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ARTIFICIAL INTELLIGENCE - REVOLUTIONIZING CLINICAL TRIAL PROCESS

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ABSTRACT

Artificial intelligence (AI) is a term that refers to the use of computers and technologies to replicate intelligent human behavior and critical thinking in a way that is equivalent to that of a human. John McCarthy coined the term AI in 1956, which he defined as "the science and engineering of creating intelligent machines." To solve not just particular but also complicated issues, artificial intelligence (AI) employs personalised information and learns from the solution it produces. Incredible advances in computer capacity, along with advances in AI technology, have the potential to change the healthcare industry. The amount of health and 'omics-related data' produced and stored has increased dramatically during the last several decades. In clinical trials, patient data may be gathered in real time and analysed using a variety of artificial intelligence (AI) techniques; mobile devices can also be utilized to improve aspects of disease diagnosis and treatment. Furthermore, AI may be employed in the discovery of novel pharmaceuticals or drug repurposing, as well as in the rapid detection and treatment of various ailments, as well as in the identification of data-driven hypotheses for researchers. In this article, we look at how artificial intelligence is beginning to transform the field of life sciences.

Keyword: Artificial intelligence, Clinical trials, Deep learning, Drug Development, Machine learning

1. INTRODUCTION

For a long time, artificial intelligence (AI) was considered as science fiction that represented in films **[1]**. However, artificial intelligence is no longer a science fiction product **[2]**. During World War II, the initial steps towards the development of computers capable of handling complicated problems were taken. Alan Turing, a talented English mathematician serving for British government, created a computer named 'The Bombe' in 1942 to break the German army's Enigma code **[3]**. He released his major work eight years later, raising the question, "Can machines think?" **[4]**. He set out to build a framework of cognitive principles, functioning, and function for his study **[5]**. In 1956, at Dartmouth Artificial Intelligence Conference, John McCarthy, Claude Shannon, Marvin Minsky, and Nathaniel Rochester invented the term "AI" **[6-9]**. Although the word "AI" has a variety of definitions, it may be defined as the study of methods and practical factors that enable the development of computers able to execute intelligent tasks including decision making without ever being explicitly programmed for such tasks **[10]**. The imitation of the cognitive processes of humans by machines (computers) is referred as artificial intelligence (AI). The process includes gathering information, creating rules for interpreting it, drawing conclusions that are definite or approximate, and self-correction. It is the art and science of developing intelligent machines, particularly smart computer programs. Among earlier revolutions including the steam engine, digital technology, and scientific & mass production, AI is now regarded as the 4th Industrial Revolution **[11]**.

Artificial intelligence (AI) is nearly everywhere, notably in the tools used by major tech firms like Facebook, Apple, Microsoft, Amazon, Google, and others. It is unexpected to assume that artificial intelligence is also revolutionizing the field of life sciences, particularly healthcare and biomedicine, with the goal of improving disease detection and patient outcomes while lowering healthcare costs **[12]**. Numerous researchers have used artificial intelligence in biomedicine for a variety of purposes, including the recognition of peptides able to modulate inflammation in healthy individuals to be used in sports nutrition **[13]**, rational drug discovery and development **[14]**, imaging of breast cancer **[15, 16]**, radiology, cardiology precision medicine studies **[17, 18]**, and clinical trials **[19-21]**.

2. Artificial Intelligence, Machine Learning and Deep Learning

During the last five decades, the world has experienced a true revolution in the field of Information Technology (IT), that has eventually result in the production and storage of massive amounts of data, not only in the field of technology, but also in other fields, offering researchers a wide range of services and products **[22]**. Big data now has unmatched potential in terms of enhancing medical outcomes and public health **[23, 24]**. Big data are directly related with computing resources, that includes structured, semi - structured and unstructured information's, due to the rising complexity and volume of data from various sources **[25]**.

The most used approach is machine learning (ML). AI encompasses a variety of approach areas, including knowledge representation, solution search, reasoning, and among them, a fundamental paradigm of machine learning. It employs statistical approaches capable of learning with or without explicit programming **[26-28]**. Machine learning is classified into three classes, supervised, unsupervised & reinforcement learning. Regression and classification techniques are used in supervised learning, and the prediction model is designed using information from the input and output source. Under the subgroup regression, it produces efficacy of drugs and ADMET predictions and under the subgroup classification, supervised machine learning provides disease diagnosis **[29]**. Feature-finding and clustering techniques are used in unsupervised learning by grouping and interpreting data purely based on the input data **[30]**. Disease subtype identification via clustering and disease target discovery through feature-finding approaches may both be achieved using unsupervised machine learning **[31]**. Reinforcement learning is primarily driven by decision-making in a given circumstance and the execution of those decisions in maximizing performance. De novo drug designs under decision making and experimental designing under execution are two examples of outputs from this type of machine learning, both of which may be accomplished using quantum and modelling chemistry **[32]**.

