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Artificial intelligence and laboratory data in rheumatic diseases

Paola Galozzi [a,*], Daniela Basso [a,b], Mario Plebani [a,b], Andrea Padoan [a,b]

[a] Department of Medicine-DIMED, University of Padova, Padova, Italy
[b] Laboratory Medicine Unit, University Hospital of Padova, Padova, Italy

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ABSTRACT

Artificial intelligence (AI)-based medical technologies are rapidly evolving into actionable solutions for clinical practice. Machine learning (ML) algorithms can process increasing amounts of laboratory data such as gene expression immunophenotyping data and biomarkers. In recent years, the analysis of ML has become particularly useful for the study of complex chronic diseases, such as rheumatic diseases, heterogenous conditions with multiple triggers. Numerous studies have used ML to classify patients and improve diagnosis, to stratify the risk and determine disease subtypes, as well as to discover biomarkers and gene signatures.

This review aims to provide examples of ML models for specific rheumatic diseases using laboratory data and some insights into relevant strengths and limitations. A better understanding and future application of these analytical strategies could facilitate the development of precision medicine for rheumatic patients.

1. Introduction

Laboratory Medicine is a discipline of medical sciences that deals with the analyses of body fluids, through the numerous existing laboratory investigations of biological samples. Despite the role of laboratory medicine in clinical decision making has been now widely and well recognized, less attention is sometimes paid to the importance of test results in the everyday human life. Indeed, laboratory medicine provides essential elements for subject's health, often precociously with respect to the onset of symptoms, enabling risk stratification and offering the basis for personalized medicine [1]. Laboratory investigations play an increasingly fundamental role in all branches of medicine, from oncology to chronic disorders, like rheumatic diseases.

Rheumatic diseases (RD) encompass a wide spectrum of heterogeneous disorders that can involve not only the joints and the musculoskeletal system, but also internal organs and other tissues. The diseases can be mainly divided into autoimmune and autoinflammatory disorders. Rheumatic autoimmune diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren's syndrome, psoriatic arthritis (PsA) and the systemic vasculitis, are chronic inflammatory disorders with multi-organ involvement. Complex interactions between a multitude of environmental and genetic factors affect disease development and progression [2]. Autoinflammatory diseases (SAIDs) are a group of disorders caused by dysregulation of the innate immune system resulting in excess pro-inflammatory cytokine secretion [3]. The clinical picture of SAIDs is extremely wide, ranging from recurrent and self-limiting fever episodes to chronic and persistent inflammatory disease course. SAIDs may exhibit multifactorial or Mendelian (recessive or dominant) inheritance [4]. The very fast development of validated assays using innovative technologies, such as massive sequencing, has made it possible to focus on many different genes simultaneously. In addition to clinical anamnestic clues, this comprehensive approach can effectively aid to fulfil the diagnosis of complex and/or heterogeneous diseases. Further, new technologies for proteomics, metagenomics, and metabolomics are uncovering new aspects of these diseases at a relatively fast rate. In the last decades, these technic advancements, in parallel with knowledge improvements of the pathophysiology of disease, have postulated a shift in the role of laboratory medicine towards predictive medicine and personalized health monitoring [5]. In future years, the convergence of artificial intelligence (AI), new technologies,

Abbreviations: AI, artificial intelligence; AUC, area under curve; CSNN, cost-sensitive neural network; CV, cardiovascular; GLM, generalized linear model; K-NN, k-nearest neighbors; LR, linear regression; ML, machine learning; NETS, neutrophil extracellular traps; OA, osteoarthritis; PBMCs, peripheral blood mononuclear cells; PLS-DA, partial least squares discriminant analysis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RD, rheumatic diseases; RF, random forest; RGIFE, rank guided iterative feature elimination; SAID, systemic autoinflammatory disease; SLE, systemic lupus erythematosus; SNP, single-nucleotide polymorphism; SVM, support vector machine.

* Corresponding author at: Laboratory Medicine Unit, Department of Medicine - DIMED, University of Padova Via Giustiniani 2, 35128 Padova Italy.
E-mail address: paola.galozzi@unipd.it (P. Galozzi).

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big data and "-omics" sciences could lead to solve the most difficult challenges facing precision medicine for rare diseases, determining also genomic determinants, avoiding patients' diagnostic/therapeutic odysseys [6].

In 2020, the European Alliance of Associations for Rheumatology (EULAR) published ten recommendations to guide the collection, analysis and use of big data in rheumatic and musculoskeletal disorders [7]. The points to consider cover aspects of data sources and data collection, privacy by design, data platforms, data sharing and data analyses, in particular through artificial intelligence and machine learning. Indeed, combined clinical and omics data have limited utility without methods for their valuable interpretation. Artificial intelligence and machine learning (ML) techniques have the capacity to identify clinically relevant patterns amongst an abundance of information, fulfilling unmet needs.

The AI and ML algorithms infer patterns from diverse clinical data types, including laboratory test results, patient symptoms or magnetic resonance imaging. The output of ML algorithms is the construction and application of a predictive model for classification, regression or clustering. In supervised learning, algorithms as are trained to recognise a pattern associated with a specific label becoming skilled at assigning this label to unseen data. Unsupervised learning algorithms instead attempts to find patterns within unlabelled data, for example by identifying clusters based upon the similarity. ML types and workflow are well reviewed elsewhere [8,9]. Successful ML requires robust and sufficiently abundant data to create a robust and generalisable model that can learn. Although the integration of data science and ML in rheumatology is at a nascent stage, ML has been applied to various data from clinical records to laboratory results. AI-based approached for RD included the analyse medical images, subtyping of patient cohorts based on medical notes, predict drug response and disease activity based on patient symptoms [10]. Recently, the importance of AI for automated image recognition and subtle patterns identification for diagnose and monitor RD progression in routine clinical practice has been emphasized by some studies [11–12]. In this review, instead, we focus on ML-driven analysis on laboratory data only, derived from sequencing analysis, transcriptomics and proteomics experiments, flow cytometry assays and haematology tests. In this way, we address the integration of AI and laboratory medicine to improve rheumatic patient identification, risk stratification, and personalized treatment.

