

## Towards revolutionizing precision healthcare: A systematic literature review of artificial intelligence methods in precision medicine

Wafae Abbaoui <sup>a,b,\*</sup>, Sara Retal <sup>c</sup>, Brahim El Bhiri <sup>b</sup>, Nassim Kharmoum <sup>d,a,e</sup>, Soumia Ziti <sup>a</sup>

<sup>a</sup> Intelligent Processing & Security of Systems (IPSS) Research Team, Faculty of Sciences, Mohammed V University in Rabat, Rabat, Morocco

<sup>b</sup> SmartLab, Moroccan School of Engineering Sciences (EMSI), Rabat, Morocco

<sup>c</sup> 2IACS Laboratory, ENSET, University Hassan II of Casablanca, Mohammedia, Morocco

<sup>d</sup> National Center for Scientific and Technical Research (CNRST), Rabat, Morocco

<sup>e</sup> Moroccan Society of Digital Health, Morocco

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### ABSTRACT

In the realm of medicine, artificial intelligence (AI) has emerged as a transformative force, harnessing the power to convert raw data into meaningful insights. Rather than supplanting the discernment of physicians, AI serves as an unprecedented enabler, equipping them with unimaginable tools. Its far-reaching applications encompass drug discovery, disease diagnosis, prognosis, treatment optimization, and outcome prediction. This technological revolution owes much to the prowess of machine learning algorithms, which adeptly process multifaceted data. Consequently, AI is poised to become an integral pillar of digital health systems, shaping and bolstering the realm of personalized medicine. The current landscape is abuzz with AI's exponential growth, fueling a surge of research ventures aimed at enhancing medical practices. By delving into the realm of precision medicine, this paper endeavors to scrutinize and evaluate recent advancements in healthcare pertaining to the utilization of machine learning (ML) and deep learning (DL) algorithms. This systematic review comprehensively encompasses previously published works, dissecting key concepts, innovations, significant contributions, and pivotal enabling techniques. Aspiring to equip readers with a profound understanding and invaluable insights, this paper proves indispensable to those dedicated to exploring the state-of-the-art and contributing to future literature in this domain.

### 1. Introduction

Amidst the captivating landscape of contemporary medicine, the concept of precision medicine took root in 2011, ushering in a remarkable era where medical treatments are meticulously tailored to match the individual characteristics of each patient [1]. In the domain of groundbreaking precision medicine, characterized by constant evolution and growth, individuals are granted personalized medical treatments and interventions for disease prevention with unmatched precision [2]. The primary objective revolves around customizing proactive and preventative therapies to elevate the overall effectiveness of medical care [3]. Precision medicine offers a plethora of assurances, including the ability to detect or predict diseases, provide precise diagnoses, and enhance treatment optimization, all while prioritizing accuracy, cost-effectiveness, and speed (Fig. 1).

In an era marked by swift progressions in AI, ML, and their allied technologies, precision medicine stands tall as a transformative force.

It capitalizes on the wealth of biological and external data, paving the way for real-time clinical management decisions tailored to each individual's unique disease journey. Unlike conventional clinical approaches, precision medicine places paramount importance on delving into comprehensive profiles of patients, encompassing their genetic makeup, physical characteristics, and metabolic patterns [1,4]. In this awe-inspiring landscape of progress, artificial intelligence emerges as the pivotal catalyst propelling the evolution of precision medicine.

Artificial intelligence, an offshoot of computer science, operates within the domain where machines undertake tasks that traditionally require human intelligence [5]. When constructing robust AI algorithms, computer systems are initially supplied with organized data, where each data point typically possesses a distinguishable label or annotation assigned by the algorithm [6]. Significantly, within the context at hand, the AI in question encompasses ML and DL, which are pivotal elements within this expansive discipline.

\* Corresponding author at: Intelligent Processing & Security of Systems (IPSS) Research Team, Faculty of Sciences, Mohammed V University in Rabat, Rabat, Morocco.

E-mail addresses: [wafae\\_abbaoui@um5.ac.ma](mailto:wafae_abbaoui@um5.ac.ma) (W. Abbaoui), [retal.sara@gmail.com](mailto:retal.sara@gmail.com) (S. Retal), [b.elbhiri@emsi.ma](mailto:b.elbhiri@emsi.ma) (B. El Bhiri), [nkharmoum@gmail.com](mailto:nkharmoum@gmail.com) (N. Kharmoum), [s.ziti@um5r.ac.ma](mailto:s.ziti@um5r.ac.ma) (S. Ziti).

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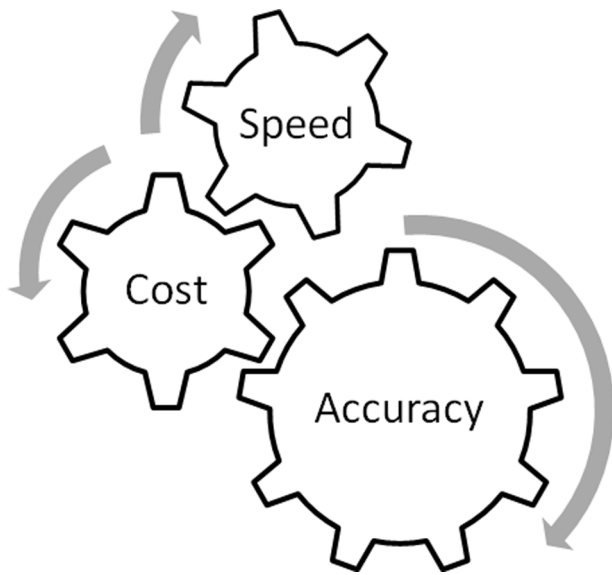


Fig. 1. Vital objectives of precision medicine.

Embarking on a mesmerizing voyage of relentless advancement, artificial intelligence permeates every aspect of society, leaving an indelible mark on the medical landscape [7]. Particularly in biomedicine and healthcare, AI pioneers transformative breakthroughs, reshaping biomedical image analysis, patient care, prognosis, and clinical decision support. With awe-inspiring speed, AI ascends to extraordinary heights, magnifying its influence within the global shift towards precision medicine [8]. Fig. 2 illustrates the integration of AI in precision medicine to enhance healthcare outcomes. Simultaneously, Fig. 3 visually captures this profound integration, illustrating how AI's transformative role enhances disease diagnosis, patient care, and contributes to the overarching goals of precision medicine.

In the context of COVID-19, the integration of several key studies significantly enhances our understanding of AI applications in gene-based diagnosis, prognosis, prediction, and medicine. Notably, one study introduced an AI method for genome sequence analysis, achieving high accuracy rates in classifying diseases. Another investigation developed a gene-based screening method using machine learning algorithms, demonstrating considerable accuracy in distinguishing between pneumonia and COVID-19. Additionally, a transcriptomic gene expression study identified potential gene targets of COVID-19, emphasizing the importance of specific genes. In terms of prognosis, a machine-learning approach accurately predicted COVID-19 mortality, while host micro ribonucleic acid (miRNA) signatures exhibited high precision in classifying COVID-19 samples. Furthermore, multi-omic data analysis and an SVM classifier were employed for prediction, identifying gene signatures and predictors of COVID-19 severity. An analysis study based on single nucleotide polymorphisms (SNPs) in genomic data revealed mutations and predicted future mutations using deep neural learning models. Collectively, these studies underscore the pivotal role of AI in advancing gene-based diagnostics, prognostics, predictions, and drug development in the context of COVID-19 [9].

An illustrative instance highlighting the valuable role of artificial intelligence during the COVID-19 pandemic is the utilization of an AI and NLP system called “COVID-19 Taxila” [10]. This system harnesses a wide range of clinical trials, publications, and pertinent sources to grant users access to the ever-evolving scientific literature regarding COVID-19. Users can leverage this system to search, analyze, and navigate the dynamic landscape of COVID-19 data. Notably, It is particularly important to emphasize that both publications and data are automatically and consistently updated, ensuring the most up-to-date information is readily available [11].

Our paper offers a comprehensive analysis of the intersection between precision medicine and AI by conducting a systematic review of the existing literature. Spanning from 2015 to 2024, we have meticulously compiled all relevant cutting-edge research in the field. We evaluate these works from diverse statistical perspectives, considering parameters such as publication year, title, type, publisher, author, keywords, methodologies, comparison metrics, datasets, organs of interest, and modalities employed. This systematic review serves as a valuable resource for readers actively engaged in this area, fostering a thorough comprehension of the present cutting-edge and offering valuable insights for future contributions in this domain.

In this article, we examined AI approaches employed in precision medicine. Unlike other recent review articles that focus solely on AI and deep learning methods within specific personalized medicine specialties, our research investigates the adaptation of AI, ML, and DL approaches across various precision medicine specialties. The remaining sections of the paper are structured as follows: The next section presents the adopted literature review planning protocol. Section 3 presents the findings of the literature review, demonstrating the application of AI, ML, and DL methods in precision medicine. Section 4 proposes public datasets for precision medicine. Section 5 delves into the discussion of challenges in precision medicine and highlights the benefits and drawbacks of different ML algorithms. Finally, the last section concludes this work.

## 2. Systematic literature review

Systematic reviews hold a unique and significant role within the healthcare landscape. They play a crucial role in shaping practice guidelines and serve as valuable sources of information for clinical decision-making, thereby informing future research endeavors [12]. Renowned for their methodological rigor, systematic reviews represent the pinnacle of evidence synthesis in healthcare. Ideally, these reviews should adhere to pre-established eligibility criteria and be conducted following a predefined methodological framework [13].

### 2.1. Unveiling the literature review methodology

This paper adopts the subsequent planning protocol for conducting the review:

#### 2.1.1. Research questions

- How are AI methods reshaping the landscape of precision medicine applications?
- Which ML algorithms dominate medical data processing, equipping healthcare professionals with vital insights?
- Which medical disciplines reap the greatest benefits from advancements in precision medicine?
- What types of data fuel the application of AI methods in medical breakthroughs?

#### 2.1.2. Literature exploration: Essential research databases

This study hinged on the utilization of *Scopus*, the well-known scientific literature database, as a cornerstone for literature searching.

#### 2.1.3. Inclusion criteria

The criteria for selecting the relevant literature in this study include the following:

- Inclusion of journal articles, conference proceedings, and book chapters.
- Indexed in the Scopus database.
- Written in the English language.
- Containing a comprehensive explanation of the methodology employed.
- Encompassing cross-sectional studies that examine changes over years.

