

AN INNOVATIVE STUDY EXPLORING REVOLUTIONIZING HEALTHCARE WITH AI: PERSONALIZED MEDICINE: PREDICTIVE DIAGNOSTIC TECHNIQUES AND INDIVIDUALIZED TREATMENT

Teja Reddy Gatla

Systems Engineer, Department of Information Technology

ABSTRACT— The key objective of this study is to fill the gap between personalized medicine and healthcare that currently exists by integrating forecasting diagnosis channels and individualized treatment made possible by artificial intelligence (AI). With advancements in big data analytics, machine learning, and deep neural networks, this research explores how AI can revolutionize healthcare by facilitating exact predictions of disease risk, diagnosis, and treatment response tailored to each patient. For instance, AI includes implementing deep neural networks for dermatologist-level classification of skin cancer and AI usage in cardiology for risk prediction and diagnosis [1]. This study outlines the existing literature and recently challenging issues in technology to explain the opportunities that AI-based personalized medicine will offer people to improve the outcome of their health, reduce the wastage of resources, and, lastly, minimize health inequalities. Secondly, this paper looks at the implications of personalized medicine approaches on the US healthcare system regarding managing chronic conditions like diabetes [1]. Today, personalized treatment plans based on the patient profile are preferred over one medication regime for all patients. Similarly, it also underscores the potential for better productivity, cost reduction, and patient-oriented treatment. Ultimately, it serves to outline the future of personalized medicine in the US with particular emphasis on two main topics, which are the persisting challenges and the opportunities for further development and adoption of such technology, such as integration of genomic data into clinical decision making to fit treatment of cancer patients.

Keywords— Healthcare, Patient outcomes, health disparities, artificial intelligence, personalized medicine, machine learning, chronic conditions, genomic data, U.S Healthcare System, AI systems, Disease Diagnosis

I. INTRODUCTION

Personalized medicine or precision medicine is a different approach to disease management, tailored to the individual characteristics of each particular patient. A conventional approach to medicine frequently uses a one-size-fits-all formula as a means of treatment, which may not address the genetic, environmental, and lifestyle individual differences that play an essential role in disease susceptibility and responses to treatment. AI in healthcare, big data analytics, machine learning, and deep neural networks are exciting areas of medicine that may yield predictive diagnostic techniques and patient-specific treatment methods[1]. The artificial intelligence integration in the health sector is another outstanding achievement, with cardiology, oncology, and dermatology being the primary beneficiaries. By using deep neural networks as an example, 5.4 million Americans every year affected by skin cancer were able to achieve a physician-equivalent level of classification in many skin cancer types. Likewise, AI-powered methods are being used in cardiology for risk prediction and diagnosis, which may impact the lives of 30 million US adults with heart diseases.

While the progress was significant, AI only scratched the surface of the growth prospects in precision medicine based on the AI application. Critical elements like data privacy and security issues, ethical implications of computer-generated decision-making, and mandatory validation and regulations of AI-based health technology are also among the vital criteria to consider [2,3]. Furthermore, inequities in healthcare infrastructure and the digital divide pose certain hurdles in applying personalized medicine strategies.

Due to data privacy and security concerns in AI-integrated medical care, AI-related privacy and security concerns appear as a significant risk. A large amount of sensitive personal health information is being accumulated, stored, and assessed, which is a starting point in case of data breach and unauthorized access. Ensuring patients' privacy takes precedence over all other factors is a must to win their trust, as per the relevant laws, such as HIPAA, in the US. Both ethical consequences of algorithmic decision-making and social challenges are reflected in artificial intelligence. AI algorithms, despite their power to master sophisticated data and produce forecasts, can also exhibit biases or accidentally inflict damage. Bias in AI algorithms can be used to maintain inequalities in healthcare outcomes, particularly among at-risk or underrepresented people [3].