Table 1: Comparison of various machine learning approaches along with their advantages and disadvantages.

Machine Language algorithms	Advantages	Limitations	Applications
Support vector machine	**It's effective for multi-dimensional feature categorization and can be utilised for semi-supervised learning.**	**Difficult to use with noisy datasets (contrast echocardiography, echocardiographic windows, or poor strain imaging)**	**Classify HFpEF-non HTN and HFpEF-HTN**

	Effective for recognition of image (echocardiography, EKG) or classification of text (EHR) Appropriate for small data sets It's applicable to both non-linear and linear relationships. (kernel)	Not suited for problems involving multi-class categorization. For large data sets, it is difficult to use Non-parametric inference (no p-values)	
Artificial neural network	**Online community support It's simple to spot probable interactions between predictor variables. Non-linear modelling capability Visualization is easy able to train a vast number of data sets Simple to use**	**Easily influenced by counter-examples (change in location or slight variations in shape) It might be difficult to pinpoint a cause-and-effect connection. Training might be challenging (require hyper-parameter tuning) Prone to over fitting Concepts of black box With an external dataset, it's difficult to generalize. Time-consuming**	**Classification of HTN treatment response HTN risk prediction**
Naive Bayes classifier	**It is good for problems of multi-class classification It's useful for text categorization.**	**If the data distribution is poor, it might be a poor classifier. Easily influenced by skewed probability (numerical variables)**	**decision-making system, risk factor identification, and HTN detection**
Fuzzy logic	**Appropriate for expert decision-making systems (mortality, cardiac arrhythmia detection, CAD in early stage)**	**Concepts are difficult to understand Is unable to comprehend complex issues No methodical approach.**	**Simple classification using variable series**
Random forest	**Effective for small datasets Scalable (very huge datasets) Effective for both regression and classification Effective for non-linear modeling Prediction speed and fast training**	**Time-consuming Prone to overfitting For large datasets, it is difficult to use**	**Simple classification using multiple decision tree**
Linear regression	**Effective for the small datasets Prediction speed and fast training Easy to understand and visualize**	**Hard to use for huge datasets Predictive accuracy is a poor Non-linear modelling is unable to manage. Cannot manage problems on classification**	**Quantitative HTN treatment**

A sub - field of Machine learning known as deep learning (DL) utilizes artificial neural network (ANN) which adapt and learn from huge amount of experimental data **[33]**. When dealing with pharmacological data sets, artificial neural networks (ANN) have become useful in addressing various complicated nonlinear interactions that exist among data **[34]**. The ability to identify novel compounds that might possibly be novel drugs, repurpose or uncover drugs that can be more effective when used singly or in combination using associated data and big data algorithm and mining techniques, and enhance the field of personalized medicine that are based on genetic markers. With the increasing quantity of data and continuing development of computer power, the rise of deep learning was observed. The versatility in the structure of neural networks like fully connected feed-forward networks, convolutional neural networks (CNNs), and recurrent neural networks (RNNs) differentiates Deep Learning as a subfield of Artificial Intelligence. With the proper integration of AI approaches, it is expected that we will see a shift into an era of reduced clinical trial failures and shorter, cheaper, and more efficient drug development procedures **[35-37]**.

The SVM (Support Vector Machine) is a machine learning model that predicts diseases depending on clinical characteristics. It's a valuable tool with the potential to be used in cohort selection in clinical trials. Researchers employed support vector machine and other machine learning models to PPD (predict postpartum depression) among patients in New York-Presbyterian Hospital and Weill Cornell Medicine during 2015 to 2017. They analyzed data from electronic health records to identify depression, anxiety, obesity, race, various forms of antidepressants, anti-inflammatory, and pain drugs as important predictors throughout pregnancy. Predict postpartum depression is one of the most common maternal morbidities after birth, with catastrophic consequences, and there are currently no efficient screening tools or high-quality treatment studies available. As a result, support vector machine may take use of a huge quantity of comprehensive patient data through EHRs to forecast PPD and execute effective clinical decision measures **[38]**.

In another instance, artificial intelligence was utilized to increase the accuracy of auscultation-based screening for congenital and valvular heart disease. Thompson *et al* created a algorithm to detect cardiac murmur that was validated objectively and quantitatively in a simulated clinical trial. As a consequence, they developed a algorithm that was highly specific for detecting abnormal murmurs in the studied data set, with levels comparable to those reported for professional auscultation, possibly making it a valuable monitoring tool for cardiovascular disease **[39]**.

