the 26 children aged 3-6 with ALL diagnosis, and 5% sodium bicarbonate was given to the other group, and it was observed that CIOM degrees were milder in the aloe vera group. CIOM formation was earlier in the other group, thus it was shown that aloe vera solution was effective in preventing CIOM formation (Pejčić et al., 2023).

20 colorectal cancer patients receiving radiotherapy were treated with 1 g aloe vera (3%) twice daily for 6 weeks and the other with placebo ointment. Significant improvement in the pre-treatment comparison of the diarrhea index, improvement in lifestyle scores, decrease in depression scores, decrease in quantitative CRP, and decrease in acute radiation proctitis were observed (Sun et al., 2020).

Benzydamine gargle efficacy study also found aloe vera gargle to be as effective as benzydamine in reducing the severity of mucositis in patients with head and neck cancer (Chen et al., 2023).

Acute radiation-induced proctitis studies have shown that aloe vera has a significant preventive effect on diarrhea, rectal bleeding, and stool urgency symptom scores. The mean lifestyle score improved significantly during radiotherapy with aloe vera. CRP levels decreased, and aloe vera topical ointment was shown to be effective in preventing acute radiation proctitis symptoms seen during radiotherapy in pelvic cancers (Mason & Thompson, 2014).

Aloe vera gel has not been shown to provide adequate protection against radiation dermatitis (Sofi et al., 2018). A study conducted on 240 metastatic solid tumor patients showed that the use of 10 ml of aloe vera three times a day in addition to chemotherapy increased the 3-year survival rate (Chang et al., 2019).

Amla (Phyllanthus Sp)

In a randomized double-blind study in which 79 hepatitis carriers participated, one group (n=40) was given 200 mg powdered frankincense 3 times a day, and the other group (n=39) was given placebo lactose for 30 days. When they were followed for 9 months; on the 30th day, 59% (n=23) of the participants became negative, while only 4% of the placebo group had HBsAg (-). Negativity continued throughout the follow-up period. 13 of the 14 positive patients who carried HBsAg but did not carry HBeAg became negative, while only 5 of the 17 people who were both positive for HBsAg and HBeAg lost their surface antigen. None of these participants had surface antigens again. No signs of toxicity were seen in any treated patient (Mullie et al., 2016).

A total of 102 cirrhotic patients (with positive elisa test or nodules) were included in a study in which Phyllanthus urinaria-CPUL (Active Compound Phyllanthus Urinaria) was applied to one group (n=52) for 3 years while the other group (n=50) was not given anything. When the development of hepatocarcinogenesis (HCC) was examined; only 2 people in the treatment group developed carcinogenesis while 9 people in the control group developed HCC. Anti-URG11 and anti-URG19 were always found positive in 2 of the 11 patients who developed HCC, while anti-DRG2 was negative. In the 2-year follow-up after treatment, the rate of HCC development was 20% (n=6) in the control group while this rate was only 1% (n=1) in the treatment group. It was stated that anti-URG19, anti-URG11 and antiDRG2 can be used as markers in estimating the therapeutic efficacy of treatment in preneoplastic HCC. CPUL active ingredient has been shown to be beneficial in preventing or delaying the progression of HBV-associated cirrhosis to HCC (Paixão et al., 2017).

Ashwagandha (Withania Somnifera)

In a non-randomized controlled study involving 100 breast cancer patients in advanced stages, one group was given chemotherapy (docetaxel-adriamycin-cyclophosphamide/5FU-Epirubicin-cyclophosphamide) while the other group was given ashwagandha root extract in addition to chemotherapy, at a dose of 2 g every 8 hours throughout the chemotherapy. When fatigue scores were examined, they were found to be significantly higher in the control group. While no variation was found in survival rates, withania somnifera was found to be potentially effective in reducing fatigue and the quality of life of cancer patients (Marzbani et al., 2019).

Literature Review of Clinical Studies on the Use of Medicinal Plants in Cancer Treatment

Many plants inhibit angiogenesis; such as calendula officinalis, turmeric, green tea, silybulum marianum.

Almost all of them lower blood sugar by different mechanisms; such as nettle, urtica dioica, plantago majus, olive leaf, olea europaea.

Many plants have antifungal, antibacterial, and antiviral properties such as St. John's Wort (Hypericum perforatum), Lemon balm (Melissa officinalis) and Calendula officinalis.

Most plants use various intracellular pathways to induce apoptosis, especially against cancer cells. Green tea (Camellia sinensis), Camphor (Cinnamomum camphora), Cranberry (Cornus Mas), Lemon (Citrus x Limon), Pumpkin (Cucurbita Pepo), Astragalus(Astragalus sp), Hibiscus (Hibuscus sp) and Turmeric (Curcuma longa) can be given as examples of plants used for this matter.

They prevent recurrence and metastasis by destroying or transforming cancer stem cells. Turmeric (Curcuma longa) Calendula off (Calendula off) Green tea (Camellia sinensis)

Many have detox properties at various levels and in different ways. Milk thistle (Silybum marianum) Artichoke (Cynara scolymus)

Some plants activate the immune system and have an immunostimulant effect. Examples of this kind are as follows: Ashwagandha (Withania somnifera), common barberry (Berberis vulgaris), black cumin (Nigella sativa), burdock (Arctium lappa), calendula (Calendula officinalis), cinnamon (Cassia cinnamomum), swallowtail (Chelidonium majus), chamomile (Matricaria chamomilla), cleavers (Gallium aparine), garlic (Allium sativum), ginger (Zingiber officinale), goldenrod (Solidago sp), grape (Vitis vinifera), green tea (Camellia sinensis), horsetail (Equisetum arvense), jiaogulan, licorice root (Glycyrrhiza glabra), long pepper (Piper longum), mallow (Malva sylvestris), mistletoe (Viscum album), sage (Salvia sp), St. John's wort (Hypericum perforatum) thyme (Thymus vulgaris) turmeric (Curcuma longa).

Some plants regulate the immune system and have an immunomodulatory effect.Aloe vera, burdock (Arctium lappa) and jiaogulan can be examples of this type of plants.

Plants like Alchemilla vulgaris and Epilobium parviflorum can prevent the formation of active hormone metabolites in hormone-dependent cancers.

Licorice root (Glycyrrhiza glabra), Willow (Salix alba) and Boswellia sp are known to have anti-inflammatory properties. Almost all of them are good antioxidants.

Black cumin (Nigella sativa), Fenugreek (Trigonella foenum-graceum), Galagan(Onopordum acanthium), Onion (Allium cepa) and Garlic (Allium sativum) are some of the plants that increase the number and functions of NK cells.

Some plants such as Peganum harmala, Valeriana officinalis, lemon balm (Melissa officinalis) St. John's wort (Hypericum perforatum) regulate the psychological state of a person. Some plants have cytotoxic effects. These plants include wormwood (Artemisia) and plantain (plantago major).

The following can regulate epigenetic mechanisms: grape (Vitis vinifera) green tea (Camellia sinensis) and turmeric (Curcuma longa) (Padma, 2015).

Even oncologists know very little about ozone therapy in cancer. This is because ozone is still not considered a treatment based on scientific evidence.

It is used to reduce the side effects of classical treatments such as ozone therapy, chemotherapy, radiotherapy or immunotherapy in cancer (Tirelli et al. 2018; Baeza-Noci & Pinto-Bonilla, 2021).

The Effects of Ozone Therapy on Cancer

Hypoxia and cancer

The hypoxic microenvironment 'allows cells to return to a primitive/blastic form' and triggers proliferation. The existence of 'hypoxic cells' in human tumors has been indirectly proven for the last 20 years. It is known that 'the presence of cells resistant to radiation due to tissue hypoxia is known in experimental animal tumors, and radiotherapy and anemia are important poor prognostic factors'.

Since cancer cells cannot survive in an oxygen-rich environment, it has been determined that if sufficient oxygen is provided, this frenzy of glucose fermentation stops, the nutrition of the tumor tissue is disrupted and the tumor cells die.

It is found that lack of oxygen facilitates the spread of cancer and that lack of oxygen causes cancerous cells to leave the primary tumor and settle elsewhere.

The reason why Dr. Otto Warburg, a scientist in Berlin who received the Nobel Prize twice in 1929 and 1944, received the Nobel Prize was his work showing the real cause of cancer. Otto Warburg's results from his scientific study indicate that the sole and final root cause of cancer is 'life without oxygen', that is, 'anaerobiosis'. Normal cells require oxygen, whereas cancer cells can survive without oxygen.

It has been shown that when normal cells taken from any embryo are forced to grow in a laboratory tube without oxygen, they take on the characteristics of cancer cells (Clavo et al., 2004).

Oncogenes in the body can initiate cancer by being stimulated by factors such as stress, pollution, radiation, as well as lack of oxygen. Therefore, cellular oxygen deficiency is an important factor thought to lead to cancer. It is determined that the CXCR4 gene is activated in the state of hypoxia, which is known as a dysfunction that develops due to lack of oxygen in the blood, cells and tissues.

The scientists determined that the activation of this gene makes it easier for cancerous cells to move to other organs, and noted that the cells escape from the lack of oxygen in the primary tumor.

Cells left without oxygen return to their primitive forms, which are anaerobic (the ability to survive without oxygen). This means that germ cells and cancer cells cannot maintain their viability in high oxygen concentrations. So, if these anaerobic microbial and cancerous cells are exposed to an environment with abundant and active oxygen for a long time, they lose their ability to survive.

If all body fluids, brain, bone marrow, and every cell are saturated with oxygen slowly and in high doses over a period of several months, microbial diseases disappear and cancer cells die (Clavo et al., 2004).

Ozone increases chemoradiosensitivity by increasing oxygenation. Thus, it increases the effectiveness of chemoradiotherapy and reduces side effects such as fibrosis formation and polyneuropathy in the long term (Tirelli et al. 2018; Luongo et al., 2017; Baeza-Noci & Pinto-Bonilla, 2021).

Acidosis and Cancer

Tumor cells have 'anaerobic metabolism'. anaerobic metabolism increases 'tissue acidification. Acidification increases the risk of invasion (relapse and local progression) and metastasis. It enables the new generation of tumor cells that grow in an acidic environment to be more aggressive. Ozone is used in the elimination of chronic tissue acidification.

When cells are deprived of oxygen, they can revert to their most primitive stages and engage in glucose reactions, getting their energy not from oxygen as normal plants and animals do, but instead from the fermentation of sugar (Estrella et al., 2013).

The rapid growth of cancer cells requires the use of very high amounts of glucose and converts glucose into lactic acid. As the acidity level of the body increases, it becomes more difficult for the cells to use oxygen. As it is known, cancerous cells can contain 10 times more lactic acid than healthy human cells (Robey & Nesbit, 2013).

After anaerobic metabolism glycolysis, ATP synthesis decreases 18-fold. Energy deprivation causes mitochondrial dysfunction, triggering apoptosis. Subsequently, necrotic cells disrupt inflammation and cell signaling. Regeneration/proliferative processes are constantly triggered (Moellering et al., 2008).

Oxidation And Cancer

Since tumor cells have a primitive life form, they have not developed mechanisms (antioxidant systems) that can protect themselves against oxidation. Tumor cells have 'low antioxidant capacity'. When ozone gas is used directly in high doses, it oxidizes and lyses the outer lipid layer of malignant cells (Menendez et al., 2008).

Ozone and oxygen derivatives, with their strong antioxidant properties, burn products and cause energy generation and the death (burning) of microbes and cancer cells. Because neither microbial agents nor cancer cells have mechanisms to protect themselves against oxygen. because they have a more primitive life form.

Normal body cells can protect themselves against the oxidizing effect of oxygen with the protective antioxidant coating they have naturally developed. It oxidizes the outer lipid layers of malignant cells, causing cell lysis and inhibiting tumor cell metabolism.

In experimental studies in which tumors were created, it has been shown that the phagocytic activities of immune cells in the blood of experimental animals increase, regardless of the stage of the tumor and the application method of ozone therapy.

Ozone creates tumor destruction by activating the phagocytosis function of macrophages. In addition to its direct antineoplastic effect, ozone also increases the production of tumor necrosis factor. TNF is produced by alpha-type macrophages and beta-type T lymphocytes when any tumor develops. It has been determined that ozone therapy increases the most important interleukin-2, which creates immune defense and antitumor resistance produced by T-helper cells.

Studies have shown that phagocyte metabolism is activated by subcutaneous injection of ozonated saline solution around the sarcoma. It has been shown that ozone selectively inhibits lung, breast, and uterine cancer cells (Megele et al., 2018).

Sensitizing Effect of Ozone Therapy to Chemoradiotherapy

The oxygen molecule has both radiosensitizing and chemosensitizing effects. Thus increasing the effectiveness of these treatments. It also reduces the application doses of these treatments and widens the dose interval. It reduces the incidence of side effects in tissues. It increases the tissue's tolerance to the side effects of such treatment. It prevents radiation fibrosis while increasing its radiobiological effects (Tirelli et al. 2018; Luongo et al., 2017; Menendez et al., 2008).

With ozone therapy, radiation-induced vascular changes, gliosis, necrosis, and oligodendrocyte demyelination decrease. Complaints related to necrosis, infarction, and demyelination, which are radiation effects on the medulla spinalis, decrease; The most prominent of these is demyelination myelopathy called LHermitte's Sign, which occurs approximately in 2-4 months. The other one is 9-15. It is paresthesia and sensory loss that develops with chronic radiation myelitis seen in months. Ozone therapy also modulates hormone metabolism and reduces hypopituitarism and growth hormone deficiency, which can develop 2-20 years after radiotherapy.

The eye is one of the organs most sensitive to radiation, and it reduces the sensitivity to radiation that will develop especially in the lens. Factors such as microaneurysm, hemorrhage, neovascularization and thrombosis in the retina that ultimately affect vision loss are reduced. It provides this with its local m Ozone therapy reduces thrombosis, ischemia, mucosal epithelium loss, pallor, telangiectasia, ulcer formation caused by radiation, and eliminates nerve damage called radiation neuritis and anticoagulation effects.

Ozone therapy is also recommended for the prophylaxis of radiation pneumonitis and fibrosis. Because fibrosis that may occur during irradiation in the lung area can cause heart failure symptoms as well as a decrease in pulmonary functions.

Ozone therapy is recommended to reduce pericardial effusion, constrictive pericarditis, delayed acute pericarditis, myocardiopathy, radiation-induced sinusoidal conduction disorders, peripheral ascites, and edema.

It has been shown that dysphagia, one of the most common symptoms after esophageal irradiation, is reduced to a minimum level with ozone therapy because it prevents fibrosis and structure formation in the esophagus. Again, ozone therapy prevents possible late complications of abdominopelvic radiation.

With ozone therapy, acid and pepsinogen secretion in the stomach is regulated. Thus, while a 20% reduction in the incidence of gastritis was observed, a 15% reduction in the incidence of gastric ulcers and a 10% reduction in perforation were reported. It has been reported that ozone therapy reduces the frequency of small bowel dysfunction, mesenteric cramps due to thrombus, diarrhea, malabsorption syndromes and developing ileus.

Painless rectal bleeding, segmental colitis, and narrowing after rectal structure, which may occur 6-12 months after radiotherapy, are reduced by ozone therapy; The incidence of severe proctitis decreases by 18%, severe rectal bleeding decreases by 15-20%, and the incidence of necrotic fistula decreases.

It reduces the frequency and degree of central vein occlusive disease in the liver. It reduces microangiopathic glomerulosclerosis and complete obliteration that can be seen in the kidneys; it prevents acute radiation nephropathy and the symptoms that develop related to it.

It is used both to prevent and treat radiation cystitis. It is used to prevent and treat hemorrhagic cystitis, ulcer, fibrosis, urethral stricture, obstructive uropathy and fistula formation that may occur due to retroperitoneal fibrosis, which can be seen in abdominopelvic irradiation.

Ozone therapy should be added to the prevention and treatment of dryness, wrinkles, telangiectasia, pigmentation changes, superficial atrophy, subcutaneous fibrosis, chronic wounds, skin ulcerations and necrosis seen after radiation on the skin. Because ozone therapy reduces the subcutaneous fibrous reaction.

It helps prevent mucosal radiation damage, mucosal intolerance, atrophy and necrosis throughout the body. It reduces the possibility of osteoporosis, avascular necrosis and fracture in bones. It prevents the formation of bone marrow fibrosis.

Ozone Therapy Dosing Protocol

Care should be taken not to apply low doses of ozone therapy during chemotherapy, as ozone therapy reduces the oxidation effect of chemotherapy. If ozone therapy is to be administered simultaneously with chemotherapy, it is recommended to do it in high doses and multipass. During radiotherapy, low-medium dose ozone multipass can be administered 2-3 times a week.

Additionally, 3-5 cc of solution taken from the cellular depression at the bottom of the tube after centrifugation, prepared from the patient's blood in the form of a tumor vaccine (minor application), can be ozonated at 80-120 gamma and injected intramuscularly.

In patients who do not receive classical treatment (chemoradiation)

If there is an active tumor; high dose (50-80 gamma) multipass every day for a total of 3-6 months, as well as a 3-5cc minor application (80-120 gamma), which we call tumor vaccine.

If there is no active tumor; low dose-multipass ozone therapy is performed 1-3 times a week for 3-6 months. Also, the tumor vaccine is from 3-5cc/20-30 gamma.

References

Akbulut, G. (2017). Tıbbi beslenme tedavisinde güncel uygulamalar. *Ankara Nobel Tıp Kitapevleri*.

Akbulut, G. (2019). Kanserde beslenme tedavisi. *Ankara Nobel Tıp Kitapevleri.*

Arafat, H. M., Omar, J., Shafii, N., Naser, I. A., Al Laham, N. A., Muhamad, R., Al-Astani, T. A. D., Shaqaliah, A. J., Shamallakh, O. M., Shamallakh, K. M., & Abusalah, M. A. H. (2023). The association between breast cancer and consumption of dairy products: a systematic review. *Annals of medicine, 55*(1), 2198256. https://doi.org/10.1080/07853890.2023.2198256

Baeza-Noci, J., & Pinto-Bonilla, R. (2021). Systemic Review: Ozone: A Potential New Chemotherapy. *International journal of molecular sciences, 22*(21), 11796. https://doi.org/10.3390/ijms222111796

Balkwill, F., & Mantovani, A. (2001). Inflammation and cancer: back to Virchow?. *Lancet (London, England), 357*(9255), 539–545. https://doi.org/10.1016/S0140-6736(00)04046-0

Balkwill, F. R., & Mantovani, A. (2012). Cancer-related inflammation: common themes and therapeutic opportunities. *Seminars in cancer biology, 22*(1), 33–40. https://doi.org/10.1016/j.semcancer.2011.12.005

Brewczyński, A., Jabłońska, B., Mrowiec, S., Składowski, K., & Rutkowski, T. (2020).

Nutritional Support in Head and Neck Radiotherapy Patients Considering HPV Status. *Nutrients, 13*(1), 57. https://doi.org/10.3390/nu13010057

Busuttil, R. A., Zapparoli, G. V., Haupt, S., Fennell, C., Wong, S. Q., Pang, J. M., Takeno, E. A., Mitchell, C., Di Costanzo, N., Fox, S., Haupt, Y., Dobrovic, A., & Boussioutas, A. (2014). Role of p53 in the progression of gastric cancer. *Oncotarget, 5*(23), 12016–12026. https://doi.org/10.18632/oncotarget.2434

Buttiron Webber, T., Briata, I. M., DeCensi, A., Cevasco, I., & Paleari, L. (2023). Taste and Smell Disorders in Cancer Treatment: Results from an Integrative Rapid Systematic Review. *International journal of molecular sciences, 24*(3), 2538. https://doi.org/10.3390/ijms24032538

Chang, V. C., Cotterchio, M., & Khoo, E. (2019). Iron intake, body iron status, and risk of breast cancer: a systematic review and meta-analysis. *BMC cancer, 19(*1), 543. https://doi.org/10.1186/s12885-019-5642-0

Chen, G., Leary, S., Niu, J., Perry, R., & Papadaki, A. (2023). The Role of the Mediterranean Diet in Breast Cancer Survivorship: A Systematic Review and Meta-Analysis of Observational Studies and Randomised Controlled Trials. *Nutrients, 15*(9), 2099. https://doi.org/10.3390/nu15092099

Clamon, G., Byrne, M. M., & Talbert, E. E. (2022). Inflammation as a Therapeutic Target in Cancer Cachexia. *Cancers, 14*(21), 5262. https://doi.org/10.3390/cancers14215262

Clavo, B., Pérez, J. L., López, L., Suárez, G., Lloret, M., Rodríguez, V., Macías, D., Santana, M., Hernández, M. A., Martín-Oliva, R., & Robaina, F. (2004). Ozone Therapy for Tumor Oxygenation: a Pilot Study. *Evidence-based complementary and alternative medicine: eCAM, 1*(1), 93–98. https://doi.org/10.1093/ecam/neh009

Coussens, L. M., & Werb, Z. (2002). Inflammation and cancer. *Nature, 420*(6917), 860–867. https://doi.org/10.1038/nature01322

Devericks, E. N., Carson, M. S., McCullough, L. E., Coleman, M. F., & Hursting, S. D. (2022). The obesity-breast cancer link: a multidisciplinary perspective. *Cancer metastasis reviews, 41*(3), 607–625. https://doi.org/10.1007/s10555-022-10043-5

Eaden, J., Abrams, K., Ekbom, A., Jackson, E., & Mayberry, J. (2000). Colorectal cancer prevention in ulcerative colitis: a case-control study. *Alimentary pharmacology & therapeutics, 14*(2), 145–153. https://doi.org/10.1046/j.1365-2036.2000.00698.x

Estrella, V., Chen, T., Lloyd, M., Wojtkowiak, J., Cornnell, H. H., Ibrahim-Hashim, A., Bailey, K., Balagurunathan, Y., Rothberg, J. M., Sloane, B. F., Johnson, J., Gatenby, R. A., & Gillies, R. J. (2013). Acidity generated by the tumor microenvironment drives local invasion. *Cancer research, 73*(5), 1524–1535. https://doi.org/10.1158/0008-5472.CAN-12-2796

Gariboldi, M. B., Marras, E., Ferrario, N., Vivona, V., Prini, P., Vignati, F., & Perletti, G. (2023). Anti-Cancer Potential of Edible/Medicinal Mushrooms in Breast Cancer. *International journal of molecular sciences, 24*(12), 10120. https://doi.org/10.3390/ijms241210120

Greten, F. R., & Grivennikov, S. I. (2019). Inflammation and Cancer: Triggers, Mechanisms, and Consequences. *Immunity, 51*(1), 27–41. https://doi.org/10.1016/j.immuni.2019.06.025

He, Y., Tao, Q., Zhou, F., Si, Y., Fu, R., Xu, B., Xu, J., Li, X., & Chen, B. (2021). The relationship between dairy products intake and breast cancer incidence: a meta-analysis of observational studies. *BMC cancer, 21*(1), 1109. https://doi.

org/10.1186/s12885-021-08854-w

Hussain, S. P., & Harris, C. C. (2007). Inflammation and cancer: an ancient link with novel potentials. *International journal of cancer, 121*(11), 2373–2380. https://doi.org/10.1002/ijc.23173

Hussain, S. P., Hofseth, L. J., & Harris, C. C. (2003). Radical causes of cancer. *Nature reviews. Cancer, 3*(4), 276–285. https://doi.org/10.1038/nrc1046

Itzkowitz, S. H., & Yio, X. (2004). Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. American journal of physiology. *Gastrointestinal and liver physiology, 287*(1), G7–G17. https://doi.org/10.1152/ajpgi.00079.2004

Itzkowitz, S. H., & Yio, X. (2004). Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. American journal of physiology. *Gastrointestinal and liver physiology, 287*(1), G7–G17. https://doi.org/10.1152/ajpgi.00079.2004

Kashyap, D., Pal, D., Sharma, R., Garg, V. K., Goel, N., Koundal, D., Zaguia, A., Koundal, S., & Belay, A. (2022). Global Increase in Breast Cancer Incidence: Risk Factors and Preventive Measures. *BioMed research international, 2022*, 9605439. https://doi.org/10.1155/2022/9605439

Kundu, J. K., & Surh, Y. J. (2008). Inflammation: gearing the journey to cancer. *Mutation research, 659*(1-2), 15–30. https://doi.org/10.1016/j.mrrev.2008.03.002

Luongo, M., Brigida, A. L., Mascolo, L., & Gaudino, G. (2017). Possible Therapeutic Effects of Ozone Mixture on Hypoxia in Tumor Development. *Anticancer research, 37*(2), 425–435. https://doi.org/10.21873/anticanres.11334

Mantovani, A., Bottazzi, B., Colotta, F., Sozzani, S., & Ruco, L. (1992). The origin and function of tumor-associated macrophages. *Immunology today, 13*(7), 265–270. https://doi.org/10.1016/0167-5699(92)90008-U

Marzbani, B., Nazari, J., Najafi, F., Marzbani, B., Shahabadi, S., Amini, M., Moradinazar, M., Pasdar, Y., Shakiba, E., & Amini, S. (2019). Dietary patterns, nutrition, and risk of breast cancer: a case-control study in the west of Iran. *Epidemiology and health, 41*, e2019003. https://doi.org/10.4178/epih.e2019003

Mason, J. K., & Thompson, L. U. (2014). Flaxseed and its lignan and oil components: can they play a role in reducing the risk of and improving the treatment of breast cancer?. *Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme, 39*(6), 663–678. https://doi.org/10.1139/apnm-2013-0420

Megele, R., Riemenschneider, M. J., Dodoo-Schittko, F., Feyrer, M., & Kleindienst, A. (2018). Intra-tumoral treatment with oxygen-ozone in glioblastoma: A systematic literature search and results of a case series. *Oncology letters, 16*(5), 5813–5822. https://doi.org/10.3892/ol.2018.9397

Melnik, B. C., John, S. M., Carrera-Bastos, P., Cordain, L., Leitzmann, C., Weiskirchen, R., & Schmitz, G. (2023). The Role of Cow's Milk Consumption in Breast Cancer Initiation and Progression. *Current nutrition reports, 12*(1), 122–140. https://doi.org/10.1007/s13668-023-00457-0

Menendez, A. S., Cepero, J., & Borrego, L. (2008). Ozone therapy in cancer treatment. *Ozone: science and energies, 30*, 398-404.