2. Methods

Relevant original papers including "machine learning" or "artificial intelligence" and rheumatic diseases' names as search terms are identified through database searching. The literature search was performed online using MEDLINE and completed in January 2023.

Original studies that applied ML methods to laboratory data obtained from rheumatic diseases patients were included. Review papers, studies not written in English or not peer reviewed were excluded. AI- and ML-based studies retained in this review were further appraised in terms of reliability according to robustness of the methods used. The explanation of features generation prior model training, the choice of parameters, the reporting of databases and packages used, and the use of reliable approaches to deal with potential over-fitting has been checked.

3. AI applications in rheumatic diseases

In RD, AI has emerged as a promising tool in several aspects, from the ability to support decision-making to improve the quality of patients care [13]. In the last decades, attempt has been made to integrate ML in laboratory medicine analysis to stratify patient and improve diagnosis, to classify risk and determine disease subtypes, to enhance the precision care, to discover biomarkers and gene signature [14,15].

Of 746 papers identified in the literature search, 241 duplicates were removed, 122 records were excluded using the criteria described above and 343 were excluded because they did not use laboratory data in ML models (Fig. 1). Forty studies were included in this review [16–55] and their major characteristics are reported in Table 1. ML and AI are most commonly applied to autoimmune rheumatic diseases, as SLE, RA and PsA. Five studies, however, are referring to rare autoinflammatory diseases [23,35,47,51,52]. Random forests (RF), linear regression (LR) and support vector machine (SVM) were the most commonly used methods. Models employing genetic and transcriptomic data have been created for all diseases; very few papers used other laboratory data as antibody titres and serum metabolites [16,18,33,46,50,53].

The application of ML can be categorized into the seven broad topics discussed below: disease identification, assessing RD risk, disease subtype classification, improving diagnosis, enhance precision care, biomarkers identification and clinical genomics analysis.

3.1. Disease identification

There are numerous classification criteria for RD that are constantly being updated to improve the quality of medical care [56]. These criteria, based on clinical symptoms and laboratory biomarkers, are used to distinguish between similar diseases and to confirm or exclude a particular disease based on inclusion and exclusion criteria. This can be difficult because many clinical and laboratory markers are non-specific and can be positive for many diseases. Different studies, as reported in Table 1, have used ML to classify patients with RD using laboratory data, as the optimisation scheme in ML can reduce variability in classification, leading to clinical standardisation.

Of relevance, the development of AI and ML algorithms, being initially trained from available data, represent a challenge for rare disease. Indeed, for some RD the prevalence of disease is so low that the inclusion of large cohort of patients is often "a mission impossible". According to these considerations, laboratory test results could empower ML generation, not only by using retrospectively collected data of RD patients, but also offering the possibility of obtaining data of individuals not affected from RD, used as reference values. This might facilitate the solution of the rare disease diagnostic paradox: from one hand the discovery of the root molecular cause comes almost immediately with the diagnosis itself, from the other hand the identification of SNP and genomic features it is not straightforward, each patient representing a specific context [6].

Logistic regression and decision trees in conjunction with the feature selection "Forward Wrapper" were employed to classify patients with SLE with or without erosive arthritis [16]. SLE-related antibodies (anti-carbamylated proteins and anti-citrullinated peptide antibodies) and arthralgia resulted the most relevant features for the ML model, achieving an area under the curve (AUC) value of 0.806. An

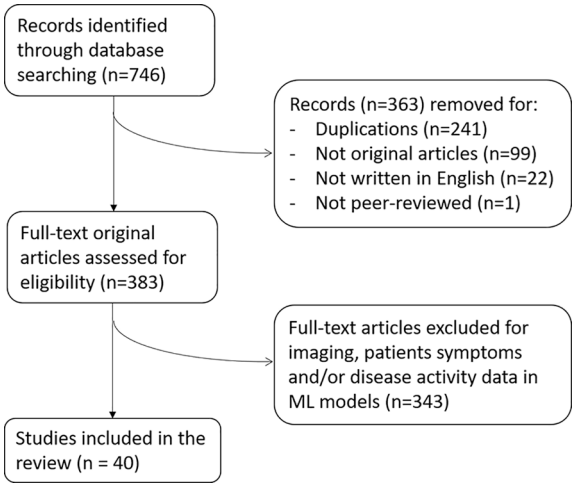

Fig. 1. The methodological flowchart.

Table 1
Studies employing machine learning in laboratory data from RD patients.