3. Artificial Intelligence in Healthcare

Artificial intelligence and associated technologies are becoming more common in society and business and are beginning to appear in the healthcare sector. These techniques have the ability to reform many patient care aspects, along with administrative procedures within providers, payers, and pharmaceutical groups. Several studies have already shown that Artificial intelligence can perform better than humans in critical healthcare activities like disease diagnosis. Algorithms are already surpassing radiologists in terms of detecting malignant tumors and directing researchers about how to establish cohorts for expensive clinical trials. However, for several reasons, it was expected that it will be several years before when AI replace humans in broad areas of medical process.

4. Real-world data and real-world evidence

In the context of healthcare and life science, Real-World Data (RWD) may be described as patient health related data or healthcare delivery, acquired outside of randomized clinical trials (RCTs) **[40]**. This information is collected from electronic health record (EHR) of patients at the hospitals and from insurance providers, from claim procedures, self-generated data of patients, and disease registries. Real-world data sources could provide a huge amount of data at the large-scale or granular level in near-real time, which can be utilized to support a variety of clinical trial designs, including RCTs, pragmatic clinical trials, huge simple trials, and observational study **[41, 42]**.

The EHR data records could be categorized as structured data (medication, and results of laboratory) and unstructured data (notes provided by physician). Unstructured data (the majority of recorded data) necessitates extensive processing before statistical tests and machine learning tasks can be performed, whereas structured data does not **[43]**.

Real-world data analysis yields Real-World evidence (RWE), which is the clinical evidence on a medical product's use as well as its risks or benefits. However, to produce high-quality real-world evidence suitable for regulatory usage and other applications of decision-making, a substantial quantity of real-world data must be gathered and translated into an analytical form, with a specific degree of data accuracy and ensured reliability, something that humans cannot achieve alone. For this objective, Artificial intelligence abilities are increasingly being used in real world data analysis **[44]**.

Three capabilities of artificial intelligence are especially applicable for generating real world evidence in the healthcare industry: robotic process automation (RPA), machine learning, and natural language processing. NLP is the interpretation that is computerized and structuring of human language that is included in unstructured data (speech recognition or physician notes) in order to indicate a certain incident or condition. It covers syntax recognition, text categorization, word interpretation based on their arrangement inside a phrase, and translation of the language in a commutative, easy to interpret, and accurate manner **[45, 46]**.

Computerized HIV risk analysis by extracting important terms from clinical text or the construction of algorithms of NLP for the diagnosis of asthma using EHRs are examples of applications of NLP **[47, 48]**. Nayor *et al* developed and verified a pipeline of NLP that determines detection rate of adenoma and serrated polyp reliably and to assess quality factors of colonoscopy **[49]**. Machine learning, on the other hand, encompasses a wide range of predictive mathematical and statistical modelling approaches that are often built on top of NLP to re-interpret and improve original assumptions after frequent use. According to a survey conducted in 2018, 60% respondents of pharmaceutical industries were employing machine learning in their RWE programs, with 95% of them expecting to adopt artificial intelligence in the upcoming years. Moreover, machine learning may be used in RWD to construct models for disease risk prediction, like atrial fibrillation, and/or to track patients' health **[50]**. Enshaeifar *et al*, for example, employed machine learning to create an algorithm to predict infections of urinary tract, which are among the top 5 causes for admissions in hospital among patients of dementia **[51]**. RPA is the third ability of AI that was employed to develop RWE. RPA is a programme that automates repetitive operations, helping to speed up processes while decreasing the rate of error made by humans **[52]**. This software was revolutionary in many fields since it performed precisely specified tasks, but it was restricted in the sense that it could not adapt to changing situations and learn from experience. RPA may also be linked to machine learning, making it more helpful in the study of real-world data. In this context, RPA may be used to gather field values from the unstructured data that is based on a programmed/scripted set, while machine learning learns from this information to generate RWE **[53]**.

5. Artificial Intelligence in Drug development

Finding effective novel drugs is a difficult task, and it is by far the most challenging aspect of drug research. A drug's development is usually a lengthy process that requires many years. This is caused by massive size of what chemical space that is expected in the order of 10^{60} molecules. [54] Drug development, on the other hand, is limited by the availability of modern technology that makes it an expensive and time-taking task that may be solved by using AI **[55]**. Artificial intelligence can recognize the difference between a lead and a hit molecule, enabling for quicker therapeutic target confirmation and design optimization of the drug structure **[56, 57]**.