Moellering, R. E., Black, K. C., Krishnamurty, C., Baggett, B. K., Stafford, P., Rain, M., Gatenby, R. A., & Gillies, R. J. (2008). Acid treatment of melanoma cells selects for invasive phenotypes. *Clinical & experimental metastasis, 25*(4), 411–425. https://doi.org/10.1007/s10585-008-9145-7

Mullie, P., Koechlin, A., Boniol, M., Autier, P., & Boyle, P. (2016). Relation between Breast Cancer and High Glycemic Index or Glycemic Load: A Meta-analysis of Prospective Cohort Studies. *Critical reviews in food science and nutrition, 56*(1), 152–159. https://doi.org/10.1080/10408398.2012.718723

Negus, R. P., Stamp, G. W., Hadley, J., & Balkwill, F. R. (1997). Quantitative assessment of the leukocyte infiltrate in ovarian cancer and its relationship to the expression of C-C chemokines. *The American journal of pathology, 150*(5), 1723–1734.

Padma V. V. (2015). An overview of targeted cancer therapy. *BioMedicine, 5*(4), 19. https://doi.org/10.7603/s40681-015-0019-4

Paixão, E. M. D. S., Oliveira, A. C. M., Pizato, N., Muniz-Junqueira, M. I., Magalhães, K. G., Nakano, E. Y., & Ito, M. K. (2017). The effects of EPA and DHA enriched fish oil on nutritional and immunological markers of treatment naïve breast cancer patients: a randomized double-blind controlled trial. *Nutrition journal, 16*(1), 71. https://doi.org/10.1186/s12937-017-0295-9

Pejčić, T., Zeković, M., Bumbaširević, U., Kalaba, M., Vovk, I., Bensa, M., Popović, L., & Tešić, Ž. (2023). The Role of Isoflavones in the Prevention of Breast Cancer and Prostate Cancer. *Antioxidants (Basel, Switzerland), 12*(2), 368. https://doi.org/10.3390/antiox12020368

Peixoto da Silva, S., Santos, J. M. O., Costa E Silva, M. P., Gil da Costa, R. M., & Medeiros, R. (2020). Cancer cachexia and its pathophysiology: links with sarcopenia, anorexia and asthenia. *Journal of cachexia, sarcopenia and muscle, 11*(3), 619–635. https://doi.org/10.1002/jcsm.12528

Philpott, M., & Ferguson, L. R. (2004). Immunonutrition and cancer. *Mutation research, 551*(1-2), 29–42. https://doi.org/10.1016/j.mrfmmm.2004.03.005

Robey, I. F., & Nesbit, L. A. (2013). Investigating mechanisms of alkalinization for reducing primary breast tumor invasion. *BioMed research international, 2013*, 485196. https://doi.org/10.1155/2013/485196

Sarasin A. (1999). The molecular pathways of ultraviolet-induced carcinogenesis. *Mutation research, 428*(1-2), 5–10. https://doi.org/10.1016/s1383-5742(99)00025-3

Shacter, E., & Weitzman, S. A. (2002). Chronic inflammation and cancer. *Oncology (Williston Park, N.Y.), 16*(2), 217–232.

Sofi, N. Y., Jain, M., Kapil, U., Seenu, V., R, L., Yadav, C. P., Pandey, R. M., & Sareen, N. (2018). Reproductive factors, nutritional status and serum 25(OH)D levels in women with breast cancer: A case control study. *The Journal of steroid biochemistry and molecular biology, 175*, 200–204. https://doi.org/10.1016/j.jsbmb.2017.11.003

Sun, Q., Xie, W., Wang, Y., Chong, F., Song, M., Li, T., Xu, L., & Song, C. (2020). Alcohol Consumption by Beverage Type and Risk of Breast Cancer: A Dose-Response Meta-Analysis of Prospective Cohort Studies. *Alcohol and alcoholism (Oxford, Oxfordshire), 55*(3), 246–253. https://doi.org/10.1093/alcalc/agaa012

Talbert, E. E., & Guttridge, D. C. (2022). Emerging signaling mediators in the anorexia-cachexia syndrome of cancer. *Trends in cancer, 8*(5), 397–403. https://doi.org/10.1016/j.trecan.2022.01.004

Tirelli, U., Cirrito, C., Pavanello, M., Del Pup, L., Lleshi, A., & Berretta, M. (2018). Oxygen-ozone therapy as support and palliative therapy in 50 cancer patients with fatigue - A short report. *European review for medical and pharmacological sciences, 22*(22), 8030–8033. https://doi.org/10.26355/eurrev_201811_16432

Zhang, X. L., & Ying, J. E. (2022). Olanzapine for the Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting: A Review to Identify the Best

Way to Administer the Drug. *Current oncology (Toronto, Ont.), 29*(11), 8235–8243. https://doi.org/10.3390/curroncol29110650

About the Authors

Dr. Hayriye Alp, graduated from Dokuz Eylül University, Faculty of Medicine in 1998. After working as a general practitioner for about 10 years, she received her anesthesia and reanimation specialization in 2012. Necmettin Erbakan Univ., where she started working in 2015. She still continues to work as a faculty member at the Faculty of Health Sciences. She also founded the GETAT Application Research Center of the same university and has 8 separate certificates. As a GETAT practitioner and trainer, she organizes courses certified by the Ministry of Health. Her areas of interest are acupuncture, phytotherapy, aromatherapy, homeopathy, prolotherapy, leeches, cupping, ozone therapy and mesotherapy.
E-mail: hayriyealp@erbakan.edu.tr **ORCID:** 0000-0002-7262-2234

Şerife AYDIN, graduated from KTO Karatay University Physiotherapy and Rehabilitation Department in 2021. In 2022, she started her master's degree education at Necmettin Erbakan University. She is currently in the thesis stage of her master's degree education and continues her studies.
E-mail: serifeaydin431@gmail.com , **ORCID:**0000-0002-9138-9300

Similarity Index
The similarity index obtained from the plagiarism software for this book chapter is 7%.

Chapter 11

Anatomical Description of Acupuncture Points and Bioresonance Therapy

Ayşe Gamze ÖZCAN
Selçuk University

İsmail ESEOĞLU
Dokuz Eylül University Vocational School of Healthcare

To Cite This Chapter

Özcan, A. G., & Eseoğlu, İ. (2024). Anatomical Description of Acupuncture Points and Bioresonance Therapy. In F. Nur Takı, S. Koçer & R. Bütüner (Eds.), *New Generation Technologies and Sustainability in Health Current Studies* (pp. 178-193). ISRES Publishing.

Introduction

Acupuncture, a traditional treatment method that has been known since ancient times, continues to be widely used today.This treatment, which has been used since ancient times, is performed by needling specific acupuncture points using special and sterile disposable needles. In order for all practitioners performing acupuncture to consistently locate these points, it is essential that the definitions of these acupuncture points be made accurately. Such definitions can only be effectively made using anatomical landmarks, which serve as the common framework among physicians (Zhang, 2021). Therefore, this chapter provides the anatomical descriptions of the locations of the back-shu, front-mu, he-sea, yuan-source, tonification, and sedation points.

Back-Shu Points

The back-shu points, located on the posterior aspect of the body, represent key points along their respective meridians. These points exert their effects through the posterior root of the spinal nerve. They are particularly effective in treating chronic conditions, diseases related to energy depletion, and disorders of the sensory organs. These points are located along the Bladder meridian and are bilaterally symmetrical. The back-shu points of all meridians are situated 1.5 cun lateral to the spinous process of the relevant vertebra. In the table below, the back-shu points for each meridian are identified by the vertebral level at which they are located (Table 1) (Cabioglu & Arslan, 2008).

Anatomical landmarks provide essential guidance in accurately locating back-shu points. For instance, BL 25 can be easily found by locating the superior border of the iliac crest; the point is situated 1.5 cun lateral to the midline at this level. Similarly, BL 14 is located at the intersection of a horizontal line drawn from the scapular spines of both scapulae with the midline of the body (Jarmey & Bouratinos, 2008).

Some of the back-shu points are located at the same level as points on the DU meridian and are positioned 1.5 cun lateral to them. For instance, BL 20 is at the level of DU 6, while BL 15 is at the level of DU 11. For the Small Intestine and Bladder meridians, the back-shu points BL 27 and BL 28 are located at the level of the first and second posterior sacral foramina, respectively. These precise anatomical descriptions ensure that practitioners can consistently and accurately locate these critical points (Cho et al., 2022).

Table 1
Back-Shu Points and Their Anatomical Locations

YIN	BACK-SHU	Anatomical Location
LUNG	BL 13	T3
PERICARDIUM	BL 14	T4
HEART	BL15	T5
SPLEEN	BL 20	T11
KIDNEY	BL 23	L2
LIVER	BL 18	T9
YANG		
LARGE INTESTINE	BL 25	L4
SMALL INTESTINE	BL 27	S1
TRIPLE BURNER	BL 22	L1
STOMACH	BL 21	T12
GALL BLADDER	BL 19	T10
BLADDER	BL 28	S2

Front-Mu Points

Front-mu points are some of the most significant points located on the anterior side of the body along the meridians. While the points on the Ren meridian are singular, those on other meridians are paired. These points exert their influence through the ventral root of the spinal nerve. Sensitivity at these points often indicates a disorder in the corresponding organ. Front-mu points are predominantly concentrated in the thorax and abdomen. Half of these points are located on the Ren meridian, distributed along the midline both above and below the umbilicus.

Several front-mu points can be easily located using anatomical landmarks. For instance, REN 12 is situated midway between the umbilicus and the xiphoid process, while REN 17 is located at the midpoint of a line drawn between the nipples in males. GB 24 and

LIV 14 are positioned at the level of the nipples on their respective sides (Table 2) (Fu, 2014).

Table 2
Front-mu Points and Their Anatomical Locations

YIN	FRONT-MU	Anatomical Location
LUNG	LU 1	Beneath the coracoid process, 6 cun lateral to the sternum
PERICARD	REN 17	The level of the 4th intercostal space
HEART	REN 14	6 cun above the umbilicus
SPLEEN	LIV 13	Below the free end of the 11th rib
KIDNEY	GB 25	The free lower end of the 12th rib
LIVER	LIV 14	4 cun lateral to the sternum at the level of the 6th intercostal space
YANG		
LARGE INTESTINE	ST 25	2 cun lateral to the umbilicus
SMALL INTESTINE	REN 4	3 cun below the umbilicus
TRIPLE BURNER	REN 5	2 cun below the umbilicus
STOMACH	REN 12	4 cun above the umbilicus
GALL BLADDER	GB 24	4 cun lateral to the midline in the 7th intercostal space
BLADDER	REN 3	4 cun below the umbilicus

He-sea Points

He-sea points are significant locations on the meridians where Qi energy is concentrated and most abundant. These points are particularly effective in treating external pathogenic conditions and are considered vital in acupuncture practice. He-sea points are primarily located around the knee and elbow joints, distributed along the meridians of both the upper and lower extremities. Each meridian has its specific he-sea point, which is found along the meridian's pathway. Below are the he-sea points for each meridian along with their precise anatomical locations. LU 5 is both the he-sea point and the sedation point of the Lung meridian. This point is located on the outer side of the biceps brachii tendon, along the transverse crease of the cubital fossa.

LI 11 serves as the he-sea and tonification point of the Large Intestine meridian. It is found at the lateral end of the transverse cubital crease when the forearm is flexed.

ST 36 is one of the most studied acupuncture points in literature. It is situated 1 fingerbreadth lateral to the tibial tuberosity and 3 cun distal to the knee joint.

SP 9 can be located by flexing the knee. The point lies just below the medial condyle of the tibia (Focks, 2008).

H 3, is found by flexing the elbow. It is located at the medial end of the transverse cubital crease, between the medial epicondyle and the ulna.

SI 8, is situated between the medial epicondyle and the olecranon. This point is easily located by flexing the elbow and is also the sedation point of the meridian.

BL 40, is located at the center of the transverse line drawn across the popliteal fossa at the knee.

KID 10 is found between the tendons of the semimembranosus and semitendinosus muscles on the medial side of the knee. The point is more easily found by flexing the knee.

P 3 is situated on the medial side of the biceps brachii tendon, on a transverse line drawn from the cubital fossa.

TB 10 is located on the posterior aspect of the arm, 1 cun above to the olecranon on the humerus. It is easily found by flexing the elbow and is also the sedation point of the meridian.

GB 34 is found between the extensor digitorum longus and peroneus longus muscles, inferior and anterior to the head of the fibula.

LIV 8, which also serves as a tonification point, is located in front of the tendons of the semimembranosus and semitendinosus muscles on the medial side of the knee. It is more easily found by flexing the knee and is situated just above the medial end of the transverse line drawn from the popliteal fossa.

These detailed anatomical descriptions ensure that practitioners can consistently and accurately locate these critical acupuncture points for effective treatment (Suh, 2015).

Table 3
He-Sea Points of the Meridians

YIN	HE-SEA
LUNG	LU 5
PERICARD	P 3
HEART	H 3
SPLEEN	SP 9
KIDNEY	KID 10

LIVER	LIV 8
YANG	
LARGE INTESTINE	LI 11
SMALL INTESTINE	SI 8
TRIPLE BURNER	TB 10
STOMACH	ST 36
GALL BLADDER	GB 34
BLADDER	BL 40

Yuan Source Points

In acupuncture, each meridian has its own Yuan source point, which is considered the most important point on the meridian. These points play a crucial role in balancing the energy (Qi) within the meridian. If the energy of the meridian is deficient, the Yuan source point, in conjunction with the tonification point, helps to increase the energy. Conversely, if the energy is excessive, the Yuan source point, along with the sedation point, helps to reduce the energy. Thus, the Yuan source points act as catalysts, adjusting the energy according to the needs of the meridian. The following section provides a detailed description of the Yuan source points for each meridian, along with their anatomical locations. These points are all located on their respective meridians (Chamberlin et al., 2011).

For the Lung meridian, this point is LU 9. It is located on the wrist, lateral to the radial artery when a hypothetical transverse line is drawn across the wrist. LU 9 also serves as the tonification point of the meridian.

LI 4 is situated between the first and second metacarpal bones. On the dorsal surface of the hand, when the first and second digits are adducted, LI 4 is the most prominent point between these bones.

ST 42 is located on the dorsum of the foot, positioned between the tendons of the extensor hallucis longus, responsible for extending the big toe, and the extensor digitorum longus, which extends the other toes. It is found at the highest point on the dorsum of the foot (Ribeiro et al., 2015).

For the Spleen meridian, this point is SP 3, located on the medial side of the foot, where the head of the first metatarsal bone meets its shaft, proximal to the metatarsophalangeal joints.

For the Heart meridian, this point is H 7, found on the medial side, in the depression lateral to the flexor carpi ulnaris tendon, on the wrist. It also serves as the sedation point of the meridian.

SI 4 is located on the ulnar side of the base of the fifth metacarpal bone.

BL 64 is located distal to the tuberosity of the fifth metatarsal bone on the foot.

For the Kidney meridian, this point is KID 3, found on the medial side of the ankle, in the depression between the medial malleolus and the calcaneal tendon (Achilles tendon).

P 7 is located between the tendons of the palmaris longus and flexor carpi radialis, on the wrist. It is also the sedation point of the meridian.

TB 4 is located between the tendons of the extensor digiti minimi and extensor digitorum muscles, on the posterior side of the wrist.

GB 40 is located in the depression anterior and inferior to the lateral malleolus, lateral to the extensor digitorum longus tendon.

For the Liver meridian, this point is LIV 3, located between the 1. and 2. metatarsal bones, on the dorsum of the foot, this point is found in the deepest and broadest part of the depression proximal to the metatarsophalangeal joints (FAN et al., 2021).

In summary, the Yuan source points on the meridians of the hand are primarily located around the wrist. LU 9, P 7, and H 7 are aligned laterally to medially along a transverse line on the anterior side of the wrist, while SI 4, TB 4, and LI 4 are located near the wrist. For the meridians of the foot, the Yuan source points are distributed around the foot and ankle.

Tonification Points

Tonification points in acupuncture are used to increase the energy of their respective meridians. Each of these points is located on its corresponding organ meridian and plays a vital role in restoring balance when the meridian's energy is deficient. The following is a detailed description of the tonification points for each meridian, including their anatomical locations.

LU 9 is located on the wrist, lateral to the radial artery when a hypothetical transverse line is drawn across the wrist. LI 11 is located at the lateral end of the transverse cubital line when the forearm is flexed at the elbow. This point is also the He-sea point of the meridian.

ST 41 is located on the ankle, between the tendons of the extensor hallucis longus, which extends the big toe, and the extensor digitorum longus, responsible for extending the other toes, at the level of the lateral malleolus. SP 2 is found on the medial side of the foot, distal to the first metatarsophalangeal joint (Kwon & Kim, 2015).

For the Heart meridian, this point is H 9, located on the lateral side of the little finger, 0.1 cun lateral to the corner of the nail at the root of the fifth finger. SI 3 is located on the medial side of the hand, proximal to the head of the fifth metacarpal bone.

BL 67 is found on the lateral side of the little toe, 0.5 cun posterior to the corner of the nail. KID 7 is located 2 cun above KID 3, in the depression between the calcaneal tendon (Achilles tendon) and the medial malleolus.

P 9 is located in the center of the distal phalanx on the palmar side, at the tip of the 3rd finger. TB 3 is found between the heads and shafts of the 4th and 5th metacarpal bones, on the posterior side of the hand.

GB 43 is located on the dorsum of the foot, between the bases of the proximal phalanges of the 4th and 5th toes. For the Liver meridian, this point is LIV 8, located on the medial side of the knee, anterior to the tendons of the semimembranosus and semitendinosus muscles. It is found just above the medial end of the transverse line drawn across the popliteal fossa and is more easily located by flexing the knee.

These tonification points are crucial for maintaining the balance of Qi within the meridians, ensuring that the body's energy is properly regulated according to its needs.

Sedation Points

Sedation points in acupuncture are used to reduce the energy (Qi) within their respective meridians. Each sedation point is located on its corresponding organ meridian and is essential for balancing excessive energy. Below is a detailed description of the sedation points for each meridian, along with their anatomical locations.

LU 5 is found lateral to the biceps brachii tendon, on a transverse line drawn across the cubital fossa. This point also serves as the He-sea point of the meridian. For the Large Intestine meridian, this point is LI 2, located on the dorsal side of the hand, at the junction of the body and base of the proximal phalanx of the second finger, on the outer edge.

ST 45 is situated on the lateral side of the 2. phalanx, 0.1 cun lateral to the corner of the nail. SP 5 is located in the depression between the medial malleolus and the metatarsal bones (Ahn et al., 2009).

H 7, which is also the Yuan source point, is found on the wrist, in the depression lateral to the flexor carpi ulnaris tendon, when a transverse line is drawn across the inner side of the wrist. SI 8 is located between the medial epicondyle and the olecranon, in the depression that becomes more pronounced when the elbow is flexed.

BL 65 is located just proximal to the head of the 5. metatarsal bone. KID 1 is located on the plantar surface of the foot, in the depression at the junction of the anterior one-third and the posterior two-thirds of the sole.

P 7 is found between the tendons of the palmaris longus and flexor carpi radialis, in the center of the wrist. TB 10 is located on the posterior side of the arm, 1 cun above the olecranon, in the depression that is easily palpable when the elbow is flexed.

GB 38 is found on the lateral side of the leg, 4 cun proximal to the lateral malleolus. For the Liver meridian, this point is LIV 2, located on the dorsum of the foot, between the bases of the proximal phalanges of the first and second toes.

These sedation points are crucial for managing excess Qi within the meridians, helping to restore balance and maintain the overall energetic harmony of the body.

Table 4
Yuan Source, Tonification, and Sedation Points of the Meridians (Focks, 2008)

YIN	YUAN SOURCE	TONIFICATION	SEDATION
LUNG	LU 9	LU 9	LU 5
PERICARD	P 7	P 9	P 7
HEART	H 7	H 9	H 7
SPLEEN	SP 3	SP 2	SP 5
KIDNEY	KID 3	KID 7	KID 1

LIVER	LIV 3	LIV 8	LIV 2
YANG			
LARGE INTESTINE	LI 4	LI 11	LI 2
SMALL INTESTINE	SI 4	SI 3	SI 8
TRIPLE BURNER	TB 4	TB 3	TB 10
STOMACH	ST 42	ST 41	ST 45
GALL BLADDER	GB 40	GB 43	GB 38
BLADDER	BL 64	BL 67	BL 65

Bioresonance Therapy

Each substance has a specific vibration pattern (frequency). The vibration pattern of any substance is not similar to the vibration pattern of another substance. Like all substances in nature, the human organism also emits different electromagnetic frequencies. Cells, tissues and organs have their own frequencies, which together determine the overall frequency spectrum of a person. These frequencies are different for each person, just like fingerprints. In fact, the frequency of the same person is different when sick and when healthy.