Publication	Disease	Aim/research question	Data types	Methods used	Sample size	Assessment	Main findings	Drawbacks
Disease identification								
Oates 2005 [21]	Lupus nephritis	To use patterns of abundance of urine proteins to identify class and disease indices.	Urine proteome	artificial neural network	20 patients	AUC > 0.85	Successfully identified protein spots that can serve as surrogates for a renal biopsy	Small sample size, need external validation
Ceccarelli 2018 [16]	SLE	To classify patients with or without erosive arthritis	Autoantibodies data, clinical and treatment data	LR, decision tree	120 SLE patients	AUC = 0.806	Relevance of ACPA and anti-CarP in determining SLE-related erosive damage	Small sample size; cross-sectional nature
Figgett 2019 [17]	SLE	To stratify SLE patients and identify disease-linked gene expression patterns	RNA sequencing data	k-means clustering, PLSDA, PCA, RF, ECOC	161 SLE patients and 57 controls	RF accuracy = 88%	Stratification of patients based on gene expression signatures may be a valuable strategy allowing the identification of separate molecular mechanisms underpinning disease	Combining matching data needed
Lu 2019 [18]	SLE	To evaluate clinical and immunologic factors associated with impending flare	Autoantibodies and 32 soluble mediators	RF	41 SLE patients	88.67% accuracy	Three subgroups of early flare patients, distinguished by greater baseline frequencies of aCD11b + monocytes, or CD86hi naïve B cells, or both	Missing data
Van Nieuwenhove 2019 [20]	JIA	To identify JIA patients	Immunophenotyping	RF, artificial neural network, SVM	72 JIA patients and 43 controls	iNKT cells AUC = 0.912	immunological pattern comprised two components: a shared signature of inflammation and a smaller set of individual immune trait changes only in JIA	Relatively limited use in diagnosis
Pinal-Fernandez 2020 [22]	myositis	To define unique gene expression profiles in muscle biopsies	Transcriptomic data	RF, linear SVM and other classification algorithms	119 myositis patients; 20 controls	Linear SVM: >91% accuracy	Usefulness of transcriptomics to tailor therapies to a specific molecular diagnosis	Small sample size
Jia 2020 [23]	AOSD	To investigate the clinical value of circulating NETs to distinguish AOSD patients with organ involvement and refractory to glucocorticoid	Cell-free DNA, NE-DNA, MPO-DNA, and citH3-DNA complexes from serum	SVM	66 AOSD patients and 40 controls	Distinguished AOSD AUC = 0.88; refractory AUC = 0.917	Circulating NETs in plasma were closely correlated with systemic score, laboratory tests, and cytokines	Small sample size
Martin-Gutierrez 2021 [19]	SLE, Sjogren disease	To identify distinct immunologic signatures to improve treatment selections	Immunophenotyping data	Supervised ML (balanced RF and sparse PLS-DA) and LR followed by k-means clustering	88 SLE/Sjogren patients and 31 controls	AUC = 0.9979	A signature of 8 T cell subsets distinctly differentiates the two endotypes	Sex and disease activity biases
Risk classification								
Almlöf 2017 [24]	SLE	To predict an individual's SLE risk	SNP genotype data	RF	1160 SLE patients and 2711 controls	AUC = 0.94	Identified novel risk genes mainly expressed in B cells	Only targets autoimmunity loci
de la Calle 2021 [25]	UA, RA	To investigate if alterations in the DNA methylation profiles of immune cells can predict the progression of UA to RA	DNA methylome	LR, RF, SVM	72 undifferentiated arthritis and 8 RA patients; 13 controls	simplified models > 25CpG: >75% accuracy	Potential early discriminants of methylation markers	Small sample size
Jalali-najafabadi 2021 [26]	PsA	To assess the impact of confounders on feature selection using information theoretic methods and characterise the risk of developing PsA using ML in a UK PsA population	Genomic data	LR, AdaBoost, XGBOOST, RF, KNN, DT and Gaussian naive bayes	1462 PsA patients	AUC = 0.53–0.55	HLA_C_*06 and HLA_B_*27 were the most important genetic features for the stratification approach that can mitigate the impact of confounders	Small sample size; cross-sectional nature of the dataset; potential phenotype misclassification
Determine disease subtype								

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Table 1 (*continued*)

Publication	Disease	Aim/research question	Data types	Methods used	Sample size	Assessment	Main findings	Drawbacks
Kegerreis 2019 [32]	SLE	To integrate gene expression data and used it to classify patients as having active or inactive disease	Whole blood trascriptomic data	Elastic GLM, KNN, RF	156 SLE patients	RF accuracy = 83%	Fine-tuning the algorithms to be informative as a standalone estimate of disease activity.	Small sample size, data imbalanced
Norgeot 2019 [31]	RA	To build a model that would most accurately predict RA disease activity in the future clinical visit	CRP, ESR and clinical/ demographic data from EHR	Longitudinal Deep Learning Model	820 RA patients	AUROC = 0.74	Building accurate models to forecast complex disease outcomes using EHR data is possible	The performance of the trained model was too low to be of immediate clinical utility
Poppenberg 2019 [34]	JIA	To predict JIA activity	PBMCs RNA sequencing data	KNN, RF, cSVM, gSVM	50 children with JIA	RF AUC = 0.94 (highest)	The models performed well in patients of different ethnicity	Small sample size
Orange 2020 [27]	RA	To refine histologic scoring of RA synovial tissue	Histologic and transcriptional data	SVM	123 RA patients	High inflammatory subtype AUC = 0.88	Identified 3 distinct molecular subtypes of RA that correlated with specific clinical phenotypes	Small sample size, lack of normal synovial tissue
Robinson 2020 [28]	SLE	To characterize the immune cell profile of patients with juvenile-onset SLE and investigate links to the disease over time	PBMCs flow cytometry data	Supervised ML (balanced RF and sparse PLS-DA) followed by unsupervised k-means clustering	67 SLE patients; 39 controls	89.6% sensitivity, 82.1% specificity, AUC = 0.909	Identified 4 potentially important subgroups among patients with SLE	Small sample size; imperfect outcome
Coelewij 2021 [29]	SLE	To predict subclinical atherosclerosis in SLE patients	Serum metabolomic data	RF, LR with and without interaction, SVM, DT	80 female SLE patients	LR with interaction AUC = 0.812 (the highest)	SLE patients with subclinical atherosclerosis plaques had a unique metabolomic profile associated with increased circulating VLDL subsets, leucine and tyrosine and reduced glycine.	small sample size, lack information of sex hormone levels
Hoi 2021 [33]	SLE	To generate an algorithm that could calculate via model fitting the presence of high disease activity	Laboratory measures and demographic data	Multinomial LR	286 SLE with 5,680 visits	AUC = 0.829	The ability to predict HDAS using simple laboratory measures and demographics is a useful application in healthcare settings where SLEDAI-2 K are not routinely performed	Small sample size
Sun 2022 [30]	Gout	To develop and validate a prediction model for renal urate underexcretion in male gout patients.	Genomic data and clinical data	linear SVC, SGD, LG	3261 male gout patients	Classifier 11 variables AUC = 0.914	4 SNPs and 7 clinical features contribute to gout	SNPs not powerful enough, only Chinese men patients
Improving diagnosis								
Patrick 2018 [39]	PsA	To predict PsA among psoriasis patients	Genomic data	LR, LDA, MARS, RF, CIF	>7000 PsA and PsC patients	AUC = 0.82	nine new loci for psoriasis and psoriasis subtypes; robust prediction of PsA and PsC can be achieved using genetic data alone.	ML analysis used different numbers of markers
Ormseth 2020 [38]	RA	To develop a miRNA panel to reliably differentiate between RA, SLE and controls	sRNA sequencing	RF	167 RA patients and 91 controls	RA AUC = 0.81, SLE AUC = 0.80	The final panel (miR-22-3p, miR-24-3p, miR-96-5p, miR-134-5p, miR-140-3p, and miR-627-5p) is associated with pathways implicated in RA pathogenesis	Not a diagnostic panel
Mulder 2021 [40]	PsA	To differentiate between psoriasis and psoriatic arthritis	Immune profile from PB cells	RF	41 PsA patients	AUC = 0.95	The PsA-specific immune profile is defined by a reduced proportion of CD4 and CD8 memory T-cell subsets, Treg cells and CD196 + and CD197 + monocytes	Differences in PASI score and DMARDs use at baseline
Ha 2022 [35]	CRMO, JIA, IFNpathies	To improve the early diagnosis of pediatric rheumatic diseases and applying machine learning to develop predictive models	Transcriptome data	RF	48 pediatric rheumatic patients	AUC = 0.80	mRNA from whole blood can provide adequate information for the differentiation. The activation and immune response of myeloid cells form participate in the biological pathways	Small sample size; disease heterogeneity; batch effects not completely avoided