6. Artificial intelligence and clinical trials

Clinical trials are aimed to assess the safety and efficacy of a therapeutic product in individuals for a particular condition or a disease. They require 6 to 7 years on an average and a considerable financial commitment. Clinical trials that are 'linear and sequential' are still the acknowledged method for ensuring the effectiveness and safety of novel drugs. Drugs are frequently tested in humans after only passing laboratory tests. Following that, humans are tested in a series of clinical studies called phase I, II, III, and IV trials. Each step of a clinical study has its own number of objectives. In general, phase I studies prove safety, trials of phase II establish effectiveness, phase III trials show efficacy in comparison to existing standard therapy, while phase IV trials indicate general benefits and risks after the approving the drugs. The participant number rises as development of drug moves from phases to phases. Drugs that are shown to be harmful or ineffective during development will not advance through all the phases of clinical trial phases **[58]**.

The long-established discrete and defined phases of randomized controlled trials (RCTs) were created primarily to evaluate mass-market pharmaceuticals and have evolved little in recent decades. Randomized controlled trials lacks the analytical strength, speed, and flexibility needed to discover complicated novel treatments for populations of patient that are smaller and frequently diverse. Furthermore, poor patient selection, enrollment, and retention, as well as challenges monitoring and maintaining patients efficiently, all contribute to increased failure rates of trial and higher research & development expenses. However, just one out of every ten molecules that enter these trials gets cleared, resulting in huge industrial losses **[59]**. These failures might be caused by inappropriate selection of patients, shortage of technology demands, or infrastructure shortage. Since there is so much digital medical data available, artificial intelligence may be used to reduce these failures.

Since AI techniques have not yet been approved by regulatory bodies such as the FDA (Food and Drug Administration) and/or the EMA (European Medicines Agency), they are not frequently employed in clinical trials. "Machine learning," "deep learning," or "artificial intelligence" are the terms appear in more than 450 interventional research (clinical trials) recorded as of July 2020 by the US National Library of Medicine. Approximately a third of these research is presently looking for the participants **[60]**. Artificial intelligence is, however, being used in the clinical trials to aid in the evaluation of exploratory aims and outcomes. Researchers are gathering data and findings with these sophisticated technologies that support the necessity for these approaches to be included in regulatory processes in order to be used in clinical trials. Artificial intelligence may be used in the following areas:

- Inclusion and stratification of patients: can aid in the better selection of individuals who will benefit from treatment
- Automated quality assurance evaluation
- Automating extraction of the quantitative imaging biomarkers
- Reducing the time of image reading
- Using the retrieved data to create multivariate models to improve the statistical power of outcomes

The patient enrolment requires one-third of the time of clinical trials. Enrolling eligible patients may increase the chances of completing a clinical study, which otherwise fails 86 percent of the time **[61]**. Artificial intelligence may help select a specific diseased cohort for enrolment in phase II & phase III clinical trials by using patient specific genome exposome profile analysis, which may help in early prediction of the possible therapeutic targets in selected patients. [62] Discovery of re-clinical compounds and estimating lead molecules prior to the beginning of clinical trial using several other facets of artificial intelligence, including predictive machine learning (PML) and other reasoning strategies, assist in earlier detection of lead compounds that might pass the clinical trial while taking consideration into the population of patients. Both machine learning and deep learning could be used to uncover semantic patterns in big sets of data, such as pictures, text, or audio, automatically. HMIs (human–machine interfaces), are a direct communication channel between a person and a technology that allows computers and people to exchange information, and NLP can comprehend and correlate data in spoken or written language. All of these AI algorithms may be used to connect huge and varied sets of data, such as medical literature, trial databases, and EHRs, in order to enhance patient–trial recruitment and matching before the beginning of the trials, as well as to constantly and automatically monitor patients throughout the trial. [63]