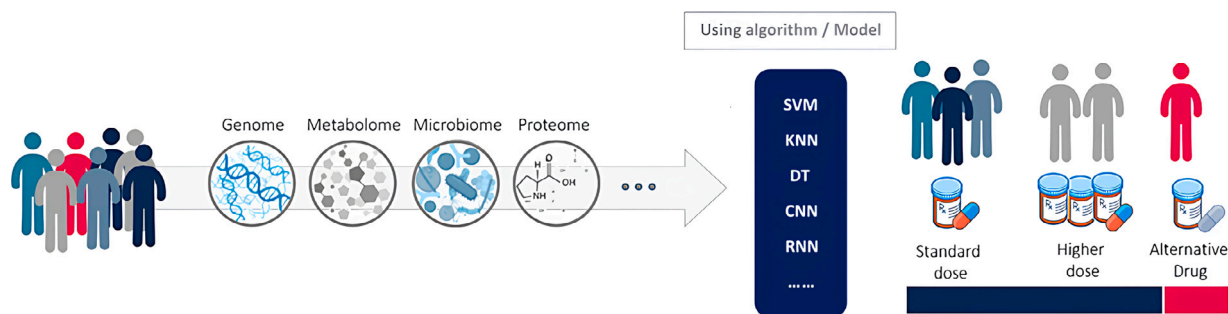


Fig. 2. AI for precision medicine.

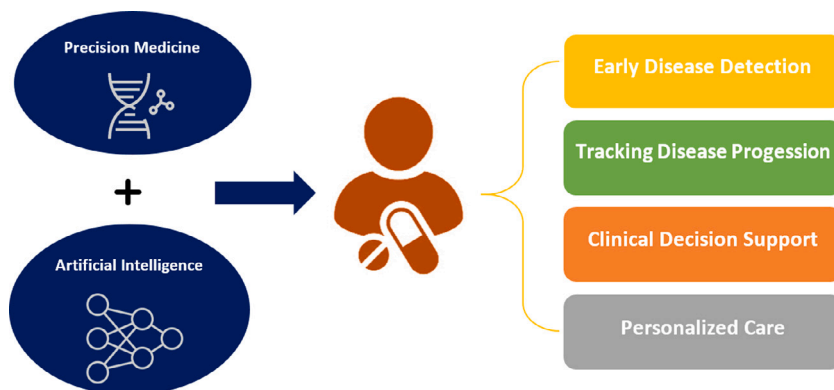


Fig. 3. Transformative integration of AI in precision medicine.

#### 2.1.4. Exclusion criteria

The following criteria were used to filter the literature for this study:

- Exclusion of studies that do not specifically examine the impact of AI on the advancement and development of precision medicine.
- Exclusion of studies that only propose ideas without presenting any experimental or comparative results.
- Exclusion of studies published before the year 2015.

#### 2.1.5. Quality criterion

Papers that specifically examine the collaboration between artificial intelligence and precision medicine and explore the resulting implications for the healthcare system.

#### 2.1.6. Selection of sources

The titles and abstracts of all publications were individually assessed by the authors, who excluded publications lacking abstracts, full texts, or English delivery. Additionally, publications unrelated to artificial intelligence and the precision medicine domain were excluded. Following this, the texts were independently and meticulously examined to ascertain if they satisfied any of the following research focus criteria: (1) artificial intelligence in precision medicine, (2) machine learning in precision medicine, or (3) deep learning in precision medicine. Articles that did not prioritize the synergy between AI and precision medicine were excluded (Fig. 4).

### 3. Findings from the literature review

#### 3.1. Pertinent literature extraction

##### 3.1.1. Publication distribution along the years

The figure presented below illustrates the number of papers published between 2014 and 2023. These statistics demonstrate a noticeable surge in interest concerning artificial intelligence applications and

diverse algorithms, which have the potential to revolutionize healthcare on a global scale, making it more efficient and personalized. The publications included in this analysis were sourced from the reputable and extensively indexed database, "Scopus". In 2014, only four articles were published, while the subsequent years witnessed a significant increase. Notably, there were 523 articles published between 2015 and 2018, followed by a remarkable surge with 3557 articles published from 2019 to 2023; The findings of this analysis indicate a growing inclination towards publishing in the field, particularly from 2017 onwards. This inclination could be attributed to the transformative impact of machine learning, deep learning models, and artificial intelligence applications, which are propelling a data-centric revolution in healthcare. Consequently, this area of research has become highly promising, attracting substantial investments from technology giants like IBM, Apple, and Google, who are actively pursuing healthcare analytics to advance precision medicine, enhance the accuracy of predictions, and improve patient outcomes (see Fig. 5).

##### 3.1.2. Publication distribution among journals and conferences

Of the 133 papers selected, 102 are articles, 23 are reviews, plus 6 conference papers, one note, and one letter (Fig. 6).

##### 3.1.3. Citation analysis

One of the indicators of the quality of a published paper is the frequency with which it is referenced or cited by other authors.

The higher the quality of the articles selected in the literature review, the more robust our research will be. To assess the impact and maintain the quality of the selected articles, we utilized the Scopus platform, which allowed us to determine the number of citations through citation analysis.

In Table 1, we present the top ten papers selected based on the number of citations, listed in descending order. Among these papers, the journal article titled "Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement" [13] received the highest number of citations (15067), surpassing all others.

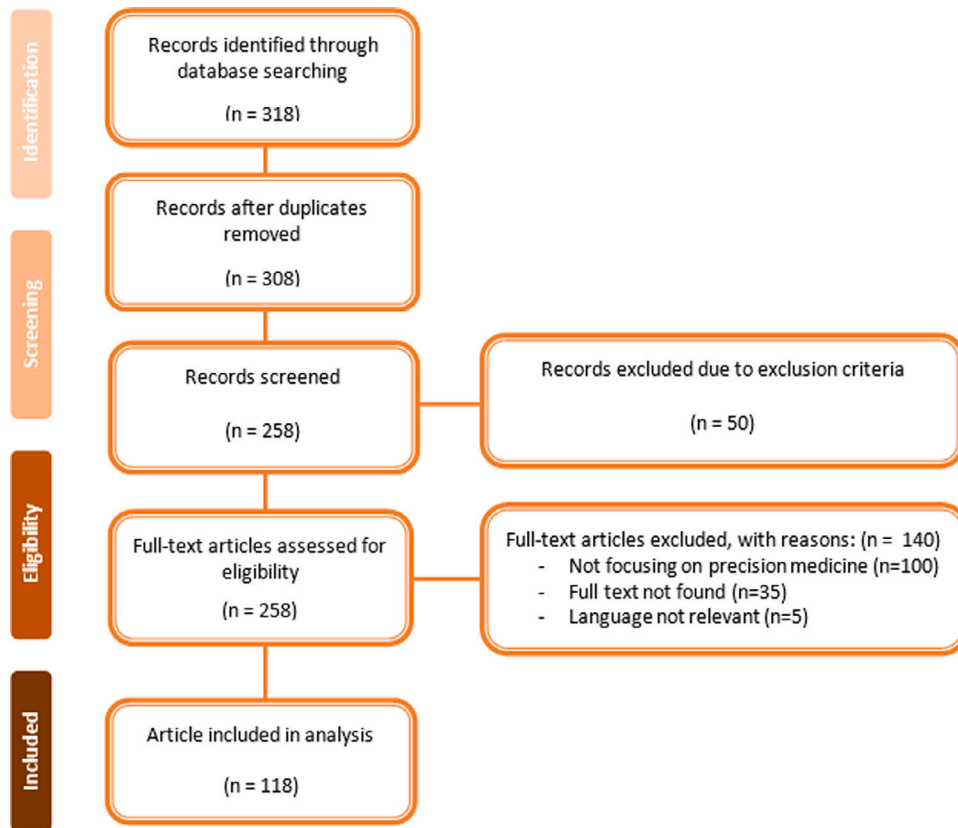


Fig. 4. The trends of search term and exclusion criteria.

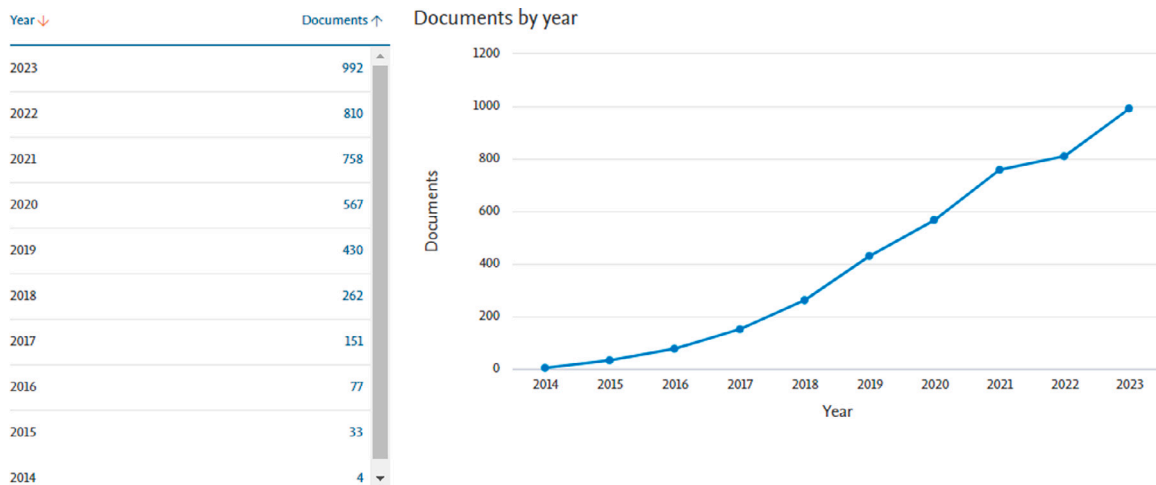


Fig. 5. The tracking of documents count by years in the Scopus database [14].

The second most cited article, with 8035 citations, was the journal article “Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: Elaboration and explanation” [12]. The third highest number of citations (7833) was attributed to the journal article titled “A survey on deep learning in medical image analysis” [15]. Taking into account the results of the citation analysis, the h-index of all the selected papers is 68.

The following figure provides a summary of the citation activity for the selected papers from 2015 to 2023 (see Fig. 7).

### 3.1.4. Word cloud of keywords in selected articles

Word cloud is a semantic and visual representation of textual content where a cluster of words that synthesize ideas and define a concept or line of reasoning presented in an article is displayed in varying sizes. The word cloud is built from the occurrence of the terms used: a word appears bigger and bolder and becomes more relevant as it is used more frequently. Word cloud is a method of visualizing the keywords in the study, which allows an intuitive understanding of the keywords and concepts in the articles.

