Machine learning approaches to improve disease management of patients with rheumatoid arthritis: review and future directions

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Structured abstract (201/200 words)
Introduction: Although the management of rheumatoid arthritis (RA) has improved in major way over the last decades, this disease still leads to an important burden for patients and society, and there is a need to develop more personalized approaches. Machine learning (ML) methods are more and more used in health-related studies and can be applied to different sorts of data (clinical, radiological, or "omics" data). Such approaches may improve the management of patients with RA.
Areas covered: In this paper, we propose a review regarding ML approaches applied to RA. A scoping literature search was performed in PubMed, in September 2021 using the following MeSH terms: "arthritis, rheumatoid" and "machine learning". Based on this search, the usefulness of ML methods for RA diagnosis, monitoring and prediction of response to treatment and RA outcomes, is discussed.
Expert opinion: ML methods have the potential to revolutionize RA-related research and improve disease management and patient care. Nevertheless, these models are not yet ready to contribute fully to rheumatologists' daily practice. Indeed, these methods raise technical, methodological, and ethical issues, which should be addressed properly to allow their implementation. Collaboration between data scientists, clinical researchers and physicians is therefore required to move this field forward.

Keywords (4-10): artificial intelligence, artificial neural networks, deep learning, diagnosis, machine learning, monitoring, prediction, random forests, rheumatoid arthritis, support vector machine.

Article highlights:

- Machine learning (ML) is a growing field in health-related research; in rheumatic diseases, ML is applied more and more to rheumatoid arthritis (RA).
- ML methods could provide interesting findings to improve disease management in RA, notably to enable an earlier diagnosis, to monitor disease activity and comorbidities, or to predict outcomes and treatment efficacy.
- However, the implementation of ML findings in current practice is limited by technical, methodological, and ethical issues. These limitations could be addressed by regulators and collaborations between clinicians and data scientists in the years to come.

1. Introduction

Rheumatoid arthritis (RA) is the most frequent autoimmune rheumatic disease, leading to extensive arthritis involving small joints, and ultimately to joint destruction (1). Early diagnosis, appropriate management of the disease and identification of factors associated with poor outcomes are therefore key issues to avoid functional impairment and deleterious consequences of the disease (2). During the last two decades, the development of targeted disease modifying anti-rheumatic drugs such as biologics, combined with paradigm shifts such as treat-to-target strategies, have contributed to the improvement of short- and long-term outcomes in RA (2,3). Nevertheless, this disease still represents an important burden for patients and for society in terms of costs, and there is a need to develop more personalized approaches, in order to enable patients to receive the treatment that will best suit their situation, as quickly as possible.

We are living in the era of Big Data (i.e., extremely large data sets that are accumulating rapidly, from various sources, and characterized by their Volume, Value, Veracity, Velocity and Variability). Novel statistical approaches are increasingly used to analyze these data (4). These methods specifically involve Artificial Intelligence (AI), i.e., the ability of a machine to mimic certain human abilities, such as calculation, learning or problem solving (5). AI includes several types of algorithms, of which the best known and most used to date are Machine Learning (ML) methods (6). These consist in models which, after “training” on a sample dataset, allow the development of predictions or decisions without being explicitly programmed to do so (7). ML includes different algorithms such as: artificial neural networks, deep learning, decision trees, support-vector machines, or Bayesian networks (8,9) (Table 1).

These methods have several applications in our daily lives, such as email filtering, speech recognition or computer vision, and are also applied to health research (10). Indeed, ML makes it possible to extract patterns within patient data and exploit these patterns to predict patient outcomes for improved clinical management (11). Even if applications of ML in rheumatology are currently hindered by the heterogeneity and complexity of rheumatic diseases, small cohort sizes and varying effect sizes of different molecular and clinical factors (12), ML studies in RA-related research are increasingly being published and provide promising potential answers to the unmet needs in this disease.

The aim of the present narrative review is therefore to describe the applications of ML methods in RA, for diagnosis, monitoring and prediction of response to treatments, and to explore future directions for AI research in RA (***Table 2***).

To ground our review, a scoping literature search in PubMed Medline was performed using the following MeSH terms: “arthritis, rheumatoid” and “machine learning” until September 2021. We will present the results of this literature review, combined with the authors’ opinion, in different sections below.

2. Usefulness for diagnosis

Detecting RA early is a key issue in rheumatology, given that the first months of the disease’s course determine the short- and long-term outcomes (2). ML may be particularly helpful to establish a diagnosis of RA, particularly in situations when other diagnoses, such as osteoarthritis or psoriatic arthritis are plausible.