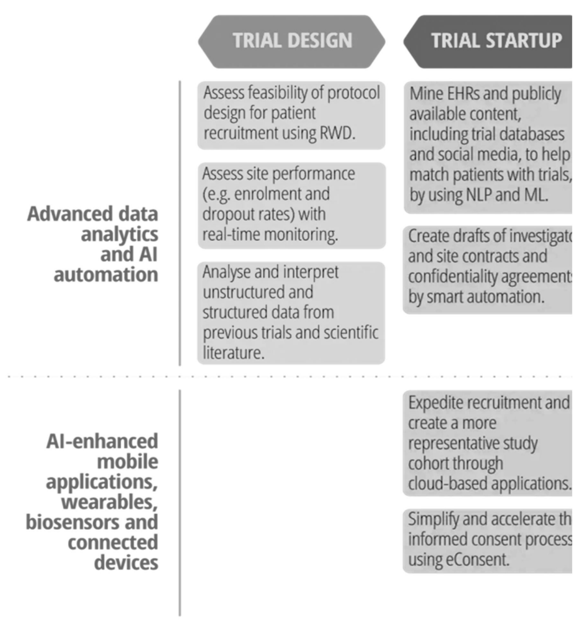

Figure 1: Applications of Artificial Intelligence enabled Clinical trials

Furthermore, dropouts from the clinical trials represents 30% of failure of clinical trial, resulting in extra recruitment needs for the study's completion, resulting in a waste of resources and time. This may be prevented by closely monitoring the participants and assisting them in adhering to the clinical trials protocol **[61]**. AiCure created mobile software to track regular medication consumption by schizophrenia patients in a Phase II study that boosted patient adherence by 25% and ensured the clinical trials success **[62]**. Clinical trial data might be aggregated, cleaned, maintained, coded, and preserved utilizing algorithms of AI with the combination of efficient digital infrastructure. Improved EDC (electronic data capture) may help in reducing the impact of errors made by humans in collection of data while facilitating system integration **[64]**.

7. Potential of AI techniques

AI offers its exceptional ability to attain quicker, cost - effective, and much more efficient biomedical research method as available data (also referred to as "Real World Data") and computer power continue to expand. Indeed, the production of huge as well as diverse amounts of clinical as well as molecular data sets from hundreds of individuals, in response to the health information digitization and advancements in high-throughput technologies, is posing novel problems in computational interpretation and analysis of bio-medical data since it expands ever larger. By working on the heterogeneous data, such as unstructured and structured data sets, Electronic Medical Records, radiopharmaceutical, and imaging data, multiomics data (proteomics, metabolomics, genomics, radiomics, etc.), and others, AI enables efficient matching of patient-trial with the improved efficient and adherence end - point evaluation **[63, 65]**.

Recent breakthroughs in artificial intelligence have resulted in a huge array of hypothesis generating systems that are data driven and seem to be a perfect fit for industry of healthcare. This transformation in the bio-medical research and innovation is prompting healthcare systems and industries to employ cutting-edge technology for collecting, storing, and analyzing the biological data **[66]**. Intelligent designing of drug for personalized therapies, is an example of an asset that is supposed to benefit from AI-assisted data analytics, providing implementable benefits and insights not just to clinical practitioners and patients, but also to strategic business decision actors and policy makers. Artificial intelligence is infiltrating the Nuclear Medicine profession, although at a slower rate, from treatment planning through scanning, analysis, and interpretations, initiating with labor-intensive tasks that are cognitively undemanding **[67]**.

Artificial intelligence has the ability to transform the clinical trials and also have a large financial impact in the sector of healthcare by aiding our knowledge of pathogenesis of the disease, the discovery of novel therapeutic biomarkers and the targets, and hence the selection of eligible participants **[68]**. AI-driven techniques will, for example, be used to identify homogeneous groups of patients who are predicted to react to therapy and exhibit measurable endpoints.

8. Conclusion and Future Perspectives

AI will play an important part in the future of healthcare. It is the crucial ability that allows precision medicine to be established, that is widely accepted as a much-needed development in treatment. Though early efforts at diagnostic and therapeutic recommendations were challenging, we think AI will ultimately dominate this field as well. Most pathology and radiology scans are projected to be analyzed by a computer at some stage, given AI's considerable breakthroughs in imaging analysis. The use of text and voice recognition for tasks like as clinical note recording and in patient communication is currently common, and this pattern will continue. In these sectors of healthcare, the most challenging task for artificial intelligence is ensuring its adoption in ordinary clinical practice, not whether the technology is sophisticated enough to be helpful. AI systems must be authorized by regulators, connected with systems of EHR, standardized to the point that comparable products operate in a similar way, taught to physicians, paid for by private or public payer organizations, and upgraded with time in the field in order for widespread acceptance to occur. These limitations will eventually be addressed, but it will take far longer than the development of modern technology themselves. As a result, we expect to see modest application of artificial intelligence in clinical practice over next 5 years, followed by more extensive use over the following decade. Furthermore, during interim analysis, clinical decision support that are guided with AI employing multi-omics techniques to increase successful treatment groups or reduce ineffective treatment groups. Finally, AI-guided clinical trials could be used to investigate unknown patterns of rare diseases such as spontaneous coronary artery dissection, arrhythmogenic right ventricular cardiomyopathy, or premature atherosclerosis using multiple cross validation, imputation, or data preprocessing techniques. AI might and will enhance all aspects of contemporary clinical trial by combining more advanced models utilizing the breadth and depth of data which are beyond standard statistical approaches.