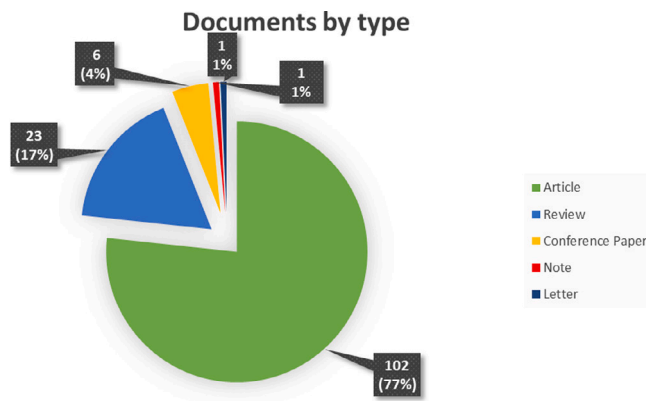


Fig. 6. Distribution of documents by type.

Table 1  
Overview of the top 10 cited articles.

Title	Publication year	Citations
Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement [13]	2015	15 067
Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: Elaboration and explanation [12]	2015	8035
A survey on deep learning in medical image analysis [15]	2017	7833
Deep Convolutional Neural Networks for Computer-Aided Detection: CNN Architectures, Dataset Characteristics and Transfer Learning [16]	2016	4039
Recent advances in convolutional neural networks [17]	2018	3348
Deep visual-semantic alignments for generating image descriptions [18]	2015	3310
Deep Learning in Medical Image Analysis [19]	2017	2860
Convolutional neural networks: an overview and application in radiology [20]	2018	2316
Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables [21]	2018	1282
Deep Learning for Health Informatics [22]	2017	1258

The process of generating the word cloud image comprises three steps. Initially, we automatically extracted the keywords from the chosen articles. Next, we conducted data cleaning, which involved combining singular and plural forms (e.g., CNN and CNNs), merging full and abbreviated terms, and considering synonyms. Lastly, we utilized Wordclouds.com, an online word cloud generator, which is free to use, to generate the word cloud from the provided text. Fig. 8 demonstrates that the font size corresponds to the frequency of the keywords. The word cloud effectively depicts that two categories of keywords are commonly employed in the selected articles. Specifically, one category encompasses keywords associated with AI and deep learning, such as artificial intelligence, deep learning, machine learning, CNN, ANN, RNN, big data, and so forth. The other category encompasses keywords

linked to precision medicine, such as personalized medicine, medical imaging, EHR, computed tomography, MRI, and so on. This analysis further validates that the identified articles are closely interconnected with AI and precision medicine.

### 3.2. Research methods analysis

#### 3.2.1. NLP model-based research attempts

Natural Language Processing (NLP) is a specialized field that holds immense potential to revolutionize Precision Medicine. By employing ML and DL techniques, NLP enables the interpretation and extraction of meaningful insights from unstructured medical data, such as electronic health records, biomedical literature, and clinical notes. Fig. 9 depicts NLP as a subset of AI that leverages diverse ML and DL approaches to achieve its objectives.

The application of NLP in clinical decision support systems (CDSS) within the field of personalized medicine has demonstrated promising results in enhancing the accuracy and efficacy of individualized therapies. In their publication [23], the authors present a framework that integrates NLP with CDSS, emphasizing the crucial aspects of data acquisition, preprocessing, feature extraction, and model development. The authors posit that incorporating NLP into CDSS holds substantial potential for advancing personalized medicine by augmenting patient outcomes, mitigating medical errors, and optimizing healthcare delivery in terms of efficiency and cost-effectiveness. Nevertheless, further research and development are imperative to fully unlock the capabilities of NLP-based CDSS in the context of personalized medicine.

#### 3.2.2. ML models-based research attempts

**Random forest** The random forest algorithm utilizes a technique in which multiple decision trees are generated using a random selection of independent variables. Its purpose is to forecast outcome labels for a particular set of samples [24]. In the field of machine learning, striking a balance between accuracy and interpretability has consistently posed a challenge. Ensemble learning methods such as random forests address this problem by combining multiple classifiers to create a highly accurate model, although interpretability is compromised in the process [25].

Random forest algorithms have found applications in various domains of precision cardiovascular medicine, including coronary computed tomography angiography, the prediction of heart failure (HF) readmission, and the development of HF risk and survival prediction models [26].

In a precision oncology investigation, the objective of the researchers was to improve the predictive power of their prediction models by incorporating radiomic variables alongside clinical data. Initially, logistic regression was employed to efficiently extract radiomic variables. Subsequently, random forests were used to integrate the radiomic (continuous inputs) and clinical (categorical inputs) information into a cohesive classifier. The findings demonstrated that the incorporation of clinical variables and the most optimal radiomic variables using random forests had a positive impact on the prediction and prognosis assessment of locoregional recurrences (LR) and distant metastases (DM) [27].

An alternative approach suggests the utilization of classification models that rely on distinct feature sets employing the random forest method. This research conducted a radiomic analysis on 85 primary tumors and 178 lymph nodes to distinguish between pathological complete response (pCR) and gross residual disease (GRD). To assess the classification performance of each feature set, random forest, and nested cross-validation methodologies were employed [28].

In a single imager magnetic resonance (MR) imaging study with a relatively large drug-naïve sample, random forest models based on cerebral radiomic features was able to distinguish attention deficit hyperactivity disorder (ADHD) patients from healthy controls with an



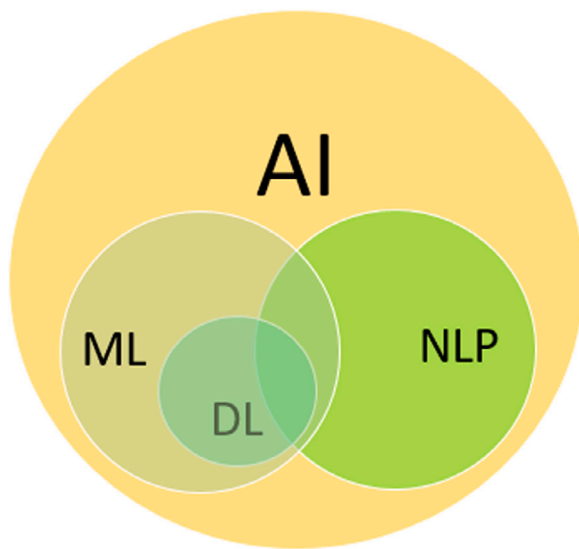


Fig. 9. NLP is a subfield of artificial intelligence that employs machine learning and deep learning approaches.

forest model emerged as the most effective predictor of mortality in this particular study [24].

The objective of the study conducted by Saeed et al. [31] aims to assess the biological properties of conditionally reprogrammed cells (CRCs) obtained from patients, with the intention of utilizing them to evaluate the effectiveness of various drugs. The researchers employed immunostaining and subsequent image analysis with Advanced Cell Classifier, a supervised machine learning algorithm called Random Forest, to quantitatively evaluate the phenotypic features of CRCs in this research.

In [32], the random forest is used in an open-source implementation called IntegratedMRF, which is used to integrate predictions of drug response from various genomic characterizations. It is worth mentioning that IntegratedMRF uses univariate or multivariate random forests that include various options for error estimation techniques. In this study, it was shown that multivariate random forests (MRF) perform better than existing approaches when drug responses are correlated. The IntegratedMRF package provides options for estimating regular random forest or MRF as a predictive modeling approach. A random forest model is generated for a single output response and MRF by default if there is more than one output response.

Another study focuses on the multivariate ensemble learning technique; MRF to increase the prediction accuracy and improve the importance ranking of variables by incorporating the interdependencies among various output responses. While the random forest model demonstrates proficiency in generating deterministic predictive models for individual drugs based on genetic profiling of cell lines, it overlooks the connections between different drug sensitivities during model development. Therefore, there is a need to investigate the extension of the random forest model using MRF, which incorporates the relationships among output sensitivities, as described by Haider et al. [33].

The research developed by Su et al. [34] proposes a method called random forests of interaction trees (RFIT), to estimate individualized treatment effects (ITEs) based on interaction trees. It should be noted that ITEs play a vital role in the advancement of precision medicine. This study demonstrated that the RFIT method outperforms the “separate regression” approach for estimating ITEs. And since the random forest is a ready-made method with high performance in predictive modeling, Su et al. [34] implemented random forest based on ITEs, which is different from the ordinary random forest of classification or regression trees.

Two studies explored the application of random forest models in understanding and predicting different aspects of prostate cancer. The first study focused on forecasting aggressive tendencies in prostate cancer using a classification model. DNA methylation alterations were used as input data, and a discovery cohort of 70 samples was divided into a training set (80% of samples) and a test set (20% of samples) through random partitioning. The model underwent training with 10,000 trees derived from the training set, resulting in a remarkable performance with a 95% AUC (Area Under the Curve) in the discovery cohort [35].

In another study, the prediction of prostate cancer mortality was conducted using random forest techniques. The authors emphasized the need for considering multiple variables and their interconnections to identify the most crucial factors for prediction. Supervised machine learning with Random Forest regression was employed to investigate intricate associations among various variables, including tumor features, race, social factors, and healthcare factors. The study examined 15 variables and their interactions, aiming to determine the relative significance of these factors in predicting prostate cancer-specific mortality [36].

Details about the application of the random forest algorithm in precision medicine can be found in [37–41] works. Additionally, Dai and LeBlanc [42] investigate gene-treatment interactions and gene-specific treatment effects on the relative risk scale using a case-only approach to trees and random forests.

**Support Vector Machine (SVM)** The support vector machine is a supervised machine learning model commonly employed for classifying data into multiple categories. The term “support vector” denotes the margin utilized by the algorithm to determine whether data belongs to a specific category or not. One of the key advantages of SVM is its ability to handle large datasets with numerous variables or dimensions. The versatility of SVM is evident in its application across various datasets, ranging from the identification of tissue and cell types based on genetic microarray expression data to the categorization of breast mammograms as having or lacking microcalcifications [43]. Due to its regularization and convex optimization benefits, SVM has become a highly favored classification algorithm, consistently demonstrating exceptional performance in a wide array of classification problems [44].

Within neuroradiology, one common challenge is distinguishing between post-treatment changes like radiation necrosis and pseudo-progression, and actual tumor progression or recurrence. There are only a limited number of studies that have utilized AI techniques to differentiate between post-treatment alterations and the growth of central nervous system (CNS) tumors. In a specific study involving 31 glioma patients who underwent surgery and chemotherapy, an SVM classifier was trained to diagnose pseudo-progression versus recurrence. The SVM classifier exhibited a sensitivity of 89.91%, specificity of 93.72%, and an AUC of 0.94, indicating its effectiveness in accurately identifying pseudo-progression [45].