Pathological agents (viruses, bacteria, heavy metals, allergens, etc.) also have their own frequencies and these frequencies disrupt the communication of the cells in the body with each other. Each of the cells in the body undergoes 2,000 or more chemical reactions per second. This situation shows that a very effective electromagnetic control is necessary for the cells to fulfill their functions in a healthy way. Otherwise, it is clear that the chaos that will arise will create a favorable ground for diseases.

The detection and treatment of pathological factors and frequencies in the body is possible with bioresonance therapy.

In bioresonance therapy, the factors that put pressure on the body are investigated first. For this, a bioresonance-specific test is applied in which 6,400 substances are scanned; this test is an examination with frequencies.

Bioresonance is a complementary therapy method to classical medicine. It is based on the principles of Chinese traditional medicine, quantum medicine and new discoveries of biotechniques.

This method, defined as ‘medicine of the future’ and ‘vibration medicine’, is applied by using computer-controlled frequency generators to give ‘patient-appropriate vibrations’. Its basis is the electromagnetic information exchange of cells. With this method, the distorted frequencies of the factors that disturb the body, organs and tissues of the body are detected and healthy frequencies, that is, the frequencies that the body needs, are sent.

After detecting the pathological frequencies, the bioresonance device applies the reverse frequency of these frequencies to the patient thanks to a magnetic cushion. According to physical laws, when the inverse of the frequency is applied, the vibration is reset.

The bioresonance device works on another frequency for each disease. The frequencies of suppressive, damaging substances and factors such as the detected heavy metals, allergies, chemicals (toxic substance), parasites, infections, fungal infections, intense electromagnetic fields, negative effects of the geographical characteristics of the experienced region on the person are eliminated.

The frequency structures of the sick person and the healthy person are different from each other. Because foreign frequencies such as viruses, bacteria, allergens, toxins, amalgams, fungi disrupt the vibrational harmony of the body and cause diseases. With the cleaning of these negative frequencies with a bioresonance device, the information exchange of the cells is restored to its regular state, and when the negative frequencies created by the substances that harm the body are eliminated, improvement is achieved. Disease does not occur in the properly functioning system of the body. Thanks to the ability of bioresonance to eliminate stress on the systems in the body, the body is protected from diseases.

Bioresonance is a therapy technique that does not use drugs and does not have the danger of radiation and microwaves. It has no side effects. The application is completely painless and personalized. It can be applied to people of all ages and sexes. It is even possible to apply it to all living things; like animals and plants.

In therapies applied with a bioresonance device, the aim is to detect the frequencies that disrupt the order and bring them to their correct vibrations. During therapy, the electrodes of the bioresonance device are placed in certain parts of the body. The electromagnetic frequencies that disrupt the frequency are determined and transferred to the device. In the device, these frequencies are purified and returned to the body. Since the pathological frequencies of the patient are normalized by inverting them with bioresonance therapy, the obstacles that disrupt the immune system are removed and the organism becomes healthy.

In this way, biological and physical frequencies are strengthened. Bioresonance therapy stimulates the body's self-healing power and strengthens the defense and immune system. Thus, the patient is healed.

Bioresonance therapies are effective in both acute and chronic diseases. It supports the body's defense system and allows the body to heal itself. These therapies can also be used effectively in cancer, HPV, Covid19 (coronavirus), detox, hormonal balance, intestinal flora, digestive system, musculoskeletal system, supporting brain functions, nervous system, allergies, smoking cessation (etc.).

In chronic diseases, classical medicine is helpless. For example, in the treatment of allergies, drugs are used only to pass the symptoms (for example, itching) for a while. Long-lasting and high-risk treatment methods (immunotherapy) show the desired result at a very small rate.

The success rate of bioresonance is quite high in the detection and treatment of chronic and acute allergies (eczema, hay fever, allergic bronchitis, allergic asthma, allergic conjunctivitis, contact dermatitis, allergic skin lesions, urticaria). The bioresonance test can reveal and treat hidden allergies as well as known allergies. One of the promising features of bioresonance is that it reveals that the main cause of some incurable chronic diseases is an 'undetected allergy'.

Bioresonance accelerates the healing of problems that cause pain. Painful spine problems such as headaches and migraines, painful joint diseases, calcifications, lumbar and neck hernia-calcifications, sports injuries and sprains, painful menstruation, painful rheumatic diseases, pains that do not go away after surgeries and pain whose cause is not understood can be cured with bioresonance therapies. Since the frequencies perceived from the pain area in the body are different from normal, cleaning these frequencies with the bioresonance method eliminates the pain. The effect of bioresonance in trauma-related pain is striking. In chronic pain, on the other hand, the passing of pain requires the treatment of the system as a whole and cleaning the load on the system. The results vary depending on how affected the body is. The effect of bioresonance on children is always stronger.

Stimulation of the lymph system and liver with detoxification in the treatment of chronic diseases is the general rule. Bioresonance stimulates the liver, stimulates the excretion of toxins, kidneys and lymph, and cleanses the kidneys and lymph system. The increase in the number of conscious patients receiving bioresonance therapy for strengthening immunity, improving overall health and detox strengthens the argument that 'bioresonance is the future medical'.

It is now recognised that the environment can control the activity of our genes. Changes in environmental factors can lead to changes in the electrical oscillation in the chromosome, which in turn can cause fluctuations in the epigenetic pattern of the organism. Disease can be thought of as a disruption of biochemical sequences and electromagnetic oscillation patterns in the body, triggered by exogenous and endogenous stimuli. Physical processes at the energy and vibrational level shape the transfer of energy and the flow of bioenergetic information in the living system. Today, many medical centers use electro-diagnostic devices to improve diagnosis and select recommended treatments. The history of these devices goes back a long way.

Nikola Tesla developed the Tesla coil in 1920 during his experiments with high-frequency phenomena. The Tesla coil is an electrically resonant transformer circuit. It is used to generate high-voltage, low-current, high-frequency alternating current electricity. Tesla collaborated with French engineer Georges Lakhovsky to complete the Multi-Wave Oscillator. Tesla and Lakhovsky thought that the cell's core, with its 'filament threads', resembled an electronic oscillating circuit that could send and receive vibrating information. Lakhovsky believed that each cell in the body has its own internal vibration rate. He hypothesized that all living cells (plants, humans, bacteria, parasites, etc.) have resonance. Lakhovsky proposed that all living cells not only produce and emit oscillations at very high frequencies, but also receive and respond to oscillations imposed on them from external sources (Lakhovsky).

In 1920, Rife, an American inventor, had finished building the world's first universal microscope. Rife was an optical engineer and technician of great skill. With this incredible microscope, he could see a living virus for the first time. Using a split spectroscope attachment, Rife carefully identified the individual spectroscopic characteristics (reflected or absorbed) of each microbe. In his work, he gradually rotated block quartz prisms to focus a single wavelength of light onto the microorganism under study. In this way, he found that each molecule oscillated at a unique frequency. Rife calculated a 'Mortality Oscillation Rate' for various pathogenic organisms and claimed to be able to destroy organisms by vibrating them at this particular rate (Rosenow, 1965, Wade, 1994, Montgomery, 2003).

In 1922, the Russian biophysicist A.G. Gurwitsch discovered mitogenetic radiation. He observed that the root of an onion in the growth phase could enhance the cellular division of another root, even if these two roots were separated by glass (Gurwitsch, 1932). This observation was the beginning of the bioresonance method with the development of the theory of biological information transfer (Basset et al., 1993). There are a total of 12 points on the human body, corresponding to the 1000 classical meridians of Chinese medicine. In 1953, Dr Reinhold Voll, a German medical doctor, developed an electronic testing device to electrically locate acupuncture points. He was successful in locating acupuncture points and demonstrating that these points have a different resistance than adjacent tissues when they encounter an electric current. Dr Voll created a diagnostic system based on the electro-conductivity of acupuncture points. He also introduced a specialized scale to effectively interpret the results. For example, he found that patients with lung cancer had abnormal readings on acupuncture points, so-called lung points. He was also successful in combining ancient acupuncture knowledge with western medicine to promote electro-acupuncture as a new method. According to Voll, the resistance of an acupuncture point is a measurement scale of the energy in a particular organ and an indicator of its ability to function. This method makes it possible to measure and record the condition and function of body organs. The overall function of the person can be recorded in this way and the source of the cause can be found.

The system developed on the basis of these findings is called 'Electro-acupuncture according to Voll' (Begher, 1989). Bioresonance is called by different terminologies. The diagnostic procedure is most commonly referred to as Electro-acupuncture according to Voll (EAV) or electrodermal Scanning (EDS), but some practitioners call it bioelectric function diagnosis (BFD), bioresonance therapy (BRT), bioenergy regulatory technique (BER), Biocybernetic Medicine (BM) calls it computerized electrodermal screening (CEDS), computerized electrodermal stress analysis (CDCSA), electrodermal testing (EDT), limbic stress assessment (LSA), meridian energy analysis (MEA) or point testing.

The German doctor Franz Morell is considered the 'father' of bioresonance therapy. In 1977, Morell, who had long-term experience in electro-acupuncture, thought that his treatments could be more precise if he could use the electromagnetic vibrations of the patient's own body. Thus, the first electronic device that could receive and return electromagnetic frequencies from the body using electrodes was manufactured (Markov et al, 2007). This method, defined as 'medicine of the future' and 'vibration medicine', is applied by using computer-controlled frequency generators to give 'vibrations suitable for the patient'. Its basis is the electromagnetic information exchange of cells. With this method, the disturbing factors of the body, the distorted frequencies of the organs and tissues of the body are detected and healthy frequencies, that is, the frequencies that the body needs, are sent. After detecting the pathological frequencies, the bioresonance device applies the reverse frequency of these frequencies to the patient through a magnetic cushion. According to physical laws, when the opposite of the frequency is applied, the vibration is reset.

The bioresonance device works on a different frequency for each disease. The frequencies of suppressive, damaging substances and factors such as heavy metals, allergies, chemicals (toxic substances), parasites, infections, fungal infections, intense electromagnetic fields, negative effects of the geographical characteristics of the region of residence on the person are eliminated. The body receives the disturbing signal from the patient through the input of information from the abdomen (or any other part of the body). This signal is processed and amplified by the bioresonance device. Following this, the reverse therapeutic signal is amplified through the modulation mat located along the spinal cord and returned to the patient. The bioresonance device allows specific parts of the total frequency spectrum to be selected for treatment (Pıhtılı et al., 2014).

In the endogenous form of bioresonance, oscillations are received using electrodes in various parts of the body and are transmitted back into the body for therapeutic purposes following an electronic inversion. In the exogenous form, oscillations of bioactive substances are transmitted into the human body following electronic inversion (e.g. an allergen) or amplification (e.g. nosodes) for therapeutic purposes (Galle et al., 2009). In this way biological and physical frequencies are amplified. Bioresonance therapy stimulates the body's self-healing power and strengthens the defense and immune system. Thus, healing is provided in the patient. Pathological factors (viruses, bacteria, heavy metals, allergens, etc.) also have their own frequencies and these frequencies disrupt the communication of the cells in the body with each other. Each of the cells in the body has 2,000 or more chemical reactions per second. This situation shows that a very effective electromagnetic control is necessary for the cells to fulfill their functions in a healthy way. Otherwise, it is clear that the chaos that will arise will create a favorable ground for diseases. The frequency structures of sick people and healthy people are different from each other.

Because external frequencies such as viruses, bacteria, allergens, toxins, amalgam, fungi disrupt the vibrational harmony of the body and cause diseases. With the cleaning of these frequencies that have a negative effect with the bioresonance device, the information exchange of the cells regains its former regular state, and when the negative frequencies created by the substances that harm the body are eliminated, healing is provided. Disease does not occur in the body's properly functioning system. Thanks to the ability of bioresonance to eliminate the stress on the systems in the body, the body is protected from diseases.

Bioresonance therapies are effective in both acute and chronic diseases. It supports the body's defense system and enables the body to heal itself. These therapies can be used effectively in cancer, HPV, Covid19 (coronavirus), detox, hormonal balance, intestinal flora, digestive system, musculoskeletal system, support of brain functions, nervous system, allergies, smoking cessation (etc.).

Conventional medicine is helpless in chronic diseases. For example, in the treatment of allergies, medication is only used to relieve the symptoms (e.g. itching) for a while. Prolonged and high-risk treatment methods (immunotherapy) show the desired result only to a very small extent.

The basic principle of bioresonance is that each person is an individual being and should be treated holistically. Therefore, every disease of a particular organism is an individual case and should be treated accordingly. Bioresonance therapy should be specially adapted to each patient. Despite increasing scientific efforts to determine the etiology and mechanisms associated with the treatment of chronic diseases, the number of these diseases is constantly increasing. One concept that defines the etiology and mechanisms of chronic diseases is based on 'Epigenetic Changes' (Angrish et al., 2018).

Epigenetic changes cause activation or silencing of a gene, which is similar to a genetic mechanism that activates a gene, such as mutation or deletion. However, epigenetic changes occur without causing a change in the base sequence and are often reversible. The genome is like the parts list of a living thing, it tells us what the living thing is made of, but it does not tell us how they work (Karaçay, 2010). The nuclear chromatin cluster is capable of electrical oscillation in the eukaryotic nucleus. The natural frequency of an oscillating chromatin region is determined by the physical properties of the DNA-protein complexes in that region, and these properties can be altered by its epigenetic state and associated protein factors (Miyamoto et al., 2015). Detection of such changes is possible using bioresonance method and therefore they can be used for early detection of chronic diseases. Bioresonance works on the basis of spectral analysis of the magnetic fields of living organisms and thus allows the therapist to distinguish between normal and abnormal frequencies emitted by the body. Electromagnetic waves, as epigenetic factors, can influence the dynamic changes of chromatin, resulting in activation or suppression of the body's biochemical processes and may play a critical role in the development or treatment of chronic diseases (Mehdipour et al., 2015).

The detection and treatment of pathological factors and frequencies in the body is possible with bioresonance therapy. In bioresonance therapy, the factors that put pressure on the body are investigated first. For this, a bioresonance-specific test is applied in which 6,400 substances are scanned; this test is an examination with frequencies. Bioresonance is a new development in the field of medicine that meets the need for early detection of disorders and organismal malfunctions that can potentially turn into disorders. Bioresonance is a method that can help both to determine the state of health and to prevent and restore it by identifying the underlying causes of a disease. The aim of bioresonance therapy is to improve health by restoring the body's energy flow, eliminating pathological conditions and restoring the body's self-healing system and treating pathological conditions that cause disease (Karakos et al.).

Bioresonance is a therapy technique without the use of drugs, radiation and microwave hazards. There are no side effects. The application is completely painless and personalized. It can be applied to people of all ages and sexes. It is even possible to apply to all living things; such as animals and plants. Each substance has a specific vibration pattern (frequency). The vibration pattern of any substance is not similar to the vibration pattern of another substance. Like all substances in nature, the human organism also emits different electromagnetic frequencies. Cells, tissues and organs have their own frequencies, which together determine the overall frequency spectrum of a person. These frequencies are different for each person, just like fingerprints. In fact, the frequency of the same person is different when sick and when healthy. The success rate of bioresonance in the detection and treatment of chronic and acute allergies (eczema, hay fever, allergic bronchitis, allergic asthma, allergic conjunctivitis, contact dermatitis, allergic skin lesions, urticaria) is quite high. Bioresonance tests can reveal and treat hidden allergies as well as known allergies. One of the most pleasing features of bioresonance is that it reveals that the main cause of some untreated chronic diseases is an 'undetected allergy'. In 1990, the pediatrician Dr. Schumacher conducted a research study in his medical practice involving 204 children with various allergies. The patients initially completed a questionnaire and then five to nine months after bioresonance treatment, the majority (83%) reported that they no longer had any allergic symptoms. Symptoms improved in 11 per cent of participants, 4.5 per cent reported no difference and 1.5 per cent could not specify. At the time, this was a revolutionary finding. The evidence level of the study was 4-5 (Schumacher, 2005). Around the same time, Dr. Schumacher published another study with patients with high fever (spring allergic rhinitis). In the spring after treatment, 43.4% of patients were no longer symptomatic, while 50.4% of patients showed improvement, indicating that efficacy exceeded 90% (Schumacher, 2005).

Bioresonance accelerates the healing of problems that cause pain. Headaches and migraine, painful joint diseases, arthritis, painful spinal problems such as lumbar and cervical hernia-calcifications, sports injuries and sprains, painful menstruation, painful rheumatic diseases, pain that does not go away after surgeries and pain of unknown cause can be treated with bioresonance therapies. Since the frequencies perceived from the pain area in the body are different from normal, cleaning these frequencies with a bioresonance method eliminates the pain. The effect of bioresonance in trauma-related pain is striking. In chronic pain, the relief of pain requires the system to be handled as a whole and the burden on the system to be relieved. The results vary according to how much the body is affected. The effect of bioresonance on children is always stronger.

In the treatment of chronic diseases, the general rule is to stimulate the lymph system and liver with detoxification. Bioresonance stimulates the liver to excrete toxins and stimulates the kidneys and lymph to cleanse the kidneys and lymph system. The increase in the number of conscious patients receiving bioresonance therapy for strengthening immunity, improving general health and detoxification strengthens the argument that 'bioresonance is the future of medicine'.

Bioresonance does not aim to replace conventional medicine, but it is of great importance as it 'complements' conventional medicine because it is a new approach that may be a new diagnostic and treatment method to prevent and deal with hidden causes in the future. Bioresonance treatments are rapidly becoming widespread both in the world and in Türkiye every day and are in demand from patients; it can already be predicted that it will become much more widespread in the near future.

References

Ahn, C.-B., Jang, K.-J., Yoon, H.-M., Kim, C.-H., Min, Y.-K., Song, C.-H., & Lee, J.-C. (2009). A study of the Sa-Ahm five element acupuncture theory. *Journal of acupuncture and meridian studies*, *2*(4), 309-320.

Cabioglu, M. T., & Arslan, G. (2008). Neurophysiologic basis of back-shu and huatuo-jiaji points. *The American Journal of Chinese Medicine*, *36*(03), 473-479.

Chamberlin, S., Colbert, A. P., & Larsen, A. (2011). Skin conductance at 24 source (Yuan) acupoints in 8637 patients: influence of age, gender and time of day. *Journal of acupuncture and meridian studies*, *4*(1), 14-23.

Cho, Y., Han, Y., Kim, Y., Han, S., Oh, K., Chae, H., Hongmin, C., & Ryu, M. (2022). Anatomical structures and needling method of the back-shu points BL18, BL20, and BL22 related to gastrointestinal organs: A PRISMA-compliant systematic review of acupoints and exploratory mechanism analysis. *Medicine*, *101*(43), e29878. https://doi.org/10.1097/md.0000000000029878

FAN, X.-s., Jun, L., SHE, Y.-f., ZHANG, J.-c., PAN, L.-j., ZHANG, X.-q., SONG, X.-d., Hao, C., GAO, Y.-y., & Xu-Liang, S. (2021). Research on the body surface resistance imbalance degree at yuan-source points of three Yin meridians of foot in the patients with primary dysmenorrhea. *World Journal of Acupuncture-Moxibustion*, *31*(3), 191-196.

Focks C. (2008). Chapter 8 - Point Categories and Point Selection, Atlas of Acupuncture, Churchill Livingstone, Pages 665-696, ISBN 9780443100284, https://doi.

org/10.1016/B978-044310028-4.50011-4.

Fu, J. J. (2014). Meridians and acupuncture points. *Handbook of traditional Chinese medicine*, *3*, 285-453.

Jarmey, C., & Bouratinos, I. (2008). *A practical guide to acu-points*. North Atlantic Books.

Kwon, H.-J., & Kim, Y.-S. (2015). General guide for Korean acupuncture & moxibustion. *Open Journal of Immunology*, *5*(3), 90-103.

Ribeiro, D. C., Moura dos Santos, A. A., Loureiro, R. P., Gonçalves, R. M., & Machado, J. P. (2015). Assessment of Short-Term Acupuncture Effect Through Electro-Conductivity Variation of Yuan-Source Acupoints. *World Journal of Traditional Chinese Medicine*, *1*(4), 48-52. https://doi.org/10.15806/j.issn.2311-8571.2015.0023

Suh, C. S. (2015). *Acupuncture anatomy: regional micro-anatomy and systemic acupuncture networks*. CRC Press.

Zhang, Y. (2021). Interpretation of acupoint location in traditional Chinese medicine teaching: Implications for acupuncture in research and clinical practice. *The Anatomical Record*, *304*(11), 2372-2380. https://doi.org/https://doi.org/10.1002/ar.24618

Angrish MM, Allard P, McCullough SD, et al. Epigenetic Applications in Adverse Outcome Pathways and Environmental Risk Assessment. Environ Health Perspect 2018; 126(4)045001 [http://dx.doi.org/10.1289/EHP2322] [PMID: 29669403]

Karaçay B., The secret of life DNA. Tubitak publications (2010).

Miyamoto K, Ushijima T. Diagnostic and therapeutic applications of epigenetics. Jpn J Clin Oncol 35:293301 (2005).

Mehdipour P, Ed. Ebrahim I M, Sharifov S, Salili M, Chernosova L. Introduction to the Impact of Bio-Resonance Technology in Genetics and Epigenetics. Dordrecht: Springer 2015

Begher FJ. Electroacupuncture nach Voll und Allergie ML-Verlag. Uelzen 1989.

Gurwitsch A. Mitogenetic radiation. Spinger-Verlag Berlin 1932

Bassett CA, Bassett L. Beneficial effects of electromagnetic fields. J Cell Biochem 1993; 51(4): 387-93

Markov MS. Expanding use of pulsed electromagnetic field therapies. Electromagn Biol Med 2007; 26(3): 257-74. [http://dx.doi.org/10.1080/15368370701580806] [PMID: 17886012]

Pihtili A, Galle M, Cuhadaroglu C, et al. Evidence for the effectiveness of bioresonance in smoking cessation: A pilot study. Forsch Komplement Med 2014; 21(4): 239-45

Galle M. Bioresonance therapy with children with allergies. Eur J Integr Med 2009; 1(4): 234-5. [http://dx.doi.org/10.1016/j.eujim.2009.08.023]

Schumacher P. Results of biophysical allergy therapy. Biophysical treatment of allergies. Thieme 2005; pp.102-9

Schumacher P. Biophysical hayfever therapy results in: Biophysical therapy of allergies. Thieme 2005; pp. 123-7i

The Effectiveness of Bioresonance Method on Human Health Periklis Karakos* , Tripsiannis Grigorios, Konstantinidis Theodoros and Lialiaris Theodoros

Lakhovsky's article and patents can be found online at:http:// www.rexresearch.com/lakhov/lakhusps.htm

Rosenow E (1965) Observations with the Rife microscope of filter-passing forms of microorganisms. Science 76:192–193

Montgomery S (2003) The rise and fall of a scientific genius: the forgotten story of Royal Raymond Rife. NZ Med J 116:1177

Wade G (1994) Dr Rife and the death of the cancer industry. http://educate-yourself.org/gw/ rifedeathofcancerindustry.shtml

About the Authors

Ayse Gamze OZCAN, MD, graduated from Istanbul University, Cerrahpaşa Faculty of Medicine in 2013. After working as a general practitioner for about 5 years, she received her anatomy specialization at Selçuk University in 2023. She still continues to work as an MD at the faculty of medicine. She has acupuncture certificate. Her main areas of interest are human anatomy, acupuncture.
E-mail: draysegamzeozcan@gmail.com, **ORCID:** 0000-0002-9946-3026

Ismail ESEOGLU, MD, graduated from Uludag University, Faculty of Medicine in 2005. He received his anesthesia and reanimation specialization in 2011. He continues to work as a faculty member at Dokuz Eylül University the faculty of health sciences. He serving as the Assistant Director at the GETAT application research center of the same university.
E-mail: ismail.eseoglu@deu.edu.tr, **ORCID:** 0000-0002-8184-8841

Similarity Index

The similarity index obtained from the plagiarism software for this book chapter is …%.