REFERENCES

[1] Ergen M. What is artificial intelligence? Technical considerations and future perception. Anatolian J. Cardiol. 2019 Oct 1;22(2):5-7.

[2] Cath C, Wachter S, Mittelstadt B, Taddeo M, Floridi L. Artificial intelligence and the 'good society': the US, EU, and UK approach. Science and engineering ethics. 2018 Apr;24(2):505-28.

[3] Haenlein M, Kaplan A. A brief history of artificial intelligence: On the past, present, and future of artificial intelligence. California management review. 2019 Aug;61(4):5-14.

[4] A.M. Turing, Computer machinery and intelligence, Mind LIX(236) (1950) 433– 460.

[5] Castelfranchi C. Alan Turing's "Computing machinery and intelligence". Topoi. 2013 Oct 1;32(2):293-9.

[6] Bini SA. Artificial intelligence, machine learning, deep learning, and cognitive computing: what do these terms mean and how will they impact health care?. The Journal of arthroplasty. 2018 Aug 1;33(8):2358-61.

[7] Mathur P, Burns ML. Artificial intelligence in critical care. International anesthesiology clinics. 2019 Apr 1;57(2):89-102.

[8] Buchanan BG. A (very) brief history of artificial intelligence. Ai Magazine. 2005 Dec 15;26(4):53-.

[9] Barry DT. Adaptation, artificial intelligence, and physical medicine and rehabilitation. PM&R. 2018 Sep 1;10(9):S131-43.

[10] Sellwood MA, Ahmed M, Segler MH, Brown N. Artificial intelligence in drug discovery. Future medicinal chemistry. 2018 Sep;10(17):2025-8.

[11] French J, Chen L. Preparing for artificial intelligence: systems-level implications for the medical imaging and radiation therapy professions. Journal of medical imaging and radiation sciences. 2019 Dec 1;50(4):S20-3.

[12] Matheny ME, Whicher D, Israni ST. Artificial intelligence in health care: a report from the National Academy of Medicine. Jama. 2020 Feb 11;323(6):509-10.

[13] Rein D, Ternes P, Demin R, Gierke J, Helgason T, Schön C. Artificial intelligence identified peptides modulate inflammation in healthy adults. Food & function. 2019;10(9):6030-41.

[14] Zhang L, Tan J, Han D, Zhu H. From machine learning to deep learning: progress in machine intelligence for rational drug discovery. Drug discovery today. 2017 Nov 1;22(11):1680-5.

[15] Mambou SJ, Maresova P, Krejcar O, Selamat A, Kuca K. Breast cancer detection using infrared thermal imaging and a deep learning model. Sensors. 2018 Sep;18(9):2799.

[16] Costa FF. Social networks, web-based tools and diseases: implications for biomedical research. Drug Discovery Today. 2013 Mar 1;18(5-6):272-81.

[17] Johnson KW, Torres Soto J, Glicksberg BS, Shameer K, Miotto R, Ali M, Ashley E, Dudley JT. Artificial intelligence in cardiology. Journal of the American College of Cardiology. 2018 Jun 12;71(23):2668-79.

[18] Krittanawong C, Zhang H, Wang Z, Aydar M, Kitai T. Artificial intelligence in precision cardiovascular medicine. Journal of the American College of Cardiology. 2017 May 30;69(21):2657-64.

[19] Mayo RC, Leung J. Artificial intelligence and deep learning– Radiology's next frontier?. Clinical imaging. 2018 May 1;49:87-8.

[20] Syed AB, Zoga AC. Artificial intelligence in radiology: current technology and future directions. InSeminars in musculoskeletal radiology 2018 Nov (Vol. 22, No. 05, pp. 540-545). Thieme medical publishers.

[21] Hosny A, Parmar C, Quackenbush J, Schwartz LH, Aerts HJ. Artificial intelligence in radiology. Nature Reviews Cancer. 2018 Aug;18(8):500-10.

[22] Oliveira AL. Biotechnology, big data and artificial intelligence. Biotechnology journal. 2019 Aug;14(8):1800613.

[23] Car J, Sheikh A, Wicks P, Williams MS. Beyond the hype of big data and artificial intelligence: building foundations for knowledge and wisdom. BMC medicine. 2019 Dec;17(1):1-5.

[24] Costa FF. Big data in biomedicine. Drug discovery today. 2014 Apr 1;19(4):433-40.

[25] Benke K, Benke G. Artificial intelligence and big data in public health. International journal of environmental research and public health. 2018 Dec;15(12):2796.

