Transforming Rheumatoid Arthritis Management: Harnessing Artificial Intelligence for Early Detection, Personalized Treatment, and Ethical Challenges

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ABSTRACT

Rheumatoid arthritis (RA) is one of the several autoimmune rheumatic diseases affecting a large population of patients; it presents with multiple comorbidities and complications and is, therefore, difficult to diagnose, treat and manage. It is acknowledged that the application of artificial intelligence (AI) in different areas of RA research and clinical management provides hopeful approaches to these challenges. This review aims to give a systematic information about the existing studies that addresses the implementation of AI into the RA including early detection, prognosis, treatment planning and decision making, drug development, and patient counselling. Substantial emphasis is placed on ML, DL, and NLP, which are instrumental in increasing diagnostic reliability, refining treatment management, and increasing patient involvement. In term of drug discovery, AI enhances speed of identifying new therapeutic agents and repurposing known medicines in treating new disorders by exploring big data and predicting drug-target relations.

Artificial intelligence has progressed into using genetic and biomarker information and predicting potential biomarkers and genetic risk factors that leads to development of RA personalized drugs and intervention plan. Additionally, AI has been used in remote care and tele medicine and tele health services, enabling better treatment, diagnosis and prognosis for patients who are hard to reach or have challenges getting the access to better healthcare. However, there are some challenges in using of AI in the process of RA. The issues of data protection; data collection and management consent, and bias within AI models and systems must be dealt to make AI fair, open, and advantageous to every patient.

Keywords: Rheumatoid arthritis, AI, machine learning, deep learning, RA diagnosis, RA prognosis

INTRODUCTION

In rheumatoid arthritis, early diagnosis is very important in the management of the disease and in preventing structural joint damage. RA is a long-term condition that causes inflammation and affects the joints predominantly and causes pain and swelling; the long-term damage of the involved joints [1]. The significance of early diagnosis in RA cannot be overstated, as the window of opportunity for effective intervention—often referred to as the "therapeutic window"—is relatively narrow [2]. During this period, the initiation of treatment with disease-modifying antirheumatic drugs (DMARDs) can significantly alter the disease course, preventing or minimizing joint damage and improving long-term outcomes [3]. Machine learning, specifically, is a disruptive tool that could be advanced for early diagnosis of RA. Most of these traditional diagnosis methods involve clinical appraisal tests, laboratory tests, and imaging studies and can sometimes delay until substantial joint damage has already occurred. On the other hand, AI models might be capable of detecting RA at much earlier stages due to the better accuracy and efficiency in comparison with analyzing only clinical data plus imaging results and biomarkers. Indeed, that time of detection is crucial because of the nature of the disease

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itself [4]. Functional damage of joints and the loss of ability are two of the most severe consequences of rheumatoid arthritis, which develops rapidly. Early detection allows for the timely administration of DMARDs, acting as a barrier against disease progression, joint damage, and loss of function. Moreover, early treatment has been shown to improve patient outcomes, including reduced disease activity, lower rates of remission, and improved quality of life [5]. However, an early diagnosis of RA is not simple, and some symptoms overlap with other diseases. This is where the real value of AI models can be shown: in the integration and analysis of huge data sets from disparate sources—including a patient's medical record, imaging studies, genetic studies, or biochemical markers—looking for an early pattern of RA, long before a person displays clinical symptoms. This might revolutionize RA diagnosis, converting it from symptom management to early intervention and prevention [6].

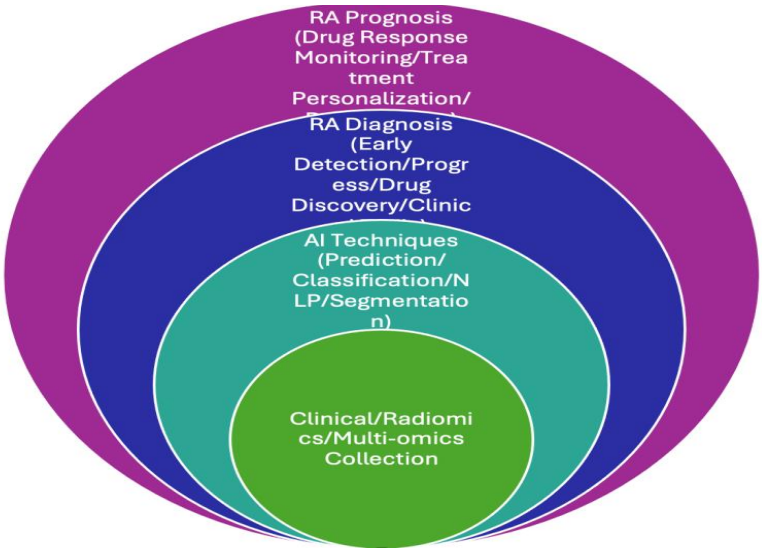

Figure 1: Artificial intelligence in the early diagnosis of diseases (RA). Data Collection: data is collected from X-ray images, electronic health records, drug information and multi omics data. Different Ai models are used for the diagnosis. Then final diagnosis and prognosis are provided by the used Ai techniques

Table 1: Studies incorporated AI for the determination of RA diseases outcomes.