2.1. Diagnosis based on Electronic Health Records

Clinical data sources are the most commonly used source of data in “big data” studies in the field of rheumatic and musculoskeletal diseases (RMDs), representing 47% of publications (13). Electronic Health Records (EHRs) are one of the most important sources of clinical data. Such data sources are interesting for health-related research, given that these data are collected routinely, and therefore reflect real-world care, which allows assessment of the benefits and risks of different medical treatments in real life conditions. Moreover, as these data are collected automatically, studies based on so called “real-world data” are faster to conduct than random controlled trials. As they gather data from thousands to millions of patients (for national healthcare EHRs) and are not formatted explicitly to provide precise clinical information (such as the severity of a given disease), ML methods may be helpful to identify patients with a given disease. Moreover, ML methods may be time-saving, given that these algorithms usually run in several seconds or minutes, whereas tens to hundreds of hours would be necessary for a physician to check the files of thousands of patients.

A first study in the Netherlands and Germany, based on Leiden and Erlangen EHRs, aimed to compare the ability of 6 different ML algorithms and a naïve word-matching algorithm to accurately identify patients with RA (14). A support vector

machine method performed well, with an area under the receiver operating characteristic curve (AUROC) of 0.98, and a positive predictive value (PPV) of 0.94. This means that almost all RA patients were identified by the algorithm (14). This method was able to identify 2,873 patients with RA from 23,300 patients in the EHR in less than 7 seconds. Another study by the same Dutch team compared the performance of a support vector machine model and manual chart reviewing in identifying RA patients; here again, the ML model performed well, with sensitivity=0.85, specificity=0.99, PPV=0.86, and negative predictive value=0.99 (15).

A Welsh study aimed to use data-driven methods to develop and validate a disease phenotyping algorithm for RA using primary care EHRs (16). In this study, data were available for 2,238,360 patients aged 16 or more, and of these, 20,667 patients were also linked in the secondary care rheumatology clinical system. Overall, 900 predictors (out of a total of 43,100 variables) in the primary care record were discovered more frequently in those with RA versus those without. Among these 900 predictors, 37 variables were selected to develop a decision tree model. The final algorithm identified 8 predictors related to diagnostic codes for RA, medication codes, such as those for disease modifying anti-rheumatic drugs (DMARDs), and absence of alternative diagnoses such as psoriatic arthritis (16). The proposed data-driven method performed as well as the expert clinical knowledge-based methods.

Thus, ML methods may be useful in accurately and quickly identifying patients with RA from EHRs, in order to consider them in clinical research studies.

2.2. Diagnosis based on biological samples

So-called “omics data” (proteomics, genomics, metabolomics, metagenomics and transcriptomics) are an important data source, and may be helpful for the diagnosis of rheumatic diseases (13). RA is characterized by the presence of auto-antibodies, such as rheumatoid factor (RF) and anti-citrullinated peptide auto-antibodies (ACPA) (17). However, RF can also be positive in other conditions, such as Sjögren’s syndrome, as well as in some infectious diseases, such as endocarditis (18,19). Conversely, around 20% of RA patients are seronegative for antibodies, which raises the question of the accuracy of the diagnosis – as other inflammatory rheumatic conditions may have clinical patterns similar to RA (20). For all these reasons,

identification of additional biomarkers is necessary to improve the diagnosis of RA and also other RMDs. A study identified a set of 12 chemokines (TGFα, EGF, CD40L, IFNγ, MIP-1β, eotaxin, TNFα, IL-1α, GRO, G-CSF, fractalkine) with levels significantly different between patients with RA, patients with osteoarthritis, and patients with no rheumatic condition (21). Based on this set, 2 artificial neural networks were developed, each diagnosing 100% of test set patients correctly. Another study revealed that serum proteins measured by multiple reaction monitoring significantly differed between patients with RA and those with psoriatic arthritis; the random forest model built for this purpose had an area under the curve (AUC) of 0.79 in a first phase and 0.85 in a second phase of validation, reflecting good performances to distinguish RA from psoriatic arthritis patients(22).