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Table 1 (*continued*)

Publication	Disease	Aim/research question	Data types	Methods used	Sample size	Assessment	Main findings	Drawbacks
							underlying JIA, CRMO and IFN-related diseases.	
Ma 2022 [43]	SLE	To seek for a feasible way for SLE accurate diagnosis	Public single-cell RNA sequencing data, enriched with PBMCs dataset integration and cellular cross talking	RF	Large-scake dataset and 43 SLE patients and 8 controls	AUC = 0.776	The interactions among the PBMC subpopulations of SLE patients may be weakened under the inflammatory microenvironment. The alterations of B cells and monocytes may be the most significant findings	Other immune cell background noise
Mc Ardle 2022 [37]	PsA	To identify serum protein biomarkers that distinguish patients and may be used to support appropriate early intervention	Proteomic data	RF	127 PsA patients	AUC = 0.79	The identified serum protein biomarker panel can separate patients	Small sample size, absence of healthy and disease controls.
Martorell-Marugan 2023 [36]	SLE, Sjogren disease	To perform differential diagnosis of similar pathologies	Transcriptome and methylome data	Multiple decision trees (XGBoost)	394 SLE/Sjogren patients and 257 controls	MCC = 0.5791 (expression), MCC = 0.5546 (methylation)	Patients assigned to a specific molecular cluster are misclassified more often and affect to the overall performance of the predictive models	The prediction capacity depends on the molecular background of the patients.
Enhance precision care								
Collins 2020 [45]	RA	To derive a prediction score for remission in RA patients with TCZ monotherapy	CRP, ESR, hematocrit and clinical/demographic data from 4 clinical trials	LR	1019 RA patients	AUROC = 0.736 in the OR-based model	The score correlated well with remission at 24 weeks and was robust to different variable selection methods.	Some inconsistency in variables between trials
Johansson 2021 [46]	RA	To derive a prediction score for remission in RA patients with TCZ monotherapy and external validated it	ESR, hematocrit and clinical/demographic data from 4 clinical trials and real-world data	LR, RF	1305 RA patients	AUROC = 0.76	The remission prediction scores, derived in RCTs, discriminated patients in RWD about as well as in RCT	Missing data
Segú-Vergés 2021 [47]	sJIA, AOSD	To investigate the optimal treat-to-target strategy for Still's disease as a proof-of-concept of the modeling approach	Trascriptomic data and treatment data	TPMS (artifical neuronal networks and sampling-based methods)	194 sJIA, 79 AOSD and 48 sJIA/AOSD patients	Accuracy 94%	More efficient role of canakinumab in the initial autoinflammatory/systemic phases that are dominated by innate immune deregulation	Limited to data available in public databases
Tao 2021 [43]	RA	To predict response to anti-TNF prior to treatment and to understand how RA patients differently respond to anti-TNF drugs	RNA sequencing and DNA methylation data	RF	80 RA patients	RNA data accuracy ADA = 85.9% and ETN = 79%; methylation data accuracy ADA = 84.7% and ETN = 88%	accurately predict the response before ADA and ETN treatment	small sample size; not all patients completed 6 months of treatment
Yoosuf 2022 [42]	RA	To detect biomarkers and signatures of treatment response to TNF inhibition expression	Transcriptomic, proteomic and flow cytometry data	Linear model (with L1 and L2 regularization), RF, SVM with an RBF kernel	39 female RA patients	Linear model AUC = 0.68; RF AUC = 0.73; SVM AUC = 0.72	Suggested new predictive models of anti-TNF treatment in RA patients	Small sample size; patients were female only
Myasoedova 2022 [44]	RA	To test clinical and genomic biomarkers to predict MTX response in patients with early RA	Genomic data, Demographic/clinical data	RF	643 RA patients	Sensitivity = 72%, specificity = 77%	Pharmacogenomic biomarkers combined with baseline DAS28 scores can be useful in predicting response to MTX in patients with early RA.	Limited generalizability
Biomarker discovery								
Swan 2015 [48]	OA	To identify putative biomarkers of O, articular cartilage degradation and synovial inflammation	Proteomic and transcriptomic data	RGIFE	193,079 genes (transcriptomics) and 1500 genes (proteomics)	accuracy > 84%	RGIFE reduces to a small number of genes or proteins including those relevant to OA, cartilage degradation and joint inflammation	bias between proteomic and trascriptomic dataset
Zhao 2022 [49]	Knee OA	To identify new biomarkers to improve the accuracy of diagnosis and treatment.	Transcriptomic data	SVM, LR	74 samples from public database	Combined AUC = 0.96	CX3CR1, SLC7A5, ARL4C, TLR7, and MTHFD2 show significant differences in cartilage, subchondrial bone and synovial tissue	No tissue-specific biomarkers, scarce clinical information

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Table 1 (*continued*)