Examination of Smartphone Applications for Assessment in Physiotherapy and Rehabilitation

Musa ÇANKAYA

Necmettin Erbakan University

Pariya POURİYAMANESH

Necmettin Erbakan University

To Cite This Chapter

Çankaya, M., & Pouriyamanesh, P. (2024). Examination of Smartphone Applications for Assessment in Physiotherapy and Rehabilitation. In F. Nur Takı, S. Koçer & R. Bütüner (Eds.), *New Generation Technologies and Sustainability in Health Current Studies* (pp. 194-210). ISRES Publishing.

Introduction

The use of smartphone apps for assessment in physiotherapy and rehabilitation is increasing daily. The digital health field is growing rapidly, and digital solutions are available for changing treatments. Therefore, the medical use of smartphones by healthcare providers and the number and use of downloadable applications that transform mobile phones into medical devices are increasing (Terry, 2010).

Smartphone apps aimed at assessing body balance must be validated and regulated to provide accurate service that supports an adequate training program guided by a therapist. Estimates suggest that more than 45,00 health, exercise, and medical apps available (Edlin JC, Deshpande RP (Powell et al., 2014). Commercial software developers are offering Mobile Health solutions. However, the risks to patient safety and professional reputation are real and some considerations need to be considered (Powell et al., 2014). In this chapter, we plan to examine smartphone applications commonly used in the clinic.

Material Methods

Mobile Phone Applications

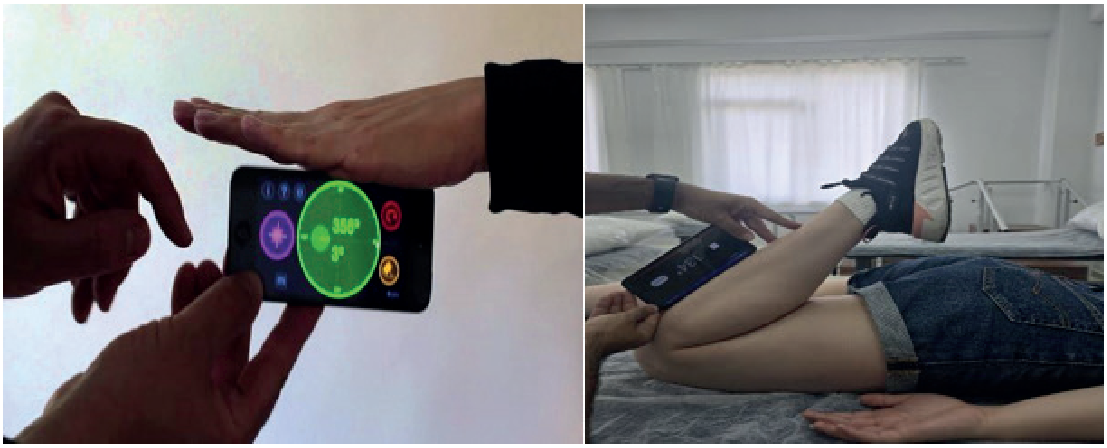
Goniometer Smartphone Applications (Clinometer, Goniometer and Electrogoniometer etc.)

Goniometers are used for assessment in physiotherapy and rehabilitation, especially for measuring range of motion. Built-in smartphone sensors (accelerometer, camera) are used to obtain useful measurements for clinical applications (Edlin et al., 2013). The advantage of smartphone-based goniometers is that they can provide simple and fast measurements through a device that is readily available at hand (Ockendon & Gilbert). Mobile medical applications are emerging technologies that need to be properly validated along with specific mobile platforms to provide safe and effective methods (Food and

Drug Administration, 2013; Milani et al., 2014).

With the development of smartphones and software applications, smartphone ownership and use is becoming widespread. Smartphone apps are easy to use, relatively inexpensive and widely available, making them like universal goniometers (Figure 1) (Keogh et al., 2019). By using apps that can be downloaded to a smartphone, these measurements can be translated into meaningful assessment data, such as joint motion. One advantage of smartphone apps is that they can be used to overcome some of the challenges associated with universal goniometer use, related to landmark identification, fixation and alignment. The ability of smartphone apps to fully overcome the disadvantages of universal goniometry may depend on the technology used and the clinician's experience with this alternative approach. Therefore, the emergence of smartphone-based goniometer apps offers clinical practitioners a new tools for integration into clinical practice (Keogh et al., 2016). Built-in sensors such as magnetometers and accelerometers are equipped to allow smartphones to measure angles and displacements (Keogh et al., 2019). It is used in motion assessment, diagnosis, and rehabilitation processes to inform and improve studies (Keogh et al., 2016; Sarac et al., 2022). The ease and availability of digital tilt measurements, especially those created as smartphone apps, has anecdotally increased the use of tilt measurements for range motion assessment. Applications have shown that the proposed method is valid and reliable for the following applications different joints, such as the knee, shoulder, hip, wrist, and ankle (Sarac et al., 2022; Keogh et al., 2016).

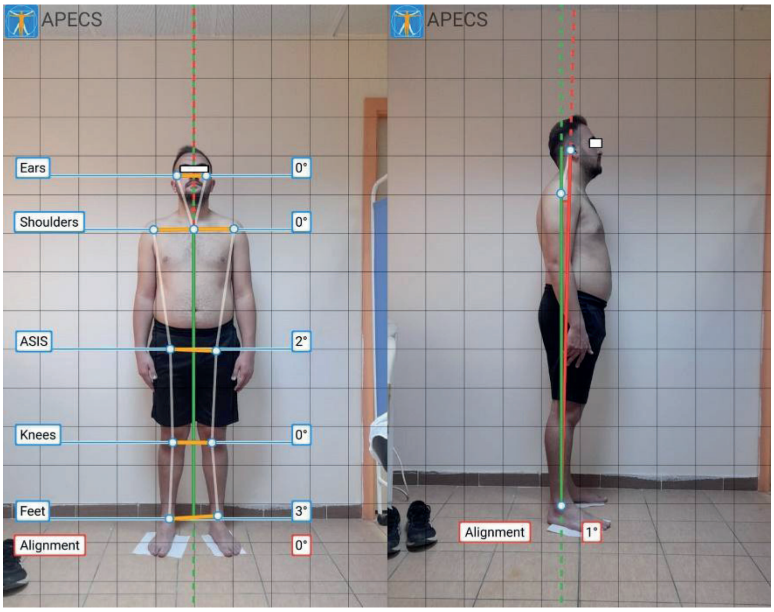
Figure 1
Smartphone Goniometer Application



Body Posture Assessment (AI Posture Evaluation and Correction System (APECS))

Digital Posture evaluation (APECS) is a software created for the evaluation of posture using non-invasive photogrammetry techniques and the prevention of posture disorders and asymmetries using various exercises (Figure 2) (Welling et al., 2023). It combines a control and diagnostic component with a posture disorder-related component. APECS offers multiple assessments, such as full and rapid posture assessment (front, back, 2 sides), dynamic posture video analysis (sagittal plane view), head-neck-shoulder assessment (forward head, rounded shoulders), and front and back trunk symmetry. APECS is already available for download in the Google Play Store. APECS performs posture assessment using markers placed on a photograph of the patient's body and uses algorithms to assess correct body symmetry (Çankaya & Takı, 2024). APECS provides rapid analysis of the anthropometric characteristics of posture. It uses standardized landmarks and anatomical angles for postural assessment. The Latin names of anthropometric landmarks and a list of relevant angles are available in the application. Previous research has shown APECS to be a reliable and valid method (Welling et al., 2023; Çankaya & Takı, 2024; Artvind, 2023). It has also been observed that assessment results are similar in individuals with different clinical experiences. APECS is inexpensive and easier to apply for researchers and clinicians than postural assessment devices (Belli et al., 2022; Bottino et al., 2023).

Figure 2
AI Posture Evaluation and Correction System



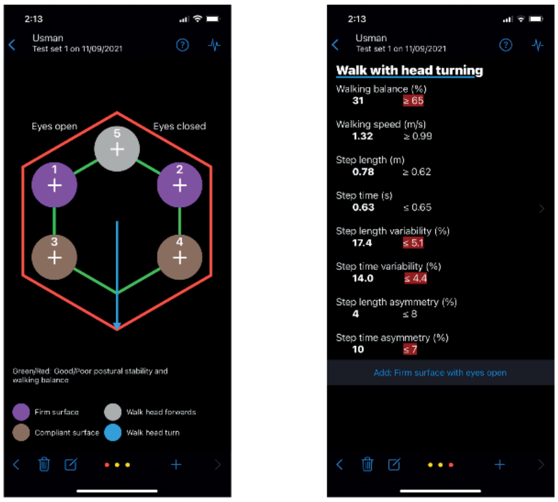
Gait and Balance Assessing (Gait&Balance smartphone application)

The Gait&Balance smartphone application (G&B App) was developed for balance assessment. The sensor works by using inertial sensors embedded in standard smartphones [16]. This tool has been validated by research as a reliable method for assessing balance and gait factors in both healthy young and older adults.(Figure 3) (Rashid et al., 2021; Olsen et al., 2023). In addition, the sensitivity of the app to age-related balance changes has supported itsvalidity in a population of healthy older adults (Olsen et al., 2023). Research on the O&M app has been conducted in high-income countries (Rashid et al., 2021; Olsen et al., 2023). There is a distinct lack of evidence on smartphone-based balance and gait measurements in low- and middle-income countries.Such research may be important in populations where standardized clinical care is not readily available. In settings where resources are limited, accessible and user-friendly technological measures can help identify adults with balance impairments and help identify risk factors that preceded falls.

The G&B app is a smartphone application that analyzes gait and balance using the smartphone's inertial sensors. G&B includes six gaits and balance assessment tasks. The gait tasks were designed to be performed at the user's preferred walking speed of approximately 10 m (Olsen et al., 2023). Each task consisted of four 6-s walks. The tasks included are: Walk in a straight line facing forward; Walk in a straight line while turning your head from side to side; There are four static test (30 seconds for each) conditions to assess postural sway, while static balance tasks are included. Users should remain as still as possible.

The G&B app has excellent validity and high reliability for postural balance and gold standard kinematic data. For walking tasks, the G&B App had moderate to excellent validity for measuring walking speed, stride length, and stride duration, but not for assessing stride length variability, stride length asymmetry, stride duration variability, and stride duration asymmetry (Shafi et al., 2023). The psychometric properties of the G&B app were investigated. When the test reliability of the application was compared with clinical measurements, it was established that the method was dependable and accurate (Berg Balance Scale, Functional Reach Test, Time Up-Go Test) (Shafi et al., 2023).

Figure 3
Gait and Balance Smartphone Application

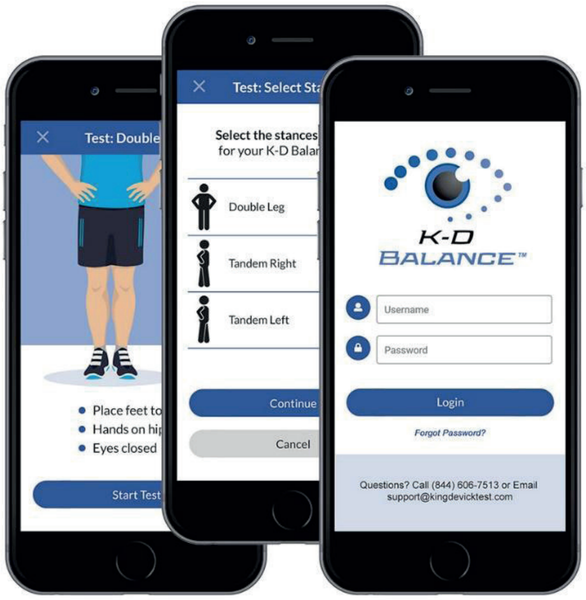


Balance Assessing (King-Devick Balance application (KDBA)

The King-Devick Balance app (KDBA) (Technologies, Downers Grove) was developed to improve the accuracy and ease of administration of clinical balance testing. The proposed mobile balance assessment app is a Food-Drug Administration approved balance evaluation software application that provides an objective measure of balance performance. The mobile balance evaluation software is compatible with multiple iPhone and Android generations. The mobile balance assessment tool uses triaxial coordinate data from the mobile device's internal accelerometers to calculate the balance score (Figure 4) (Zhang et al., 2019). The K-D Balance app is an existing application for phone products that measures triaxial coordinate data through a mobile device's internal accelerometer to provide a quantitative assessment of balance performance. The balance points were derived from the algorithm (Zhang et al., 2019).

The KDBA assesses three basic balance postural metrics: double stance, and right/left tandem stance. The mobile balance assessment tool does not include single-leg stances in the test procedure because of the significant variability in single-leg stance measurements. The balance assessment uses postures used in other balance testing protocols, including the double-leg and tandem postures in the Berg Balance Scale assessment. The double leg only assesses two-foot postures (Starling et al., 2016; Krause et al., 2020). The KDBA, via an iPhone or iPod Touch, is secured to the patient with a hands-free, wearable device holder to stabilize the device. After step-by-step voice guidance for each posture, an objective balance score is automatically derived by sensing the individual's movements using the device's built-in accelerometer (Starling et al., 2016). Athletic trainers, physiotherapists, physicians, and other healthcare professionals can assess a patient's KDBA. The reliability measures of the KDBA (ICC, 0.42) were moderate to good. This lower-than-expected reliability can be partly attributed to the use of old, young,, adult, healthy and active individuals with limited variability among participants (Krause et al., 2020).

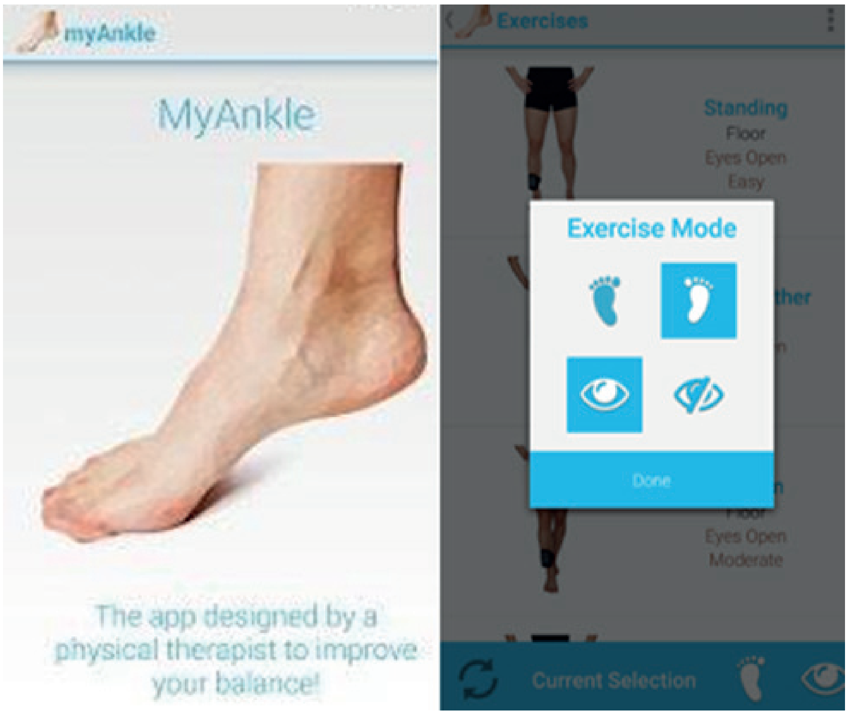
Figure 4
King-Devick Balance Application



Standing Balance MyAnkle Application

MyAnkle is a free mobile phone application designed for patients to assess and track their standing balance. MyAnkle smartphone application was developed to assess standing balance as an alternative to the Berge Balance Scale for assessing overall balance between patients and healthy volunteers with eyes closed (Figure 5) (Shah et al., 2016). The validity and reliability of the MyAnkle smartphone app showed significant results when assessed with eyes closed. However, when the app was used with eyes open, no distinction could be made between patients and healthy subjects. Like the Biodex Balance system, one-week test-retest reliability appears insufficient for accurate follow-up, and clinicians should therefore be cautious with these findings (Abdo et al., 2020; Polechońsk et al., 2019). As cell phone technology advances and embedded accelerometers are developed, myAnkle may provide more robust measurements of standing balance. The position of the ankle may provide higher detection sensitivity in the execution of more difficult exercises. In terms of ease of application and feasibility, the ankle is a preferred application for the evaluation of balance and gait (Shah et al., 2016).

Figure 5
MyAnkle Application



Assessing Postural Balance in Daily Life (Y-MED Application)

Y-MED is a smartphone application using an accelerometer sensor on a smartphone that has been evaluated for reliability and validity used to assess postural balance in activities of daily living. However, the validity and reliability of Y-MED for balance assessment in patients old with chronic low back pain has not been validated (Amin et al., 2022).

Gait Analysis Method (OneStep Smartphone Application)

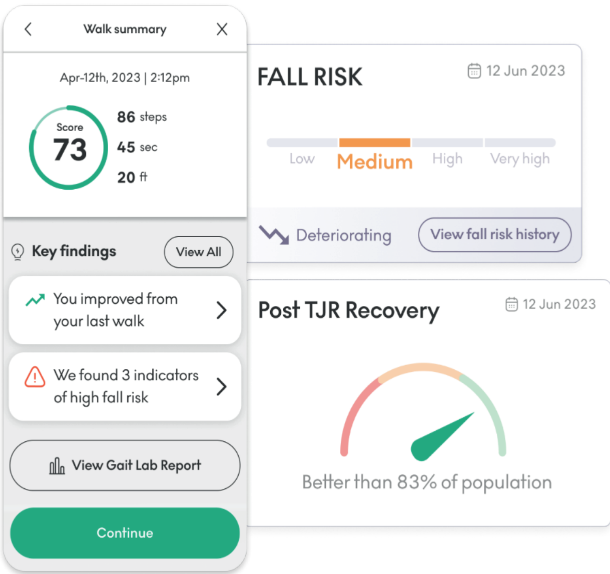
The OneStep app (Celloscope Ltd.) records data from a smartphone's standard integrated inertial measurement unit (IMU) (sampling rate 100 Hz) and extracts time-oriented gait parameters based on the user's movement/activity and the position of the device (left/right front or back pocket automatically detected) (Rozanski & Putrino, 2022). The recorded motion is converted into a digital representation gait using OneStep's proprietary algorithms (Marom et al., 2024). The machine learning models then determine various gait parameters from this representation. Note that calibration is not required. After segmentation of the gait cycle, variables such as cadence, speed, hip spacing, base width, stride and stride lengths, stance, and double support times can be calculated. Each recorded gait was categorized as "in-app" (initiated by the patient pressing the "Start (Walk) button" or background (collected automatically if movement activity is detected). The information is analyzed identically by the same algorithms and displayed on the user interface (Rozanski & Putrino, 2022). The full spatiotemporal results will be accessible by the assigned therapist.

An Outline of OneStep's Gait Analysis Method:

The system converts the raw signals from the IMU into a standard representation of the user's movements (patent application US20200289027A1) (Figure 6) (Shahar & Agmon., 2021). First, the raw signal was divided into gait cycles. Then, the acceleration of each cycle was integrated into the displacement of the sensor along the cycle, considering the orientation of the sensor in space. This generates the sensor's trajectory through each gait cycle in an inertial reference frame that moves at the sensor's average velocity, thus constraining the sensor to achieve a closed-form trajectory with six degrees of freedom throughout the gait cycle (Christensen et al., 2022). As a result, this process produces a representation of each gait cycle based solely on the user's movement and body position of the device. The matrix is divided into 100 units over time to provide a standardized representation in the form of a 6×100 matrix. The deep learning models then obtain this standardized representation of the motion and estimate values for various gait parameters, including spatiotemporal parameters, for each gait cycle. These models are based on regression models using convolutional layers trained on labeled data of gait parameter values and 6 degrees of freedom representations of the motion of the corresponding cycle (Christensen et al., 2022).

OneStep offers comprehensive solutions for digital physical therapy and remote motion analysis. Innovative technology transforms any smartphone into a clinically validated motion analysis lab. OneStep is a platform that can accurately capture more than 40 gait parameters and range of motion and functional movement assessments, such as Time Up-Go, without the need for wearable devices (Rozanski & Putrino, 2022). By analyzing patients' movements throughout their daily life, it gains greater clinical insight into the patient's condition and evidence of their true functional mobility outside the clinic. Using predictive analytics, OneStep is the app that tracks changes in gait trends over time that are associated with an increased risk of falls, providing healthcare professionals with information to intervene at the right time, every time.

Figure 6
One-Step Smartphone Application

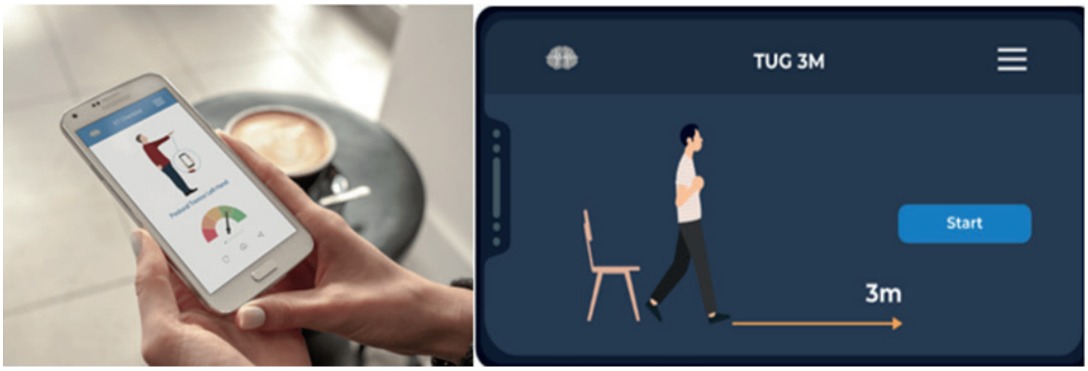


Movement Disorders (Mon4t Clinic Application)

The Mon4t Clinic Application (Encephalog) is used to perform standardized motor and cognitive tests. Using smartphone-integrated sensors (no additional hardware needed), quantitative biomarkers are obtained from each test. The Mon4t Clinic is also used to assess static posturography and tremors, along with cognitive tests. The Mon4t Clinic application was developed by Zhong et al (Figure 7) (Zhong & Rau, 2020). Mon4t uses the integrated triaxial accelerometer, gyroscope, and magnetometer found in any standard smartphone to calculate gait parameters such as time up and go completion time, segment durations (e.g. stand up, turn), stride length, distance and step-to-step variability and more (Willemse et al., 2024). Mon4t Clinic Application, 10-meter time up and go, Finger tapping test, Tremor, Static Balance, Cognitive-Stroop, Cognitive-Verbal Memory test can be performed.