The analysis of genomics data with ML methods may be also helpful in RA diagnosis (23–30). Based on random forest models, a study identified a set of 9 mRNAs (CFL1, COTL1, ACTG1, PFN1, LCP1, LCK, HLA-E, FYN, and HLA-DRA) enabling to distinguish RA samples from healthy samples, with AUCs between 0.95 and 1.00 according to the models (31). Another study, based on a panel of micro-RNAs (miR-22-3p, miR-24-3p, miR-96-5p, miR-134-5p, miR-140-3p, and miR-627-5p), used ML methods to differentiate RA patients from systemic lupus erythematosus (SLE) patients and healthy subjects; these methods differentiated RA from control subjects in discovery (AUC=0.81) and validation cohorts (AUC=0.71), seronegative RA (AUC=0.84), RA patients in remission (AUC=0.85), and patients with SLE (AUC=0.80) versus controls (32). Random forests, k-nearest neighbors, support vector machine, naïve-Bayes and a tree-based method applied to a set of 16 genes (*TMOD1, POP7, SGCA, KLRD1, ALOX5, RAB22A, ANK3, PTPN3, GZMK, CLU, GZMB, FBXL7, TNFRSF4, IL32, MXRA7*, and *CD8A*) were used to distinguish RA from osteoarthritis, with a good accuracy for each of these methods (0.91 to 0.96) (33).

Genomics data have also been used to identify RA sub-types in patients based on histologic data from synovial tissue samples. The severity of RA symptoms is variable from patient to patient, and it has been reported that this may be the result of distinctive gene expression profiles (34,35). To investigate these findings, a study applied consensus clustering techniques to gene expression data in order to identify different synovial sub-types. 129 synovial samples were used to identify 20 histologic features, which were used to cluster the gene expression data from a subset of 45

samples 1000 times each into 2, 3, or 4 groups. The ML algorithm was able to identify 3 subgroups: a high inflammation subgroup characterized by extensive infiltration of leukocytes (AUC=0.88), a low inflammation subgroup characterized by enriched growth factor β, glycoprotein, and neuronal gene pathways (AUC=0.71), and a mixed subgroup (AUC=0.59) (36).

Thus, these studies indicate the value of ML methods to improve diagnosis based on -omics, and ultimately, to potentially enable the development of novel biological tests to diagnose RA (33,37,38). Moreover, apart for diagnosis, novel systems for disease phenotyping from mild to severe by means of and on terms identified by ML could be of utmost importance for basic research (disease pathophysiology), clinical management (e.g. patients at-risk for fast versus slow progression) and ultimately for deciding how tightly the control of the disease should be pursued.

2.3. Diagnosis based on imaging and image recognition

Numerous big data studies in RMDs are based on imaging data (13). Given that a single imaging exam compiles a huge amount of data, this field is particularly conducive to the use of ML methods (39,40).

In a study based on 1000 hand photographs from 280 patients with hand arthritis, ML algorithms were developed to classify those patients as having RA, osteoarthritis or psoriatic arthritis (41); the reference diagnosis was provided by a physician after a 45-minutes consultation. These algorithms were able to classify inflammatory arthritis with an accuracy of 96.8% and a precision of 97.2%.

It has been established that some imaging techniques, and particularly ultrasonography (US), depend on the examinator's experience (42,43). In this context, ML may aid diagnosis by automatically analyzing US images. A literature review identified 11 main ML methods currently used in ultrasound computer-aided diagnosis systems, and RA was one of the 4 rheumatic conditions for which these innovative systems were used the most, with an overall accuracy of more than 75% (44). Combining US images with clinical and biological information may also allow a faster and more accurate diagnosis of RA; a Japanese team used a pretrained convolutional neural network algorithm, AlexNet, to classify patients as RA or non-RA, based on US images and clinical settings (45). The accuracy of this method was of 90 to 98%, and agreement between this algorithm and clinical diagnosis was satisfactory (Cohen's kappa=0.79 to 0.87).

ML methods may also be applied to other imaging techniques. A study based on diffuse optical tomography of proximal interphalangeal joints showed that the use of a polynomial SVM classifier helped for diagnosing RA with a sensitivity of 100.0% and a specificity of 97.8% (46). Other studies developed automated algorithms to detect synovitis on magnetic resonance imaging (MRI), and compared results from the algorithm with the semi-quantitative RAMRIS scoring system (47,48). The correlation between automated algorithms and RAMRIS was good, with r=0.70 to 0.90. These results indicate the potential of ML methods applied to MRI for clinical applications in RA.

2.4. Diagnosis based on sensors

RA symptoms may fluctuate over the day, and clinical examination may be normal if the patient comes to the clinic after the flare has resolved. Sensors are devices such as accelerometer or thermal infrared cameras, that may be wearable, and that are more and more used to gather data from RA patients (50).