Publication	Disease	Aim/research question	Data types	Methods used	Sample size	Assessment	Main findings	Drawbacks
Geng 2022 [50]	RA	To analyze and evaluate the effectiveness of the detection of single autoantibody and combined autoantibodies in RA	Multiple autoantibodies and patient symptoms	CSNN model	309 RA patients	Sensitivity = 92%, specificity = 86%, accuracy = 90%, AUC = 0.90	Simply relying on single antibody and combined multiple antibodies did not have high diagnostic sensitivity and specificity	Error in the sensitivity of single autoantibody tests
Clinical genomics analysis								
Briggs 2010 [54]	RA	To investigated epistatic interactions with a well-established genetic factor (PTPN22 1858 T) in RA	Genomic data	LR, RF	1624 RA patients and 2506 controls	NA	SNP variants within CDH13, MYO3A, CEP72 and near WFDC1 showed significant evidence for interaction with PTPN22, affecting susceptibility to RA.	No clear standard
Accetturo 2020 [51]	FMF	To reduce the number of MEFV variants with ambiguous classification	Genomic data	REVEL	216 missense variants	AUC = 0.879	Reclassification of 96 MEFV variants, reducing the VUS proportion from 61.6% to 17.6%	Small number of variants
Catalina 2020 [53]	SLE	To determine the contribution of genetics, serology, and clinical manifestations to gene expression profile	Genomic and serological (autoantibodies and cell types) data	LR, GLM, SVM	1566 SLE patients	LR AUC = 0.94, GLM AUC = 0.97, SVM AUC = 0.91	ML determines a gene signature characteristic to distinguish African ancestry SLE and was most influenced by genes characteristic of the perturbed B cell axis in patients	Data can have complex and often contradictory effects
Adato 2022 [52]	FMF	To predict the mutation type carried by a patient based on the countries of origin to understand the epidemiology of FMF	Genomic data	LR	1781 FMF patients	AUC = 0.67–0.86	A strong geographic association in North Africa for p.Met694Val, Europe for p.Val726Ala, and west Asia for p.Glu148Gln	Low penetrance variants underrepresented
Xiao 2022 [55]	RA	To investigate how neuropeptides and m6A played an important role in the underlying pathogenic processes of SFs that contribute to the development of RA	Single-cell RNA sequencing data	RF, SVM-RFE	Two RA and two OA patients from public databases	AUC = 0.667	Differential expression of neuropeptides GHR and NPR2 in SFs, influenced by the m6A methylation-related genes IGFBP2 and METTTL3	Data were not validated at the single-cell level

AOSD: adult onset Still's disease; AUC: area under the curve; CIF: Canonical Interval Forest; CRMO: Chronic Recurrent Multifocal Osteomyelitis; CRP: C-reactive protein; CSNN: cost-sensitive neural network; DMARDs: disease-modifying antirheumatic drug; DT: decision tree; ECOC: error-correcting output code; EHR: electronic health registry; LDA: Linear Discriminant Analysis; ESR: erythrocyte sedimentation rate; FMF: Familial Mediterranean Fever; GLM: Generalized linear model; iNKT: Invariant natural killer T; JIA: juvenile idiopathic arthritis; KNN: K-nearest neighbor; LR: Logistic regression; MARS: Multivariate adaptive regression spline; na: not applicable; OA: osteoarthritis; PASI: Psoriasis Area Severity Index; PB: process-based; PBMCs: peripheral blood mononuclear cells; PCA: principal component analysis; PLS-DA: partial least squares discriminant analysis; PsA: psoriatic arthritis; PsC: psoriasis; RA: rheumatoid arthritis; RF: random forest; RGIFE: Real-Time Intermediate Flow Estimation; SGP: Stochastic Gradient Push; SLE: systemic lupus erythematosus; SVM: support vector machine; TCZ: tocilizumab; UA: undifferentiated arthritis.

unsupervised k-mean ML method identified four clusters in transcriptomic data of 30 SLE patients [17]. An SVM approach was then applied, confirming that the classification software was able to classify patients with 88% accuracy. Classification of early or late flare in 34 SLE patients was achieved by means of independent RF models, built using either gene expression data of immune pathways, autoantibodies and soluble mediators and immune cell subset from flow cytometry data [18]. ML models showed three subgroups of early flare patients, distinguished by greater baseline frequencies of activated CD11b + monocytes, or CD86hi naïve B cells, or both. Similarly, a signature of 8 T cell subsets (total CD4 + and CD4 + Temra T cells, total CD8 + and CD8 + naïve, Tem, Temra, responder T cells, and CD25-CD127- T cells) was identified in ML models to distinctly differentiate SLE from primary Sjogren's syndrome with high accuracy (AUC = 0.9979) [19]. The detected altered immunopathogenic processes had predictive value in determining long-term disease progression in terms of disease activity and damage. In addition, immune phenotyping data set from patients with juvenile idiopathic arthritis (JIA) was used to generate an algorithm capable of discriminating 72 JIA patients from 43 healthy controls with approximately 90% accuracy [20]. RF models identify invariant natural killer T cells as primary predictive immunological change in JIA (AUC = 91.18%). Urine test data was also used to build models for classification patients with renal disease of SLE (lupus nephritis) [21]. Neural networks were trained on normalized protein abundance to predict histological class with a sensitivity over 86%. The models identified six protein dots that can be used as a combined marker to classify patients with high sensitivity. ML models can also be trained on transcriptomic data to classify muscle biopsies from 119 patients with different types of myositis [22]. The SVM algorithm allowed for accurate classification in over 90% of muscle biopsies and also identified a gene expression profile uniquely overexpressed in different myositis patients, useful to tailor therapies. Due to the difficulty in diagnosing Adult-onset Still's disease (AOSD) and the complexity of the disease features, the identification of predictive models to distinguish patients who are susceptible to developing life-threatening complications is crucial. The use of neutrophil extracellular traps (NETs) as laboratory data for training ML algorithms to discriminate AOSD patients with organ involvement could be useful in this regard [23]. Support vector machines were used for modelling circulating NETs signature and found to distinguish AOSD patients from controls (AUC = 0.88) and stratify patients with liver and cardiopulmonary system involvement (AUC > 0.7).