In the context of dementia prognostic research, the systematic literature review (SLR) revealed that SVMs were widely utilized. Among the 37 selected studies and 38 proposed models, SVMs were employed in 30 studies, making them the most popular ML approach by a significant margin. This includes both traditional SVMs and their variations. Notably, all 30 studies implemented SVMs to predict the likelihood of mild cognitively impaired (MCI) patients developing Alzheimer's disease (AD) [46].

Another work that tests a precision medicine approach for AD treatment, using SVM analyses is [47]. The objective of this study is to evaluate the predictive capability of a baseline blood proteomic companion diagnostic in determining the response to a non-steroidal anti-inflammatory drug (NSAID) treatment. The original dataset was divided into five equally sized subsamples, with one subsample allocated for testing and the remaining four used for training. To predict the treatment response, an SVM model was created, employing the radial basis function kernel and implementing five-fold cross-validation. The

SVM model utilized a cost value of 100 and a gamma value of 0.001. The study findings reveal that the overall NSAID companion diagnosis accurately classified 89% of the subjects who were randomly assigned to the NSAID treatment group.

In [48], the purpose is to investigate how SVMs can be used to predict dementia and to confirm their effectiveness using statistical analysis. The proposed computational method is based on a new approach that uses an ensemble of SVMs for dementia classification, using MRI data and parameters from a mini-mental state examination (MMSE). Data are from the Open Access Series of Imaging Studies (OASIS-2) longitudinal collection of 150 subjects on 373 MRI data. In the present study, considering the total brain value with MMSE and clinical dementia ratio (CDR), the SVM approach produced an accuracy of almost 70%.

In the context of cancer prediction, the utilization of machine learning algorithms with gene expression data aids in identifying the correlation between genetic information and cancer, thereby promoting the advancement and implementation of precision medicine. In light of the inherent gene sequence, a technique known as oriented feature selection SVM (OFSSVM) was proposed by Shen et al. [49]. This novel classification approach combines fused lasso and elastic net as regularization for linear SVM, employing huberized hinge loss as the loss function. Experimental findings demonstrate that OFSSVM strikes a favorable balance between interpretability and classification accuracy, surpassing traditional methods in terms of comprehensive evaluation.

The research developed by Huang et al. [50] introduces a software platform, available as open-source, that enables the prediction of cancer drug response. This platform utilizes a highly flexible SVM algorithm in conjunction with a standard recursive feature elimination (RFE) approach. In this study, SVM models were constructed using gene expression and drug sensitivity profiles, specifically targeting seven commonly prescribed chemotherapeutic drugs for ovarian cancer treatment. The findings of this research are promising, as the models achieved an overall predictive accuracy exceeding 80% in the used dataset.

In a research conducted by Nanmaran et al. [51], the authors examined the impact of image fusion on an enhanced brain tumor classification model. It is important to note that image fusion combines the input images, resulting in fused images that contain more valuable information, making them more suitable for classification tasks. The utilization of high-quality fused images leads to improved classification outcomes compared to the use of individual input images. The SVM classifier achieved remarkable performance with a maximum accuracy of 96.8%, precision of 97.5%, recall of 95.12%, sensitivity of 97.43%, and an F1 score of 96.29%. These results surpass the performance of SVM, k-nearest neighbors (KNN), and decision tree classifiers when only magnetic resonance imaging (MRI) or single-photon emission computed tomography (SPECT) image features are provided as inputs. The proposed method is compared against existing approaches and yields satisfactory outcomes. This novel fusion-based cancer classification model holds great potential for more effective application in personalized medicine.

For further information about the use of the SVM algorithm in precision medicine research, papers [52–55] are recommended. On the other hand, a predictor based on the SVM algorithm can be found in [56].

**Decision tree** Decision-tree-based algorithms are a valuable class of algorithms, particularly suitable for datasets of moderate size. These algorithms utilize decision trees to classify data by repeatedly partitioning it based on the most informative biomarker. The biomarker with the highest “information gain” statistically is considered the most informative. Combining decision trees into ensembles, such as a random forest, significantly enhances their effectiveness. Boosting, a technique that assigns higher weights to challenging samples during training, can be applied to train these ensembles. Tree-based models are highly favored

due to their versatility, ease of training, and their ability to handle correlated or unnecessary features without overfitting. Consequently, they have gained wide popularity [57].

Artificial intelligence has been employed to swiftly predict patients at high risk, allowing for their prioritization and potentially reducing the mortality rate. A study conducted at Tongji Hospital in Wuhan, China, involved training a gradient-boosted decision tree model using electronic health records (EHRs) of 375 discharged patients, utilizing clinical measures as input features. The model achieved an impressive accuracy rate of 93%. By utilizing this model, physicians can promptly identify critical situations and take appropriate actions. Additionally, the model identified three essential clinical indicators: lactic dehydrogenase, lymphocyte count, and high sensitivity C-reactive protein [11].

In precision medicine, accurately identifying mutations during sequencing that are crucial for disease diagnosis and treatment poses a significant challenge. To address this, the present study introduces a novel approach, proposed by Do Nascimento et al. [58], which focuses on developing a decision tree algorithm that can be easily implemented by non-computer experts in clinical settings. This method aims to improve the average accuracy of current pathogenicity predictors by modeling a decision tree and discretizing attributes obtained from integrated databases. To validate the proposed method, its accuracy is evaluated and compared with 17 supervised machine learning algorithms and 4 classical pathogenicity predictors. The results demonstrate that the decision tree algorithm outperforms all other assessed variables, achieving an accuracy of 91% for true neutrals, 8% for false neutrals, 9% for false pathogens, and 92% for true pathogens.

Generally, precision medicine aims to determine the most suitable treatments for patients based on their specific characteristics. In line with this goal, Sysoev et al. [59] introduced a novel approach for identifying subgroups within categorical treatment scenarios. This method involves the construction of a decision tree that displays the probabilities associated with each treatment being the optimal choice for a particular group of patients. Additionally, the decision tree provides labels indicating the recommended treatments. Thus, a decision-maker can see the patient characteristics on which the treatment recommendation is based.

The objective of a study developed by Hendriks et al. [60] involves creating clinically interpretable, data-driven clinical decision trees (CDTs) to model guideline recommendations. To evaluate the proposed approach, the researchers employed the Dutch national breast cancer guideline. The findings from this research demonstrate that an interactive decision support application successfully integrated 60 CDTs, covering the entire guideline. Moreover, it was possible to classify 89% of the total data elements using existing classification and coding systems. It should be noted that these data elements were derived from pathology reports (49%), clinical reports (12%), radiology (27%), and multidisciplinary teams (12%).

Recently, novel approaches have been developed that aim to maximize the predicted clinical reward by employing decision trees to directly estimate individual treatment rules (ITRs). With the objective of maximizing rewards, a new reward function and decision tree algorithm was proposed by Doubleday et al. [61], recognizing the widespread use of decision trees in clinical practice owing to their straightforward interpretability. In this work, the researchers enhanced the effectiveness of a single-tree decision rule by employing an ensemble decision tree algorithm known as ITR random forests.

To explore the possibility of differentiating syndromes in patients with IgA nephropathy based on clinicopathological parameters, Gu et al. [62] proposed a method to infer patients’ traditional Chinese medicine (TCM) syndromes using a decision tree. In the present study, data were collected on the types of TCM syndromes, clinicopathological characteristics, and demographic information. Decision tree models based on classification and regression trees were then constructed to

distinguish between different syndrome types. These models were employed to classify TCM syndromes using objective variables, specifically the clinicopathological parameters of 370 IgA patients. The models were subsequently validated using a separate set of 94 patients. To investigate the impact of pathologic parameters on model accuracy, MEST scores<sup>1</sup> were included in the model. Despite both the models with and without pathological features achieving comparable accuracy in the training data, the model incorporating MEST scores exhibited superior performance and demonstrated a notable advantage during validation.

The objective of a study by Pei et al. [64] is to employ a decision tree method as a supportive system for swiftly and automatically identifying individuals who may have diabetes. In this particular investigation, the researchers introduced a decision tree-based classifier that utilized 9 easily attainable and non-invasive patient characteristics as predictive variables to detect potential diabetes cases from a database containing annual health checkup reports from a prominent Chinese hospital. The construction of the decision tree involved using a training dataset (N = 7305), while the model's evaluation was performed using a separate test dataset (N = 3131). The results demonstrated high accuracy, precision, recall, and an area under the receiver operating characteristic curve (AUC) value of 94.2%, 94.0%, 94.2%, and 94.8% respectively, for identifying potential diabetes cases. Additionally, the structure of the decision tree indicated that age held the utmost significance as a feature.

Additional materials exploring the implementation of decision trees in the healthcare field can be found in [65–67]. In a related study, Kasbekar et al. [68] utilized a decision tree to develop an evidence-based tool for predicting the risk of amputation in diabetic foot patients. On the other hand, Das et al. [69] introduced a sparse high-order interaction model with a rejection option (SHIMR) as an interpretable ML model for medical diagnosis. The authors of this study employed a decision tree with an extensive rule to explain the diagnosis to the patient, while SHIMR utilizes a weighted sum of concise rules.

*K-means* stands as one of the most commonly employed clustering algorithms, offering an efficient data partitioning solution for high-dimensional datasets. This algorithm is known for its simplicity and faster computation when compared to hierarchical clustering. Despite being an unsupervised learning technique in pattern recognition and machine learning, the *k-means* algorithm and its extensions are consistently affected by the initializations, specifically the predefined number of clusters. Proper initialization of centroids is crucial in the *K-means* algorithm, as inadequate initialization can result in suboptimal solutions and yield unsatisfactory outcomes [70–72].

A comprehensive analysis was conducted on a cohort of 8980 newly diagnosed diabetes patients from the Swedish All New Diabetics in Scania cohort, utilizing the *k-means* algorithm and hierarchical clustering. The clustering process incorporated six variables, namely anti-glutamate decarboxylase antibody, glycosylated hemoglobin, age at diagnosis, body mass index, as well as Homeostatic Model 2 estimates of  $\beta$ -cell function and insulin resistance. By linking these clusters with prospective patient records, including information on problem incidence and medication prescriptions, the study's findings were validated through the Scania Diabetes Registry (n=1466), newly diagnosed diabetics in Uppsala (n=844), and the Vaasa Diabetes Registry (n=3485). This research represents a significant advancement in the field of precision medicine for diabetes by integrating diagnostic

<sup>1</sup> The MEST score, a composite measure in the Oxford classification of IgA nephropathy (IgAN), encompasses four histologic components: mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S), and interstitial fibrosis/tubular atrophy (T). These individual elements combine to form the MEST score, and each component is independently correlated with renal outcome [63].

data and healthcare system information, contributing to more accurate and clinically relevant patient classification [21].