Strict planning and regulation of AI-motivated healthcare technologies are necessary to guarantee their safety, effectiveness, and dependability. Unlike old counterparts, in control of AI, algorithms can grow and mature gradually and obtain more data and experience to help them learn. This dynamism creates an environment that makes it complex to introduce standard protocols for AI-driven healthcare technology validation and regulation [4]. Also, the rate of the latest technological advancement goes beyond the regulatory frameworks such that it is needed that they can be done continuously and make necessary adjustments of quality and safety to meet the standard. Equally, disparities in healthcare access and the digital divide burden the equitable use of personalized medicine techniques. Social-economic alignment, geographical location, and cultural problems could be the main obstacles surrounding people and the direct use of healthcare technology that uses AI in diagnostic tools and treatments. The health literacy inequity and the digital literacy disparity are the other factors that increase the gap between healthcare access and utilization [5].

Resolving these challenges requires a multidisciplinary approach based on partnerships among healthcare providers, strategists, technologists, ethicists, and community members. Practical strategies to mitigate data privacy and security risks include robust encryption, anonymizing data as much as possible, and having transparent consent processes before data sharing. Ethical principles and frameworks for AI in healthcare

could put fairness, transparency, and accountability at the top of auditing and algorithmic bias fix mechanisms. Agencies should apply agile regulatory policies to try to find a balance between initiating innovations and protecting patients, which can comprise adaptive licensing models and post-market surveillance systems as components of regulatory strategies. Besides, efforts to bridge the bridges and advocate for advocates should also include expanding healthcare services, improving health literacy, and addressing the social determinants of health. Through a holistic approach, AI-driven personalized medicine can transform the healthcare delivery system and bring about favorable patient outcomes for everyone. This paper aims to examine the research problem of the implementation of individualized therapies, which are AI-based in the health system of the USA, to explore the relevant funding, and to emphasize the importance and benefits of such an approach. Considering current trends and exploring prospects, this paper attempts to present the field of personalized medicine and how AI can transform healthcare and future delivery.

II. RESEARCH PROBLEM

The main problem that will be solved in this study is the disproportion between the potential of personalized medicine with AI and its practical usage in healthcare systems. AI is not a complete cure -it has a lot of problems and barriers impeding the speedy adoption of personalized medicine by patients-which is made more evident by the visible progress of AI in the healthcare sector [6]. These challenges range from data privacy, security, and ethical issues of algorithmic decision-making to requiring robust verification and regulation of AI-driven healthcare technologies, and there are imbalances in accessing healthcare and the digital divide, among other things. The research topic is the challenge of integrating AI into healthcare systems for the practical use of personalized medicine. This study will analyze the challenges and their implications, suggest strategies to overcome them, and create an appropriate system [7]. This study pays due attention to the bottlenecks to discover the power of personalized medicine, bring desirable changes in patient treatment, and provide healthcare services.

III. LITERATURE REVIEW

A. ADVANCEMENTS IN AI-DRIVEN HEALTHCARE TECHNOLOGIES

The development of Explainable AI (XAI) is one of the The last decade has seen exceptional breakthroughs in AI-driven healthcare technologies, such as predictive analytics, image recognition, and language processing. It is a machine learning algorithm based on Deep neural networks that has shown incredible breakthroughs in complicated medical imaging and diagnostic categories, disease prognosis, drug response, and treatment. On the other hand, deep learning algorithms can compete with or even excel human dermatologists in identifying malignancy on skin images. Another capability of AI in this field is the creation of AI-based diagnostic devices for different medical branches, such as neuroimaging, clinical pathology, and cardiology, that allow for faster and more precise diagnoses [8].

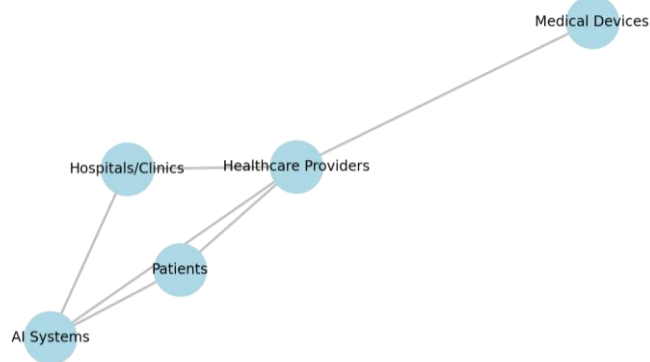


Fig. 1 Entity-Relationship Diagram for AI in Healthcare

The role of AI-driven healthcare technologies in medical diagnosis, treatment, and patient care has dramatically changed and improved the landscape of medicine. Machine learning algorithms, notably deep neural networks, have shown extraordinary abilities to process complicated medical data (structured as electronic health records, medical pictures, and genomic sequences). To illustrate this, researchers have successfully created AI algorithms designed to recognize various diseases, including skin cancer, cardiovascular diseases, and neurodegenerative conditions, based on medical imagery or clinical information. While these advancements may help detect diseases at an earlier stage and develop custom treatment regimes aimed at reducing morbidity and mortality rates, they are still under research, and there needs to be more evidence to validate their success.