Study	Algorithms Used	Data Size	Primary Data Type	Validation/Testing Method	Objective	Key Findings
Gola et al. (2021)	Model-based MDR, Random Forest, Elastic Net	RA: 868, Controls: 1194	Omics Data	Nested 10-fold cross-validation	Disease prediction	Elastic Net model, AUC = 0.86
O'Neil et al. (2021)	LASSO Regression	At-risk: 127, ACPA-: 47, ACPA+: 63, Progressors: 17	Omics Data	Full dataset (models 1 & 2), dependent test set (model 3)	Identify RA susceptibility markers	Model 3 (Validation, n=34): Accuracy = 91.2%, AUC = 0.931
Jin et al. (2021)	Logistic Regression, Random Forest	Arthritis: 2272, No arthritis: 6151	Clinical and Lab Data	Not Applicable	Link between eye diseases and arthritis risk	Cataract OR = 1.331 (1.057–1.664), Other Eye Diseases OR = 1.428 (1.174–1.730)

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Negi et al. (2013)	Support Vector Machine (SVM)	Discovery: RA = 706, Controls = 761, Replication: RA = 927, Controls = 1148	Omics Data	Replication set, cross-validation	Identify RA-associated SNPs	Four SNPs associated with RA (Highest OR = 1.42)
Kruppa et al. (2012)	LASSO Regression, Logistic Regression, Random Jungle	RA: 707, Controls: 738	Omics Data	10-fold cross-validation, Dependent test set	Identify SNP-RA associations	Random Jungle Model: AUC = 0.8925, Sensitivity = 80.09%, Specificity = 80.48%

Table 1 shows various studies applied artificial intelligence (AI) and machine learning (ML) models to improve the determination and prediction of rheumatoid arthritis (RA). Gola et al. 2021 had a supervised machine learning model on the prediction of RA in 868 RA patients and 1,194 controls. A model validation was nested within 10-fold cross-validation, with an excellent area under the curve of 0.86, showing good prediction [7]. O'Neil et al. applied the LASSO technique to determine which markers of RA susceptibility in a group of 127 at-risk individuals who were either ACPA-negative, ACPA-positive, or progressors. Combining a full dataset with a dependent test set for validation, the third model designates an accuracy of 91.2% and AUC = 0.931; the model was efficient in ascertaining the protein markers associated with RA susceptibility [8]. The study by Jin et al. (2021) investigated arthritis risk through eye diseases, employing a combination of algorithms based on logistic regression and Random Forest. A comparison was done between the clinical and laboratory data of 2,272 arthritis patients with data from 6,151 individuals who did not have arthritis. Although detailed validation of the method was not applicable, the research noted important associations with cataracts (OR = 1.331) and other eye diseases (OR = 1.428) in significantly enhanced risk for arthritis, thereby observing a possible link between ocular health and risk of arthritis [9]. Negi et al. (2013) search to target the identification of single nucleotide polymorphisms associated with RA, using a supervised ML model, the Support Vector Machine. The study was conducted in 2 phases of discovery and replication on omics data that included 706 RA patients and 761 controls in the discovery phase, and 927 RA patients with 1,148 controls in the replication phase. Four SNPs were found to be strongly associated with RA, and the highest OR was 1.42 [10]. Kruppa et al. (2012) tested a combination of LASSO regression, logistic regression, and Random Jungle classifiers to define associations between SNPs and RA. The study included 707 RA patients and 738 controls, tested in 10-fold cross-validation along with dependent test set validation. The AUC of the Random Jungle model was 0.8925, with a sensitivity of 80.09% and specificity of 80.48%, showing that this model really discriminates RA patients from controls based on genetic data [11].

AI in Predicting Disease Progression and Flares

Rheumatoid arthritis (RA) is a chronic disease that progress with time, in terms of severity and locality. Therefore, it becomes imperative to detect the onset of RA as early as possible. This increases the chances of damage control happening at the joints. However, it's not easy. Onset and progress of RA depends upon several clinical and lifestyle factors of a patient. There are several attempts have been made to use AI to leverage these factors and understand who are the most vulnerable patients at an increased risk of the disease's progression. Attempts have been made to predict the likelihood of joint damaged, timing of flares and overall patient outcomes in the current work, getting further expanded into patient treatment strategies, patient monitoring and intervention strategies [12]. In the prediction of disease progression and flares in RA, several AI techniques are employed to provide insights into the dynamics of the disease. They include predictive analytics based on patient history and biomarkers [13].