The Mon4t Clinic Application, an inclusive screening protocol, supports patient selection and increases the likelihood of enrolling suitable candidates. Subsequently, a quantitative assessment of motor and cognitive symptoms can reduce inter- and intra-rater variability. The tests were performed using the participants' smartphones as a medical device. The application will enable decentralized clinical trials that can last for several years. Furthermore, Mon4t's platform can provide ready reference data for patients and healthy controls. Mon4t improves the result quality and shortens the time to market (Karlinsky et al., 2022).

Figure 7
Mon4t Clinic Application



Hand Rehabilitation (Hand Therapy Application)

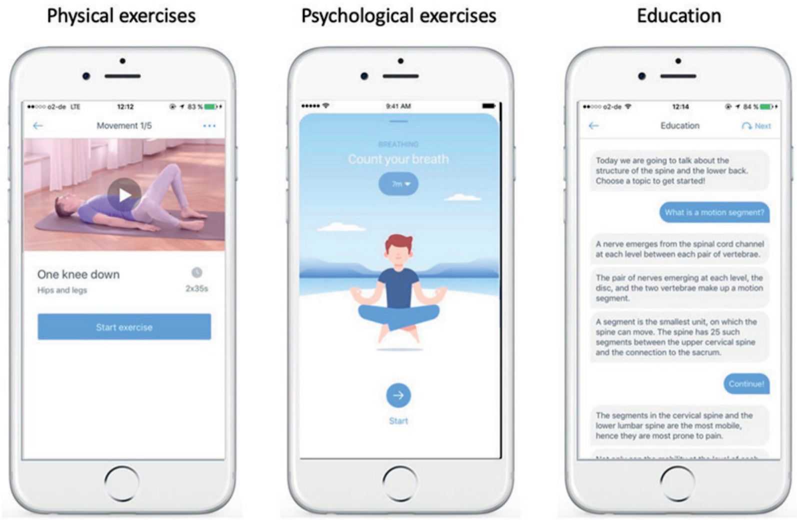
Hand injuries are common. They account for up to 35% of accident and emergency admissions. The Hand Therapy application is an exercise prescription app that enables patients to access high-quality treatment information anytime and anywhere (Figure 8) (Gerber, 2009; Wang et al., 2017). The Hand Therapy smartphone app was developed by hand therapists at Chelsea Hospital Foundation Trust. It is designed with the patient's experience in mind to provide quick access to treatment information and exercises on smartphones and tablets. The app offers tailored exercise programs to help patients identify the activities that are important to them. Our goal is to help patients return to optimal function or manage long-term conditions. The app's design is perfect for clinicians working in busy clinics, as it can be downloaded quickly without an exhausting setup. Easy-to-follow videos ensure that exercises are performed correctly, which is crucial for successful outcomes. The app aims to empower patients to self-manage their recovery. This will save clinicians time and allow them to focus on other aspects of treatment (Gerber, 2009; Wang et al., 2017).

Figure 8
Hand Therapy Application

Back Pain Treatment (Kaia Back Pain Application)

The Kaia application (Kaia Health Software, Munich, Germany) is a multiplatform application for Android, iOS, and native web applications (Figure 9). The Kaia app was launched in September 2016. Classified as a medicinal product. It is an app available in the App Store (iOS), Google Play Store (Android) or as a native website. The application consists of three parts: (1) education program specific to back pain, (2) physiotherapy/physical exercise practices, and (3) learning mindfulness/relaxation techniques (Figure 3) (Huber et al., 2017). The programs are updated each day depending on the progress of individual patients. In the education section, it includes specific training on pain and a broad education process specific to back pain. There are more than 30 different training units in the app. In the exercise section up to 5 exercises per day are designed for each user and are ranked depending on the difficulty of the exercise (Priebe et al., 2020). The content for each patient is compiled from a large history of exercises and skills archived in the app and updated daily (or at each login). This content is continuously adapted according to the patient's information, practice, and progress. Thus, the exercise program and exercise content are tailored to the patient. The exercises are based on German, international, and standard textbooks in the field. The section on mindfulness and relaxation techniques includes units on breathing techniques, body analysis, visualization, and progressive muscle relaxation. People who download the app must provide information about the location and intensity of their back pain. Each day, users who log in to the app are also asked to record their current pain level and the quality of their sleep the previous night in a pain diary. The level of pain was recorded on an 11-point numerical scale (0=no pain, 10=excruciating pain). The quality of sleep was rated on another 11-point scale (0=worst imaginable,10=best imaginable). The content of the education section covered a wide range of educational content related to general pain and specific pain types. There are over 30 different training units in the app. It is based on content from current and standardized textbooks in the field, as specified in over 30% international guidelines (Priebe et al., 2020).

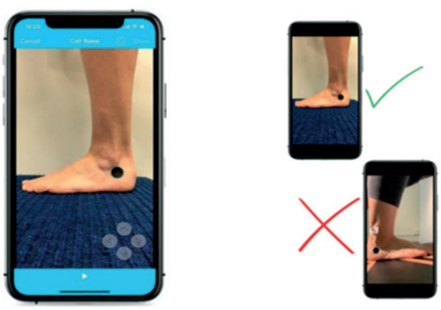
Figure 9
Kaia Back Pain Application



Calf Raise Test (Calf Raise Application)

The Calf Raise app (CRapp) was developed for Apple (iOS) users to facilitate objective measurement, repetition of laboratory-based measurements that are difficult to measure in clinics, and standardization of the Calf Raise Test (CRT) (Figure 10) (Fernandez et al., 2023). CRapp uses computer vision algorithms to track a circular marker placed on an individual's foot from videos. While the algorithms have been shown to be valid and reliable for the following barbell movement during weightlifting compared to 3D motion capture, it has not yet been validated in its application to CRT. CRT is a test used in rehabilitation and sports medicine to assess gastrocnemius muscle function (Fernandez, 2023). In general, CRT results (i.e. repetitions, positive work, total height, peak height, fatigue CRapp index and peak power) can be easily obtained from video using this application in a clinical setting. The app can also provide step-by-step guidance on the correct form of the movement. For example, starting position: standing with feet shoulder-width apart. Descent: Lower the heels back down in a controlled manner. Repetitions and sets: recommendations for how many repetitions and sets to perform the exercise (Fernandez et al., 2023; Fernandez, 2023).

Figure 10
Calf Raise Application

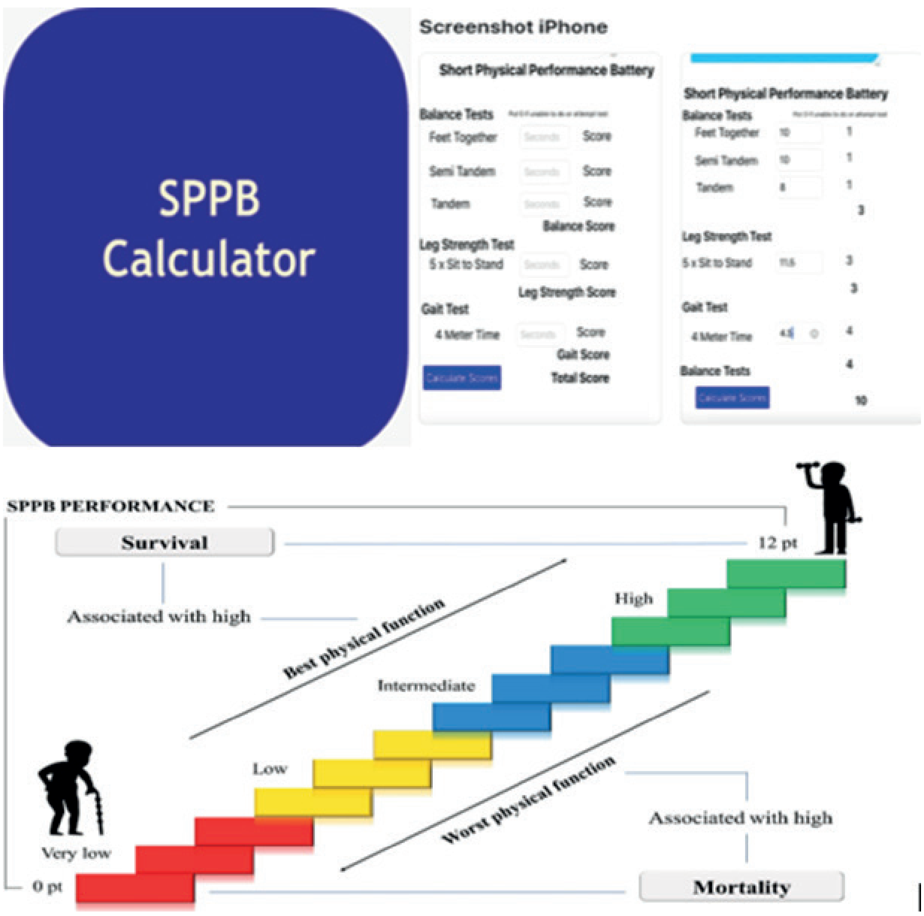


Physical performance tests (Short Training Session of the Physical Performance Battery)

Short Physical Performance Battery (SPPB) application is used in the field of physiotherapy to assess the physical performance of adult individuals by measuring their physical abilities such as walking speed, balance, sitting, and standing (Figure 11). In the clinic, these tests are preferred for detecting age-related physical decline, assessing adult individuals, monitoring physical decline, determining rehabilitation processes, comparing and researching treatment outcomes, and collecting data in clinical trials (Lauretani et al., 2019). However, physical performance measurements are important for not only assessing functional status but also monitoring the overall clinical evolution of older adults. The SPPB Test usually consists of three main parts: Gait Speed Test measures walking speed over 4 meters. Balance Test includes tests such as standing on one leg. Sit and Stand Test includes movements of up and sitting down. Each of these tests assesses an individual's specific physical abilities and forms the basis of treatment plans (Amiss & Cottrell, 2022). This application is an available method to calculate the results of the SPPB functional test. There is no need to remember the end times for each score. The application is easy to use. The SPPB is an easily applicable tool and the method of choice for assessing the ability to predict adverse health status like dependence on activities of daily living, hospitalization, frailty syndrome and death (de Fátima Ribeiro Silva et al., 2021).

Figure 11

Pelvic Floor Muscle Strength Test (Squeezy Application)



Pelvic Floor Muscle Strength Test (Squeezy Application)

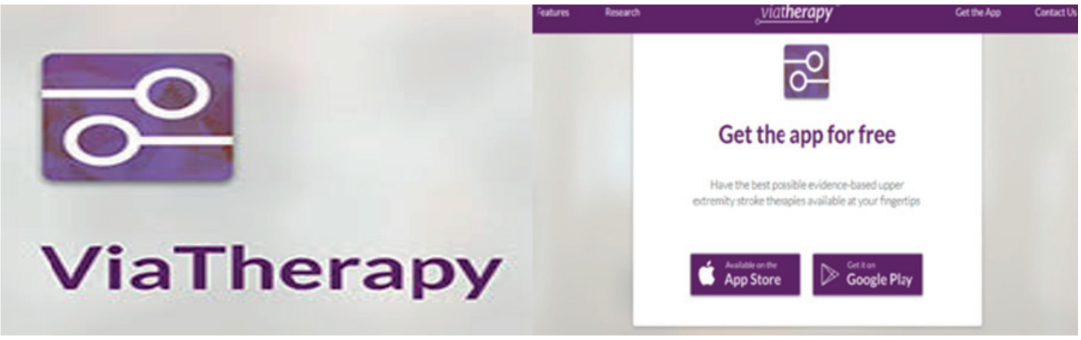
The Squeezy pelvic floor muscle exercise smartphone app (Propagator Ltd, London, UK) was released through the Apple App Store in September 2013. This is an evidence-based and peer-reviewed mobile device program designed to educate and motivate women to do exercises to strengthen their pelvic floor muscles (Figure 12) (Robson, 2017). Squeezy is a mobile application for strengthening pelvic floor muscles. This application aims to increase pelvic muscle strength and eliminate various health problems by using a personalized exercise program. With this application, a personalized exercise program, exercise guidance, progress monitoring, education, and information are provided. This application also has applications in physiotherapy for incontinence treatment and rehabilitation. It is particularly preferred to support home treatment processes and to facilitate individuals to exercise independently (Sudol et al., 2019). Using the exercise library in this application, the physiotherapist can use different exercises and techniques, select appropriate exercises for the patient's needs and teach them to the patient through the application. Feedback and corrections provide user feedback to assess whether the exercises are performed correctly. Using this feedback, physiotherapists can teach patients the correct techniques of exercises (Sudol et al., 2019).

Figure 12
Squeezy Application

Stroke Rehabilitation (ViaTherapy Application)

ViaTherapy is a health app used in physiotherapy. In order to enhance their physical health, the proposed app will provide users with various tools and resources (Figure 13) (Hancock et al., 2019) [45]. This app represents about 5 years of work by an international panel representing stroke and rehabilitation researchers and related disciplines, including clinicians from Medicine (Physiatry and Neurology) and Physical and Occupational Therapy. The primary target group of the proposed algorithm is the rehabilitation service providers who are actively involved in the rehabilitation of people with arm disability after stroke. Collective expertise spans research interests in epidemiology, motor control, and knowledge translation. The content of this application includes different exercise programs, patient monitoring and feedback tools, rehabilitation programs, and personalized training programs. ViaTherapy and similar applications increase the interaction between physiotherapists and patients and improve the efficiency of treatment processes. This application is used in Cerebral vascular disease rehabilitation to improve upper extremity rehabilitation outcomes (Bernhardsson et al., 2023). In this application, specific exercise goals can be created for patients. These goals help patients to be motivated and increase their adherence to treatment. In addition, patients are motivated by receiving badges when they fulfill the specified tasks, thus ensuring the continuity of treatment (Hancock et al., 2019).

Figure 13
ViaTherapy Application



Results

In this section, information about the applications used in the field is provided. The number of apps is very high, and the number of apps is increasing daily. Different levels of evidence suggest that digital physiotherapy evaluation can be compatible with face-to-face physiotherapy rehabilitation evaluation and that the two types of assessment can results are pretty similar in terms of validity and reliability. The highest validity was observed for the limb, while the lowest validity was found for postural assessment and clinical observations. Variability and certainty of evidence suggest that digital evaluation should not completely replace face-to-face assessment, particularly in relation to key aspects of physiotherapy such as diagnosis. However, it suggests that it may be important for patients who are likely to benefit from remote access. There was a high level of agreement between the two types of assessment for several components suggests that digital physiotherapy assessment is a suitable alternative to face-to-face assessment. Digital applications may be a useful way to provide environmentally friendly access; however, having access to digital tools, technical skills and enough time are all things that may hinder widespread implementation of digital assessment [47,48]. Patients' preferences and preferences for easier assessment methods that are more tailored to their needs should be considered. Despite expressing high satisfaction with digital assessment, most patients prefer face-to-face contact whenever possible. It would be great to look at some different views on how digital assessment could be a good thing for patients, physiotherapists and society. Furthermore, the level of evidence for digital physiotherapy assessment is limited, with certainty of evidence ranging from extremely low to high for the different assessment components examined. To get a clearer picture of the advantages of digital physiotherapy assessment, we need to do more research. (Morera et al., 2016).

References

Terry, M. (2010). Medical apps for smartphones. *Telemedicine and e-Health*, *16*(1), 17-23. doi: 10.1089/tmj.2010.9999. https://doi.org/10.1089/tmj.2010.9999

Powell, A. C., Landman, A. B., & Bates, D. W. (2014). In search of a few good apps. *Jama*, *311*(18), 1851-1852. https://doi.org/10.1001/jama.2014.2564

Edlin, J.C. & Deshpande, R.P. (2013) Caveats of smartphone applications for the cardiothoracic trainee. *The journal thoracic cardiovascular surgery*, 146, 1321-1326. https://doi.org/10.1016/j.jtcvs.2013.08.033

Ockendon, M. & Gilbert, R. E. (2012) Validation of a smartphone accelerometer-based knee goniometer. *The journal of knee surgery*, 25, 341-345. https://doi.org/10.1055/s-0031-1299669

Food and Drug Administration. (2013). Guidance for industry and food and drug administration staff. *Mobile Medical Applications. US Department of Health and Human Services Food and Drug Administration*.

Milani, P., Coccetta, C. A., Rabini, A., Sciarra, T., Massazza, G., & Ferriero, G. (2014). Mobile smartphone applications for body position measurement in rehabilitation: a review of goniometric tools. *PM&R*, *6*(11), 1038-1043. https://doi.org/10.1016/j.pmrj.2014 .05.003.

Keogh, J.W.L. Cox, A, Anderson, S, Liew, B, Olsen, A, Schram, B, Furness, J. (2019). Reliability and validity of clinically accessible smartphone applications to measure joint range of motion: A systematic review. *PLoS One.* 14(5), e0215806. https://doi.org/10.1371/journal.pone.0215806.

Keogh, J.W. Espinosa, H. G. & Grigg J. (2016). Evolution of smart devices and human movement apps: recommendations for use in sports science education and practice. *Journal of Fitness Research*, *5*, 14-15

Sarac, D. C., Yalcinkaya, G., and Unver, B. (2022). Validity and reliability of a smartphone goniometer application for measuring hip range of motions. *Work*, *71*(1), 275-280. https://doi.org/ 10.3233/WOR-213626.

Welling, A., Gurudut, P., Shirodkar, G., Shetye, N., & Khan, S. (2023). Validation of non-radiographic APECS software in comparison with standard radiographic measurement of full-length lower limb hip-knee-ankle angle in elderly obese women. *Physiotherapy Quarterly*, *31*(1), 90-94. https://doi.org/10.5114/pq.2023.119865

Çankaya M & Takı F. N. Comparison of Postural Assessment and Awareness Using Al Posture Evaluation and Correction System in Individuals Receiving Posture Training. *International Journal of Occupational Safety and Ergonomics*, 2024:4:250

Arvind, N. (2023). Evaluation of the Effectiveness of the Active Correction Exercises in Forward Head Posture in Young Adults. *INTI JOURNAL*, (19), 1-6.

Belli, G., Toselli, S., Latessa, P. M., & Mauro, M. (2022). Evaluation of self-perceived body image in adolescents with mild idiopathic scoliosis. *European Journal of Investigation in Health, Psychology and Education*, *12*(3), 319-333. https://doi.org/10.3390/ejihpe12030023.

Bottino, L., Settino, M., Promenzio, L., & Cannataro, M. (2023). Scoliosis Management through Apps and Software Tools. *Int J Environ Res Public Health*, *20*(8), 5520–5530. https://doi.org/10.3390/ijerph20085520

Rashid, U., Barbado, D., Olsen, S., Alder, G., Elvira, J. L., Lord, S., ... & Taylor, D. (2021). Validity and reliability of a smartphone app for gait and balance assessment. *Sensors*, *22*(1), 124-132. htps://doi.org/10.3390/s22010124

Olsen, S., Rashid, U., Allerby, C., Brown, E., Leyser, M., McDonnell, G., ... & Taylor, D. (2023). Smartphone-based gait and balance accelerometry is sensitive to age and correlates with clinical and kinematic data. *Gait & Posture*, *100*, 57-64. https://doi.org/10.1016/j.gaitpost.2022.11.014

Shafi, H., Awan, W. A., Olsen, S., Siddiqi, F. A., Tassadaq, N., Rashid, U., & Niazi, I. K. (2023). Assessing gait & balance in adults with mild balance impairment:

G&B app reliability and validity. *Sensors*, *23*(24), 9718. https://doi.org/10.3390/s23249718

Zhang, C. Talaber, A. Truong, M. & Vargas, B. B. (2019). KD Balance: An objective measure of balance in tandem and double leg stances. *Digital Health* 5:2055207619885573. https://doi.org/10.1177/205520761988557

Starling, A. J. Leong, D. F. Bogle, J. M. & Vargas, B. B. (2016). Variability of the modified Balance Error Scoring System at baseline using objective and subjective balance measures. *Concussion*, *1*(1). https://doi.org/10.2217/cnc.15.5

Krause, D. A., Anderson, S. E., Campbell, G. R., Davis, S. J., Tindall, S. W., & Hollman, J. H. (2020). Responsiveness of a balance assessment using a mobile application. *Sports Health*, *12*(4), 401-404. https://doi.org/10.1177/1941738119888656

Shah, N. Aleong, R. and So, I. (2016). Novel use of a smartphone to measure standing balance. *JMIR Rehabil Assist Technol*, *3*(1), e4511. https://doi.org/10.2196/rehab.4511

Abdo, N., ALSaadawy, B., Embaby, E., & Youssef, A. R. (2020). Validity and reliability of smartphone use in assessing balance in patients with chronic ankle instability and healthy volunteers: A cross-sectional study. *Gait & Posture*, *82*, 26-32. https://doi.org/10.1016/j.gaitpost.2020.08.116

Polechoński, J. Nawrocka, A. Wodarski, P. & Tomik, R. (2019). Applicability of smartphone for dynamic postural stability evaluation. *BioMed Research International*, *2019*(1), 9753898. https://doi.org/10.1155/2019/9753898

Amiss, E. & Cottrell, M. (2022). Evaluation of a Novel Step Training Mobile App Intervention in Cardiopulmonary Rehabilitation: A Single-Arm Prospective Cohort Study. *Games for Health Journal*, *11*(5), 330-336. https://doi.org/10.1089/g4h.2021.0142

Rozanski, G. & Putrino, D. (2022). Recording context matters: Differences in gait parameters collected using the OneStep smartphone application. *Clinical Biomechanics*, *99*, 105755. https://doi.org/10.1016/j.clinbiomech.2022.105755

Marom, P. Brik, M. Agay, N. Dankner, R. Katzir, Z. Keshet, N. & Doron, D. (2024). Reliability and Validity of the OneStep Smartphone Application for Gait Analysis among Patients Undergoing Rehabilitation for Unilateral Lower Limb Disability. *Sensors*, *24*(11), 3594. https://doi.org/10.3390/s24113594

Shahar, R. T., & Agmon, M. (2021). Gait analysis using accelerometry data from a single smartphone: Agreement and consistency between a smartphone application and gold-standard gait analysis system. *Sensors*, *21*(22), 7497. https://doi.org/10.3390/s21227497

Christensen, J. C., Stanley, E. C., Oro, E. G., Carlson, H. B., Naveh, Y. Y., Shalita, R., & Teitz, L. S. (2022). The validity and reliability of the OneStep smartphone application under various gait conditions in healthy adults with feasibility in clinical practice. *Journal of Orthopaedic Surgery and Research*, *17*(1), 417. https://doi.org/10.1186/s13018-022-03300-4.