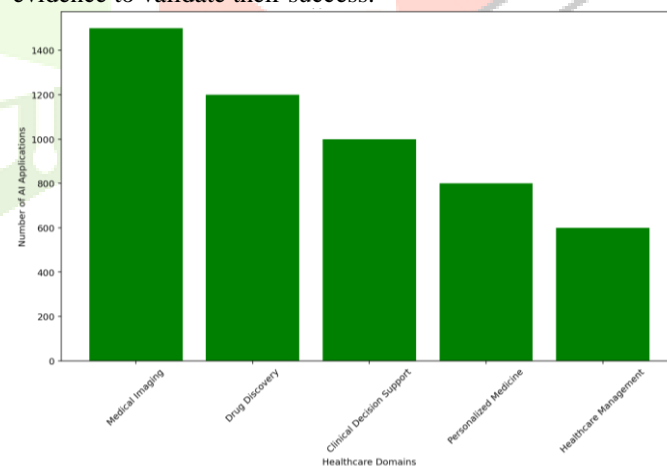


Fig. 2 AI applications in healthcare

AI applications in medicine also cover the areas of diagnosis, treatment planning, and process management. AI-aided predictive analytics can be used to track disease progress and to determine the size of populations at risk in the event of a high rate of disease. Moreover, the analytics can be constructed with patient characteristics to create individualized treatment plans. Moreover, robot-assisted virtual assistants and AI bots are used nowadays to ensure remote patient monitoring, medication adherence, and patient education, which, in essence, widens access to healthcare and boosts patient engagement [8,9]. However, as these technologies adopt these technologies to evolve further, they can open prospects for revolutionizing medical delivery by making it possible for doctors to access and interpret data and for creating a more personalized, efficient, and patient-centered model of delivering care.

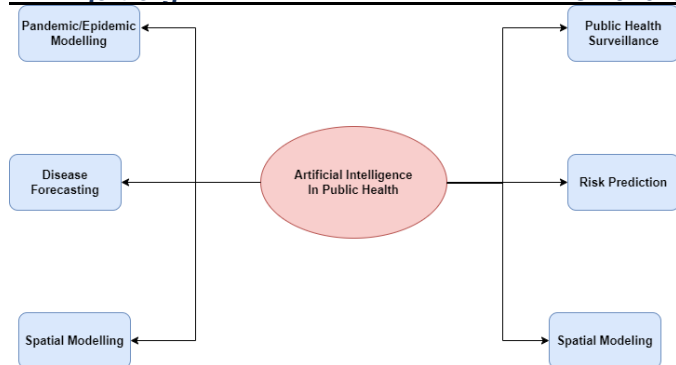


Fig. 3 Predictive modeling of AI in public health.

Moreover, AI-based techniques are used in healthcare technologies and are critical in translational biomedical research and drug discovery. One of the first steps of drug discovery relies on big data analytics and machine learning algorithms to help scientists identify new drug targets, predict drug responses, and advance the development of precision drugs for different diseases. For example, AI algorithms have been utilized to analyze tumor genomes and find drug efficacy and resistance biomarkers, leading to targeted cancer treatment [10]. Additionally, AI-based drug repurposing approaches have expedited the identification of existing drugs with potential therapeutic benefits for new indications, offering cost-effective solutions for drug development and reducing time-to-market for new treatments.