In an alternative research study, a fresh classification system was proposed by researchers using *k-means* clustering to assess the severity of bipolar disorder (BD). The objective was to provide physicians with a user-friendly, cluster-based approach that could assist in personalized medicine and shared decision-making. Through the study, 12 distinct profiles spanning five life domains were identified, allowing patients to be categorized into five clusters. These profiles encompassed various factors, such as the number of hospitalizations and suicide attempts, comorbid personality disorder, number of comorbid physical illnesses, body mass index, metabolic syndrome, cognitive functioning, permanent disability caused by BD, overall functioning, leisure-time functioning, and the patient's perception of functioning and mental health. The researchers found initial evidence supporting the validity of the classification system, as all profiles exhibited significant increases in severity across the clusters. Additionally, the more severe clusters necessitated more complex pharmacological treatments [73].

In their study, Horvat et al. [74] investigated the associations between genetic alterations and MRI features, including both qualitative and quantitative aspects, in primary rectal adenocarcinoma. They achieved this by employing consensus clustering of 34 computed texture features, utilizing the *K-means* algorithm, and considering the Euclidean distance as a similarity metric for the texture features. The resulting clusters were then examined to determine the prevalence of genetic mutations within each cluster.

A study carried out by Li et al. [75] introduces a novel method within the N-of-1-pathways framework using *k-Means* clustering of transcript fold change (FC) followed by gene set Enrichment (kMen) analysis. In this work, the authors demonstrated that kMen is resilient against overall transcriptome variability and supports both bidirectional response detection and unidirectional route responses (background noise). In two simulation simulations, kMen outperforms the other N-of-1-pathways approaches. Then, they applied kMen to identify patient-level transcriptional pathway response to antiretroviral therapy in 20 HIV-infected patients using a clinical case study on publicly available data.

*K-means* like several clustering methods are commonly used for patient stratification, an important aspect of tailoring personalized treatment for complex diseases. A method called entropy-based consensus clustering (ECC), introduced by Liu et al. [76], effectively addresses challenges related to high-throughput molecular data, such as noise, heterogeneity, dimensionality, and interpretability. ECC employs an entropy-based utility function to combine base partitions into a consensus partition that closely aligns with them. The authors also discovered an interesting equivalence between the entropy-based utility function and the distance function used in classical *K-means*, enabling an efficient solution to the complex utility maximization problem. To validate ECC's effectiveness, the study conducted experiments on 110 synthetic and 48 real datasets, including 35 cancer gene expression reference datasets and data from 13 cancer types, spanning four molecular data types sourced from The Cancer Genome Atlas.

In 2017, a study conducted by Niedzielski et al. [77] aimed to determine the inherent radiosensitivity of patients. The researchers employed *K-Means* clustering on esophageal expansion response to achieve this objective. Through the clustering process, three distinct patient radiosensitivity subgroups were identified: radiosensitive, radio-normal, and radioresistant. The analysis was performed around the 30th fraction of radiation therapy treatment using expansion-response data. Subsequently, this information was transformed into a dichotomous variable to identify the patients with high radiosensitivity. The obtained radiosensitivity information was then integrated into a toxicity prediction modeling method. The method utilized lasso penalized logistic regression within a repeated cross-validation procedure to improve the accuracy of esophagitis prediction models.

Survival and drug response are critical factors in cancer research that significantly influence a patient's prognosis. In an effort to address this, Malik et al. [78] introduced a novel framework for integrating multiple omics data in the later stages of breast cancer. This framework employed unsupervised regression and clustering techniques, specifically K-means clustering, to effectively categorize patients into responders and non-responders based on their predicted half-maximal inhibitory concentration (IC50) values, represented as Z-score. The IC50 threshold value, which distinguished the two groups, was recorded for each drug and subsequently utilized to evaluate and validate the predictive capability of the drug response model.

Meng et al. [79] conducted a comparative analysis of the GuidedSparseKmeans method, the sparse K-means method without outcome guidance, and the two-step clustering method. The evaluation was performed on simulation datasets as well as on gene expression profiles of breast cancer and Alzheimer's disease. For the gene expression profiles, the researchers utilized regular K-means with pre-selected genes using the Cox score. The clustering performance was assessed using the adjusted rand index (ARI), which measures the similarity between the clustering outcome and the true underlying clustering (ranging from 0 for random agreement to 1 for perfect agreement). Additionally, the researchers employed the Jaccard index to evaluate the similarity of the selected genes to the intrinsic genes. The Jaccard index calculates the ratio of the number of genes present in both genes sets to the number of genes present in either gene set (ranging from 0 for no intersection between the gene sets to 1 for identical gene sets).

Other works that use k-means algorithms are [80–83]. For instance, Zhu et al. [80] applies the k-means algorithm within a genomic framework to predict disease relapse and assess the response to specific chemotherapies. They employ the k-means classification algorithm to identify groups with either low or high gene expression linked to disease recurrence. Similarly, Li et al. [81] implement the k-means algorithm to examine the feasibility of the Swedish scheme for categorizing newly diagnosed Chinese adults with diabetes. By employing 6 clinical parameters, patients are classified into 5 subgroups using both k-means and Two-Step methods. In another investigation, Oldham et al. [82] employ k-means to analyze variables that indicate clinical risk in patients with exercise intolerance. Lastly, Elmer et al. [83] compare the predictive outcomes of k-means and group-based trajectory modeling (GBTM) using longitudinal data after cardiac arrest.

### 3.2.3 ANN model-based research attempts

Given their significance, robust capacity for self-learning, and intricate biological information processing abilities, ANN models have found extensive application in the field of diagnosing, prognosing, analyzing medical images, and treating significant diseases. A retrospective study conducted by [84] endeavors to develop a neural network model that can effectively predict the long-term survival rates of patients with gastric cancer before undergoing surgery, enabling an assessment of the tumor's condition prior to the operation.

Within the field of plastic surgery, plastic surgeons have the potential to use ANNs to anticipate postoperative complications arising from craniofacial surgery, drawing parallels with how ANNs have already been utilized to predict the recurrence of cardiovascular disorders [85].

At large, DL applications encompass a range of methodologies that harness sophisticated ANN architectures. These methodologies demonstrate the ability to model and learn anticipated correlations across diverse data types, holding immense potential to transform the landscape of omics research and precision medicine applications [86].

In 2019, a study was conducted by Vogiatzi et al. [87] to develop and validate an efficient ANN for predicting live birth based on parameters that exhibit a statistical correlation. The dataset utilized in this study consisted of 257 infertile couples who underwent a total of

426 IVF<sup>2</sup>/ICSI<sup>3</sup> cycles between 2010 and 2017. For each cycle, a comprehensive set of 118 parameters was collected. To ensure robustness, the data was subjected to cross-validation by randomly splitting it and repeating the training and testing procedure 10 times. The findings of the study demonstrated a stable performance of the constructed ANN, as indicated by the relatively low standard deviation of the performance indices observed between the training and test sets throughout the validation process. This consistency underscores the reliability of the ANN as a medical decision support tool. Furthermore, the validation of the system provided valuable insights into its clinical value, positioning it as a reliable approach for routine use in IVF units. Its user-friendly environment further enhances its practical applicability in real-world scenarios.

In an effort to accurately predict breast cancer (BC) using ANNs, the researchers focused on the calibration process by implementing the Hosmer–Lemeshow goodness-of-fit test. The resultant architecture of the network comprised three layers: an initial layer incorporating 36 input nodes, a hidden layer containing 1000 nodes, and an output layer consisting of 1 node. By conducting cross-validation on a dataset consisting of 62,219 records, the network was trained and its performance was compared to the predictive ability of eight radiologists. The comparison revealed that the radiologists achieved an AUC value of 0.939, whereas the ANN achieved an AUC value of 0.965, demonstrating the superior predictive capabilities of the ANN. Hence, the ANN serves as a dependable tool for facilitating diagnostic decisions [88].

According to the American Cancer Society, an estimated 3.3 million individuals are diagnosed with skin cancer annually. To assess the risk of developing non-melanoma skin cancer (NMSC), 13 specific patient attributes were utilized, including gender, age, body mass index (BMI), diabetic status, smoking status, emphysema, asthma, race, Hispanic ethnicity, hypertension, heart disease, vigorous exercise habits, and stroke history. These input parameters were adjusted to values ranging from 0 to 1 and used to construct an ANN model. The model consisted of an input layer with 13 nodes, two hidden layers with 13 nodes each, and an output node. The study employed a dataset comprising 462,630 examples, where 70% were allocated for training purposes and the remaining 30% for validation. The evaluation of the model yielded an AUC value of 0.81. The study concluded that the risk estimates provided by the model could potentially be enhanced by incorporating two critical factors: radiation exposure and personal medical history, which are key considerations in skin cancer research [89].

A research group published a paper on ANNs, in which they compared the ANNs' results to those from subjective evaluation, Logistic Regression (LR) models, and the Risk of Malignancy Index, and found that the ANNs had a 93.5% specificity and a 95.9% sensitivity. They then proposed and tested Simple Rules based on ultrasound features and found that using the Simple Rules as a triage test produced better results. When the Simple Rules produced an inconclusive result, they then conducted a second stage test using the subjective assessment of the ultrasound examiner, which proved to be the best second stage test, achieving a sensitivity of 91% and specificity of 93% [90].

One of the most popular immunosuppressive agents for preventing acute rejection after solid organ transplantation is tacrolimus. Over 70% of kidney transplant patients received this powerful medication in 2004. Tacrolimus, however, needs to be used carefully because of its low therapeutic index and substantial inter- and intra-individual variability in bioavailability. It is crucial to note that while drug-related toxicities like nephrotoxicity, neurotoxicity, and new-onset diabetes are more likely to occur when tacrolimus overdoses, acute rejection is more likely to occur when tacrolimus is underdosed. As a result, there is an increasing need to develop better techniques for figuring out the right dose in a clinic environment. The application of ANN in this study led to highly accurate predictions of the warfarin maintenance dose, more than 70% of patients in the low ( $\leq 21\text{mg/}$ ) and median dose (21–49 mg) subgroups have been correctly identified [91].

<sup>2</sup> In vitro fertilization.

<sup>3</sup> Intracytoplasmic sperm injection.

### 3.2.4 DL models-based research attempts

Deep learning is a subset of machine learning that utilizes artificial neural networks (ANNs) and draws inspiration from the complexity of the human cognitive system. By incorporating multiple hidden layers, deep learning architectures can capture intricate nonlinear relationships and express complex hypotheses [92]. This characteristic empowers DL to excel in various applications, such as automatic lesion detection, providing suggestions for differential diagnoses, generating preliminary radiology reports, and even serving as a personalized treatment recommendation system. Additionally, DL offers a valuable framework for advancing medical research across different domains.