Such devices may be helpful for early RA diagnosis. Thermal imaging enables the detection of inflammation in a joint, by detecting variations of temperature in specific joints, and therefore may help in diagnosing RA at an early stage – in other terms, in the first weeks after symptoms onset, before the occurrence of structural damage. An Indian team proposed a ML method called modified multi-seeded region growing, to classify knees as having arthritis or not based on thermographs, with 91% accuracy, then to classify arthritis as RA or other kind of arthritis (51). This method allowed the diagnosis of RA at an early stage with 73% accuracy, and an AUC of 0.72.

Another team proposed using wearable sensor-enabled gloves, also based on thermal infrared camera technologies, to measure finger movements and then assess the presence of stiffness, which is a clinical sign of RA (52). However, the glove is a complex device, which is not easily implementable in patients' daily lives. Different ML methods may be applied to analyze data from sensors, such as k-nearest neighbors or decision trees (50).

3. Usefulness for monitoring

3.1. Monitoring the disease

After RA is diagnosed, proper monitoring of the disease is key. To this end, ML methods may provide interesting tools, to assess disease activity or structural progression on imaging and/or detect flares.

Wearable activity trackers continuously register a patient's movements and may therefore capture changes reflecting the evolution of symptoms or the occurrence of a flare. From the raw accelerometer data, the use of machine learning makes it possible to deduce the types of physical activity performed (53). Recent methodology allows to automatically apply a threshold to predictions by confidence levels, in addition to a logical filter to correct for infeasible sequences of activities. An example of the use of trackers in RA patients is to automatically correlate task performance with symptom level. In one study, patients were asked to perform a specific exercise several times a week without any supervision, such as standing up from a chair and sitting down five times. The activity tracker was used to remotely collect the time taken to perform the five repetitions. Varying the time taken to perform this exercise provided passive and automatic information about a patient's pain and stiffness (49). In the French Study ActConnect, activity tracker was used to detect flares in patients with RA or spondyloarthritis based on the variation in the number of steps taken during the day (54). Overall, data from 155 patients (1,339 weekly flare assessments and 224,952 hours of physical activity assessments) were analyzed using multiclass Bayesian methods, which performed well when compared with patient-reported flares (mean sensitivity 96%, mean specificity 97%, mean positive predictive value 91% and negative predictive value 99%). In another study, wrist and walking movements were tracked by a smartphone sensor to detect symptoms. This study used the gyroscope and the accelerometer of a smartphone to measure movement, with pattern recognition using unsupervised machine learning algorithms including Gaussian mixture model. A link was observed between objective measurements and the participant-reported information on pain, discomfort, and mobility (55).

Wearable devices may also be used to monitor a specific joint. A study proposed a wearable device to monitor patients' hand movements during a game aiming to help the rehabilitation of the wrist (56). Data were then computed and analyzed by an artificial neural network, which provided a score determining if the patient performed well or not. The results were also transferred to the patient's rheumatologist and physiotherapist, to guide her/him to improve rehabilitation.

Beyond the analysis of sensor data, the use of machine learning is also found with imaging. Indeed, a regular assessment of RA patients also involves repeated imaging, and particularly radiographs or ultrasonographs of the joints. However, the comparison of radiographs or MRI images may be time-consuming (57), and US exams may depend on the physician's experience. Thus, automatic analysis of the images may be helpful to monitor the disease in RA patients. The ML methods used to this end are mostly artificial neural networks (58,59), and especially deep learning (60,61).

3.2. Monitoring comorbidities

RA is associated with comorbidities, which are related to the disease itself (particularly, cardiovascular comorbidities) or may be to the consequences of RA treatments (e.g., DMARDs increase the risk of infection, and glucocorticoids the risk of osteoporosis) (62). Consequently, identifying and monitoring such complications is a cornerstone of global care in RA. ML methods may be helpful for this purpose.

Several studies used ML and especially deep learning algorithms to better characterize arterial tissue and the atherosclerotic plaque in RA patients (63). These methods analyze morphology and texture features extracted from US images, and can detect atherosclerotic changes in the arterial wall (64–66). Recently, Lekadir et al. used a deep learning model to characterize US images of the carotid into three classes: lipid, fibrous, and calcified plaques (67). Thus, ML methods are relevant to assess patients' cardiovascular risk, ensure their US follow-up, monitor the effectiveness of the management of cardiovascular risk factors, and thus may help to prevent the occurrence of cardiovascular events.

4. Usefulness for prediction

4.1. Prediction of response to treatment

The early initiation of a DMARD is key in the management of RA, but this early initiation does not guarantee an accurate response to the treatment, and intensification of therapy may be required to achieve remission. It is therefore crucial to predict patients' response to a given treatment, to adapt the management of RA proposing the best therapeutic option.