B. CHALLENGES IN DATA PRIVACY AND SECURITY

AI-based drug repurposing approaches, on the other hand, have brought forth a promising technology that could be used for locating existing drugs that were previously unknown to contain medicinal properties for new indications, providing hopefully cheaper solutions for drug development and reduced time to launch to market for new treatment. One of the most challenging aspects of implementing AI-led personalized medicine is preserving the confidentiality and security of health data. However, there are more and more electronic health records (EHRs), wearable devices, and medical imaging archives nowadays, which generate serious problems for health organizations as the need to guarantee the safety of patients' confidential data regarding the prevention of illegitimate use, breaches, or cyberattacks is on the rise. Furthermore, using AI for clinical workflows necessitates in-depth data sharing and interoperability triggered by the fear of privacy, especially regarding data governance, confidentiality, and compliance with policy frameworks such as the Health Insurance Portability and Privacy Act (HIPAA) [11]. These challenges require effective encryption protocols, such as role-based access controls and audit trails, to keep patients' privacy and ensure data integrity throughout the AI life cycle.

In the face of astonishing opportunities propelled by AI-based healthcare solutions, data privacy, and security risk lingers as a giant ominous shadow. The influx of electronic health records (EHRs), wearable devices, and health-related applications connected to medicine has produced an enormous amount of information and its different kinds that must be stored [11]. These huge detective pools consisting of patients' medical history, diagnostic pictures, and the list of their genetic constructions are attractive to cybercriminals looking for the exploitation possibilities of each healthcare IT system. Moreover, healthcare networks are more likely to be interconnected due to their expansion to third-party vendors. While they make access to information easy, there is a higher risk of data theft and unauthorized access.

Another crucial point is compliance with statutory frameworks; for instance, the Health Insurance Portability and Accountability Act (HIPAA) imposes strict necessities on healthcare organizations to secure medical data and ensure

confidentiality, integrity, and availability [11,12]. While compliance can be achieved, it faces a very technically demanding environment, similar to the one in AI-based healthcare technologies that operate on vast data sharing and interoperability to train algorithms and produce valuable insights. Achieving data access balance with privacy and security necessitates robust technology-agnostic encryption protocols and access controls to enable security and audit trails to protect sensitive information throughout its lifespan.

Data privacy and security problems can only be addressed if healthcare organizations are encouraged to adopt a more conscious attitude toward cybersecurity. This includes developing a culture of security awareness among healthcare personnel, repeatedly training and education programs on data protection best practices, and creating incident response protocols for a practical flash-front approach to mitigation and response to data security breaches. Secondly, collaboration among healthcare providers, technological vendors, and governmental agencies is needed to design standard frameworks and rules for AI-based clinics' safety and consistency requirements in a dynamic regulatory environment. Thoroughly assessing these challenges enables healthcare organizations to deepen trust between patients and stakeholders while eliminating risks and realizing the full potential of AI as a personalized medicine driving better outcomes [12].

C. ETHICAL IMPLICATIONS OF ALGORITHMIC DECISION-MAKING

Applying artificial intelligence algorithms in medicine provokes various ethical considerations such as fairness, transparency, and responsibility in decision-making. AI algorithms can analyze large datasets and generate predictions, but their inclination to bias could augment the disparities in healthcare outcomes. For instance, biases in data and algorithmic design can result in a differential recommended treatment or diagnostic error, causing more detrimental effects for marginalized populations than those that are underrepresented [13]. Besides, the transparency of AI algorithms creates a dilemma for physicians and patients in understanding and interpreting algorithmic predictions. Also, it raises questions about how to maintain informed consent, patient autonomy, and the physician's duty of care.

AI algorithms complementing healthcare choice-making processes pose morally severe issues that must be well handled. Algorithmic biases could magnify or systematize the unevenness of health interventions' outcomes as an emerging issue. AI models utilize historical data, which can be inherently prejudiced because healthcare, diagnosis, and treatment may all be systematically biased [13,14]. This, in turn, AI algorithms might unwittingly enable the persistent notions of unfairness by providing tailored differential treatments for various social groups or diagnostic outcomes. There is a bias issue in algorithmic decision-making because AI algorithms cannot be immediately transparent or accountable, which makes it hard to spot bias, leading to questions about fairness, transparency, and algorithmic decision-making.