3.2. Risk classification

Patients with RD frequently are at increased risk for future cardiovascular (CV) events or pulmonary manifestation. Circulating markers, as Krebs von den Lungen-6 glycoprotein (KL-6), anti-citrullinated peptide antibodies and natriuretic peptides, could aid in CV or lung disease risk stratification as reported for systemic sclerosis [57] or rheumatoid arthritis [58,59]. Although the small sample size of these studies may limit the interpretation of the results, these non-invasive strategies using biomarkers may have the potential to facilitate risk assessment.

In addition, AI offers the opportunity to make an early estimate of risk by exploiting the interactions between different risk factors and laboratory data. SNPs and genotype data can be used to identify disease risk markers, as reported by Almlöf and colleagues for SLE patients building a RF model [24]. The model identified 40 risk genes, half of which not previously linked to SLE. A small study assessed the DNA methylome of patients with undifferentiated arthritis using supervised and unsupervised methods to distinguish a methylation pattern as risk pattern to develop RA [25]. Despite the small sample size, a distinct methylation signature was observed, useful for detecting early disease determinants in these patients. Other authors studied the most appropriate risk assessment method to select the optimum number of features from genomic data from PsA and psoriatic patients [26]. They applied 7 supervised ML-based algorithms, identifying a stratification approach to mitigate the impact of confounding that lead to the expected identification of HLA-B*B27 as the predominant risk factor for PsA in psoriasis.

3.3. Determine disease subtypes

Due to the overlapping clinical features and the lack of specific diagnostic criteria for many RD, defining important subtypes of disease is of growing interest. However, validation of subtypes identified by supervised or cluster ML models is not easy to accomplish.

ML models based on gene expression data from synovial biopsy samples have been used to refine histological subtyping of RA patients [27]. Consensus clustering revealed three clusters of patients: low-, mixed or high-inflammatory RA subtype based on histological evaluation. Synovial histological features of the same 45 biopsy samples were used as input data to train several binary SVM models to discriminate inflammation subtypes. The cross-validated model based on the histological scores was successful in classifying the highly inflammatory subtype (AUC = 0.88). Robinson and colleagues applied supervised ML approaches for classifying and clustering 67 juvenile-onset SLE patients using both demographic and flow cytometry data [28]. Balanced RF and partial least squares discriminant analysis (PLS-DA) algorithms were able to select 28 immune cell subsets as important variables from peripheral blood mononuclear cells (PBMCs). These variables were used as input to the k-means clustering algorithm that identified 4 clusters with differences in T cell frequencies among SLE patients. In 80 female SLE patients, it was possible to define subtypes of the disease based on the presence of lipoprotein-derived metabolites [29]. Different ML tools (univariate LR, lasso LR and RF) identified 4 metabolites associated with subclinical plaque. Logistic regression with interactions differentiated between patients with SLE with subclinical plaque and patients with SLE with no subclinical plaque groups with greatest accuracy of 0.800. Three ML prediction models for renal urate underexcretion in gout patients were built using reliable genetic variants and clinical data [30]. Four SNPs were selected as the most important contributors for clustering gout patients. Combining these SNPs to other 7 clinical features helped to optimize the models with AUC approximately 0.9.

One of the main interests for clinicians and patients is the definition of the disease activity state. As many RD are rare disorders, this can be particularly challenging; however, ML holds specific promise to improve strategies from available laboratory information (Table 1). An earlier study used structured data from electronic health record data (i.e. disease activity score, erythrocyte sedimentation rate and C reactive protein levels, treatment data and autoantibodies dosage) to predict disease activity index in RA patients [31]. In another study, generalized linear model (GLM), RF, k-nearest neighbor (k-NN) and hierarchical clustering models using gene expression data were compared for their ability to accurately classify patients with active or inactive SLE in independent datasets [32]. The strong performance of the RF model suggests that nonlinear decision tree-based classification methods are most appropriate for SLE diagnosis. In addition, routinely available laboratory data were suitable for creating an accurate model to calculate high disease activity in SLE patients [33]. Seven laboratory parameters and three demographic variables were found to be significantly associated with active disease building an algorithm with an accuracy of 88.6%. Four different ML approaches were used to create predictive models of JIA activity from by PBMCs transcriptome data [34]. Although the variability of gene expression within patients is challenging, the ML models were able to predict JIA status well, with a training accuracy > 74% and a test accuracy > 78%.

3.4. Improving diagnosis

There is ample evidence that early diagnosis leads to better outcomes in patients with inflammatory rheumatic diseases and that the first 12 weeks after the onset of symptoms represent a therapeutic window of opportunity [60,61]. There is great interest in applying ML to laboratory

data to obtain new tools for differential diagnostic approaches. For example, predictive RF models were built based on blood transcriptome data of 48 children with autoinflammatory diseases, 46 children with viral infection and 35 controls [35]. The cross-validation results confirmed that a model could differentiate paediatric RD from controls (AUC = 0.8) and from viral infection cases (AUC = 0.7). Moreover, other models could differentially distinguish RD with AUC > 0.8. Similarly, gene expression and methylation data from 651 individuals (SLE patients, Sjogren's syndrome patients and controls) were used with ML methodologies to predict the correct disease diagnosis [36]. Following a feature selection strategy, the authors identified the most informative subset of genes and methylated sites that improve the prediction model with a mean accuracy of 0.7926. Coupling cutting-edge serum proteomics data with multivariate ML analysis, Mc Ardle and colleagues differentiated between PsA and RA patients with an AUC in the range of 0.79–0.85 [37]. In another study, different ML algorithms were applied to select a microRNA panel that identified patients as having RA, SLE or neither disease [38]. A RF algorithm was used as a feature selection technique to identify differentially expressed microRNAs in 167 RA and 91 control samples. Based on the results, six microRNAs were selected and the panel reliably distinguished between RA patients and controls with an AUC of 0.81.