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Predictive Analytics Based on Patient History and Biomarkers

There are several use cases where authors have experimented with Serological biomarkers such as Rheumatoid Factor (RF) and anti-citrullinated protein antibody (ACPA). These biomarkers although are helpful in understanding the progress of RA, but they are always not detected in the early stages. Nevertheless, AI could see pattern recognition techniques, in association with several other biomarkers, and patient characteristics such as multi-omics data (genomics, proteomics and metabolomics) to predict early RA [14]. Biomarkers are now measured for disease severity, prognosis, and response to treatment [2]. With the fast-evolving area of AI, especially machine learning, new biomarkers from proteomics, metabolomics, or transcriptomics data have been discovered. Machine learning algorithms can analyze large datasets of biological samples from RA patients to identify biomarkers that predict disease outcomes. These predictive biomarkers can be used to tailor treatment strategies to individual patients, improving the efficacy of therapies and reducing the risk of adverse effects [15].

Several studies use proteomics analysis using mass spectrometry for the identification of diagnostic biomarkers. These studies use small sample size having higher number of input variables. This type of data pattern makes decision tree-based algorithms best suited for the analysis of such datasets, as it has the ability to effectively manage the high dimensional input data relative to the number of samples. Similarly Geurts et al. also demonstrated that a boosted decision tree algorithm outperformed support vector machines and k-nearest neighbors [16]. Recently, non-coding RNAs have also gained significant attention as potential diagnostic biomarkers for RA [17]. According Ormseth et al.., LASSO variable selection method along with logistic regression is also helpful in developing microRNAs (miRNAs) panel which can differentiate RA patients from controls. The panel of upregulated miR-22-3p, miR-24-3p, miR-96-5p, miR-134-5p, miR-140-3p, and miR-627-5p achieved an AUC of approximately 0.8 which distinguish both seropositive and seronegative RA patients from controls. However also signify other autoimmune diseases, which make it difficult to differentiate between RA and systemic lupus erythematosus [18]. Several studies utilize proteomics analysis using mass spectrometry for the identification of diagnostic biomarkers. Higher input variables with a small sample size are studied. Decision tree-based algorithms have the ability to effectively manage high-dimensional input data relative to the number of samples. Hence, decision tree algorithms are the best fit for analysis on such datasets. Similarly, Geurts et al. also demonstrated that a boosted decision tree algorithm outperformed support vector machines and k-nearest neighbors [22]. Recently, non-coding RNAs have gained significant attention as potential diagnostic biomarkers for RA [23]. According to Ormseth et al., penalizing variable selection in logistic regression using the Least Absolute Shrinkage Selection Operator (LASSO) method is also helpful in developing a microRNA (miRNA) panel that can differentiate RA patients from controls. To distinguish both seropositive and seronegative RA patients from controls, the panel of upregulated miR (22-3p, 24-3p, 96-5p, 134-5p, 140-3p, and 627-5p) achieved an AUC of approximately 0.8. However, these miRNAs also signify other autoimmune diseases, making it difficult to differentiate between RA and systemic lupus erythematosus [24].

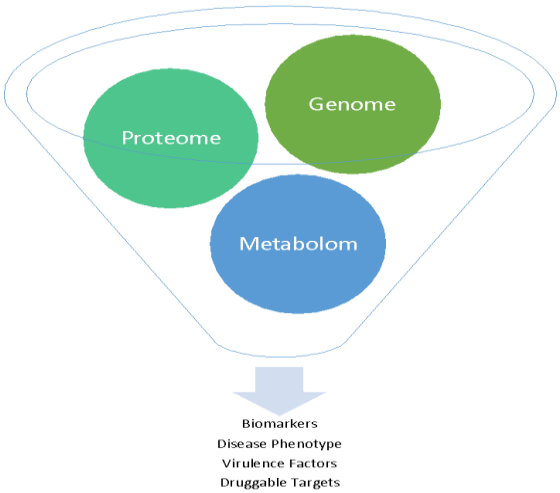

Figure 2. Multi-omics data integration of Proteomic, Genomics and Metabolomic data and its usage in predicting RA disease or RA disease biomarker outcomes.