Moreover, artificial intelligence in healthcare raises complex questions of patient autonomy, informed consent, and the doctor's right to care. AI algorithms provide guesses that suit complex statistical models and can result in difficulties clinicians and patients encounter when interpreting the predicted recommendations. The obscuring factor can diminish patients' trust in doctors and their autonomy to elect because the patient may feel that the choice is made on the doctor's behalf [14]. This also raises questions concerning allocating accountability and attribution in situations where algorithm-induced suggestions harm individual patients or their well-being. The benefits of AI healthcare technologies should be carefully considered, along with ethical principles such as

beneficence, non-maleficence, justice, and respect for patient autonomy. Therefore, collaboration between clinicians, ethicists, policymakers, and technology developers should be maintained to discuss and solve the ethical issues emerging with the technology.

D. VALIDATION AND REGULATION

The validation and regulation of AI-driven healthcare technology is imperative to ensure safety, efficacy, and reliability and prevent any hazardous implications for patients. Regulatory traditional frameworks might not be well suited when applying these to medical devices and software due to the characteristics of AI algorithms and the challenges they pose, which evolve as more data is processed and they advance experience. Therefore, regulatory bodies like the Food and Drug Administration (FDA) confront the complicated undertaking of modifying the present conventional regulatory paradigms in conceding to the ever-changing nature of AI-guided healthcare technologies[14,15]. Developing regulatory frameworks that balance innovation with patient safety to adaptive licensing models and post-market surveillance mechanisms is the most crucial step, which can steer the innovation simultaneously and ensure that AI innovations in healthcare meet high quality and safety standards. Similarly, international harmonization of regulations and integration of cross-border partnerships are significant for AI-driven healthcare technologies to disseminate and be accepted globally due to avoiding fragmentation and enabling interoperability across the global markets.

E. HEALTHCARE DISPARITIES AND THE DIGITAL GAP

Even though AI-driven personalized medicine presents much transformative potential in healthcare, there are difficulties in the distribution of healthcare within the community and the digital divide that is challenging to overcome as it relates to the user-friendly implementation of the AI the user-friendly implementation of AI. Socio-economic issues, geographical positions, and cultural difficulties can break people's desires to receive help with advanced healthcare technologies like AI-based diagnostic tools and treatments [15,16]. Also, healthcare disparity further worsens the inequities in healthcare access and utilization, where health literacy and digital literacy levels play a significant role, particularly among vulnerable groups. Healthcare services should be expanded, and there should be more health literacy among the people, bridging the digital divide[17]. Policy efforts to address access barriers and promote health equity will be the only option to achieve this. Capitalizing on the holistic nature of AI-driven personalized medics, healthcare systems now have the power to revolutionize their delivery patterns and provide additional benefits to patient outcomes for all.

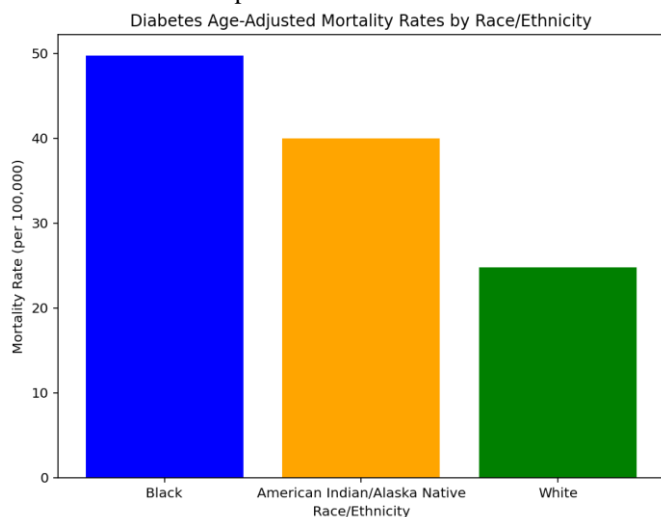


Fig. 4 Mortality Impacts due to health Disparities on minority groups

IV. SIGNIFICANCE AND BENEFITS TO THE U.S

Implementing AI-driven Personalized Medicine in the United States is a significant move with many benefits beyond the immediate impact. First and foremost, using AI in healthcare careers can boost patients' outcomes through quicker detection and more accurate diagnosis and treatment options based on personal patient statistics. These could include the management and avoidance of chronic diseases, reduction in hospitalization, and paved quality of life for patients across many states [18]. Furthermore, AI-powered health technologies have been discovered to be an obvious way of making the system more efficient and, consequently, reducing the dimension of the cost of healthcare service delivery and improving healthcare resource allocation. By rationalizing clinical workflows, automating administrative tasks, and optimizing treatment protocols, AI makes it possible for healthcare providers to accomplish more in less time and develop cost-effective solutions that enrich both patients and healthcare systems[18].