[26] Bishop CM. Model-based machine learning. Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences. 2013 Feb 13;371(1984):20120222.

[27] VoPham T, Hart JE, Laden F, Chiang YY. Emerging trends in geospatial artificial intelligence (geoAI): potential applications for environmental epidemiology. Environmental Health. 2018 Dec;17(1):1-6.

[28] Lee JG, Jun S, Cho YW, Lee H, Kim GB, Seo JB, Kim N. Deep learning in medical imaging: general overview. Korean journal of radiology. 2017 Aug 1;18(4):570-84.

[29] Gunčar G, Kukar M, Notar M, Brvar M, Černelč P, Notar M, Notar M. An application of machine learning to haematological diagnosis. Scientific reports. 2018 Jan 11;8(1):1-2.

[30] Koohy H. The rise and fall of machine learning methods in biomedical research. F1000Research. 2017;6.

[31] Young JD, Cai C, Lu X. Unsupervised deep learning reveals prognostically relevant subtypes of glioblastoma. BMC bioinformatics. 2017 Oct;18(11):5-17.

[32] Chen H, Engkvist O, Wang Y, Olivecrona M, Blaschke T. The rise of deep learning in drug discovery. Drug discovery today. 2018 Jun 1;23(6):1241-50.

[33] Grys BT, Lo DS, Sahin N, Kraus OZ, Morris Q, Boone C, Andrews BJ. Machine learning and computer vision approaches for phenotypic profiling. Journal of Cell Biology. 2017 Jan 2;216(1):65-71.

[34] Gobburu JV, Shelver WH. Quantitative structure–pharmacokinetic relationships (QSPR) of beta blockers derived using neural networks. Journal of pharmaceutical sciences. 1995 Jul;84(7):862-5.

[35] Labovitz DL, Shafner L, Reyes Gil M, Virmani D, Hanina A. Using artificial intelligence to reduce the risk of nonadherence in patients on anticoagulation therapy. Stroke. 2017 May;48(5):1416-9.

[36] Jiang F, Jiang Y, Zhi H, Dong Y, Li H, Ma S, Wang Y, Dong Q, Shen H, Wang Y. Artificial intelligence in healthcare: past, present and future. Stroke Vasc. Neurol. 2, 230–243.

[37] Fleming N. How artificial intelligence is changing drug discovery. Nature. 2018 May 1;557(7706):S55-.

[38] Wang S, Pathak J, Zhang Y. Using electronic health records and machine learning to predict postpartum depression. InMEDINFO 2019: Health and Wellbeing e-Networks for All 2019 (pp. 888-892). IOS Press.

[39] Thompson WR, Reinisch AJ, Unterberger MJ, Schriefl AJ. Artificial intelligence-assisted auscultation of heart murmurs: validation by virtual clinical trial. Pediatric cardiology. 2019 Mar;40(3):623-9.

[40] Leite ML, de Loiola Costa LS, Cunha VA, Kreniski V, de Oliveira Braga Filho M, da Cunha NB, Costa FF. Artificial intelligence and the future of life sciences. Drug Discovery Today. 2021 Nov 1;26(11):2515-26.

[41] Zou KH, Li JZ, Imperato J, Potkar CN, Sethi N, Edwards J, Ray A. Harnessing real-world data for regulatory use and applying innovative applications. Journal of Multidisciplinary Healthcare. 2020;13:671.

[42] FDA U. Use of real-world evidence to support regulatory decision-making for medical devices: guidance for industry and Food and Drug Administration staff. Rockville, MD: US Food and Drug Administration. 2017.

[43] Gehrmann S, Dernoncourt F, Li Y, Carlson ET, Wu JT, Welt J, Foote Jr J, Moseley ET, Grant DW, Tyler PD, Celi LA. Comparing rule-based and deep learning models for patient phenotyping. arXiv preprint arXiv:1703.08705. 2017 Mar 25.

[44] B. Davis, J. Morgan, S. Shah, Second annual real-world evidence (RWE) benchmarking survey (2018), Deloitte, London, 2018

[45] Matheny M, Israni ST, Ahmed M, Whicher D. Artificial intelligence in health care: the hope, the hype, the promise, the peril. Washington, DC: National Academy of Medicine. 2019 Dec.

[46] Cleary M. Artificial intelligence: the key to unlocking novel real-world data. Value Outcomes Spotlight. 2019;5(2):16-9.

[47] Wi CI, Sohn S, Ali M, Krusemark E, Ryu E, Liu H, Juhn YJ. Natural language processing for asthma ascertainment in different practice settings. The Journal of Allergy and Clinical Immunology: In Practice. 2018 Jan 1;6(1):126-31.