Methotrexate (MTX) is the first line DMARD for most RA patients (3). Thus, several studies aimed to predict insufficient clinical response to this conventional synthetic DMARD (csDMARD). A study based on the Dutch REACH cohort aimed to assess the performance of multiple regression and 3 ML methods (LASSO, random forest and XGBoost) to predict insufficient response to MTX at 3 months, (68). To this end, features related to RA pathogenesis (RF status, ACPA status, and Disease Activity Score 28 [DAS28] components) or to MTX metabolism (e.g., single nucleotide polymorphisms (SNPs) in ATP-binding cassette (ABC) transporter genes and erythrocyte folate) from 355 RA patients were computed to build the models. The 4 models performed well to predict insufficient response to MTX, with AUC=0.77 for multiple logistic regression, AUC=0.76 for LASSO, AUC=0.71 for random forest, and AUC=0.70 for XGBoost. Furthermore, the most important features were baseline DAS28 components. Another study aimed to analyze whole blood samples from RA patients at 2 time points (pretreatment and 4 weeks following initiation of MTX), to identify gene expression biomarkers of the MTX response (69). Data were analyzed by the means of a random forest model. Based on this method, a significant overrepresentation of type I interferon signaling pathway genes in non-responders at pretreatment (p-value < 0.0001) and at 4 weeks after treatment initiation (p-value < 0.0001) was identified. Finally, a study of the Swedish Rheumatology Quality Register aimed to predict the 1-year persistence to MTX initiated as the first ever csDMARD in new-onset RA (70); in this study, data on phenotype at diagnosis, demographics, medical disease history and medication use were analyzed by four different ML methods (LASSO, support vector machine, random forest and XGBoost). Among these methods, LASSO regression performed best (AUC=0.67) to predict the persistence to MTX. Finally, to predict the response to csDMARD (MTX, hydroxychloroquine, leflunomide and sulfasalazine) at 6 months, a study used random forest and support vector machine methods to identify predictors among serum biomarkers (71). This work demonstrated that baseline plasma concentrations of resolvin D4, 10S, 17S-dihydroxy-docosapentaenoic acid, 15R-Lipoxin (LX)A4 and n-3 docosapentaenoic-derived Maresin 1 were predictive of csDMARD responsiveness at 6 months.

The question of response prediction is also important for biologic DMARDs (bDMARDs). Artificial neural networks were used to predict response to infliximab and identified 9 clinical predictors of good to moderate response: ESR, tender joint

count, albumin level, monocyte level, red blood cell level, prednisone intakes, MTX intakes, HbA1c and previous bDMARD intakes (72). This method displayed good performances, with 92% accuracy, 96.7% sensitivity and 75% specificity. A random forest algorithm was used to predict the response at 6 months for adalimumab and etanercept, based on gene expression and/or DNA methylation profiling on peripheral blood mononuclear cells (PBMCs), monocytes, and CD4+ T cells prior to anti-TNF treatment (73). The models using differential genes reached an accuracy of 85.9% for adalimumab and 79.0% for etanercept, and models using differentially methylated positions reached an overall accuracy of 84.7% and 88% for adalimumab and etanercept, respectively. Thus, analyzing molecular signature in RA by the means of ML methods can predict patients' response to TNF-inhibitors, prior to treatment initiation. Another study, using a Gaussian process regression model to analyze data on patient demographics, baseline disease assessment, treatment, and single-nucleotide polymorphism array, showed this method performed well to predict response to TNF inhibitors (74); baseline DAS28 score could better predict response to therapy than genetic biomarkers, but genetic biomarkers improved the predictive accuracy of the model. Genes such as EPPK1 (75), HMMR, PRPF4B, EVI2A, RAB27A, MALT1, SNX6 and IFIH1 (76) were identified thanks to ML methods as potential predictors of the response to TNF inhibitors.

Thus, it appears that both clinical and -omics data are relevant predictors of response to biologics, and ML methods are interesting tools to identify them (77,78). However, these methods are not yet implemented in clinical practice.

4.2. Prediction of outcomes

Accurately predicting patients' outcomes in RA can allow to anticipate the potential complications of the disease and adapt the treatment strategy if needed.

ML methods may be useful to predict outcomes related to RA itself, such as flares or radiographic progression. Deep learning (79,80), k-nearest neighbors, naïve Bayes classifier, random forest (81) and support vector machine (82) methods were proposed to predict the evolution of disease activity and the occurrence of flares, based on patients' clinical and biological features. These methods all had good predictive performances, with AUC between 0.75 and 0.91, and identified predictors of flare such as change of bDMARDs, clinical disease activity (DAS28 ESR), disease duration, joint pain, inflammatory markers, age and duration of treatment (79–83).