AI-based personalized medicine is not only result-oriented but can also act as a catalyst for creating new markets and increasing the GDP of the United States. The evolution and promotion of AI-based medical devices, various applications (software), and virtual health solutions open new opportunities for entrepreneurship, employment, and industry expansion. Investors in startups and tech companies focusing on using AI algorithms to contribute to a healthcare area can enlarge the US healthcare market and position it as a world leader in innovative healthcare [19]. Additionally, by allocating resources for AI-driven healthcare technology research and development, the United States can create an environment of collaboration between academia, industry, and governmental organizations, which will assist innovation, scientific discoveries, and advances that may bring about life-changing healthcare discoveries on a global scale. Besides, AI-empowered personalized medicine can detect and spur healthcare inequalities elimination and health equity improvement in the United States. AI may steer medical treatment to the demands of any given patient population to mitigate disparities in healthcare, access consequences, and quality of care.

V. FUTURE IN THE U.S

The future of AI-powered personalized medicine has an enormous potential to revolutionize the healthcare delivery system in the US. The more technology develops and matures, and the AI algorithms become more accurate, the more they will penetrate clinics, research labs, and even managerial systems in the healthcare industry. Improved prognostic methods and tailored treatment plans enabled by AI are increasing. Consequently, healthcare providers are now more able to make treatment more precise and improve it to match the needs and characteristics of each patient precisely. The increasing trend towards individualized medicine can affect the healthcare system, improve patient wellness, cut healthcare costs, and optimize efficiency in healthcare service providing [19].

Additionally, the evolution and development of AI-based personalized medicine in the United States will be guided by future technological advancements, regulatory frameworks, and healthcare policies. Regulatory bodies, including the Food and Drug Administration, will be essential in elections and enforcing AI-powered healthcare solutions due to verification and regulation functions. Besides that, policymakers and healthcare stakeholders should deal with ethical, legal, and social considerations of AI in healthcare contexts, including subjects like data protection, algorithmic bias, and fair access

to care. Through partnerships between academia, industry, government, and patient advocacy organizations, AI-assisted personalized medicine can make sufficient use of the country's potential to expand further population health and world innovations that will lead it to keep the top position globally in healthcare innovation.

VI. CONCLUSION

The main aim of this paper was to assess the capability of AI-based personalized medicine to overhaul healthcare in the United States. This paper has been critical of AI being the driving force of healthcare technologies in that through an analysis of some of the technological issues inhabiting AI, the application of AI, and its significance when it comes to personalized medicine, this paper has presented the magnitude at which AI revolutionizes the processes of providing quality care, delivery of care, and the whole healthcare. The future of AI-driven personalized medicine in the US must be examined through essential considerations like data privacy and security, ethical issues, regulatory challenges, and health disparities. AI-driven personalized medicine offers a new paradigm of care in medicine, which is focused on the individual and would directly address each patient separately. On the other hand, implementation of AI in the medical field requires combined efforts from healthcare systems' practitioners, decision-makers, regulators, and developers to drive these complex challenges and barriers the focus. By cultivating teamwork and creativity and focusing on fairness and consumer facilitation, a country can use the transforming power of Artificial Intelligence-based personalized medicine to cope with health issues, improve the healthcare system state, and drive innovations in the future.