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A variety of studies have used machine learning methods to develop coding and non-coding RNA panels in serum or plasma that can be used for the accurate diagnosis of rheumatoid arthritis. In a recent investigation on peripheral blood cells, Liu et al. analysed 52 gene expression profiles that are differentially expressed in RA patients. Subsequent protein-protein interaction analysis revealed nine hub genes—HLA-E, FYN, CFL1, COTL1, ACTG1, PFN1, LCP1, LCK, and HLA-DRA—that play pivotal roles in immune regulation and RA pathogenesis. To distinguish RA patients from healthy individuals, machine learning models using bootstrap aggregating methods (Random Forest) and logistic regression models on these nine messenger RNAs (mRNAs) achieved an area under the curve (AUC) of 0.97 or higher. In another study on gene expression profiling to predict the development of RA in patients with undifferentiated arthritis over 28 months of follow-up, Pratt et al. identified a 12-gene transcriptional signature in peripheral blood CD4+ T cells. The sensitivity in autoantibody tests was higher among anti-citrullinated protein antibody (ACPA)-positive patients, but the new gene expression signature had a better true positive and true negative rate in seronegative patients. Interestingly, the expression of several of these genes was influenced by IL-6-mediated upregulation of STAT3. When combined with the Leiden prediction rule, the 12-gene risk metric yielded an AUC of 0.84—higher than the application of the Leiden rule alone (AUC = 0.78)—for the prediction of undifferentiated arthritis in seronegative patients with RA progression, suggesting the clinical applicability of these biomarkers [29, 30].

AI in Imaging Analysis for Rheumatoid Arthritis:

AI techniques, particularly deep learning, are increasingly being used to analyze imaging data in predicting RA progression. Deep learning models can analyze baseline MRI or ultrasound images to identify subtle changes in joint structures that are predictive of future damage or flare-ups. These imaging features can be incorporated into predictive models to provide disease progression insights that are not easily apparent with common imaging assessments alone [25]. In AI, several techniques are being employed in the analysis of imaging data related to RA. Some of these include deep learning models, which may involve image segmentation and classification; radiomics; and detailed image features that come from an automated scoring system [26].

Deep Learning Models for Image Segmentation and Classification:

Deep learning is most appropriate for image analysis because of its inherent multilayer neural network structure, so it naturally popularizes the use of convolutional neural networks for deep learning models in segmenting and classifying images taken to investigate RA. This process partitions an image into meaningful regions or segments for further analysis [27]. These AI segmentation models are implemented to automatically delineate joint structures and pinpoint areas of inflammation or erosion in RA. Image classification is just categorizing detected images into classes either related to the severity of joint damage or being present or absent of specific pathological features like bone erosion or synovitis in RA. Such classifications could be used by clinicians to make more precise diagnoses and hence, treat patients with appropriate treatments [28].

Radiomics

Radiomics has evolved as a field in which large numbers of quantitative features are derived from medical images and can be analyzed to predict the disease outcome. This approach may offer the possibility for some imaging features, which are sub-visible at the level of the human eye, to either be related to the disease or predictive of activity in the case of RA. Radiomics is a technique of extracting textual shape and intensity features from medical images, which can be used in combination of the above-mentioned biomarkers or on its own in predicting diseases outcomes. Such predictions can guide clinicians on taking more informed decisions about the intensity and duration of treatment, which will ultimately yield better patient results [29, 30].

Automated Scoring Systems:

Another application of AI in analyzing RA images is automated scoring systems. Scoring systems with artificial intelligence algorithms are able to automatically assign scores to imaging studies—be it the Sharp/van der Heijde scoring system for X-rays or the OMERACT-EULAR scoring system for ultrasound—based on some standardized criteria [4]. An important advantage of such automated scoring systems is that they provide

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standardization for image studies, thereby reducing the variabilities among different observers. This standardization is most crucial in clinical trials, as scoring needs to be consistent to evaluate new treatment results on patient outcomes [31]. Radiography continues to be the primary method for assessing structural joint damage in rheumatoid arthritis (RA). In a study conducted by Hirano et al., [32], X-ray images of RA patients were used to train and develop a deep convolutional neural network (CNN) designed specifically to evaluate joint destruction. The model's ability to assess joint erosion and joint space narrowing was found to be on par with evaluations made by rheumatologists, highlighting its effectiveness in clinical settings [33]. According to Hirano et al., they used x-ray images of RA patients for training and developing a convolutional neural network (CNN) model to predict joint destruction. The performance is highly comparable to the expert Rheumatologists in clinical practice [33]. Similarly, models based on hand x-rays achieved a similar performance. [34]. Despite of these high performances, radiography images may underestimate the number and size of erosion in the affected area due to its protectional nature [35] which are most often overcome by using CT images as shown in [36]