Regarding radiographic progression, a study used a support vector machine classifier to identify SNPs predicting structural damage progression on X-ray (84). Overall, the ML model identified 85 SNPs combined with patients' clinical information as predictors of radiographic progression, with an AUC of 0.79; this model performed better than classical approaches such as GWAS (AUC=0.65) and SPOT (AUC=0.74).

ML methods may also help in predicting morbimortality related to RA. Random survival forests were used to identify predictors of mortality in two Spanish cohorts: age at diagnosis, median ESR, and number of hospital admissions were shown to display the best predictive capacity for this outcome, and the elaborated model had specificity and sensitivity of 0.79–0.80 and 0.43–0.48 after 1 year and 7 years of follow-up, respectively (85). An American cohort study aimed to identify predictors of serious infection risk in RA compared with non-inflammatory rheumatic diseases: the LASSO model revealed a major role of moderate and high disease activity (86). Finally, LASSO and random forests were used to explore the risk factors for osteopenia or osteoporosis in RA patients (87). These models identified higher serum 25-hydroxyvitamin D3 level and using tumor necrosis factor inhibitor in the last year as protective factors, whereas aging, lower body mass index, and increased serum uric acid were risk factors for bone loss.

5. Limitations of machine learning and future directions

5.1 – Limitations of machine learning methods

Although promising, ML methods have several limitations which is slowing down their implementation in daily practice.

As ML methods used to date are mostly "supervised", large datasets are needed to train the models adequately. Additionally, the accuracy of these data must be guaranteed, as poor quality data could lead to erroneous results and therefore, to erroneous conclusions; nevertheless, implementing data quality control can be time consuming, expensive, and laborious (88). Moreover, standardization of data (especially imaging data) acquisition is still challenging.

A model based on ML methods is only able to answer a specific question based on a given dataset, but is currently unable to solve a multitude of different problems. Human expertise and intervention are therefore still required to build, train and validate ML models. Furthermore, most models do not pass external validation when applied to other datasets. Moreover, most studies focus on the "performances"

of the models, but do not consider or discuss the clinical relevance of their findings. This explains why, even though the number of publications related to ML is increasing, only a few models are implemented in daily practice.

In this review, we presented some models which achieve a performance of 1 or 100% in terms of AUC, accuracy or precision for example. This may indicate either that the model is perfect and classifies groups without error, or that the model is overloaded and may lead to poor implementation of cross-validation strategies (11).

ML methods are complex, and the process leading to the findings is often unclear: this “black box” phenomenon constitutes a scientific and ethical issue, given that results from medical research have consequences on patients’ health and lives. In this context, it seems crucial to be able to explain and justify the decisions taken by the machine.

This naturally leads to the question of the integration and real-world use of ML methods (89). Indeed, as with any new technology, this requires an initial transitional period for professionals to get used to it. Conversely, the lack of understanding, coupled with a certain degree of complacency which may appear, can lead to an over-reliance on ML for decision making. These two aspects mandate to clearly define prerogatives and clinical best practices when using ML, and AI systems more generally in clinical situations. Indeed, the efficiency and accuracy of ML methods do not preclude the involvement of a human healthcare professional: this “human guarantee” is even mandatory by law in some countries (90).

Another ethical issue raised by ML is the consequence of such methods on a patient’s daily life. Indeed, care should be taken to ensure that patients identified by these new technologies as being at greater risk of a poor prognosis do not suffer deleterious consequences, particularly in economic terms (for example, by paying higher insurance costs). The guarantee of data anonymity and medical confidentiality is therefore crucial.

5.2 – Future directions

The limitations mentioned above should not be seen as unsolvable problems. On the contrary, they pave the way for directions to be taken in machine learning research. Thus, to enable the creation of large databases while ensuring quality control of these data, data collection methodology should be standardized; moreover, standardization could facilitate research results to be interoperable and reliable. A

possibility would be using existing core outcome measurement sets, as proposed for example by the OMERACT (91).

To limit human intervention in the building, training and validation of ML algorithms (for time-sparing purposes) as much as possible, the development of so called “evolutionary algorithms” might help designing models, in order to find the optimum parameters for the models automatically (92).

Furthermore, after the elaboration of a ML model, validation studies should be performed, on the one hand, to test the reproducibility of the results on other datasets, and on the other hand, to assess the clinical relevance of the findings. Thus, collaboration between data scientists, health researchers and physicians is key to implement ML tools in rheumatology practice; this point has been raised in the recent EULAR points to consider for the use of big data and AI in rheumatic diseases (93). To address these different points, a research agenda was proposed by EULAR, with several working points related to data collection, data analyses, training, interpretation, and implementation of findings (93). The execution of this research agenda is ongoing.