ML has also been employed to predict the insurgence of PsA among psoriasis patients utilizing 200 genetic markers of >7,000 patients [39]. The authors were able to identify nine new loci for psoriasis (AUC of 0.82) and suggested that robust prediction of PsA can be achieved using genetic data alone. To discriminate PsA from psoriasis, it has been studied a disease-specific immune profile from the phenotype of peripheral blood immune cells [40]. Using a RF-based algorithm coupled with in-deph flow cytometry, Mulder and colleagues found that PsA exhibited increased proportions of differentiated CD4 + CD196 + CD183-CD194 + and CD4 + CD196-CD183-CD194 + T-cells and reduced proportions of CD196 + and CD197 + monocytes, memory CD4 + and CD8 + T-cell subsets and CD4 + regulatory T-cells (AUC = 0.95). Identification of altered levels of B cells and monocytes, subpopulations of PBMCs, in SLE patients was a useful information for building a RF model to distinguish patients from controls [41]. The model could accurately identify not only SLE (AUC = 0.776) but also RA (AUC = 0.967) and multiple sclerosis (AUC = 0.775) in PBMCs patient dataset. This ML model may be feasible for accurate diagnosis of chronic autoimmune diseases.

3.5. Enhance precision care

Personalised care is valuable for laboratory medicine, in general as well as for RD, characterized by variability within the disorders and presence of several comorbidities. The use of AI is a way to implement precision care and treatments. In a small cohort of 39 women with RA starting anti-TNF therapy, researchers assessed differences in multiomics from PBMCs [42]. ML models using transcriptomic data at baseline showed high predictive utility in classifying RA patients based on response to anti-TNF treatment. Interestingly, transcriptomic data-based models predict response with higher accuracy compared with models with clinical data. Anti-TNF-therapy and other RA therapies, which is often determined in laboratory, require a careful assay evaluation since standardization of assays have not still achieved and well-defined consideration for defining clinical useful cut-off [62]. In a study from Tao et al., RF models were built to predict response to anti-TNF therapy in RA patients using expression and DNA methylation data from PBMCs [43]. Transcriptomics data built a model most accurate in predicting response to adalimumab, whereas the model with methylation data accurately predicted response to etanercept. Others have proposed the application of RF model to predict methotrexate response in patients with early RA [44]. In this model, the incorporation of genetic data in the prediction algorithm improved prediction accuracy with 72% of sensitivity. In addition, data from several randomized controlled trials (RCTs) in RA were examined and a remission prediction score for patients treated with tocilizumab was derived and validated with AUCs showing good discrimination [45]. The study presented an accurate design and rigorous statistical analysis. The score correlated well with remission at 24 weeks and was robust to different variable selection methods. Interestingly, this prediction rule was subsequently tested in real-world data, finding that the RCT model could discriminate patients as well as the real-world model with AUC from 0.76 [46]. Combining artificial neuronal networks, sampling-based methods and AI, Segú-Vergés and colleagues create a model to identify optimal treat-to-target strategies for Still's disease [47]. The expression data from systemic juvenile idiopathic arthritis and AOSD – two form of the Still's disease – point towards a more efficient role of canakinumab in the initial phase of the disease to prevent the development of destructive complications. In lights of these insights, future development of personalized therapeutic treatments for RA might be defined using ML and disease genetic phenotypes.

3.6. Biomarker discovery

The comprehensive molecular phenotyping through omics data and ML appears a very attractive approach to identify emerging biomarkers to target novel treatment and to improve disease diagnosis. For OA, ML-based feature reduction methods were performed to identify biomarkers associated with the disease [48]. The RGIFE method described was tested on several proteomics OA datasets, identifying ten inflammatory-associated proteins known to be linked with cartilage matrix degradation. The reduced transcriptomics datasets, instead, varied in size and utility, given the unknown function of a large number of identified genes. Another recent paper identified five potential useful diagnostic biomarkers related to knee OA in gene expression datasets [49]. The SVM model showed significant differences of these biomarkers in the cartilage and subchondral bone tissue.

While not researching new biomarkers, the work of Geng and colleagues [50] is interesting because it analysed and evaluated the effectiveness of the detection of single or combined autoantibodies in RA patients. The cost-sensitive neural network prediction (CSNN) model used had instead a high diagnostic sensitivity and specificity (0.90 and 0.86, respectively), better that simply relying on single antibody and combined multiple antibodies.

3.7. Clinical genomics analysis

AI can improve the comprehensive analysis of a large volume of genetic data to address variant classification and to identify molecular relationships between complex features in the omics data and the RD. For rare autoinflammatory diseases, the use of AI methods to improve the classification of many uncertain significant gene variants could result in a more accurate diagnosis and a better interpretation of clinical consequences and drugs response. For example, variant interpretation of *MEFV* gene in Familial Mediterranean Fever (FMF) have been simplified and improved using REVEL (rare exome variant ensemble learner), a novel metaprediction tool [51]. The authors, calculating a REVEL score for all missense variants, proposed a reclassification of 96 *MEFV* variants, greatly reducing the variant of uncertain significance proportion from 61.6% to 17.6%. A logistic regression approach can be used to determine the origin of different *MEFV* variants, suggesting that specific variants could be pathogenic in certain ethnicities [52]. For example, p.Met694Val showed an increased likelihood to be present in North Africa with an AUC of 0.86, while p.Val726Ala in Europe (AUC of 0.83). An additional study used ML to predict ancestry using gene expression data in SLE patients [53]. LR, SVM and GLM algorithms have been trained by 752 genes known to discriminate patients by ancestry. The ML models accurately identified African ancestry SLE patients from their gene expression data and identified genes associated with B cells as important for distinguishing African ancestry SLE to European ancestry SLE

patients. In another study, RF and logistic regression were employed to predict genetic interactions between identified risk genes in RA [54]. The authors stated that the genetic contribution to RA risk is complex and novel candidate genes (*CDH13, MYO3A, CEP72, WFDC1*) were recognize to modify the effect of *PTPN22*-associated risk for RA. Similarly, ML was used to find genetic interactions between neuropeptide, N6-methyladenosine (m6A) and RA pathophysiology-related genes [55]. The SVM model showed the highest accuracy for predicting m6A factors associated with *GHR* and *NPR2*.