A groundbreaking technique named DeepSurv was introduced in a study by Katzman et al. [93]. DeepSurv is a state-of-the-art approach to survival analysis, utilizing a deep neural network that builds upon the Cox proportional hazards model. This method effectively captures the complex connections between a patient's covariates and the effectiveness of treatment, allowing for the creation of individualized treatment recommendations.

In a separate study, Futoma et al. [94] elaborated a comparative analysis of various models' effectiveness in predicting hospital readmissions. This analysis was carried out utilizing an extensive EHR database. Moreover, DL approaches were employed by the researchers to tackle the five specific conditions outlined by the Centers for Medicare and Medicaid (CMS) as criteria for penalizing hospitals.

Moreover, DL has opened new avenues for customizing healthcare by offering remarkable capabilities and effectiveness in analyzing vast amounts of unstructured multimodal data stored in hospitals, cloud providers, and research institutions. DL systems have the potential to continuously evolve and produce outcomes in situations where human interpretation is challenging, leveraging the availability of data. Consequently, disease diagnoses can be expedited and enhanced, while uncertainty in the decision-making process can be minimized. However, it is important to acknowledge that the integration of data across different health informatics disciplines may pose a constraint for deep learning when it comes to supporting the advancement of precision medicine in the future [22].

In several medical interventions, many patients are saved by image-guided interventions. For this, image registration should be seen as the most challenging problem to solve. Because the latter is primordial to the image-guided intervention where e.g. precision medicine cannot be carried out without the correct utilization of image registration techniques. However, the ability to use deep neural networks with contemporary many-core GPUs (Graphics Processing Unit) has lately led to significant advancements in the field of machine learning. With registration being no exception, it has created a potential opportunity to contest many medical applications in more time- and cost-efficient methods [95].

An interesting study, where deep convolutional networks were used by Roth et al. [96] to classify medical images according to specific organs or bodily parts. They specifically used 4298 axial 2D CT scans to train their deep network on these five bodily parts: the neck, lungs, liver, pelvis, and legs. Their research produced an average AUC (area under the receiver-operating characteristic curve) value of 0.998 and an anatomy-specific classification error of 5.9%.

Deep neural networks (DNNs) have revolutionized various aspects of brain image analysis. In several brain image segmentation challenges, convolutional neural networks (CNNs) have played a significant role and achieved outstanding performance. In the brain tumor segmentation challenges of 2014 and 2015 (BRATS), as well as the longitudinal multiple sclerosis lesion segmentation challenge of 2015 and the ischemic stroke lesion segmentation challenge (ISLES) of the same year, leading teams achieved remarkable results by leveraging the power of CNNs. Additionally, CNNs were successfully employed in the MR brain image segmentation challenges of 2013 (MRBrains). It is important to note that while these techniques have primarily focused on brain MR imaging, deep learning-based analysis can also be extended to

other brain imaging modalities like computed tomography (CT) and ultrasound (US). This demonstrates the versatility and potential of deep learning approaches across various brain imaging techniques, facilitating advancements in accurate segmentation and analysis in different modalities [15].

In [97], a deep learning model is proposed for medical imaging. However, the reconstruction of 3D images from DICOM files typically requires strict supervision to ensure consistent metadata, such as slice thickness and image resolution. To overcome this challenge, a novel algorithm has been proposed that can reconstruct 3D images from medical images in the DICOM format with varying metadata and resize them to facilitate processing. This algorithm preserves annotations by projecting them onto the resized images, which enables the use of original annotations as ground truths for machine learning methods. Experimental results demonstrate that this method can handle diverse DICOM files and accurately project annotations onto the resized images. Such an approach is expected to have a significant impact on deep learning in personalized medicine, as it can enable more efficient and accurate processing of large 3D image data sizes.

Overall, when there are lots of samples available during the training phase, deep learning methods are quite successful. For instance, the ImageNet Large Scale Visual Recognition Challenge (ILSVRC) offered access to over a million annotated images. However, medical applications usually suffer from a scarcity of images, typically fewer than 1000. This limited availability of training samples poses a significant challenge in the application of deep learning to medical imaging, as it hinders the creation of deep models without encountering overfitting issues [19].

The research developed by Mohammedqasem et al. [98] introduces an encouraging novel framework for medical datasets characterized by a high proportion of missing values, leveraging deep learning optimization models. By combining the Data Missing Care (DMC) Framework with Grid-Search optimization, the study achieved model robustness and enhanced deep predictive training specifically tailored for COVID-19 patients. This proposed framework underwent testing on three medical datasets, including COVID-19 and cervical cancer, and demonstrated a remarkable enhancement in accuracy and efficiency. Evaluation metrics approached ideal values for all deep learning classifiers employed. The formula put forth in this study holds the potential to replace traditional formats in optimization, thereby enhancing the overall evaluation performance of classifying medical datasets with substantial missing values. Consequently, it emerges as a valuable tool for personalized medicine.

Transitioning to the domain of cancer detection, Danaee et al. [99] pioneered a deep learning methodology with a particular focus on identifying critical genes for diagnosing breast cancer. The procedural steps of their approach encompassed: (i) Employing a Stacked Denoising Autoencoder (SDAE) to convert high-dimensional gene expression profiles into more interpretable lower-dimensional data. (ii) Evaluating the extracted representation using benchmarking supervised learning algorithms, including ANN, SVM with linear and Radial Basis Function (RBF) kernel; (iii) Uncovering interactive genes that could function as potential clinical biomarkers for cancer diagnosis. Through an autoencoder-based deep learning model, this proposed approach extracts functional features of genes and identifies highly relevant genes that may play crucial roles and serve as clinical biomarkers for breast cancer diagnosis. The potential extension of this work to identify cross-cancer biomarkers from input gene expression would present a promising avenue for further exploration in this field [100].

Deep learning holds immense significance for the advancement of precision medicine, signifying its potential to revolutionize healthcare. For further exploration of the intersection between deep learning and precision medicine, we suggest referring to the following papers: [101–107].

**Convolutional Neural Network (CNN)** CNN, which is a subset of artificial neural networks and have demonstrated remarkable performance in numerous computer vision tasks, are increasingly being recognized and utilized in various fields, including the medical domain. By incorporating essential components such as convolution layers, pooling layers, and fully connected layers, CNNs are designed to efficiently and autonomously learn hierarchical spatial features through the iterative process of backpropagation [20].

CNN is inspired by the natural visual system of living beings. Deep CNNs have achieved state-of-the-art performance in the processing of text, speech, video, and images [17]. Recently, medical imaging has been proven to be greatly impacted by an adaption of CNN deep learning methods to enhance disease detection and image processing. More precisely, CNN deep learning methods have been successfully applied for medical image segmentation in several recent applications [108]. In a recent study by Grøvik et al. [109], the focal intention revolved around conceiving and evaluating a fully CNN to achieve an automatic detection and segmentation of brain metastases, utilizing multisequence MRI data as the network's input.

In a preliminary study, Huynh et al. [110] showcased the potential of CNNs in computer-aided diagnosis (CADx) by directly learning features from image data, eliminating the need for analytically extracted features. Given the challenges of training CNNs from scratch in medical imaging, such as limited sample sizes and variations in tumor presentations, transfer learning can be employed. By utilizing CNNs initially pre-trained for non-medical tasks, tumor information can be effectively extracted from medical images, thereby reducing the dependence on extensive datasets.

In a separate study focusing on histology, Mobadersany et al. [111] introduced a computational approach for extracting patient outcomes from digital pathology images. They demonstrated the effectiveness of survival convolutional neural networks (SCNNs) in integrating information from histological images and genomic biomarkers into a unified framework. This framework enables the prediction of outcomes over time and exhibits superior predictive accuracy compared to the current clinical approach for estimating overall survival in patients diagnosed with glioma. These findings underscore the growing importance of deep learning in precision medicine and highlight the expanding potential of computational histology analysis in future pathology practices

In the field of precision radiology, Oakden-Rayner et al. [112] conducted proof-of-concept trials with the aim of demonstrating the potential of regularly obtained cross-sectional computed tomography (CT) imaging as a comprehensive gauge of an individual's health and disease status, specifically in predicting their longevity. Using computational image analysis techniques, they showcased the effectiveness of deep learning with CNNs in the field of radiomics research. Their approach involved designing a CNN model to predict all-cause mortality, which necessitated certain modifications to accommodate the unique attributes of CT image data. This research underscores the considerable promise of computational image analysis when applied to routinely collected medical images, thus advancing the initiatives of precision medicine.

To identify ureteral stones in CT slice volumes, Långkvist et al. [113] developed a computer-aided detection (CADE) system. The method was evaluated on a substantial dataset comprising 465 patients. A CNN was employed directly on the high-resolution CT volumes, and annotations by an expert radiologist were used for evaluation. The system achieved a sensitivity of 100% with an average of 2.68 false positives per patient, demonstrating its effectiveness in identifying ureteral stones.

Given the rapid progress of CNN-based techniques, a study conducted in 2019 presented a swift and efficient 3D CNN-based computer-aided detection/diagnosis (CAD) system designed for breast cancer. Using a test set of 171 tumors, the system achieved sensitivities of 95%, 90%, 85%, and 80% with corresponding false positives per patient values of 14.03, 6.92, 4.91, and 3.62 (with six passes). While the

methods showed usability, reducing false positives while maintaining 100% sensitivity requires further work [114].

In 2018, an automated system for brain tumor segmentation was developed by Hussain et al. [115] utilizing a deep convolutional neural network (DCNN). The researchers incorporated advanced neural network optimization techniques such as batch normalization and dropout. Furthermore, they introduced a novel ILinear nexus architecture by integrating non-linear activation and inception module. This innovative approach demonstrated significant advancements in accurately segmenting brain tumors, showcasing the potential of deep learning in medical image analysis.

In another work concerning prostate cancer, conducted by Rampun et al. [116], a CAD system was put forth, accompanied by a collection of informative texture descriptors extracted from T2-weighted (T2 W) MRI images. The authors gathered 418 samples from 45 patients and employed a 9-fold cross-validation approach to thoroughly examine and assess the proposed approach. The experimental outcomes demonstrated that the method competes favorably with current CAD systems that utilize multimodal MRI, highlighting its effectiveness in prostate cancer detection and diagnosis.

In order to explore the impact of various factors on the performance of CNNs, such as CNN architectures, dataset properties, and transfer learning, a study conducted by Shin et al. [16] focused on thoraco abdominal lymph node detection. In their research, they conducted experiments utilizing five distinct CNN architectures that had previously demonstrated state-of-the-art performance in a variety of computer vision tasks.