Extending and standardizing the use of ML methods will lead to ever more new and exciting applications in rheumatology. For instance, voice analysis has shown its usefulness in the monitoring of patients with multiple sclerosis, since voice patterns are affected during flares (94). Similarly, changes in the larynx can occur with disease progression in RA patients. Thus, vocal biomarker identification and tracking is being developed as it may be useful for patient monitoring (95). ML applied to voice represents a cost effective and efficient way to help monitor certain symptoms of RA patients.

Another potential field is the monitoring and analysis of patient experience using the enormous amounts of data generated on social media platforms. This type of analysis has already been conducted to investigate the perception of DMARD treatments for RA (96). The use of social media, though still in its infancy regarding its use in rheumatology, represents a challenging yet promising endeavour, which may complement traditional approaches, particularly as concerns patient safety and experience (97).

6. Conclusion

ML methods are numerous and diversified, and lead to applications in health in general, with promising though not yet fully implementable findings in RA management ***(Table 2)***. ML models may be used in the diagnosis of RA, based on clinical, radiological and -omics data. These methods may also be applied in the monitoring of RA and its associated comorbidities. Finally, ML algorithms may also help in the prediction of the response to treatment, and of short- and long-term outcomes.

However, the implementation of these methods in rheumatologists' daily practice is still an issue, for technical, methodological, and ethical reasons. These limitations should encourage clinical researchers in the field of RA to standardize their practices, and strengthen collaboration between data scientists, clinical researchers, and physicians to develop relevant tools for the management of RA.

7. Expert opinion

Artificial intelligence, and particularly ML, is a rapidly growing field in medical research (10,12). ML methods are extremely diverse, each with potentially interesting properties, such as recognition, classification, clustering, or prediction (11). This explains the growing interest shown by rheumatologists and researchers, as these methods have the potential to impact RA management, including shifting or extending the scope and roles of all those involved in patient care – from nurses to the patients themselves. The use of ML could augment current practice to provide more personalized care or assist in managing situations outside of the usual context of care while awaiting physicians' decisions.

As discussed above, several models have been developed, based on diverse data sources, to enable an earlier and more accurate disease diagnosis (14-49); as it has been demonstrated that there is a window of opportunity in RA, and that the first months of the disease are crucial for disease prognosis (98), using ML methods may result in sooner treatment initiation and therefore, faster disease activity control, and better long-term outcomes for the patient (99). ML methods may also help monitoring the disease (50-64), and thus detect flares faster, which could also result in quicker treatment adjustment and thus, in achieving remission again. Disease activity control is indeed key in RA management, since chronic inflammation of the joints results in pain, joint destruction, and functional impairment, which impact patients' daily lives, and particularly, their ability to work (100). Achieving remission as fast as possible,

with the help of ML methods, could therefore help reduce the economic burden of RA on society (101).

Furthermore, the prediction ability of ML methods could which treatment patients have the best response to, and therefore help find the best therapeutic approach for each patient (65-84). It has been established that some patients with more severe forms do not respond to the first lines of conventional or biological treatments recommended by the learned societies (3); it is therefore essential to identify these patients as soon as possible, in order to offer them an adapted therapeutic strategy and to improve their short and long-term prognosis. Consequently, identifying new predictive factors could impact treatment management and therefore, treatment guidelines in RA.

Although promising, implementation of ML methods in routine practice is not feasible presently, for technical, methodological, and ethical reasons.

Technical issues are related to the fact that huge amounts of validated data are required to properly train “supervised” ML models – which represent most ML methods used nowadays (88). Indeed, depending on the physician or research team, disease parameters are not assessed in the same way (e.g., disease activity can be assessed in 28 or 44 joints, or using erythrocyte sedimentation rate or C reactive protein), which results in heterogeneous data. A crucial and time consuming data management process is therefore required to homogenize the data, and check if the data are adequately computed in the database. A potential solution would be to standardize the way data are computed by the means of recommendations for good research practice (91,93), or to develop validated “equivalence” scales to homogenize data collected in different ways for a same disease parameter.

Methodological issues are mostly related to the fact that, although providing interesting results on specific datasets, only a few ML models are applicable to other datasets (88). As a matter of fact, most ML models presented previously have good predictive performances, but this could reflect “overfitting” of the models to the dataset they were trained on. Additional validation studies, not focusing on “technical” performances of the models but rather on their clinical relevance, are therefore required. Consequently, to move this field forward, a strong collaboration between ML experts and RA experts is needed (93).