Zhong, R. & Rau, P. L. P. (2020). A mobile phone–based gait assessment app for the elderly: development and evaluation. *JMIR mHealth and uHealth*, *8*(5), e14453. https://doi.org/10.2196/14453

Willemse, I. H. Schootemeijer, S. van den Bergh, R. Dawes, H. Nonnekes, J. H. & van de Warrenburg, B. P. (2024). Smartphone applications for Movement Disorders: Toward collaboration and reuse. *Parkinsonism & Related Disorders*, 105988 https://doi.org/10.3233/JPD-240091

Karlinsky, K. T., Netz, Y., Jacobs, J. M., Ayalon, M., & Yekutieli, Z. (2022). Static balance digital endpoints with Mon4t: smartphone sensors vs. Force plate. *Sensors*, *22*(11), 4139. https://doi.org/10.3390/s22114139

Gerber, J. (2009). The occupational therapy perspective of activity orientation in hand rehabilitation

Wang, B., McDaid, A., Aw, K. C., & Biglari-Abhari, M. (2017, September). Design and development of a skinny bidirectional soft glove for post-stroke hand rehabilitation. In *2017 Intelligent Systems Conference (IntelliSys)* (pp. 979-987). IEEE. https://doi.org/10.1109/IntelliSys.2017.8324248

Huber, S. Priebe, J. A. Baumann, K. M. Plidschun, A. Schiessl, C. & Tölle, T. R. (2017). Treatment of low back pain with a digital multidisciplinary pain treatment app: short-term results. *JMIR rehabilitation and assistive technologies*, *4*(2), e9032. https://doi.org/10.2196/rehab.9032

Priebe, J. A., Haas, K. K., Moreno Sanchez, L. F., Schoefmann, K., Utpadel-Fischler, D. A., Stockert, P., ... & Toelle, T. R. (2020). Digital treatment of back pain versus standard of care: the cluster-randomized controlled trial, rise-uP. *Journal of pain research*, 1823-1838. https://doi.org/10.2147/JPR.S260761.

Priebe, J. A., Utpadel-Fischler, D., & Toelle, T. R. (2020). Less pain, better sleep? The effect of a multidisciplinary back pain app on sleep quality in individuals suffering from back pain–a secondary analysis of app user data. *Journal of Pain Research*, 1121-1128. https://doi.org/10.2147/JPR.S232792.

Fernandez, M. R. Athens, J. Balsalobre-Fernandez, C. Kubo, M. and Hébert-Losier, K. (2023). Concurrent validity and reliability of a mobile iOS application used to assess calf raise test kinematics. *Musculoskeletal Science and Practice*, 63, 102711. https://doi.org/10.1016/j.msksp.2022.102711

Fernandez, M. R. (2023). *Scientific Investigation of the Calf Raise Test Using the Calf Raise Mobile Application to Inform Test Administration and Interpretation* (Doctoral dissertation, The University of Waikato).

Lauretani, F., Ticinesi, A., Gionti, L., Prati, B., Nouvenne, A., Tana, C., ... & Maggio, M. (2019). Short-Physical Performance Battery (SPPB) score is associated with falls in older outpatients. *Aging clinical and experimental research*, *31*, 1435-1442. https://doi.org/10.1007/s40520-018-1082-y

de Fátima Ribeiro Silva, C., Ohara, D. G., Matos, A. P., Pinto, A. C. P. N., & Pegorari, M. S. (2021). Short physical performance battery as a measure of physical performance and mortality predictor in older adults: a comprehensive literature review. *International journal of environmental research and public health*, *18*(20), 10612. https://doi.org/10.3390/ijerph182010612

Robson, M. (2017). The Squeezy pelvic floor muscle exercise app: user satisfaction survey. *J Pelvic Obstet Gynaecol Physiother*, *75*(9), 64-68.

Sudol, N. T., Adams-Piper, E., Perry, R., Lane, F., & Chen, K. T. (2019). In search of mobile applications for patients with pelvic floor disorders. *Urogynecology*, *25*(3), 252-256. https://doi.org/10.1097/SPV.0000000000000527

Hancock, N. J., Collins, K., Dorer, C., Wolf, S. L., Bayley, M., & Pomeroy, V. M. (2019). Evidence-based practice 'on-the-go': using ViaTherapy as a tool to enhance clinical decision making in upper limb rehabilitation after stroke, a quality improvement initiative. *BMJ Open Quality*, *8*(3), e000592. https://doi.org/10.1136/bmjoq-2018-000592

Bernhardsson, S., Larsson, A., Bergenheim, A., Ho-Henriksson, C. M., Ekhammar, A., Lange, E., ... & Bornhöft, L. (2023). Digital physiotherapy assessment vs conventional face-to-face physiotherapy assessment of patients with musculoskeletal disorders: A systematic review. *PloS one*, *18*(3), e0283013. https://doi.org/10.1371/journal.pone.0283 013

Morera, E. P., de la Torre Díez, I., Garcia-Zapirain, B., López-Coronado, M., & Arambarri, J. (2016). Security recommendations for mHealth apps: Elaboration of a developer's guide. *Journal of medical systems*, *40*, 1-13. https://doi.org/10.1007/s10916-016-0513-6

About the Authors

Musa ÇANKAYA, PhD, is Lecturer Doctor at Necmettin Erbakan University in Konya, Türkiye. He holds a PhD in physiotherapy and rehabilitation from Necmettin Erbakan University. Her main areas of interest are orthopedic rehabilitation, electrophysical agents, validity and reliability studies.
E-mail: mcankaya@erbakan.edu.tr, **ORCID:** 0000-0002-2093-5036

Pariya POURİYAMANESH, B.SC., is a fresher in physiotherapy and rehabilitation master at Necmettin Erbakan University in Konya, Turkiye. She holds bachelor's degree in physiotherapy and rehabilitation from Necmettin Erbakan University.Her main areas of interest are Pediatric rehabilitation, Tele-rehabilitation, Women's health.
E-mail: 24842401701@ogr.erbakan.edu.tr, **ORCID:** 0009-0005-3142-3510

Similarity Index

The similarity index obtained from the plagiarism software for this book chapter is 10%.

Acupuncture and Homeopathy Applications in Chronic Neuropathic Pain

Hayriye ALP

Necmettin Erbakan University

To Cite This Chapter

Alp, H. (2024). Examination of Smartphone Applications for Assessment in Physiotherapy and Rehabilitation. In F. Nur Takı, S. Koçer, & R. Bütüner (Eds.), *New Generation Technologies and Sustainability in Health Current Studies* (pp. 211-219). ISRES Publishing.

Introduction

Acupuncture accepts the body as a combination of soul and body, apart from a physical structure. It is a very successful treatment method in the treatment of chronic pain. Some of the factors in its success can be considered to evaluate the concept of organ functionally. Organs are alive in acupuncture; vitality is provided by life energy called dew. Pathogens that interrupt the flow that clogs the raw flow creates diseases. Acupuncture needles are immersed in special spots on Bonghan channels and regulate the raw flow by electron transfer (Lin et al., 2017). Acupuncture is a needling method and can be used in the treatment of many diseases such as chronic pain. The effects of acupuncture can be explained by neurophysiological studies. These effects are not only local effects, but also effects on general, central nervous system. The acupuncture needle spreads from the local needling through viscero-cutaneous, cutaneous-visceral, cutaneous-muscular reflexes. Thus, it provides a dermatomal effect. The acupuncture stimulation then reaches the upper centers via the medulla spinalis, and finally the periaquaductal neurons in the mesencephalon; β-endorphine, encephalin, serotonin are released. Acupuncture points are points in close relationship with the lymphatic system and vascular structures Acupuncture points are shown to have low electrical resistance points and calcium concentration increases as a result of needle stimulation of the point (Shang, 1989).

With the needling of the acupuncture point, the transition from the brain to the spinal core, the thalamus, sensory cortex, periacuaductal neurons are activated and the pain control system is activated (Bear et al., 2007; Guyton & Hall, 2007). Acupuncture stimulation stimulates endorphinergic and encephalinergic neurons, which are associated with the cortex and hypothalamus. With synaptic connections, serotonergic neurons in the bulb are activated (Merskey & Bogduk, 1994; Chen et al., 1996).

Analgesia is also important neurotransmitters encephalin and serotonin (Pintov et al., 1997). Encephalin is released from periaquaductal neurons in mesencephalon. It shows affinity for delta and mu_1 receptors. In painful stimuli, their oscillations increase and play an important role in analgesic mechanisms. While the μ_1 receptors are abundant in the raphe nucleus and periaquaduktal neurons, the delta and kappa receptors are located in the spinal cord. Enkefalins bind to µ1 receptors at the supraspinal level and to delta receptors at the spinal level and show an analgesic effect. Encephalins have been shown to inhibit in the posterior cord on A delta and C fibers in the presynaptic and postsynaptic area (Guyton & Hall, 2007; Chen et al., 1996). Electroacupuncture has its analgesic effect on serotonin receptors (5-HT (1A) and 5-HT (3) (Chang et al., 2004).

Pathological meridians were detected primarily with the diagnosis of pulse in each patient with chronic pain. Then the Yuan points of pathological meridians were pinned. In those with cervical discopathy, cervical Back-Shu points and other relevant points were used. The needles were immersed in a depth of 0.5-1 cun by taking the feeling of dew; He stayed for 20 minutes during the session. A current of 2 Hz was given with the electroacupuncture device over the needles.

In ear acupuncture, zero point, jerome, shen-men cervical vertebra and lumbal vertebrae points were used. Permanent vaccaria seed, magnetic ball, intradermal acupuncture needles were used in the ear.

UB-10; Tianzhu; It is in the posterior hairline, where M. Trapezius adheres to the lower edge of the occiput bone. It is at the level of C1-C2 vertebrae.

UB-13; The Feishi; It is the back-Shu point of the lung. The spinous protrusion of the T3 vertebra is at the level of its lower edge,

DU-14; The Dazhu; It is located under the processus spinous of the C7 vertebra.

DU-20; Baihui; both ears are at the intersection of the line drawn from the apex. This point is a general physiological and coordination point in every acupuncture treatment.

Also; Lumbar Back-Shu points were obtained in those with lumbar discopathy.

UB-21; Weishu; T12 vertebra's spinous protrusion,.

UB-23; The Shenshen; The kidney's Back-Shu point. The spinous protrusion of the L2 vertebra is at the level of its lower edge, 1.5 cun lateral to the posterior midline.

UB-24; The Qiaish; the L3 vertebra is at the level of its lower edge

UB-25; The Dachangsh; The Large Intestine is the Back-Shu point. The spinous protrusion of the L4 vertebra is at the level of its lower edge, 1.5 cun lateral to the posterior midline. Krista iliaka is the upper limit.

UB-27; The Xiaochangsh; The Small Intestine is the Back-Shu point.

UB-28; The Pangguangsh; It is the back-shu point of the bladder. At the level of the 2nd sacral foramen, 1.5 c from the posterior midline (Çevik, 2016).

Homeopathy

Intracellular pathological pathways; It seems logical to update it as homeopathy, which is a regulation treatment based on the principle of transforming energy level, substrate level, enzyme cofactor level, pH, enzymes (amount and activity) into normal biochemical pathways through processes such as compartmentalization and hormonal control. If this theory is accepted as true; Healing with homeopathic medicines should be as follows: It is achieved by the sick body emitting the frequencies of pathological pathways and processing pathological biochemical reactions, resulting in reduction and oxidation reactions according to these biochemical pathways. It should be acknowledged that what is meant by the law of similimum, the basic law of homeopathy, is that the frequencies of homeopathic medicines match the frequencies of the patient. The sickening photons are canceled or the missing photons are added by the resonance effect until the normal frequency pattern is restored. This situation continues until the biochemical pathological pathway is healed. This is what determines potency and repetition time. The reason why medications are frequently given in acute diseases is; It is the active disruption and restoration of pathological pathways.

Example Studies of Pharmacodynamic Mechanisms

It is clear that further in vivo and clinical studies of these raw materials need to be carried out in order not to be overshadowed by the negative perspective on homeopathy. However, it should be noted that these raw materials are not commercially patentable, that is, they are not economically monopolized. A few notable examples of pharmacodynamic effects are as follows:

- Podophilylum 4D-increases free radical production and reduces adhesion in human neutrophil cells. The combined preparation (4D-6D) containing Arnica, Calendula, Hypericum, Symphytum increases chemotaxis and cell movement in 3T3 fibroblasts.

- The combined preparation containing calcium fluoride, magnesium phosphate and acidium silicium (6D-12D) induces osteogenesis in rat osteoballasts.

- The combination of magnesium phosphate and manganese phosphate (8D) causes a decrease in free radical production in human neutrophils.

- Apis C3, C5, C7 The homeopathic composition containing (RWPE) causes gene expression changes in different groups of human prostate cells.

- Gelsemium (C5 and C9); increases the production of neurosteroids in rat neurons.

- Lycopodium (C5); It induces apoptosis in cervical cancer HeLa cells.

- Mercurius sol. (C6); in mouse peritoneal macrophages; increases the production of interferon G.

- Ruta (C6).

- (30D) Rhus Tox; It increases COX2 specific gene expression in primary mouse chondrocytes, induces the inflammation response responsible for PGE2 release, inhibits collagen 2 differentiator specific gene expression.

- Acon, Ars, Asa-f, Cal-C, Chelid, Cinnamon, Conium, Echinesia, Rhus-Tox- It has been reported that the combination of Gelsemium, Ipec, Phos, Thuja, Sil, Sulph 7D-24 inhibits TNF release in macrophages in human macrophage cells.

- Thuja 1M induces gene expression in DLA cells.

- Carcinocin C200 induces P53 gene apoptosis.

Effects of 12 Minerals

Nr 1 can be used for tissue hardening, scars, hardened lymph nodes, varicose veins, hemorrhoids, sagging, calluses, wounds, bruises, scratch marks, and nail bed infections.

Nr 2 can be used in the treatment of muscle cramps, muscle stiffness, stiff neck, tension-type headache, barking cough in children, restless heartbeat, excessive sweating, and post-bone fracture.

Nr 3 can be used for first aid purposes in injuries, contusions, sprains, infections, throbbing pains, redness, feeling of warmth, swelling, scratches, joint infection, acute pains, sunburn, burns (combined with nr 8).

Nr 4 can be used for cough accompanied by white mucus sputum, skin granules, capillary cracks, varicose veins, adhesions, in the extinguishing phase of the infection, and bursitis.

Nr 5 can be used for foul-smelling non-healing wounds, necrosis, ulcers, tissue crushing, extreme fatigue pain, tennis elbow, golfer's shoulder, muscle fatigue, paralysis, and heart strain.

Nr 6 can be used for flaking in the corneal upper layer of the skin, inflammatory upper skin diseases (eczema, psoriasis, neurodermatitis), feeling of pressure in the upper epigastrium, and discharge from the nose and sinuses containing yellowish-brown mucus.

Nr 7 can be applied for lightning-like and shifting pains; gas cramps, menstrual complaints, nervous skin itching, headaches starting from the neck (forehead and temples), angina pains (around the heart).

Nr 8 can be used in cases where the moisture balance of the skin is disrupted (moist skin rashes), dry mucosa, cartilage degeneration with decreased fluid amount, fibers, ligament-tendon, gout disease, lumbar disc degeneration, and complaints after insect bites.

Nr 9 helps to restore acid-base balance and adjust tissue pH If it is found in sufficient amounts in cells and tissues, the body easily eliminates acidity and helps detox.

Nr 10: It is an important mineral in xenobiotic excretion. It resolves under-eye edema that cannot be eliminated during weight loss.

Nr 11 It contains silicon, broken nails, deep forehead lines are indicators of deficiency. There is sensitivity to light. When silicon support in the connective tissue decreases, bruising occurs easily, nails separate in layers, and sweat smells.

Nr 12 It treats not only acid but also other harmful substance excretion; it does this by increasing the permeability of the connective tissue.

Shussler mineral substances may be available on the market with different excipients and may have different tablet pressing pressures. Those that do not use wheat starch and do not contain gluten should be preferred.

According to Dr. Receweg's homotoxin doctrine, diseases occur as a result of interaction with toxins. When all detox mechanisms of the organism are exhausted, toxins begin to accumulate first in the extracellular matrix and then in the intracellular environment. According to this mechanism, first acute diseases, then chronic diseases, and finally autoimmune diseases and cancer begin to emerge. The issue that Dr. Shüssler underlines is the loss and consumption of functional substances and building blocks and the depletion of stores of vitamins and bioactive substances. The common goal of all complementary treatments is to reverse these processes as much as possible. For this, the person must first be relaxed and then the waste-toxins must be detoxified; such as regulating nutrition, repairing scars and disruptive areas, arranging the sleeping area and lifestyle.

Method

Mineral tablets for first aid purposes in cases of sprains and contusions can be dissolved in a little water, mashed and applied thickly to the damaged area. (For open and bleeding lesions, number 3 can be applied, if there is crushing and bruising, number 11 can be added to this)

Since in burns the body loses fluid rich in sodium and chloride; By immersing the burned part in cold melted nr 8 water, nr 3 can be added to meet the electrolyte needs of the cell fluid and to relieve the pain.

Odorless and non-irritating gel and cream gel forms can be applied locally for sensitive skin and can be easily tolerated. Water-based ointments may be preferred so that they can be easily absorbed through the oily layers of the skin. Paraffin, paraben, petroleum jelly, triethanolamine; Since they do not contain fragrance, they can be used on all types of sensitive skin. Ointment forms can be applied in a thin layer, especially before going to bed at night, and covered with a thin gauze. Cream-gel forms, on the other hand, have a more effective use on the mucosa because they have a hydrophilic ointment liquid with a low oil content.

Zinc Preparations

Zinc Sulfate: The most used and least absorbable preparation, may cause stomach complaints and conspolition.

Zinc Picolinate: The Form with the best absorption

Zinc Gluconate: Absorption is good

Zinc Citrate: Good absorption, good taste

Zinc Bisglicinate: Absorption is quite good

Zinc Acetate: Available in lozil form

Zinc Oxide: Available in pomad form, used in wound care

Graphites also in Restless Leg Syndrome is also used.

Graphites:

* pain in the back, arms and legs,

numbness in hands, cramps in legs, arthritis

* thickening, hardening, deformities in the nails

* Calluses on hands and knees, wrists, cold extremities, hot feet, bad smell, feeling of taking the foot out of bed.

Kalium Bromatum:Used in restless hand movements. The patient shakes his hands, his hands are fidgety, he looks restless. He tries to relieve his restlessness by constantly moving his hands and fingers. There may be numbness throughout the body. Can also be used in Night terrors (like stramonium)

Magnesium carbonicum: There is also restlessness in the legs here, the reason is severe pain. These people cannot sleep due to extreme pain. There is a different uneasiness than Zincum.

*Pain is at the forefront in Mag-Car.

*In Zincum, there is restlessness due to the urge to move.

Zincuım Metallicum

Restlessness, abnormal and involuntary movements, twitching and even convulsions

Hypersensitivity of the nervous system is a distinctive feature of the zincum group of remedies.

In the beginning, there is overstimulation and mental overactivity in the mind. This state of hyperarousal is often followed by collapse, resulting in mental dullness, dissatisfaction, deep depression, and even suicidal thoughts. While initial excessive mental arousal creates an angry, angry and violent state, mental activities slow down over time, and mental deterioration such as slowness of speech, scattered - disjointed thoughts, use of wrong words and confusion develops.Over time, functional deficiency of Zinc, the most essential mineral for the brain, becomes evident.There are many complaints on the mental level in Zincum.

<u>At the beginning:</u> There is a lot of arousal, sensitivity, irritability, anger

Dissatisfied, complaining about everything, unsatisfied people

There are too many thoughts in the head, the connections between thoughts break down over time.

<u>After:</u> There is difficulty in understanding, he cannot understand what is asked immediately, he first repeats the question and then says the answer (ecospeech).

Mistakes in speaking and writing

Depression and suicidal ideation

Thoughts of death comfort the patient, but if these thoughts continue, he may attempt suicide.

General worsening after suppressed skin rashes, cortisone medications used for eczema, etc.

<u>Feeling good during the period:</u> general deterioration as a result of suppression of menstruation

Restlessness is felt especially in the feet and legs

Contractions in a single muscle group, twitches, tremors, fasciculations, convulsions, tremors occurring in Parkinson's disease, facial tics

Headache occurs especially in the occipital region at the back of the head. It is relieved by applying pressure or tying it tightly. Its severity increases after drinking wine and alcohol.

Due to the hyperactivity in the GI tract, there is severe hunger and overeating that occur at 11:00 am. Sometimes indigestion and vomiting may occur after eating.

Difficulty urinating, especially unable to urinate while standing, urinating more easily when sitting or leaning back

Urinary incontinence during convulsions, after coughing or sneezing

Premature ejaculation in men, increased sexual desire

Restless children constantly move their legs and feet, they cannot fall asleep at night, there may be sudden movements and contractions in the muscles even during sleep.

Peripheral neuropathy, numbness or burning.

Zincuım Phosphoricum

There is great reluctance to do anything mentally. They do not want to read books, study, think, or comment. Doing these causes great fatigue and as a result, reluctance occurs and they become failure and lazy.

Having lustful dreams, increased sexual desire

Severe nervous tremors

There is vertigo that gets worse when lying down, the patient is irritable.

Phosphor structure has zincum properties. Someone who is lively, attractive and has increased sexual desire as a phosphor structure, has poor memory and concentration as a zincum characteristic, overeating, especially around 11:00.

Restless legs, dullness in the brain, lack of concentration, excessive hunger and overeating at 11.00 o'clock, attractive young girls, menstrual delay, first menstruation has not started yet, Zinc phos can be given here.

Zincum also delays the onset of the first menstrual period.

Phosphorus, tuberculinum and calcarea have early puberty.

In Calcarea, there is actually a delay in normal development such as walking, speaking, teething, and the first occurrence of menstruation occurs early. So there is Puberty Precox

Discussion

There are many Cochrane reviews on non-pharmacological interventions for pain and many Cochrane reviews evaluating acupuncture treatment under pain conditions (Manchikanti et al., 2017). 22 relevant Cochrane reviews were found, concluding that some acupuncture therapy concluded that it was probably useful for the treatment of certain pain conditions. Most of the opioid uses (80%) used in painful conditions in America result in addiction, and after a while tolerance problems arise (Singh, 1999).

Non-steroidal anti-inflammatory drugs used non-opioid have gastrointestinal system problems, nausea, abdominal pain, stroke, heart attack, kidney failure and acute and chronic bleeding side effects (Singh, 1996). Among rheumatoid arthritis (RA) and OA patients alone, there are 16,500 deaths per year from NSAID-related gastrointestinal complications, and as of 2000, 25% of adverse drug reactions reported have been linked to prescription NSAID use (Singh, 2000). It is recommended by the Disease Control and Prevention Centers (CDC) and the USA as the first line of care. Centers such as the FDA, National Institutes of Health (NIH) make acupuncture among the first non-pharmacological methods to be tried at the top of the list in the treatment of pain (Ernst & White, 2001). As a result of systematic reviews and surveys, acupuncture proved to be reliable when performed by appropriately trained people (White, 2004).

Vickers et al. found acupuncture superior to sham group in pain and functions. It was observed that the effect of acupuncture continued with a decrease of approximately 15% when monitored for 1 year.

Referances

Bear, M. F., Connorsand, B. W. & Paradiso, M. A. (2007). Chemical control of the brain and behavior. In: M.F. Bear, B. W. Connorsand M.A. Paradiso (eds.) *Neuroscience Exploring the Brain.Phladelphia.* Lippincott Williams &Wilkins, pp. 481-508.