For further information about how CNN is used in precision medicine for image segmentation, articles [117–121] are recommended. In addition, a deep learning-based hierarchical brain tumor classifier using CNN can be seen in [122].

**Recurrent neural network (RNN)** Recurrent neural networks are a specific type of ANN designed to handle temporal data. These networks have the ability to greatly enhance tasks involving natural language processing, speech recognition, and handwriting recognition.

The study led by Choi et al. [123] aimed to present a novel framework for predicting the diagnosis of heart failure (HF). Using a 12-month of observation, the RNN model yielded a remarkable area under the curve (AUC) value of 0.777, surpassing the AUCs of alternative supervised ML algorithms such as SVM, k-nearest neighbors (KNN), logistic regression, and multilayer perceptron (MLP). These research findings lead to the conclusion that RNN is the most efficient method for accurate HF diagnosis prediction.

In an intriguing exploration by Karpathy and Li. [18], a captivating study showcased a novel multimodal architecture of RNN designed to generate textual descriptions based on input images. The experimental results from this study revealed that the phrases generated by the RNN architecture surpassed the capabilities of the retrieval-based baseline and consistently produced meaningful qualitative predictions.

In a research study aimed at examining and predicting unplanned readmission to the intensive care unit (ICU), cutting-edge deep learning techniques were employed to leverage the sequential nature of the data. The researchers introduced an RNN architecture featuring Long Short-Term Memory (LSTM) layers to improve the predictive model by incorporating the temporal aspects of the data. Furthermore, the model integrated low-dimensional representations of medical concepts as inputs. To evaluate, test, and elucidate the proposed methods, a dataset comprising more than 40,000 patient records and 60,000 ICU admission records spanning a 10-year period was utilized. The results of this study indicate that the LSTM-based solution proposed can effectively capture the high volatility and unstable condition of ICU patients, which are crucial factors contributing to ICU readmission. By employing this data-driven approach, the associated costs and penalties can be minimized by preventing the inappropriate discharge or transfer of patients at a high risk of ICU readmission [124].

**Table 2**  
Compilation of publicly available datasets for precision medicine.

Reference	Description of the data set
[125]	Infrared Chemical Image of a Breast Cancer Tissue Microarray
[126]	CT scans of COVID-19 patients
[127]	Data for “Deep learning-based model for diagnosing Alzheimer’s disease and tauopathies”
[128]	Metabolic syndrome and risk of lung cancer: An analysis of Korean National Health Insurance Corporation database
[129]	Data set from “Absolute Treatment Effects for the Primary Outcome and All-cause Mortality in the Cardiovascular Outcome Trials of New Antidiabetic Drugs — A Meta-Analysis of Digitalized Individual Patient Data”

RNNs are designed to leverage sequential information, allowing them to process input data of varying lengths, such as speech and text. However, there are situations where the current output is influenced by both past and future inputs. To address this, Bi-directional Recurrent Neural Networks (BRNNs) have been developed and are commonly used. A notable example is the work conducted by Fergadis et al. [138], where they presented a deep learning system for the Document Triage Task. This task involves automated systems that receive a list of PubMed identifiers (PMIDs), which are biomedical abstracts, and provide relevance-ranked judgments for triage purposes. In their study, the authors described a hierarchical bi-directional attention-based RNN as a reusable sequence encoder architecture for document classification. The sequence encoder comprises two bi-directional RNNs with an attention mechanism that identifies and captures essential phrases, words, or sentences within a document. This mechanism is followed by a dense layer responsible for classification. The results demonstrated that the RNN model effectively captures contextual information from text without the need for annotations and regardless of the dataset’s tokenization options.

Mechanical ventilation (MV) is a sophisticated and essential treatment process used to treat seriously unwell patients. By generating forces and releasing reactive oxygen species, it affects acid–base balance and can potentially lead to prognostically significant biotrauma, negatively influencing outcomes. In this study, RNN modeling was assessed by Mamandipoor et al. [139] for its use in predicting the outcomes of patients on mechanical ventilation using conventional mechanical ventilation parameters. The outcome of this analysis revealed that among patients receiving mechanical ventilation and its subset admitted with respiratory diseases, the RNN-based model performed better than random forest and logistic regression.

Train-of-Four ratio (TOFR) monitoring is widely employed as a means to evaluate the level of muscular relaxation. However, it is essential to acknowledge that this standard method only provides static data. In a research conducted by Wang et al. [140], they employed deep learning methods based on RNN to predict real-time TOFR for cisatracurium. This was accomplished by incorporating temporal sequence data and static factors. To obtain precise and trustworthy patient-specific predictions, transfer learning was carried out by patient similarity, which has theoretical relevance for clinical research in precision medicine.

In a radiology study, Banerjee et al. [141] introduced a novel model known as the domain phrase attention-based hierarchical recurrent neural network (DPA-HNN). This innovative model effectively combines information related to pulmonary emboli (PE) by utilizing a comprehensive dataset comprising more than 7370 clinical thoracic computed tomography free-text radiology reports obtained from four prominent healthcare centers. The study’s findings highlight the potential of recurrent neural networks (RNNs) in automating the classification of imaging text reports, offering diverse applications such as prioritizing radiology patients, generating cohorts for clinical research,

**Table 3**  
Salient features of AI-based research attempts.

Research attempt	AI model	Usage of the benchmarking repository	Performance measure used
[130]	SVM KNN DT	Kaggle	Accuracy: 96.80% Sensitivity: 97.43% Precision: 97.50%
[131]	LR  SVM Linear  SVM Radial  KNN  NB  DT  RF	Syl-het Diabetes Hospital in Bangladesh	Accuracy: 89% F1 Score: 91% Recall: 91% Precision: 92% Accuracy: 90% F1 Score: 92% Recall: 91% Precision: 94%  Accuracy: 98% F1 Score: 98% Recall: 98% Precision: 98%  Accuracy: 98% F1 Score: 98% Recall: 98% Precision: 98%  Accuracy: 86% F1 Score: 88% Recall: 88% Precision: 89%  Accuracy: 97% F1 Score: 97% Recall: 97% Precision: 97%  Accuracy: 98% F1 Score: 98% Recall: 98% Precision: 98%
[132]	NN	The Cancer Genome Atlas	Accuracy: 94% AUC: 98%
[133]	Deep Learning	HAM10000	Accuracy: 94.4%
[134]	CNN	Physionet PCG dataset	Accuracy: 97% Precision: 94.4% Sensitivity: 94.6% Specificity: 94.6%
[135]	GAN/AE	Normal Controls (NCs) Xuanwu cohort	SSIM: 0.929 ± 0.003 PSNR: 31.04 ± 0.09 MSE: 0.0014 ± 0.0001
[136]	GAN/GNN	Genotype-Tissue Expression (GTEx) project (v8)	
[137]	Transformers	IBM Exploys Therapeutic dataset	MLM Accuracy: 67% PLOS F1 Score: 66%

- LR — Logistic Regression
- NB — Naive Bayes
- NN — Neural Network
- GAN — Generative Adversarial Network
- AE — Auto Encoder
- GNN — Graph Neural Network
- SSIM — Structural Similarity Index Measure
- PSNR — Peak Signal-to-Noise Ratio
- MSE — Mean Squared Error

screening eligibility for clinical trials, and evaluating the utilization of imaging.

For more details regarding the RNN and its algorithms in neural drug design and sensitivity prediction, refer to [142]. In addition, [143,

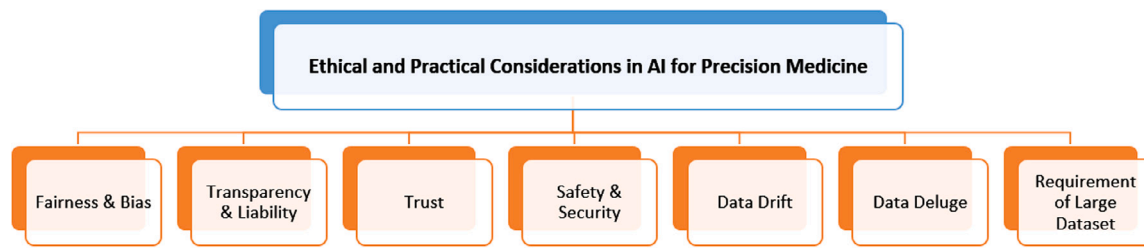


Fig. 10. Key ethical and practical considerations in applying AI to precision medicine.

Table 4  
Research attempts and application focus.

Research attempt	Application focused
[130]	Investigating the role of image fusion in brain tumor classification models based on ML algorithm
[131]	Early detection of type-2 diabetes mellitus
[132]	Survival prediction model for breast cancer patient
[133]	Skin lesion classification
[134]	Classification of anormal and abnormal phonocardiogram (PCG) signals
[135]	Identification of individual brain atrophy in AD and mild cognitive impairment (MCI)
[136]	Testing digital twin model in clinical scenarios, monitoring patient conditions, and detecting inflammatory cytokines related to the renin-angiotensin pathway, particularly in the context of SARS-Cov2 infection
[137]	Prediction of severe COVID-19 disease progression

[144] discuss deep models and architectures based on RNN algorithms for risk prediction.

#### 4 Public data sets for precision medicine

Table 2 presents a compilation of publicly available datasets that can be utilized for testing and evaluating artificial intelligence techniques in the realm of precision medicine. These datasets serve as valuable resources for new researchers to develop, test, and compare different machine learning methodologies in medical applications. The first dataset, introduced by Tang et al. [125], encompasses mid-infrared spectroscopy chemical images of a breast cancer tissue microarray. The second dataset, proposed by Schätz et al. [126], consists of CT scans of patients diagnosed with COVID-19. Moving on, [127] put forth the third dataset, which aims to develop a deep learning model for diagnosing Alzheimer’s disease and tauopathies. The fourth dataset, proposed by Sin et al. [128], seeks to analyze the risk of lung cancer based on the presence of metabolic syndrome, its components, and the count of metabolic syndrome components. Finally, the fifth dataset, proposed by Akbulut and Kuss. [129], contains five variables “OutcomeType” (with values “AllcauseMortality” or “PrimaryOutcome”), “Study” (denoting the respective cardiovascular outcome trial), “Treatment” (denoting the respective study treatment or placebo), “Event” (denoting if the respective has been observed (Event=1) or not (Event=0)), and “SurvivalTimeMonths” (denoting the respective time to the event or censoring in months). For further information about the data set, see their references.

#### 5 Discussion

The main objective of this study was to evaluate the effectiveness of various ML algorithms within the realm of precision medicine. Due to the substantial variability in clinical data and research parameters across studies, a meaningful comparison could only be made by establishing a common benchmark dataset and scope. The precision medicine field must advance cautiously, avoiding overselling, and

making sure that any claims are supported by substantial evidence. Therefore, we have chosen to present only some of the challenges related to the design of AI-based methods and their application to precision medicine.