[48] Feller DJ, Zucker J, Yin MT, Gordon P, Elhadad N. Using clinical notes and natural language processing for automated HIV risk assessment. Journal of acquired immune deficiency syndromes (1999). 2018 Feb 1;77(2):160.

[49] Nayor J, Borges LF, Goryachev S, Gainer VS, Saltzman JR. Natural language processing accurately calculates adenoma and sessile serrated polyp detection rates. Digestive diseases and sciences. 2018 Jul;63(7):1794-800.

[50] Hill NR, Ayoubkhani D, McEwan P, Sugrue DM, Farooqui U, Lister S, Lumley M, Bakhai A, Cohen AT, O'Neill M, Clifton D. Predicting atrial fibrillation in primary care using machine learning. PloS one. 2019 Nov 1;14(11):e0224582.

[51] Enshaeifar S, Zoha A, Skillman S, Markides A, Acton ST, Elsaleh T, Kenny M, Rostill H, Nilforooshan R, Barnaghi P. Machine learning methods for detecting urinary tract infection and analysing daily living activities in people with dementia. PloS one. 2019 Jan 15;14(1):e0209909.

[52] AIIM. Intelligent information management glossary: what is robotic process automation? www.aiim.org/what-is-robotic-process-automation [Accessed July 1, 2021].

[53] Bhatnagar N. Role of robotic process automation in pharmaceutical industries. InInternational Conference on Advanced Machine Learning Technologies and Applications 2019 Mar 28 (pp. 497-504). Springer, Cham.

[54] Segler MH, Kogej T, Tyrchan C, Waller MP. Generating focused molecule libraries for drug discovery with recurrent neural networks. ACS central science. 2018 Jan 24;4(1):120-31.

[55] Vyas M, Thakur S, Riyaz B, Bansal KK, Tomar B, Mishra V. Artificial intelligence: the beginning of a new era in pharmacy profession. Asian J Pharm. 2018 Apr 1;12(2):72-6.

[56] Mak KK, Pichika MR. Artificial intelligence in drug development: present status and future prospects. Drug discovery today. 2019 Mar 1;24(3):773-80.

[57] Sellwood MA, Ahmed M, Segler MH, Brown N. Artificial intelligence in drug discovery. Future medicinal chemistry. 2018 Sep;10(17):2025-8.

[58] Sedgwick P. Phases of clinical trials. BMJ. 2011 Sep 28;343.

[59] Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J. Clinical development success rates for investigational drugs. Nature biotechnology. 2014 Jan;32(1):40-51.

[60] Delso G, Cirillo D, Kaggie JD, Valencia A, Metser U, Veit-Haibach P. How to Design AI-Driven Clinical Trials in Nuclear Medicine. InSeminars in Nuclear Medicine 2020 Oct 17. WB Saunders.

[61] Fogel DB. Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: a review. Contemporary clinical trials communications. 2018 Sep 1;11:156-64.

[62] Mak KK, Pichika MR. Artificial intelligence in drug development: present status and future prospects. Drug discovery today. 2019 Mar 1;24(3):773-80.

[63] Harrer S, Shah P, Antony B, Hu J. Artificial intelligence for clinical trial design. Trends in pharmacological sciences. 2019 Aug 1;40(8):577-91.

[64] Mayorga-Ruiz I, Jiménez-Pastor A, Fos-Guarinos B, López-González R, García-Castro F, Alberich-Bayarri Á. The Role of AI in Clinical Trials. InArtificial Intelligence in Medical Imaging 2019 (pp. 231-243). Springer, Cham.

[65] Uribe CF, Mathotaarachchi S, Gaudet V, Smith KC, Rosa-Neto P, Bénard F, Black SE, Zukotynski K. Machine learning in nuclear medicine: part 1—introduction. Journal of Nuclear Medicine. 2019 Apr 1;60(4):451-8.

[66] Shah P, Kendall F, Khozin S, Goosen R, Hu J, Laramie J, Ringel M, Schork N. Artificial intelligence and machine learning in clinical development: a translational perspective. NPJ digital medicine. 2019 Jul 26;2(1):1-5.

[67] Nensa F, Demircioglu A, Rischpler C. Artificial intelligence in nuclear medicine. Journal of Nuclear Medicine. 2019 Sep 1;60(Supplement 2):29S-37S.

[68] Wolff J, Pauling J, Keck A, Baumbach J. The economic impact of artificial intelligence in health care: systematic review. Journal of medical Internet research. 2020;22(2):e16866.