Chen, Z., Hedner, J., & Hedner, T. (1996). Substance P-induced respiratory excitation is blunted by delta-receptor specific opioids in the rat medulla oblongata. *Acta physiologica Scandinavica*, *157*(2), 165–173. https://doi.org/10.1046/j.1365-201X.1996.485232000.x

Chang, F. C., Tsai, H. Y., Yu, M. C., Yi, P. L., & Lin, J. G. (2004). The central serotonergic system mediates the analgesic effect of electroacupuncture on ZUSANLI (ST36) acupoints. *Journal of biomedical science*, *11*(2), 179–185. https://doi.org/10.1007/BF02256561

Çevik, C . (2016). Medikal Akupunktur 3.Baskı. *Kuban Matbaacılık:*162-225.

Ernst, E., & White, A. R. (2001). Prospective studies of the safety of acupuncture: a systematic review. *The American journal of medicine*, *110*(6), 481–485. https://doi.org/10.1016/s0002-9343(01)00651-9

Guyton, A. C. & Hall, J. E. (2007). Textbook of medical physiology. *WB Saunders, Philadelphia*

Lin, D., Huang, X., Zhuang, W., & Lin, L. (2017). [From Bonghan system to primo vascular system: the thought on the substantial study on meridian points] *Zhongguo zhen jiu = Chinese acupuncture & moxibustion*, *37*(1), 95–101. https://doi.org/10.13703/j.0255-2930.2017.01.025

Manchikanti, L., Kaye, A. M., Knezevic, N. N., McAnally, H., Slavin, K., Trescot, A. M., Blank, S., Pampati, V., Abdi, S., Grider, J. S., Kaye, A. D., Manchikanti, K. N., Cordner, H., Gharibo, C. G., Harned, M. E., Albers, S. L., Atluri, S., Aydin, S. M., Bakshi, S., Barkin, R. L., … Hirsch, J. A. (2017). Responsible, Safe, and Effective Prescription of Opioids for Chronic Non-Cancer Pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines. *Pain physician*, *20*(2S), S3–S92.

Merskey, H. M. & Bogduk, N. (1994). Classification of chronic pain. *IASP Press,* Seattle.

Pintov, S., Lahat, E., Alstein, M., Vogel, Z., & Barg, J. (1997). Acupuncture and the opioid system: implications in management of migraine. *Pediatric neurology*, *17*(2), 129–133. https://doi.org/10.1016/s0887-8994(97)00086-6

Shang C. (1989). Singular point, organizing center and acupuncture point. *The American journal of Chinese medicine*, *17*(3-4), 119–127. https://doi.org/10.1142/S0192415X8900019X

Singh, G., & Triadafilopoulos, G. (1999). Epidemiology of NSAID induced gastrointestinal complications. *The Journal of rheumatology. Supplement*, *56*, 18–24.

Singh, G., Ramey, D. R., Morfeld, D., Shi, H., Hatoum, H. T., & Fries, J. F. (1996). Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis. A prospective observational cohort study. *Archives of internal medicine*, *156*(14), 1530–1536.

Singh G. (2000). Gastrointestinal complications of prescription and over-the-counter nonsteroidal anti-inflammatory drugs: a view from the ARAMIS database. Arthritis, Rheumatism, and Aging Medical Information System. American journal of therapeutics, 7(2), 115–121.

White A. (2004). A cumulative review of the range and incidence of significant adverse events associated with acupuncture. *Acupuncture in medicine : journal of the British Medical Acupuncture Society*, *22*(3), 122–133.

About the Author

Dr. Hayriye Alp, graduated from Dokuz Eylül University, Faculty of Medicine in 1998. After working as a general practitioner for about 10 years, she received her anesthesia and reanimation specialization in 2012. Necmettin Erbakan Univ., where she started working in 2015. She still continues to work as a faculty member at the Faculty of Health Sciences. She also founded the GETAT Application Research Center of the same university and has 8 separate certificates. As a GETAT practitioner and trainer, she organizes courses certified by the Ministry of Health. Her areas of interest are acupuncture, phytotherapy, aromatherapy, homeopathy, prolotherapy, leeches, cupping, ozone therapy and mesotherapy.

E-mail: hayriyealp@erbakan.edu.tr **ORCID:** 0000-0002-7262-2234

Similarity Index

The similarity index obtained from the plagiarism software for this book chapter is 13%.

Medical Image Processing: Applications of Artificial Intelligence

Yunus Emre GÖKTEPE
Necmettin Erbakan University

Yusuf UZUN
Necmettin Erbakan University

To Cite This Chapter

Göktepe, Y. E. & Uzun, Y. (2024). Medical Image Processing: Applications of Artificial Intelligence. In F. Nur Takı, S. Koçer & R. Bütüner (Eds.), *New Generation Technologies and Sustainability in Health Current Studies* (pp. 220-234). ISRES Publishing.

Introduction

Today, medical image processing has become one of the most important functions of modern medicine. Medical imaging methods offer significant convenience in many areas such as diagnosis of diseases, treatment planning, and monitoring of patients. These techniques provide an auxiliary specialty for doctors to study the internal structure of the human body in detail. In this way, processes such as early diagnosis of diseases, treatment process and monitoring of the general health status of patients can be carried out more precisely and reliably (Li et al., 2023).

Medical imaging methods allow diseases to be detected in the early stages. For example, the practice of mammography plays a vital role in the early detection of breast cancer. Similarly, computed tomography (CT) and magnetic resonance imaging (MRI) are crucial in the early detection of various types of cancer and other serious diseases (Remeseiro & Bolon-Canedo, 2019).

Medical images help doctors more accurately create treatment plans for patients. Radiotherapy, surgical interventions, and other treatment methods can be applied more sensitively, reliably, and effectively thanks to medical images. In addition, the effectiveness of the treatment process can also be monitored through these images, so that treatment strategies can be revised if necessary (Sharma et al., 2020).

Imaging techniques play a major role in planning and performing surgical interventions. Especially in minimally invasive surgeries, surgeons can perform more precise and safe operations by using medical images before and during the operation. In the management of chronic diseases, regular monitoring of patients provides monitoring of the course of the disease. In this way, the progression of diseases and responses to treatment can be continuously monitored and treatment processes can be adjusted accordingly (Wang et al., 2021).

In recent years, the development of artificial intelligence and machine learning techniques has increased the efficiency and accuracy of medical image processing. Artificial intelligence-based algorithms analyze large data sets, allowing for the development of more accurate diagnoses and prognostic models. These technologies minimize errors caused by the human factor, especially in the analysis of complex images, and accelerate the diagnostic processes (Mohd Sagheer & George, 2020).

In the future, medical image processing is expected to become even more important. Technological advances will allow for the development of higher resolution and more detailed imaging techniques, while artificial intelligence applications will further improve diagnosis and treatment processes. In addition, it is envisaged that medical image processing, along with personalized medicine approaches, will play a central role in the creation of patient-specific treatment plans (Mohd Sagheer & George, 2020).

In recent years, artificial intelligence and deep learning techniques have revolutionized the field of medical image processing. These technologies offer significant advantages in many areas such as analysis, classification, segmentation, and anomaly detection of medical images. Artificial intelligence and deep learning accelerate medical image processing processes, improve their accuracy, and provide healthcare professionals with more reliable diagnostic and treatment options (Rizwan I Haque & Neubert, 2020).

This chapter comprehensively discusses the use of artificial intelligence techniques in the field of medical image processing. Medical imaging techniques, which are one of the cornerstones of modern medicine, offer indispensable tools in critical processes such as early diagnosis of diseases, treatment planning, and monitoring of patients. Artificial intelligence and deep learning have the potential to improve the quality of healthcare by increasing the accuracy and effectiveness of these processes. In this section, the effects of artificial intelligence and deep learning techniques on medical image processing, current applications and future perspectives will be examined in detail. The department aims to provide information and examples for academics, researchers, and health professionals to help them understand innovations and practices in this field.

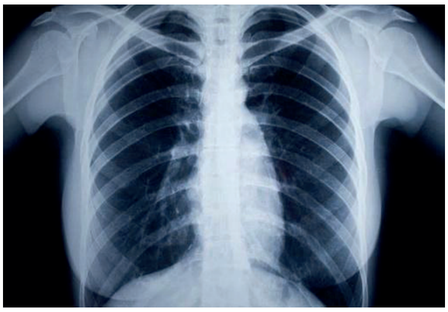
Medical Imaging Techniques

X-ray

X-ray imaging is a medical imaging technique that examines the internal structure of the human body using electromagnetic radiation. X-rays were discovered by Wilhelm Conrad Rontgen in 1895 and have been widely used in medical imaging ever since (Zhao et al., 2024).

X-rays are electromagnetic waves with a very short wavelength and high energy. These rays are absorbed in different amounts by tissues of different densities as they pass through the body. As X-rays pass through body tissues, they are more absorbed by dense structures such as bone, but less by soft tissues and air-filled cavities. These different levels of absorption create a contrast on the detector, creating an image. The bones appear white, the air-filled cavities appear black, and the soft tissues appear in shades of gray. X-rays are produced by accelerating electrons into a metal target in an X-ray tube. The resulting X-rays pass through the body and fall on the detector or film, and in this way, the image is obtained. An example of an X-ray image is shown in Figure 1.

Figure 1
X-ray Imaging (X-Ray, 2024)



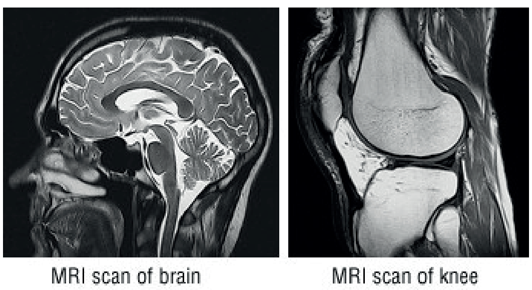
It is widely used in the diagnosis of bone fractures, dislocations, deformities, and other diseases of the skeletal system. It is also important in the evaluation of joint and spine problems. It is used in the diagnosis and monitoring of lung diseases (e.g., pneumonia, tuberculosis, and lung cancer). Chest X-rays also provide information about heart enlargement and other mediastinal structures. It is used in the diagnosis of dental and oral diseases such as dental caries, periodontal diseases, tooth root infections, and problems with jawbones. It is a special X-ray imaging technique used in the early diagnosis of breast cancer. It provides detailed images of breast tissue and helps detect masses and microcalcifications. It is a technique that provides live X-ray imaging. This method is used during interventional procedures such as examinations of the gastrointestinal tract, angiography, and catheter insertion. It is used in the evaluation of intra-abdominal organs (for example, intestinal obstruction, stones, and foreign bodies) (Zhao et al., 2024).

X-ray imaging is a fast and easy-to-apply technique. It is cost-effective. It provides high accuracy in the diagnosis of skeletal systems and some soft tissue diseases. It is necessary to limit exposure due to the use of ionizing radiation. Since soft tissue contrast is low, it may be insufficient for a detailed evaluation of some organs and tissues. It should be used with caution during pregnancy.

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is a medical imaging technique that creates detailed images of the body's internal structure using strong magnetic fields and radio waves. Body tissues are largely made up of water, and the hydrogen atoms in water molecules contain protons (Al-Lami et al., 2024). The MRI machine aligns the magnetic moments of these protons by creating a strong magnetic field. An example of an MRI image is shown in Figure 2.

Figure 2
MRI Imaging (MRI, 2024)



The device sends a short pulse of radio waves. These radio waves disrupt the protons' aligned state, absorbing their energy and causing them to rotate. When the radio wave is interrupted, the protons try to return to their original alignment. In this process, they release energy, which is detected by the detectors of the MRI machine. The alignment times (relaxation times) of protons vary depending on the type of tissue and environmental factors. The collected signals are processed by a computer to create detailed cross-sectional images of different tissues. MRI can provide cross-sectional images from a variety of angles (transverse, longitudinal, and diagonal) (Al-Lami et al., 2024).

MRI plays an important role in a wide range of medical diagnoses because it is a non-invasive technique and does not use radiation. MRI is considered the gold standard in diagnosing diseases of the brain and spinal cord. Brain tumors, stroke, multiple sclerosis (MS), cerebrovascular diseases, and degenerative diseases can be visualized in detail with MRI. MRI provides detailed and accurate information in imaging joints, muscles, tendons, and connective tissues. Sports injuries, arthritis, soft tissue tumors, and bone infections can be detected by MRI. MRI is an important tool in the structural and functional evaluation of the heart. It is used in the diagnosis of heart muscle diseases, heart valve diseases, and congenital heart diseases. Cancer diagnosis and staging can be done with whole-body scans. The size, location, and spread of tumors can be determined by MRI. Treatment response can also be monitored. It is used in the evaluation of liver, pancreas, biliary tract, and intestinal diseases. It is especially useful in conditions such as inflammatory bowel diseases and cirrhosis of the liver. It is used in the evaluation of the pelvic organs (uterus, ovaries), especially in the diagnosis of endometriosis, fibroids, and ovarian cysts. It can also be used in combination with mammography in breast cancer screening (Al-Lami et al., 2024).

MRI does not use radiation, so it is safe, especially in pediatrics and pregnancy. It provides detailed and clear images with high soft tissue contrast. It can distinguish various types of tissues and their abnormalities with high accuracy. Metal implants can be incompatible with pacemakers and other ferromagnetic devices. It is cost-effective and the shooting time is longer than other imaging methods. It can create discomfort for patients with a fear of confined spaces (claustrophobia).

Computed Tomography

Computed Tomography (CT) is an advanced medical imaging technique that creates cross-sectional images of the body's internal structures using X-rays. The CT scanner consists of X-ray tubes and detectors arranged in the form of a ring. X-rays are absorbed at different rates by tissues of different densities as they pass through the body. A CT scanner scans a specific area of the body in multiple sections (slices). These sections are a combination of images of X-rays taken from different angles. The collected data is processed by a computer to create detailed, cross-sectional images of the body's internal structures. These images allow the creation of a three-dimensional model of a specific region. In some cases, contrast agents (ionic or non-ionic) may be used for clearer imaging of blood vessels, organs, or tissues. These substances absorb X-rays better, highlighting certain structures (Navran et al., 2024). An example of a CT image is shown in Figure 3.

Figure 3
CT Imaging (Tomography, 2024)

CT scans have a wide range of applications in various fields of medicine. In trauma patients, CT scans are used to quickly and accurately assess internal bleeding, organ damage, or fractures. It is vital for brain hemorrhages, strokes, and other emergencies. CT is a fast and effective method for diagnosing brain and spinal cord diseases. Brain tumors, hemorrhages, strokes, aneurysms, and infections can be detected by CT. CT scans play a critical role in cancer diagnosis, staging, and monitoring of treatment response. The size, location, and spread of tumors can be evaluated in detail. It is used in the evaluation of the heart and coronary arteries. It is an important tool in the diagnosis of coronary artery disease, heart failure, and other heart diseases (Navran et al., 2024).

CT scans are commonly used in the diagnosis and monitoring of lung diseases (e.g., lung cancer, pneumonia, and emphysema). It is also effective in assessing emergencies such as pulmonary embolism. It is used in the evaluation of the liver, pancreas, kidneys, and other abdominal organs. Intra-abdominal tumors, stones, inflammations, and other pathologies can be visualized with CT. CT scans provide detailed and accurate information in the evaluation of bone fractures, joint diseases, and bone tumors. It is also used for surgical planning and monitoring. CT angiography is used to evaluate blood vessels. Aneurism, stenosis, and other vascular pathologies can be detected by CT angiography.

CT scans provide fast, high-resolution images. It can view bone, soft tissue, and blood vessels in detail. Ideal for rapid diagnosis and treatment planning in emergencies. Better visualization of certain structures can be achieved with contrast agents. It uses ionizing radiation, so limiting exposure is necessary. There is a risk of allergic reactions to contrast agents. It should be used with caution during pregnancy. It is a costly method and in some cases, alternative methods such as MRI may be preferred.

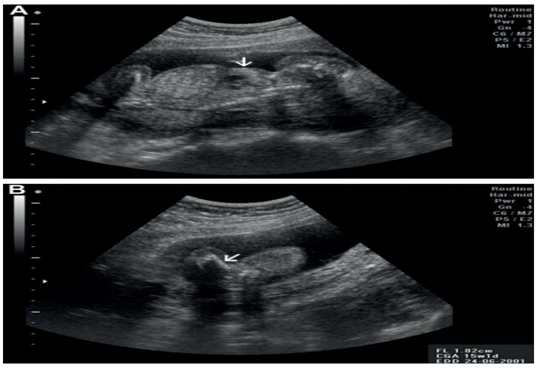
Ultrasonography

Ultrasonography is a medical imaging technique that creates images of the internal structures of the body using high-frequency sound waves. The use of sound waves makes this method radiation-free and safe (Meomartino et al., 2021).

The ultrasound device uses a transducer (probe) containing piezoelectric crystals. These crystals, when excited by electric current, produce sound waves of high frequency and send these waves to the body. Sound waves sent to body tissues are reflected from tissues of different densities and properties (create echoes). These reflections are again detected by the transducer and converted into electrical signals. The received electrical signals are processed by the ultrasound device and converted into real-time two-dimensional or three-dimensional images of the internal structures of the body. These images can be viewed and saved on the monitor. Doppler ultrasound is used to provide information about blood flow and mobile structures. The Doppler effect determines the speed and direction of blood flow by measuring the frequency changes of sound waves reflected from motile blood cells (Meomartino et al., 2021).

Ultrasonography is widely used in various fields of medicine with a wide range of applications. Pregnancy follow-up and fetal development assessment. It provides information about the position, age, sex, and health status of the fetus. An assessment can be made about the condition of the placenta, amniotic fluid, and uterus. It is used in the diagnosis of gynecological diseases, cysts, and tumors. It is used in the diagnosis and monitoring of cardiovascular diseases. Evaluation of heart valves, heart muscle, and heart cavities. With echocardiography, the functions and structural anomalies of the heart are visualized. An example of an ultrasonography image is shown in Figure 4.

Figure 4
Ultrasonography Imaging (Chen et al., 2013)



Evaluation of abdominal organs such as liver, gallbladder, pancreas, kidneys, spleen, and bladder. Diagnosis of stones, tumors, cysts, inflammation, and other pathologies. Examination of the thyroid gland, lymph nodes, and neck structures. Detection of thyroid nodules, cysts, and tumors. Evaluation of muscle, tendon, connective tissue, and joint structures. Diagnosis of sports injuries, tendonitis, bursitis, and other soft tissue problems.

Abdominal, brain, and hip ultrasonography in infants and children. Detection and monitoring of congenital anomalies. Evaluation of the kidneys, bladder, prostate, and testicles. Diagnosis of stones, cysts, tumors, and prostate diseases. Evaluation of blood vessels and blood flow. Detection of thrombosis, aneurysm, stenosis, and other vascular diseases. Ultrasonography does not contain radiation, so it can be used safely in pregnant and pediatric patients. It provides real-time imagery, which allows monitoring of moving structures and dynamic processes. It is cost-effective and has wide accessibility. It is a non-invasive and usually painless method. Sound waves may be insufficient to visualize tissues behind structures such as air or bone. Detailed imaging of deep tissues can be difficult. It is a user-dependent method; Operator experience and skill can affect image quality.

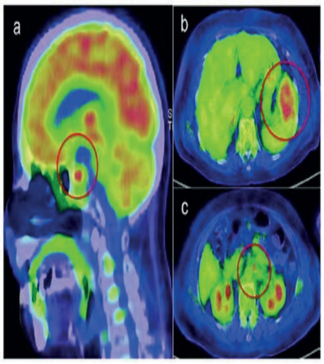
Pozitron Emissions Tomography

Positron Emission Tomography (PET) is an advanced nuclear medicine imaging technique that visualizes the biological functions of the body using radioactive materials.

PET scans use biological molecules (usually glucose, water, or oxygen) labeled with positron-emitting radioactive isotopes. These isotopes have short half-lives and are usually analogs of substances naturally present in the body. Radioactive isotopes emit positively charged particles called positrons. These positrons collide with electrons in the body and enter the annihilation process, during which two gamma photons with an energy of 511 keV are emitted. Detection of Gamma Photons: The PET scanner consists of detectors arranged around the body. The reciprocal gamma photons emitted because of annihilation are detected by the detectors and the source points are determined by measuring the time differences of these photons reaching the detectors. The collected data is processed by a computer and converted into three-dimensional images of the body's biological functions. PET images show the distribution of metabolic activity, blood flow, and other biochemical processes (Katal et al., 2024). An example of a PET image is shown in Figure 5.

Figure 5

PET Images (Kumabe et al., 2015)



PET scans have a wide range of applications, especially in the fields of oncology, neurology, and cardiology. PET is used in cancer diagnosis and staging, based on the principle that cancerous cells show an increase in glucose uptake due to their high metabolic activity. FDG-PET (fluorodeoxyglucose-PET) is particularly common. PET is used to determine the location of primary tumors and metastases. It helps in the planning of treatment and the direction of surgical interventions. Changes in the metabolic activity of tumors after chemotherapy, radiotherapy, or immunotherapy can be monitored with PET.

PET is used for early detection and monitoring of Alzheimer's disease, Parkinson's disease, Huntington's disease, and other neurodegenerative diseases. Changes in glucose metabolism and neurotransmitter levels in the brain are displayed. It is used for the determination of epileptic foci and surgical planning. It is used to investigate biochemical changes in the brain in schizophrenia, depression, and other psychiatric disorders. PET is used to evaluate blood flow (perfusion) and oxygen utilization of the heart muscle. It helps in the diagnosis of coronary artery disease, ischemic heart disease, and myocardial infarction. It is used to determine living heart tissue (viability) and to identify areas of ischemia. PET can image biological and metabolic activities in high resolution. It provides high accuracy in diagnosing early-stage diseases and monitoring treatment response. Since it provides functional imaging, it provides more comprehensive information when used in conjunction with anatomical imaging techniques (CT and MRI). It uses radioactive substances, so limiting exposure and careful handling is necessary. It is costly, and logistical challenges can be experienced due to the short half-life of radioactive isotopes. Contrast resolution may be limited, and in some cases may need to be supplemented with other imaging methods (Katal et al., 2024).

Artificial Intelligence Algorithms and Techniques

Image segmentation is the process of distinguishing between different regions or objects in an image, and it occupies an important place in the field of artificial intelligence. It is especially used in areas such as medical imaging, autonomous driving, and object recognition.

U-Net

U-Net is a convolutional neural network (CNN) architecture developed specifically for medical imaging data. It was introduced in 2015 by Olaf Ronneberger and colleagues. U-Net has a "U" shaped structure and consists of two main parts: an encoder (downsampling) and a decoder (upsampling). While the encoder part gradually reduces the images by extracting features at lower resolutions; The decoder part is used to bring these properties back to the original resolution. U-Net is notable for its ability to reconstruct low-resolution details in high resolution. It performs particularly well on limited data sets and is widely used in medical imaging applications. Medical image segmentation (e.g., tumor detection and organ segmentation) is used in areas such as biomedical imaging (Liu & Wang, 2024).

Mask R-CNN

Mask R-CNN is a deep learning model that can perform object detection and segmentation tasks simultaneously. Mask R-CNN is an extension of Faster R-CNN and uses the RoIAlign (Region of Interest Alignment) method for object detection (Sapkota et al., 2024). Mask R-CNN makes a classification, a boundary box prediction, and a segmentation mask prediction for each object. It performs both object detection and segmentation tasks with high accuracy. It precisely defines the boundaries of objects and produces segmentation masks at the pixel level. It is used in areas such as object detection and segmentation, autonomous driving, video analytics, and industrial automation (Aljabri & AlGhamdi, 2022).