- Data protection and privacy: Precision medicine places significant emphasis on each patient’s health data within the framework of big data and AI. The adoption of decentralized sensors and measurement devices has undoubtedly enhanced the regular gathering of personal health and environmental data. However, the challenge of safeguarding patient data from breaches has resulted in limited data accessibility. This limitation hampers model training and hinders the realization of its full potential.
- Standardization of data entry and storage: Recently, there has been a dramatic increase in the volume, velocity, and variety of data in the field of biomedical research. It is certain that by effectively managing data collection, storage, and standardization, the overall quality of medical data can be uniformly enhanced. However, failure to do so may lead to unforeseen errors that are difficult to detect or explain using human judgment.
- Necessity for new analytic tools and algorithms: The deeper challenge lies in the need to create systematic approaches for comprehending data effectively. This entails constructing models and algorithms that empower biomedical scientists and clinicians to optimize the utilization of various data types in diagnosing and predicting outcomes. Therefore, in order to adopt precision medicine, clinicians must possess advanced tools that enable them to propose and investigate potential treatments based on real-time analysis of patient data. The tools should cover complex elements, including the patient’s genetic makeup, surrounding environmental conditions, and existing health conditions, in accordance with established literature and care guidelines.
- Training and education of the different stakeholders: Physicians are under unprecedented stress as a result of the rapid evolution of AI in handling the exponential expansion of medical knowledge and learning new skill sets. Therefore, gains in precision medicine may be unrestricted if stakeholders adapt to these changes, healthcare providers shorten pathways that ease access to specialists and appropriate care, and organizations and payers support a cost-effective field.

The challenges outlined above underscore the critical importance of addressing ethical and practical considerations in the integration of AI in precision medicine, as illustrated in Fig. 10.

The benefits and drawbacks of various ML algorithms are outlined in Table 5. Moreover, the research attempts, benchmarking repositories, and performance measures associated with each AI model are detailed in Table 3 and Table 4, respectively. These tables provide a comprehensive overview of the diverse applications and performance evaluations of the ML models.

#### 6 Conclusion

In conclusion, the transition towards a data-driven healthcare system not only heralds profound implications for patients, clinicians, and

**Table 5**  
Benefits and drawbacks of different machine learning algorithms.

ML algorithm	Benefits	Drawbacks
Random forest	<ul style="list-style-type: none"> <li>– Enhances decision trees by mitigating overfitting and reducing variance, leading to improved accuracy.</li> <li>– Suitable for addressing classification and regression problems alike.</li> <li>– Demonstrates effectiveness with both categorical and continuous variables.</li> <li>– Automatically handles missing values without requiring manual intervention.</li> <li>– Exhibits greater resilience to noise compared to other approaches.</li> </ul>	<ul style="list-style-type: none"> <li>– More complex and computationally expensive compared to other algorithms.</li> <li>– Prioritizes variables or attributes with a wide range of possible values when estimating variable importance.</li> <li>– Prone to overfitting, which can occur more readily in this approach.</li> <li>– It is a difficult tradeoff between the training time and the increased number of trees.</li> <li>– It is like a black box algorithm, with very little control over what the model does.</li> </ul>
SVM	<ul style="list-style-type: none"> <li>– More effective in high-dimensional spaces.</li> <li>– Less risk of overfitting.</li> <li>– Applicable to both regression and classification problems.</li> <li>– Exhibits strong performance in classifying semi-structured or unstructured data, such as texts, images, and more.</li> <li>– Relatively memory efficient.</li> </ul>	<ul style="list-style-type: none"> <li>– Selecting a suitable Kernel solution function can pose challenges.</li> <li>– Training time can be prolonged when dealing with large datasets.</li> <li>– Performance may deteriorate in the presence of noisy data.</li> <li>– Understanding and interpreting the resulting model, weights, and variable impacts can be difficult.</li> <li>– The generic SVM approach is limited to binary classification unless extended to handle multiple classes.</li> </ul>
Decision tree	<ul style="list-style-type: none"> <li>– Highly intuitive and easy to understand and interpret.</li> <li>– Data preparation is easier.</li> <li>– Supports multiple data types, including numeric, nominal, and categorical.</li> <li>– Building a decision tree is unaffected by missing values in the data.</li> <li>– Applicable to both classification and regression tasks.</li> <li>– Capable of producing robust classifiers that can be validated using statistical tests.</li> </ul>	<ul style="list-style-type: none"> <li>– Overfitting i.e. it is a high variance algorithm. As a result, it can easily overfit and produce complex decision rules because it lacks an inherent mechanism to stop.</li> <li>– It is affected by noise i.e. a little bit of noise can make it unstable which leads to wrong predictions.</li> <li>– Susceptible to instability, i.e. small change in the data can result in significant alterations to the decision tree's structure.</li> <li>– Reliant on the order of attributes or variables, influencing the resulting tree.</li> <li>– Training the model often entails a longer time compared to other methods.</li> <li>– Limited performance in regression.</li> </ul>
K-Means	<ul style="list-style-type: none"> <li>– Relatively efficient and easy to implement.</li> <li>– Possesses a high degree of flexibility, allowing for effortless adaptation to changes. If any issues arise, modifying the cluster segment enables seamless adjustments to be made in the algorithm.</li> <li>– It has linear time complexity and it can be used with large datasets conveniently.</li> <li>– With a larger number of variables, k-means may be computationally faster than hierarchical clustering.</li> <li>– the outcomes are easily interpreted.</li> </ul>	<ul style="list-style-type: none"> <li>– The selection of the initial centroids is random.</li> <li>– Unable to handle noisy data or outliers.</li> <li>– Generates clusters with consistent sizes, even when the input data varies in size.</li> <li>– Performs poorly when applied to a global cluster.</li> <li>– Different initial partitions can lead to divergent final clusters.</li> </ul>
ANN	<ul style="list-style-type: none"> <li>– Relevant for both classification and regression scenarios.</li> <li>– It has a parallel processing capacity.</li> <li>– Capable of identifying intricate nonlinear relationships between dependent and independent variables.</li> <li>– It has fault tolerance i.e. corruption of one or more cells of ANN does not prevent it from generating output.</li> <li>– It can be executed in any application.</li> </ul>	<ul style="list-style-type: none"> <li>– There is no proper rule to determine the structure.</li> <li>– Training the network for a complex classification problem can be computationally demanding.</li> <li>– Pre-processing of predictor or independent variables is necessary.</li> <li>– It needed high processing time for big neural networks.</li> </ul>
CNN	<ul style="list-style-type: none"> <li>– Automatically identifies important features without the need for human supervision.</li> <li>– Demonstrates exceptional accuracy in image recognition and classification tasks.</li> <li>– Weight sharing is a notable advantage of CNNs.</li> </ul>	<ul style="list-style-type: none"> <li>– Sufficient training data is required for CNNs to achieve effectiveness.</li> <li>– The computational speed of CNNs tends to be slower due to operations like max pooling.</li> <li>– Absence of spatial invariance capability towards input data.</li> </ul>
RNN	<ul style="list-style-type: none"> <li>– It is the best example of Long Short Term Memory.</li> <li>– Its ability to retain the memory of previous inputs makes it particularly valuable for time series prediction.</li> <li>– It can be combined with convolutional layers to effectively capture pixel neighborhood information.</li> </ul>	<ul style="list-style-type: none"> <li>– The computational process of this neural network is time-consuming.</li> <li>– Training an RNN poses significant challenges and is often a difficult task.</li> <li>– Processing very long sequences using an activation function can become cumbersome and tedious.</li> </ul>

society at large but also marks a pivotal shift from a model of mass curative medicine to personalized care across all medical specialties. This transformative journey requires the capability to aggregate vast datasets from diverse sources and harness expertise in utilizing them, with the ultimate goal of achieving precision medicine in clinical practice through the integration of advanced AI methods.

While there exists a perspective that perceives AI's medical applications as a potential substitute for physicians, we emphasize that this should not lead to the supplanting of doctors. Rather, those doctors who embrace AI, including cutting-edge technologies such as augmented reality (AR) and virtual reality (VR), will supersede those who do not. The integration of AR and VR can enhance medical training, im-

prove surgical procedures, and provide immersive experiences for both clinicians and patients. To address concerns about autonomy, doctors must apply a diagnostic approach that involves engaging with patients to formulate hypotheses and possess the capacity to comprehend the underlying reasons behind proposed decisions, deviating from them if necessary. AI, when embraced by doctors, can fulfill its mission as a secure, effective, and proven aid to patient treatment and healthcare enhancement, notwithstanding the need to surmount numerous technical and regulatory obstacles to transform the AI-based approach to precision medicine from a vision into a tangible reality.

According to the analysis conducted, it is abundantly clear that research in the fields of AI and precision medicine is active, pointing towards a future where the convergence of these two poles, will lead to the design and optimization of diagnostic, therapeutic intervention, and prognostic pathways. This convergence holds promise for reducing the burden of certain cancers, cardiovascular diseases, and other ailments, consequently lowering healthcare costs. The endless scope of work in AI-based precision medicine, including the integration of AR and VR, extends far beyond our current conclusions, with the ever-evolving landscape of technology and medical discoveries suggesting unexplored horizons for AI application in personalized care.

While our systematic literature review provides valuable insights into the current landscape of AI-based precision medicine, it is essential to acknowledge certain limitations. The dynamic nature of both AI technologies and precision medicine may result in rapid advancements or changes not fully captured in our analysis. Additionally, the diversity in methodologies and reporting standards across the reviewed studies poses challenges in making direct comparisons. These limitations highlight the need for continuous updates and vigilance in tracking the evolving intersection of AI and precision medicine.

As we recognize that our current analysis is a step in a dynamic journey, we encourage researchers to continue these investigations to shape the future of precision medicine. Embracing the rapid evolution of technology, including the integration of AR and VR, holds the potential for notable advancements in personalized treatment design, disease prevention, and healthcare cost optimization. In summary, this research establishes a foundation, yet there is much more to be discovered and accomplished in the exciting field of AI-based precision medicine.

#### CRedit authorship contribution statement

**Wafae Abbaoui:** Writing – review & editing, Writing – original draft, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Sara Retal:** Writing – review & editing, Validation, Supervision, Investigation, Formal analysis, Conceptualization. **Brahim El Bhiri:** Writing – review & editing, Validation, Project administration, Investigation. **Nassim Kharmoum:** Writing – review & editing, Validation, Investigation. **Soumia Ziti:** Writing – review & editing, Validation, Project administration, Investigation.

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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