AI in Personalizing Treatment Plans for RA Patients

The approach of developing individual treatment program for rheumatoid arthritis is described as a paradigm shift from the mass/treatment program and is an idea that seeks to design interventions that fit the specific needs of the patients. RA is accepted as a condition that commonly causes variation in terms of manifestation and response to therapy. This variation requires that treatment plans be personalized based on patient characteristics, including the intensity of their illness, genetic susceptibility, other conditions, and therapeutic histories [37]. AI is mainly effective for creating newer strategies in the treatment planning of patients affected by rheumatoid arthritis (RA). By processing clinical records, genotype, phenotype, and behaviour significant information for the right drug choices, right dose and right timing of drug delivery is helped by the use of AI. This means to develop a treatment plan specifically designed to achieve better therapeutic outcomes for the patients with RA by reducing possible side effects as much as possible to better the quality of the lives of the patients [38]. Personalized medicine in RA is highly important for positive patient outcome [39]. For example, there are various DOMARDs and biologics affect differently to different patients based on their genetic composition, stage of the disease and their individual characteristics. Personalizing treatment plans allows for the selection of the most appropriate therapy for each patient's unique condition, thereby improving therapeutic efficacy [40].

AI Tools for Monitoring and Predicting Treatment Response in RA

Because of the long-term nature of the diseases, monitoring the response of the patients to the drugs is highly crucial in disease management. Monitoring makes the clinician to make early modifications in the therapy procedures thus improving the overall therapeutic process and minimising toxic effects. Modern technology in particular artificial intelligent application brings new ways in monitor responses to therapy in patients with RA to enhance the process of patient care [38]. At present, a wide range of treatment options are available for RA patients which includes NSAIDs, glucocorticoids, conventional synthetic DMARDs, biological DMARDs and oral small molecules [41]. Although there are several treatment options, finding the best option is so far the most challenging task for the doctor. The challenge is due to the vast choice of forms and much reliance on trial and error in the assignment of therapies.

Additionally, this challenge is compounded by a limited understanding of the efficacy and safety of these drugs across diverse patient populations [42]. Methotrexate is still the first drug of choice in RA treatment [43]. Artacho et al. evaluated whether differences at an individual level in gut microbiota composition might represent predictive biomarkers of response to MTX in newly diagnosed patients with RA. The faecal specimens were obtained from 26 patients undergoing MXT therapy for the first time and for these samples, 16S rRNA sequences are analysed. An AUCROC score of 0.84 was obtained using a predictive approach based on the mycobiome abundance features in predicting MXT treatment response [44]. Furthermore, there are studies that determine the MXT repones rate in 9 months using machine learning algorithm on a cohort of 493 and 239 patients. Models such as LightGBM have been used in several other experiments in predicting response, have reportedly achieve an AUCs of 0.72 on external validation test set [45]. The Light Gradient Boosting Machine (LightGBM) model achieved AUCs of 0.73 and 0.72 in training and external validation

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sets, respectively [45]. Analysis by Lim et al. utilized exome sequencing data from 349 patients using 95 genetic factors and 5 non-genetic factors, achieved an AUC score of 0.828 [42]. Similarly, Plant et al. experimented with gene expression data from blood samples of RA patients before 4 weeks of using MTX treatment to predict response rate at six month's time using a L2 regularized logistic regression, achieving an AUCROC score of 0.78 [46]. In an another study, an hybrid approach was taken to integrate anti-TNF treatment and biomarkers from 29 healthy donors and 104 RA patients predicted treatment response with 0.91 [47]. The approach of embedding demographical, clinical and genetic features in the Optimal Model Embedded Gaussian Process Regression in the DREAM RA Responder Challenge was innovative towards predicting anti-TNF treatment response at 24 months apart with 0.6 AUCROC score [48]. Also, kim et al. worked on 11 datasets containing 256 synovial tissue samples and four machine learning models achieving an AUCROC score of 0.87 with ASA pathway driven model and 0.9 with DEF driven model [49]. Figure 3 presents a radar chart comparing AUCROC score reported in all methods discussed above.