The ethical issues raised by ML in RA research are linked to the so-called “black box” phenomenon: in other terms, the mechanisms leading from an input to an output

are unclear for most ML algorithms (102). Not being able to explain results that will have consequences on the management and therefore the health of patients is a major concern. A better understanding of the theoretical aspects of machine learning algorithms is therefore fundamental in order to have full confidence in these methods. Another ethical question that arises is the consequences of advances in ML on patients' everyday lives (103). Indeed, patients could suffer deleterious consequences if their health information were to be communicated to their insurance companies or their employers. The guarantee of data anonymity and medical confidentiality is therefore more important than ever. In this perspective, the General Data Protection Regulation, which is in place in Europe (104), should not be perceived as an obstacle to research, but as a way to ensure the confidentiality of patients' data to avoid deleterious consequences on their daily lives.

Future research in the field of machine learning should therefore address all these issues, with a view to implementing these methods in current practice. A research agenda was elaborated by the EULAR task force on Big Data and Artificial Intelligence use in RMDs, with several working points related to data collection, data analyses, training, interpretation, and implementation of findings (93). The execution of this research agenda is ongoing.

Future efforts should be inspired by the evolutions of ML in other fields, especially other medical areas. Fields dealing with easily digitizable data or at the very least data which is easily handled by computers (in terms of processing) are of particular interest in this regard. In cardiology and radiology for instance, ML projects are numerous (105,106). Such projects could provide interesting starting points to address some of the concerns that have been raised.

Given its potential, ML is part of the future of medical research, and particularly in RA-related research. Nevertheless, given the current limitations, it is clearly not the only way, and more classical basic and clinical approaches are still relevant to improve the management of the disease. In the years to come, we believe that progress will be made at least regarding the technical and methodological limitations of ML, which will certainly help to implement these methods, and ultimately improve the management of RA patients.

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Table 1: types of machine learning algorithms

Type of learning	Definition	Examples of algorithms	Examples of application
Supervised learning	The algorithm maps an input to an output, based on example input-output pairs (107).	Logistic regression, Bayesian networks, random forests, support vector machine, artificial neural networks, deep learning, LASSO, k-nearest neighbors, XGBoost	Object recognition in computer vision (108), vocal recognition (Siri…)
Unsupervised learning	The algorithm is not provided with any pre-assigned labels or scores for the training data and must therefore first self-discover any naturally occurring patterns in that training data set.(109)	Hierarchical clustering, k-means clustering, principal component analysis, deep learning	Phenotypic stratification of cardiac risk (110), personalized movie propositions on Netflix
Weak supervision learning	This technique uses models based on new generated data which can be incomplete, inexact, or inaccurate. They typically use programs to de-noise or predictively label data (111).	Transductive support vector machines, convolutional neural networks,	Snorkel (112), the BREXIT tweet classifier, Image recognition
Transfer learning	This focuses on storing the knowledge gained while solving one problem and applying it to a different but related problem (113).	Markov logic networks, Bayesian networks	Cancer subtype discovery (114), medical imaging, spam filtering
Semi-supervised learning	This type of learning combines a small amount of labeled data with a large amount of unlabeled data during training (115)	Semi-supervised clustering, semi-supervised support vector machine	Analysis of urban flow (116)
Reinforcement learning	It consists, for the machine, in learning the actions to take, from experiments, in order to optimize a quantitative reward over time (117).	Monte Carlo, Q-learning, State–action–reward–state–action (SARSA)	Gaming (AlphaGo Zero) (118)

Table 2: summary of data sources and machine learning methods used in rheumatoid arthritis for diagnosis, monitoring and prediction

Application	Data source	Machine learning methods used
Diagnosis	Electronic Health Records	SVM
	Omics	ANN, RF, k-NN, SVN, naive Bayes, consensus clustering
	Imaging	CNN, SVM
	Sensors	Modified multi-seeded region growing, k-NN, decision trees
Monitoring	Sensors	Bayesian methods, ANN
	Imaging	ANN, deep learning
Prediction	Clinical data (cohort or register)	LASSO, RF, ANN, SVM, XGBoost
	Omics	RF
	Clinical and omics data combined	Deep learning, k-NN, naïve Bayes, RF, SVM

Footnote: ANN: artificial neural network; CNN: convolutional neural network; n-NN: k-nearest neighbors; LASSO: Least Absolute Shrinkage and Selection Operator; RF: random forests; SVM: support vector machine