REFERENCES

- [1] D. C. Mohr, M. N. Burns, S. M. Schueller, G. Clarke, and M. Klinkman, "Behavioral Intervention Technologies: Evidence review and recommendations for future research in mental health," *General Hospital Psychiatry*, vol. 35, no. 4, pp. 332–338, Jul. 2013, doi: <https://doi.org/10.1016/j.genhosppsych.2013.03.008>
- [2] P. Bamidis et al., "Ethical Issues of Social Media Usage in Healthcare," *Yearbook of Medical Informatics*, vol. 24, no. 01, pp. 137–147, Aug. 2015, doi: <https://doi.org/10.15265/iy-2015-001>
- [3] L. Fernández-Luque and T. Bau, "Health and Social Media: Perfect Storm of Information," *Healthcare Informatics Research*, vol. 21, no. 2, p. 67, 2015, doi: <https://doi.org/10.4258/hir.2015.21.2.67>. Available: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4434065/>.
- [4] R. Schnall, S. Bakken, M. Rojas, J. Travers, and A. Carballo-Dieguez, "mHealth Technology as a Persuasive Tool for Treatment, Care, and Management of Persons Living with HIV," *AIDS and Behavior*, vol. 19, no. S2, pp. 81–89, Jan. 2015, doi: <https://doi.org/10.1007/s10461-014-0984-8>
- [5] N. Tripp et al., "An emerging model of maternity care: Smartphone, midwife, doctor?" *Women and Birth*, vol. 27, no. 1, pp. 64–67, Mar. 2014, doi: <https://doi.org/10.1016/j.wombi.2013.11.001>. Available: <https://www.sciencedirect.com/science/article/abs/pii/S187151921300423X>.
- [6] M. Terry, "Twittering Healthcare: Social Media and Medicine," *Telemedicine and e-Health*, vol. 15, no. 6, pp. 507–510, Jul. 2009, doi: <https://doi.org/10.1089/tmj.2009.9955>
- [7] Sumeet Dua, U Rajendra Acharya, and Purna Dua, *Machine Learning in Healthcare Informatics*. Berlin, Heidelberg Springer Berlin Heidelberg, 2014.
- [8] Ivo De Lotto, M. Stefanelli, and European Coordinating Committee For Artificial Intelligence, *Artificial intelligence in medicine: proceedings of the International Conference on Artificial Intelligence in Medicine*, Pavia, Italy, 13-14 September 1985. Amsterdam; New York: North-Holland; New York, N.Y., USA, 1985.
- [9] E. T. Keravnou, *Artificial intelligence in medicine: 6th Conference on Artificial Intelligence in Medicine Europe, AIME '97*, Grenoble, France, March 23-26, 1997: proceedings. Berlin; New York: Springer, 1997.
- [10] Hans Jürgen Ohlbach, *GWAI-92: advances in artificial intelligence: 16th German Conference on Artificial Intelligence*, Bonn, Germany, August 31-September 3, 1992: proceedings. Berlin; New York: Springer, 1993.
- [11] S. Miksch, J. Hunter, and Elpida Keravnou-Papailiou, *Artificial intelligence in medicine: 10th Conference on Artificial Intelligence in Medicine, AIME 2005*, Aberdeen, UK, July 23-27, 2005; proceedings. Berlin: Springer, 2005.
- [12] G. Freiherr and Research Resources Information Center, *The seeds of artificial intelligence: SUMEX-AIM*. Bethesda, Md.: US Dept. Of Health, Education, And Welfare, Public Health Service, National Institutes Of Health; Washington, DC, 1980.
- [13] A. Armoni, *Effective Healthcare Information Systems*. IGI Global, 2001.
- [14] K. A. Wager, F. W. Lee, and J. P. Glaser, *Managing health care information systems: a practical approach for healthcare executives*. San Francisco, CA: Jossey-Bass, 2005.
- [15] E. L. Drazen, J. B. Metzger, J. L. Ritter, and M. K. Schneider, *Patient Care Information Systems*. Springer Science & Business Media, 2012.
- [16] J. G. Anderson, C. Aydin, and SpringerLink (Online Service), *Evaluating the Organizational Impact of Healthcare Information Systems*. New York, NY: Springer New York, 2005.
- [17] J. Rodrigues, *Health information systems concepts, methodologies, tools, and applications 2*. Hershey [UA] Med. Information Science Reference, 2010.
- [18] C. On, *Health IT, and patient safety: building safer systems for better care*. Washington, DC: National Academies Press, 2012.
- [19] W. Horn, "Artificial intelligence in medicine and medical decision making Europe," *Artificial Intelligence in Medicine*, vol. 20, no. 1, pp. 1–3, Sep. 2000, doi: [https://doi.org/10.1016/s0933-3657\(00\)00049-x](https://doi.org/10.1016/s0933-3657(00)00049-x)