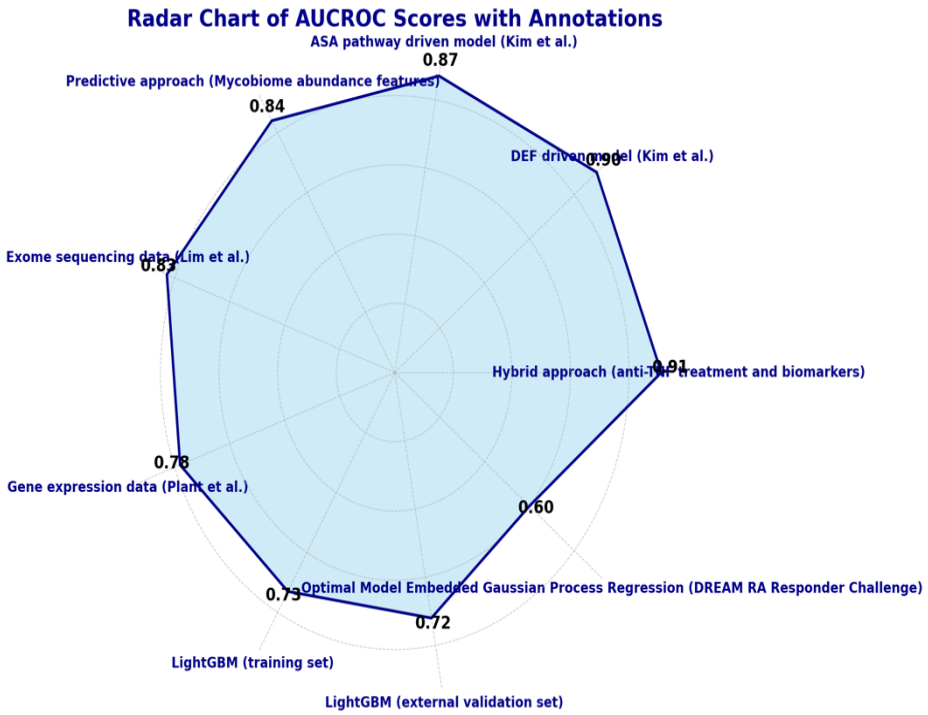

Figure 3. Radar Chart highlighting AUCROC score of predicting RA treatment response using ML techniques in several studies. These studies have used MTX and Anti-TNF

AI in Drug Discovery and Development for Rheumatoid Arthritis

There has been a continuous effort in the field of drug discovery, not only RA but also for several other diseases. AI has played crucial role in reducing the time for finding the right drug. The integration of AI into the drug discovery process has increased the pace of drug development, enhanced the precision of drug-target interaction, and reduced the costs related to new drug introduction [50].

Target Identification and Validation

One of the major applications of AI in drug discovery is target identification and validation. In particular, machine learning models can sift through large volumes of genomic, proteomic, and metabolomic data to identify possible biological targets from which to develop a drug. Many of these algorithms have been able to pinpoint proteins or biological pathways said to be associated with particular diseases and thus can provide important information in guiding the development of new therapeutics [51]. ML-based approaches like Kronecker regularized least squares (KronRLS) evaluate the similarities between drugs and protein molecules to determine drug-target binding affinity (DTBA). This capability is crucial for selecting optimal targets that are druggable, safe, and effective [52].

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Virtual Screening and Drug Design

AI play an important role in the virtual screening and drug designing, which are key steps in discovery of drugs. The use of virtual screening tools for effective drug development requires three-dimensional protein target structures to interact with potential drug molecules. This accelerates drug discovery, allowing researchers to identify more promising drug candidates for experimental testing [53]. This has proven to be an invaluable strategy in the optimization of drug design because molecular docking simulations can predict the preferred orientation of a drug candidate when bound to a target protein using artificial intelligence algorithms. For example, massive data on chemical structures and pharmacokinetic properties are analyzed with deep learning models to predict the efficacy and safety of potential drugs [54].

This complicated and expensive process of discovering and developing new treatments for rheumatoid arthritis typically consumes many years of research and billions of dollars. The hope provided by artificial intelligence in this field brings innovative ways to aid the discovery of novel therapeutics and optimally structure development pipelines. AI has the advantage of analyzing large datasets to identify patterns and predict possible outcomes, useful across many stages of drug discovery, from identifying novel drug targets to repurposing existing drugs [55].

AI Algorithms in Drug Discovery

AI-driven methods of drug discovery have significantly revolutionized the processes through data-driven analytics, machine learning (ML), and rapid simulation, which are at opposite to the traditional highly manual research, experimentation, and testing. There are several different ways to assist drug discovery process as shown in Figure 4.

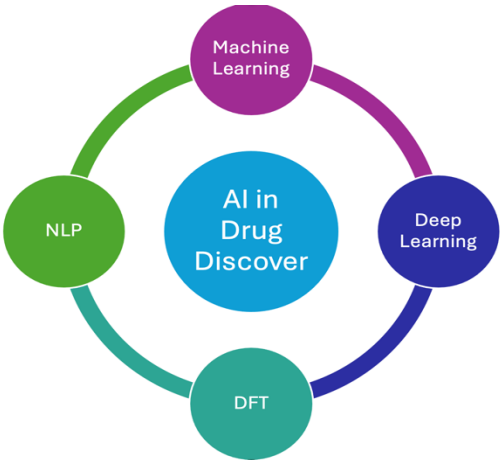

Figure 4. Algorithms of AI in Drug Discovery process.