DeepLab

DeepLab is a set of convolutional neural network architectures specifically targeted to achieve high-quality segmentation results. It was first introduced in 2015 and is available in several versions (DeepLabv1, DeepLabv2, DeepLabv3, and DeepLabv3+). By using "atrous" (or "dilated") convolutions, DeepLab is enabled to process a larger area with a smaller number of parameters. DeepLabv3+, on the other hand, tries to capture details better with its encoder-decoder structure. It provides detailed segmentation results at high resolution. It performs well for a variety of image resolutions and object scales. Semantic segmentation is used in areas such as urban planning and agriculture imaging (Zhan & Chen, 2024).

SegNet

SegNet is a convolutional neural network designed specifically for segmentation tasks. It was introduced in 2015 by Vijay Badrinarayanan et al. SegNet has an encoder-decoder structure. In the encoder section, the properties are extracted and in the decoder part, these features are converted into detailed segmentation masks. SegNet implements "max pooling" and "unpooling" at each level of feature maps. It preserves the details of images in high resolution. It is especially successful in applications such as urban image segmentation and road networks. Semantic segmentation is used in areas such as urban planning and traffic analysis (Jonnalagadda & Hashim, 2024).

Fully Convolutional Network

Fully Convolutional Network (FCN) is an approach that transforms classification networks into segmentation networks by replacing convolutional neural networks with completely convolutional layers. It was introduced in 2015 by Jonathan Long and his friends. Instead of classification using standard CNNs, FCN ensures that each pixel receives a class label. Convolutional layers can process images in high resolution. Thanks to its completely convolutional structure, it provides flexibility and high-resolution segmentation. It is used in areas such as semantic segmentation and image analysis (Wan et al., 2024).

Image Classification

Image classification is the process of dividing an image into specific categories and has an important place in the field of deep learning. One of the commonly used artificial intelligence algorithms in image classification is Convolutional Neural Networks (CNNs). CNNs are deep learning models specifically designed to process and classify image data (Liu et al., 2023).

Convolutional Neural Networks

Convolutional Neural Networks (CNNs) is an artificial neural network architecture developed to process image data. It is very effective in learning the local relationships and characteristics within the images. The CNN architectural structure consists of 4 basic layers. Convolutional layers use small, animated kernels to extract features (edges, corners, and textures) from images. Filters create feature maps by scrolling over the image. Activation layers, usually activation functions such as ReLU (Rectified Linear Unit), make the values obtained after the convolution process non-linear. Pooling operations, such as pooling layers, max-pooling, or average-pooling, reduce the size of feature maps and summarize important information. This improves the overall performance of the model and reduces the computational cost. Fully connected layers, after the properties are extracted, these properties are assigned to specific classes using fully connected layers. These layers enable the neural network to be converted into output classes (Raquib et al., 2024).

CNNs can learn local features in images and infer higher-level meanings by combining those features. Convolutional filters use the same filter on the entire image, reducing the number of parameters and enabling more efficient learning. It performs well with large data sets and deep network structures, making more complex and diverse classification tasks possible. It is successfully used in areas such as human face recognition, object recognition, facial expression analysis, disease detection, tumor classification, and organ segmentation. Popular CNN architectures; LeNet-5, AlexNet, VGGNet, ResNet and Inception applications (Abut et al., 2024).

Feature Extraction and Selection

Medical imaging is a tool used to diagnose and monitor a variety of health problems, and extracting meaningful information from these images is critical. Feature extraction is a technique used to extract meaningful information from images. In medical images, this process allows the identification of diseased areas, organ structures, or other important signs. Methods such as noise removal and normalization are used as image pre-processing processes. Texture properties, shape features, color features, and quantitative properties are used to extract features (Nagarajan et al., 2016).

Anomaly Detection

Anomaly detection in medical images is critical for the early and accurate identification of diseases and pathological changes. Artificial intelligence and machine learning techniques make this process more effective. Deep learning methods are used especially in processes such as cancer diagnosis, determining the location and size of tumors, and classifying abnormal tissue regions. Autoencoders are used in anomaly detection, especially in determining the deviations of images from normal (Durairaj et al., 2024). Generative Adversarial Networks (GANs) are used in processes such as creating and detecting anomalies in medical images, especially in the simulation and detection of rare diseases. One of the machine learning methods, Support Vector Machines (SVM) anomaly detection can perform especially when working on high-dimensional features and small data sets. Decision Trees and Random Forest are especially used in anomaly detection and classification tasks in data sets. K-Nearest Neighbor (K-NN) is used in anomaly detection and classification processes in medical images. Image Processing Techniques are used in the detection and analysis of tumors or lesions (Huérfano-Maldonado et al., 2023).

Application Areas

Disease Diagnosis

Artificial intelligence is creating a major revolution in the diagnosis of diseases in the field of medicine. The use of artificial intelligence in the early diagnosis and management of serious health problems such as cancer, heart disease, and neurological disorders is rapidly becoming widespread.

Image processing and deep learning methods are successfully used in cancer diagnosis. Artificial intelligence is used to detect tumors and abnormal tissues in X-rays, mammography, CT, MRI, and pathology images. In particular, CNNs are widely used in this field. By extracting features such as the size, shape, and texture of the tumor from medical images, it can classify the type and stage of cancer using these features. Artificial intelligence can be used in the genetic profiling of cancer and the creation of individual treatment plans. By extracting meaningful biomarkers from genomic data, it is possible to identify the type of cancer and offer personalized treatment options (Ganeshkumar et al., 2022).

In diagnosing heart diseases, artificial intelligence is used in echocardiography and cardiac MRI images to analyze heart structures and functions. This evaluates heart muscle abnormalities, valve problems, and blood flow. Deep learning algorithms are very good at detecting arrhythmias and other heart rhythm disorders from ECG data. By analyzing electronic health records (EHR) and other patient data, AI can identify heart disease risk factors and make early diagnoses. Machine learning algorithms use this data to build risk prediction models (Ganeshkumar et al., 2022).

In diagnosing neurological disorders, artificial intelligence is used in brain MRI and CT images to detect abnormalities and diseases in the brain. It is used in the diagnosis of neurological disorders such as Alzheimer’s, Parkinson’s, and MS (Multiple

Sclerosis). By analyzing fMRI data, which evaluates brain activity, it can detect early signs of neurological diseases. Artificial intelligence can be used to identify and analyze biomarkers that can be used in the diagnosis of neurodegenerative diseases. By analyzing the clinical signs and test results of neurological disorders, artificial intelligence can improve the diagnosis and prognosis of diseases (Pandya et al., 2019).

Detecting diseases in their early stages increases treatment success rates. Artificial intelligence can create personalized treatment plans by analyzing individual patient data. In addition, it can quickly and accurately analyze large amounts of medical data, reducing the workload of healthcare professionals and improving diagnostic accuracy. In addition to these, the privacy and security of medical data is an important issue in artificial intelligence applications. The decisions of the models need to be understandable and explainable. The integration of artificial intelligence solutions into clinical settings and adoption by healthcare professionals can take time (Pandya et al., 2019).

Current Research and Developments

Medical image processing is making great strides with the rapid development of artificial intelligence and deep learning techniques. Next-generation deep learning models such as Vision Transformer (ViT) and Swin Transformer are achieving great success in image processing tasks. These models show better anomaly detection and classification performance in medical images. Models trained on large data sets are adapted to the field of medical imaging using transfer learning, thus achieving high performance even in small data sets (Fu et al., 2024).

Combining different medical imaging modalities such as MRI, CT, PET, and ultrasound allows for more comprehensive and accurate diagnoses. These techniques combine the strengths of different images to improve diagnostic accuracy. The combination of data from different imaging modalities allows for more comprehensive analyses and more reliable diagnoses (Yang et al., 2024).

Real-time image analysis techniques are being developed for surgical robots and other medical devices, thus providing instant decision support systems during surgery. Artificial intelligence-supported systems provide instant feedback to doctors in diagnosis and treatment processes, helping them to make faster and more accurate decisions. Autonomous devices powered by artificial intelligence automate imaging processes, resulting in faster and more accurate results. These devices provide great advantages, especially in remote areas or where resources are limited. Robotic systems provide accurate and reproducible imaging positions, increasing image quality, especially in surgical interventions (Demirkol et al., 2024).

Quantum computing is opening new horizons in the field of medical image processing. Quantum algorithms perform complex calculations by processing large-scale image data faster. Quantum technologies enable images to be obtained with higher resolution and less radiation exposure in medical imaging. Integrated diagnostic systems powered by artificial intelligence offer more comprehensive and personalized analyses for early diagnosis and prognosis of diseases. Artificial intelligence creates advanced prognostic models to predict disease progression and predict treatment outcomes (Wei et al., 2023).

Conclusions

In this chapter, the role and applications of artificial intelligence in the field of medical image processing are examined in detail. Medical image processing is critical for early diagnosis of diseases, treatment planning, and patient follow-up. Various imaging techniques such as X-ray, MRI, CT, ultrasound, and PET are indispensable tools in accurate diagnosis and treatment processes. These techniques assist doctors in identifying diseases by providing detailed images of the body's internal structures.

Artificial intelligence and deep learning are transforming medical image processing processes. Deep learning algorithms such as CNN, U-Net, and Mask R-CNN provide high accuracy rates in tasks such as image segmentation, classification, and anomaly detection. These methods make significant contributions to clinical decision support systems by detecting complex structures and abnormalities in medical images.

It is used in various fields such as bone fractures, lung diseases, and dental health. Its basic principle is to create images by reflecting different densities of textures. It provides detailed images of soft tissues and is used in the diagnosis of diseases of the brain, spinal cord, joints, and muscles. MRI creates images using a magnetic field and radio waves. It provides cross-sectional images of the body and provides a detailed examination of the internal organs. It creates 3D images using X-rays and computer technology. It provides images of internal organs and tissues using sound waves. It is used in various fields such as pregnancy tracking, heart diseases, and liver diseases. It displays metabolic activities using radioactive materials and is used in the diagnosis of cancer, heart diseases, and neurological disorders.

Using algorithms such as U-Net and Mask R-CNN, organs, tumors, and other structures in medical images are highlighted. CNNs are used in the classification of medical images and are critical for disease diagnosis. Extracting meaningful features from medical images is essential for accurate diagnosis and treatment. Artificial intelligence techniques enable early diagnosis of diseases by detecting abnormalities in medical images. It plays a huge role in diagnosing cancer, heart disease, and neurological disorders. Early diagnosis of diseases and personalized treatment plans are created by methods such as image analysis, clinical data analysis, and genomic data. In the field of medical image processing, significant advances are being made in areas such as advanced deep learning models, multi-modal imaging, real-time analysis, autonomous imaging, quantum computing, and data privacy. These advances make medical image processing processes faster, more accurate, and safer.

The use of artificial intelligence in the field of medical image processing brings revolutionary changes in healthcare. Deep learning algorithms and other artificial intelligence techniques complement human expertise in the analysis of medical images, enabling faster and more accurate diagnoses. However, for these technologies to be successfully implemented, challenges such as data privacy, security, model transparency, and clinical integration must be overcome. In the future, with the further development of AI-powered medical image processing technologies, significant advances are expected in areas such as early detection of diseases, personalized treatment plans, and improvement of patient outcomes. These developments will contribute to the provision of more efficient and effective services in the health sector.

References

Abut, S., Okut, H., & Kallail, K. J. (2024). Paradigm shift from Artificial Neural Networks (ANNs) to deep Convolutional Neural Networks (DCNNs) in the field of medical image processing. *Expert Systems with Applications*, *244*, 122983.

https://doi.org/https://doi.org/10.1016/j.eswa.2023.122983

Al-Lami, B. S., Al-Lami, B. S., & Al-Lami, Y. S. (2024). PET/CT in comparison with PET/MRI as an imaging modality in the management of Gliomas: A systematic review and meta analysis. *Journal of Medical Imaging and Radiation Sciences*, *55*(2), 330-338. https://doi.org/https://doi.org/10.1016/j.jmir.2024.02.008

Aljabri, M., & AlGhamdi, M. (2022). A review on the use of deep learning for medical images segmentation. *Neurocomputing*, *506*, 311-335. https://doi.org/https://doi.org/10.1016/j.neucom.2022.07.070

Chen, C.-P., Chang, T.-Y., Lin, M.-H., Chern, S.-R., Su, J.-W., & Wang, W. (2013). Rapid detection of K650E mutation in FGFR3 using uncultured amniocytes in a pregnancy affected with fetal cloverleaf skull, occipital pseudoencephalocele, ventriculomegaly, straight short femurs, and thanatophoric dysplasia type II. *Taiwanese journal of obstetrics & gynecology*, *52*, 420-425. https://doi.org/10.1016/j.tjog.2013.05.003

Demirkol, A. S., Sahin, M. E., Karakaya, B., Ulutas, H., Ascoli, A., & Tetzlaff, R. (2024). Real time hybrid medical image encryption algorithm combining memristor-based chaos with DNA coding. *Chaos, Solitons & Fractals*, *183*, 114923. https://doi.org/https://doi.org/10.1016/j.chaos.2024.114923

Durairaj, A., Madhan, E. S., Rajkumar, M., & Shameem, S. (2024). Optimizing anomaly detection in 3D MRI scans: The role of ConvLSTM in medical image analysis. *Applied Soft Computing*, *164*, 111919. https://doi.org/https://doi.org/10.1016/j.asoc.2024.111919

Fu, L., Chen, Y., Ji, W., & Yang, F. (2024). SSTrans-Net: Smart Swin Transformer Network for medical image segmentation. *Biomedical Signal Processing and Control*, *91*, 106071. https://doi.org/https://doi.org/10.1016/j.bspc.2024.106071

Ganeshkumar, M., Sowmya, V., Gopalakrishnan, E. A., & Soman, K. P. (2022). Chapter 10 - Unsupervised deep learning-based disease diagnosis using medical images. In A. K. Bhoi, V. H. C. de Albuquerque, P. N. Srinivasu, & G. Marques (Eds.), *Cognitive and Soft Computing Techniques for the Analysis of Healthcare Data* (pp. 203-220). Academic Press. https://doi.org/https://doi.org/10.1016/B978-0-323-85751-2.00011-6

Huérfano-Maldonado, Y., Mora, M., Vilches, K., Hernández-García, R., Gutiérrez, R., & Vera, M. (2023). A comprehensive review of extreme learning machine on medical imaging. *Neurocomputing*, *556*, 126618. https://doi.org/https://doi.org/10.1016/j.neucom.2023.126618

Jonnalagadda, A. V., & Hashim, H. A. (2024). SegNet: A segmented deep learning based Convolutional Neural Network approach for drones wildfire detection. *Remote Sensing Applications: Society and Environment*, *34*, 101181. https://doi.org/https://doi.org/10.1016/j.rsase.2024.101181

Katal, S., Patel, P., Lee, J., Taubman, K., & Gholamrezanezhad, A. (2024). Total Body PET/CT: A Role in Musculoskeletal Diseases. *Seminars in Nuclear Medicine*. https://doi.org/https://doi.org/10.1053/j.semnuclmed.2024.05.009

Kumabe, A., Kenzaka, T., Nishimura, Y., Aikawa, M., Mori, M., & Matsumura, M. (2015). A rare case of anasarca caused by infiltration of the pituitary gland by diffuse large B-cell lymphoma. *BMC Endocrine Disorders*.

Li, J., Chen, J., Tang, Y., Wang, C., Landman, B. A., & Zhou, S. K. (2023). Transforming medical imaging with Transformers? A comparative review of key properties, current progresses, and future perspectives. *Medical Image Analysis*, *85*, 102762. https://doi.org/https://doi.org/10.1016/j.media.2023.102762

Liu, L., Sun, H., & Li, F. (2023). A Lie group kernel learning method for medical image classification. *Pattern Recognition*, *142*, 109735. https://doi.org/https://doi.org/10.1016/j.patcog.2023.109735

Liu, M., & Wang, S. (2024). Early macular edema recognition after cataract surgery based on U-Net assisted optical coherence tomography. *Journal of Radiation Research and Applied Sciences*, *17*(3), 100990. https://doi.org/https://doi.org/10.1016/j.jrras.2024.100990

Meomartino, L., Greco, A., Di Giancamillo, M., Brunetti, A., & Gnudi, G. (2021). Imaging techniques in Veterinary Medicine. Part I: Radiography and Ultrasonography. *European Journal of Radiology Open*, *8*, 100382. https://doi.org/https://doi.org/10.1016/j.ejro.2021.100382

Mohd Sagheer, S. V., & George, S. N. (2020). A review on medical image denoising algorithms. *Biomedical Signal Processing and Control*, *61*, 102036. https://doi.org/https://doi.org/10.1016/j.bspc.2020.102036

MRI. (2024). *MRI imaging*. Retrieved 24.07.2024 from https://www.health.harvard.edu/a_to_z/magnetic-resonance-imaging-mri-a-to-z

Nagarajan, G., Minu, R. I., Muthukumar, B., Vedanarayanan, V., & Sundarsingh, S. D. (2016). Hybrid Genetic Algorithm for Medical Image Feature Extraction and Selection. *Procedia Computer Science*, *85*, 455-462. https://doi.org/https://doi.org/10.1016/j.procs.2016.05.192

Navran, A., Kayembe, M. T., Gouw, Z. A. R., Vogel, W. V., Karssemakers, L., Paul de Boer, J., Donswijk, M. L., Schreuder, W. H., Owers, E., van den Brekel, M., & Al-Mamgani, A. (2024). FGD-PET/CT three months after (chemo)radiotherapy for head and neck squamous cell carcinoma spares considerable number of patients from a salvage neck dissection. *Radiotherapy and Oncology*, *198*, 110407. https://doi.org/https://doi.org/10.1016/j.radonc.2024.110407

Pandya, M. D., Shah, P. D., & Jardosh, S. (2019). Chapter 3 - Medical image diagnosis for disease detection: A deep learning approach. In N. Dey, A. S. Ashour, S. J. Fong, & S. Borra (Eds.), *U-Healthcare Monitoring Systems* (pp. 37-60). Academic Press. https://doi.org/https://doi.org/10.1016/B978-0-12-815370-3.00003-7

Raquib, M., Hossain, M. A., Islam, M. K., & Miah, M. S. (2024). VashaNet: An automated system for recognizing handwritten Bangla basic characters using deep convolutional neural network. *Machine Learning with Applications*, *17*, 100568. https://doi.org/https://doi.org/10.1016/j.mlwa.2024.100568

Remeseiro, B., & Bolon-Canedo, V. (2019). A review of feature selection methods in medical applications. *Computers in Biology and Medicine*, *112*, 103375. https://doi.org/https://doi.org/10.1016/j.compbiomed.2019.103375

Rizwan I Haque, I., & Neubert, J. (2020). Deep learning approaches to biomedical image segmentation. *Informatics in Medicine Unlocked*, *18*, 100297. https://doi.org/https://doi.org/10.1016/j.imu.2020.100297

Sapkota, R., Ahmed, D., & Karkee, M. (2024). Comparing YOLOv8 and Mask R-CNN for instance segmentation in complex orchard environments. *Artificial Intelligence in Agriculture*, *13*, 84-99. https://doi.org/https://doi.org/10.1016/j.aiia.2024.07.001

Sharma, M., Agrawal, S., & Deswal, S. (2020). Chapter 6 - Application of hybrid computational intelligence in health care. In S. Bhattacharyya, V. Snášel, D. Gupta, & A. Khanna (Eds.), *Hybrid Computational Intelligence* (pp. 123-148). Academic Press. https://doi.org/https://doi.org/10.1016/B978-0-12-818699-2.00007-X

Tomography, C. (2024). *Computed Tomography*. Retrieved 24.07.2024 from https://www.nibib.nih.gov/science-education/science-topics/computed-tomography-ct

Wan, Z., Lan, H., Lin, S., & Dai, H. (2024). Defect detection and repair algorithm for structures generated by topology optimization based on 3D hierarchical fully convolutional network. *Biomimetic Intelligence and Robotics*, *4*(2), 100149. https://doi.org/https://doi.org/10.1016/j.birob.2024.100149

Wang, S., Celebi, M. E., Zhang, Y.-D., Yu, X., Lu, S., Yao, X., Zhou, Q., Miguel, M.-G., Tian, Y., Gorriz, J. M., & Tyukin, I. (2021). Advances in Data Preprocessing for Biomedical Data Fusion: An Overview of the Methods, Challenges, and Prospects. *Information Fusion*, *76*, 376-421. https://doi.org/https://doi.org/10.1016/j.inffus.2021.07.001

Wei, L., Liu, H., Xu, J., Shi, L., Shan, Z., Zhao, B., & Gao, Y. (2023). Quantum machine learning in medical image analysis: A survey. *Neurocomputing*, *525*, 42-53. https://doi.org/https://doi.org/10.1016/j.neucom.2023.01.049

X-Ray. (2024). *X-Ray Imaging*. Retrieved 24.07.2024 from https://lifeofmedical.com/x-ray-rontgen-nedir/

Yang, Q., Chen, N., & Zhang, S. (2024). CT, MRI, and 18F-FDG PET/CT imaging of multiple bone brown tumors secondary to parathyroid adenoma: A case report. *Asian Journal of Surgery*. https://doi.org/https://doi.org/10.1016/j.asjsur.2024.04.114

Zhan, W., & Chen, J. (2024). SADNet: Space-aware DeepLab network for Urban-Scale point clouds semantic segmentation. *International Journal of Applied Earth Observation and Geoinformation*, *129*, 103827. https://doi.org/https://doi.org/10.1016/j.jag.2024.103827

Zhao, J., Huang, Q., Liang, D., Chen, Y., & Wang, G. (2024). Chapter 9 - Deep learning for medical image reconstruction: Focus on MRI, CT and PET. In S. K. Zhou, H. Greenspan, & D. Shen (Eds.), *Deep Learning for Medical Image Analysis (Second Edition)* (pp. 247-278). Academic Press. https://doi.org/https://doi.org/10.1016/B978-0-32-385124-4.00019-2

About the Authors

Yunus Emre GOKTEPE, PhD, is an Assistant Professor at Necmettin Erbakan University. The author's areas of expertise are bioinformatics, artificial intelligence, and machine learning. He is still serving as a faculty member of the Department of Computer Engineering, Seydisehir Ahmet Cengiz Engineering Faculty at Necmettin Erbakan University in Konya, Türkiye.
E-mail: ygoktepe@erbakan.edu.tr,**ORCID:** 0000-0002-8252-2616

Yusuf UZUN, PhD, is an Assistant Professor of Computer Engineering at Necmettin Erbakan University in Konya, Türkiye. He holds a PhD in Mechanical Engineering from Necmettin Erbakan University. His main areas of interest are artificial intelligence, autonomous systems, and augmented reality applications. He also works as the Rector's Advisor at Selcuk University.
E-mail: yuzun@erbakan.edu.tr, **ORCID:**0000-0002-7061-8784

Similarity Index

The similarity index obtained from the plagiarism software for this book chapter is 11%.

New Generation Technologies and Sustainability In Health:Current Studies was published from selected articles invited by the editors.

This edition includes sustainability, artificial intelligence, augmented reality, robotic solutions, etc., which are used in today's technology used in healthcare. it consists of 14 chapters. All applications are reviewed by at least two international referees. The purpose of the book is to provide readers with the opportunity of a technology scientific peer-reviewed publication from current technologies in health.

New Generation Technologies and Sustainability In Health:Current Studies is published by ISRES Publications.

ISRES Publishing