Machine Learning (ML)

ML consists of many algorithms which, in general, learn patterns and make predictions. These algorithms in most cases are dependent on structured data and feature engineering, where relevant features of data have to be chosen before training [56]. ML models, which are simpler and less computationally intensive than deep learning models, perform better on small space but may struggle with sample having non-linearity in associations [57]

Deep Learning (DL)

Unlike ML techniques, DL uses artificial neural networks with many layers to automatically learn the data representations, without any prior feature engineering being done. Models under deep learning are very effective at dealing with unstructured data; for instance, they are very effective in both image and text processing. They are resource-intensive and have less interpretability because of their complex architecture [58].

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Gong et al. demonstrated the use of ML in screening polymers for gene delivery by applying high performance algorithms to understand structure-function associations and to predict transfection based on polymer properties. This computational approach proved effective in predicting biological outcomes in silico, showcasing the utility of ML in drug discovery [59].

High-Throughput Density Functional Theory (DFT)

High throughput DFT is a computational technique that focuses on the atomic level understanding of the materials and has applications in areas such as drug discovery. It enables the quick calculation of binding energies and affinities for drug molecules to target proteins, making the screening of potential drug candidates more efficient [60]. DFT also predicts physicochemical properties like solubility and metabolic stability, aiding in the selection of compounds with favourable ADMET profiles. DFT is helpful in understanding the small fragments that binds to a target protein. This leads to formation of several fragment-based drug design[61].

Natural Language Processing (NLP)

Text mining is one of the evolving part of artificial intelligence where, in particular, natural language processing deals with human language. These algorithm study and understand data, features and information from sources like scientific articles, patents, and clinical trial repositories. It identifies drug names, target proteins, and other disease-related information by NLP models, assisting researchers in the collection of crucial data required for the discovery of new drugs [62].

Text mining

Text mining has different strategies to identify existing drugs and their application in new therapies. Analysis of the scientific literature by AI models may throw up drug candidates with proven efficacies against certain diseases or targets, therefore opening the door for drug repurposing studies and studies based on polypharmacology [63]. These AI models, when developed, build knowledge graphs that integrate a wide variety of data sources ranging from clinical trial outcomes and genomic data to chemical databases. These graphs build complex relationships between drugs, targets, diseases, and biological pathways, thereby enabling comprehensive analyses and generation of new hypotheses [64].

In order to take advantage of such capabilities, there are number of text mining applications that leverages AI. Jang et al., for example, developed a novel tool PISTON that predicts side effects using NLP and topic modelling [65]. Similarly, DisGeNET supports the subject of gene-disease and variant-disease relationship by providing number of practical use cases such as analysing adverse drug reaction, molecular pathways and therapy targets [66]. Also, a protein2protein interaction software based up of STRING database predicts the interaction between proteins and chemicals [67]

Drug Repurposing:

Drug repurposing is the technique by which new therapeutic utilities of existing drugs are found; it can significantly reduce the time and cost involved in drug development [68]. Among them, AI has made a remarkable achievement in this aspect through network-based methodologies. The potential for drug repurposing with artificial intelligence has recently gained huge consideration by pharmaceutical companies and research organizations to speed up legacies in making discoveries. Some studies in RA have suggested a computation-based approach in drug discovery [69].

In one of the studies related to drug and disease data, an approach was taken to construct genetic disease network and subsequently a drug-ranking algorithm which identified innovative drugs for RA diseases [70]

It was further supported by another pre-clinical study that indicated pirfenidone, originally used in the treatment of anti-pulmonary fibrosis, inhibited inflammation and angiogenesis via multiple pathways in collagen-induced arthritic rats. This suggests the possible use of pirfenidone in the treatment of RA; however, there is a need for further studies in humans to confirm its therapeutic efficacy in RA [71].

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Machine Learning for Predicting Drug Efficacy and Safety:

One of the crucial steps of drug development is not just finding the right drug but understanding which candidate is fit for the drug to answer: will it work and be safe? AI, mainly through the use of machine learning models, has a repertoire of tools for making more accurate predictions in the earlier developmental stages of the candidate drugs. Machine learning algorithms are very promising for making predictions, especially when they can be developed by learning historical data from clinical trials, preclinical studies, and real-world evidence concerning the potential activity or safety of a new drug candidate in patients [72]. These models take into account pharmacokinetics and pharmacodynamics of the drugs and the genotype information of the patients to work. Similarly, AI is used to predict adverse effect given the candidate is part of the clinical trial

By analysing data from previous drugs and known side effects, AI can identify patterns that might suggest a high risk of toxicity or other safety concerns [73].

AI in Patient Education and Self-Management for Rheumatoid Arthritis

The management of rheumatoid arthritis should be carried out in a comprehensive and individual basis to give best quality of life considering outcome of the disease in the future. It is therefore imperative that the management of the disease involves the patient and their cooperation with the doctors as well as their compliance with the laid treatment plans [74]. Today, artificial intelligence is used as an effective means of improving the patient's knowledge and self-management. Self-management tools based on AI can provide RA patients with personalized, timely, and constant encouragement to enable them to have more decision-making power and assume a greater amount of responsibility for their health and treatment than in the past. These tools include all over AI based conversational bots for instant guidance and information including virtual health companion for your daily leading health management application for tracking symptoms and taking medications. On the other hand, with the help of the predictive models, these applications provide specific self-management interventions for clients. The chatbots possess NLP and Machine Learning along with the ML algorithms to interact to patients where it asks questions, gives related information and educates regarding their status of disease [75].

Another AI-driven tool for self-management in RA is the use of personalized health management apps to monitor patients' symptoms, track medication adherence, and offer personalized recommendations based on real-time data. These automated apps offer self-monitoring of daily symptoms, such as pain levels, joint stiffness, and fatigue [76] which will help in rightful intervention and further decrease in the pain severity.

AI in Remote Monitoring and Telemedicine for Rheumatoid Arthritis

With the advancement of AI, it is now possible to offer tele services to RA patients in the rural area or those with limited access to the specialized care. AI has been used in real-time monitoring, one to one facetime with the doctor, through continuous data collection, provide custom disease management plans. [77]. Moreover, there are several AI powered wearables that analyses the patient health in the Realtime and provides a 360 degree view of the condition for rightful intervention.[78]. Several AI techniques such as cloud enabled large scale data munching, processing, transformation and predictions are behind remote monitoring and telemedicine for RA [79]

Ethical and Legal Considerations in AI for Rheumatoid Arthritis

AI has been crucial in predicting RA outcomes, diagnosis, treatment management, prognosis and many more. With more sophisticated algorithms and integration of several types of clinical and non-clinical data, precision has improved over the time. Moreover, there are studies that shows impact of real time assessments. However, this comes at a cost of ethical and legal challenges [80]. This makes addressing biases in AI models all the more important, in order to ensure that applications do not inadvertently harm some patient groups over the others. This might lead to misrepresented outcomes of care where certain patients receive either better or worse care based on such factors as race, gender, or socioeconomic status. The development and deployment of AI in

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the management of RA can support a goal that all patients should be assured of high-quality, fairly administered, and transparently accounted care [81].

A number of AI techniques and frameworks are under development to take on these ethical and legal problems associated with the treatment of RA. It includes fairness-aware algorithms, interpretability models, and frameworks for the deployment of ethical AI. Fairness-aware algorithms have been developed to identify and reduce biases in AI models, whereby the outcomes created by such models are fair across the diversity of patient groups. It is in fields related to healthcare that these algorithms really matter. Biased AI models could result in unequal treatment, diagnosis, and outcomes [82]. Interpretability of models means the AI tool is designed such that artificial intelligence systems may easily become more transparent in making decisions, and the reasons behind these decisions are therefore more understandable and human interpretable. In healthcare, where the AI model would generally work like a black box, giving virtually no insight into how it arrives at its recommendations, interpretability is important for the building of trust in the system by clinicians and patients [83].

CONCLUSION

AI applications help to manage the disease and improve the outcomes in multiple aspects, including early diagnosis, individualised treatment decision making, ongoing assessment, drug development, and patient engagement in case of rheumatoid arthritis (RA). Using AI methods, healthcare practitioners can get a higher diagnostic rate, determine personalized care plans, and control outcomes of the disease over time as well as increase patients' involvement and responsibility for their health. One interesting application of AI is early detection of RA because the earlier the diagnosis is made, more efficiently can DMARDs be used to start preventing joint damage. In terms of treatment AI consider patient genetic makeup, disease characteristics, and treatment history which lead to the development of effective therapeutic approaches. AI driven tools provide real time monitoring of treatment response and progression of disease, which enables healthcare providers to adjust treatment plans, result in better disease control and also minimize the adverse effects of treatment. The use of AI also enables healthcare providers to quickly identify novel therapeutic target and also help in repurposing of the already available drugs. These interventions reduce the cost and time required for the introduction of new treatment method in market. Moreover, AI has the ability of integrating and analysing multi-omics data which contribute in better understanding of the genetic and molecular factors related to RA. This result in adaptation of more tailored and preventative healthcare strategies.

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