4. Drawbacks of AI applications in RD

Overall, different limitations have been found in every paper included in this review. The majority of the studies presented small sample size and are concentrated more on a single -omics component than on the integration of various data types and with clinical data. In the future, it will be crucial to gather larger, more representative samples of multiomics data and completely include the various data types into ML models. A few studies have used multiomics data [42,48], but more rigorously designed longitudinal studies and a greater dataset will be required. It would be useful to have international large-scale programs (e.g. European programs) that guarantee the ability to share the datasets of various specialized centers for rare diseases, as RD. This would require further efforts for overcoming privacy and legislative regulation issues. A bias by gender, disease activity or treatments was reported for some research that focused the analysis on specific patient subsets [19,30,40,42,49]. In these cases, the main findings should be assessed in the light of how missing data may affect the outcome of the ML analysis performed.

5. Challenges

ML is an effective and powerful way for analysing laboratory big data, as it can recognize scheme which are not so easy for humans to detect. However, multiple challenges need to be overcome for an efficient integration of AI and laboratory medicine to improve RD (Table 2).

In particular, regulatory and ethical challenges to guarantee data privacy and patient safety appeared of particular relevance for RD [63]. Indeed, being these diseases rare, data need to be acquired from different hospitals of centres specialized for RD. In a recent paper about bioethics aspects of big data in RD, Manrique et al identified privacy, informed consent, impact on the medical profession and justice as main areas of concern [64]. To date, most ML studies are based on retrospective data, as they used existing datasets, sometimes not sufficient robust. The predictive power of a model depends on the quality of the data [65]; indeed the "mantra" garbage in, garbage out is often used to depict the concept that poor data quality returns useless results [66]. Thus, a careful pre-processing of dataset is essential, also when laboratory tests results are queried by laboratory information system (LIS). Indeed, patient results could include non-numeric results that should be converted and anonymized before used [67]. Comparing multiple algorithms to find the most appropriate one for the dataset is a good practice to increase the confidence of the ML outcomes. It is also important to improve the awareness of health personnel about the strengths and weaknesses of data science, prompting the develop of digital skills and competences. ML can also prove challenging in the selection of the most appropriate algorithm *a priori*. This might require implementation of multiple ML models dependent on the desired outcomes, the specific type of data and the sample size. Although there are no cut-off limits for sample size, the general indication is the more the better [68]. Interpretation and identification of machine bias become quite challenges when complex and interdependent data are analysed [69]. Not all biases can be resolved using overrepresented training dataset, since they can be embedded into this data. Developing tools for addressing machine bias is necessary not only to solve these issues, but also to be free from human bias. A multidisciplinary approach by bioinformaticians, clinicians and laboratory staff in close collaboration may help to fit the interpretation [70]. However, the most important and yet most critical practical aspect of ML is model validation. In fact, biomedicine ML models may uncover relationship without biological meaning, derived from a reductionist approach or data noise. In this case, it is essential that the studies are rigorously and appropriated performed with larger open datasets. In medical settings, ML models frequently lack the ability to significantly generalize beyond their training distribution and may be prone to data leaking and overfitting. This makes external validation using a set of new data points that come from other cohorts, facilities, or repositories of utmost importance [71].

Other practical aspects have been determined to limit the development of AI and its tools, namely as ML, in clinical laboratories. In a recent survey conducted in medical laboratories, it has been shown that research on AI is limited by equipment not adequate for implementing high technological tasks, such as those required by AI. Although the lack of technological infrastructure might be due to a shortage of economic resources, the problem could not the be easily solved by updating computer software (such as laboratory LIS), since this action still might not benefit this issue [72]. Moreover, other important challenges have been raised during the 3rd Strategic Conference of the European Federation of Laboratory Medicine in 2022 [73]. It will be the responsibility of laboratory experts to create the instruments, guidelines, and experimental methods that will improve the evaluation of the performance, quality, safety, and effectiveness of ML models used in patient care. In their well-reported work, Lennerz and colleagues present one such tool, a diagnostic quality model recommended for understanding the intricate details of clinical ML implementations [74]. Another key aspect is the development of user confidence in AI systems through accuracy, reproducibility and replicability [75]. Proving the reproducibility and replicability of AI studies raises unique challenges. Release of datasets, source code, and trained models enables independent results verification [76]. This is also essential for facilitating the successful translation of ML applications into clinical practice.

Table 2
Limitation of machine learning.

Challenges	How they could be overcome
Data privacy and patient safety	Active involvement of health personnel; avoid providing full access to any potential interested entity
Inter-operability of AI solutions	Use of structured data
Poor quality of the input data	Careful pre-processing of data; comparing the algorithms to find the most appropriate for the dataset; larger datasets
Correct algorithm selection	Implementation of multiple ML models; several attempts based on the desired outcome, the type of data and the sample size
Interpretation and identification of machine bias	Multidiscliplinary approach to assess the results
Validation of ML models	Studies must be rigorously and appropriated performed; larger open datasets
Reproducibility	Perform cross validation; provide rationale for final model selection; include external validation for final method performance evaluation
Clinical translation of ML application in laboratory medicine	Interpret the results and performance of the selected model in relevant subgroups and clinical scenario

6. Future perspective

During last few years, laboratory medicine has evolved to a highly technological medical discipline, generating large amount of data every year. As the next inevitable evolutional step, these big data sources are now meeting AI algorithms, that might assist us in data integration and making sense of the masses of diagnostic data collected [67,77]. Data, indeed, might come from several sources, as clinical, imaging or

laboratory dataset, often not interoperable one another [78]. This is the case when clinical records are combined with diagnostic test results. The need to figure out how to combine and interpret those different data could be resolved with AI solutions, such as by using natural language processing (NLP) tools [14,15]. Regarding data integration, it should be mentioned that for combining data, some fundamentals standardization prerequisites should be achieved in each centre, such as the interconversion of measurement unit, the specification of the analytical platforms, the sample collection and handling modality, etc… Thus, data integration is of fundamental importance for applying ML in RD and, more in general, in all rare diseases.

Currently, there is an increasing number of AI algorithms that support specific diagnostic tasks in different RD, paving the way for new perspective in biomedicine. A variety of other uses for ML are in various stages of development, including smart technology, wearables and health monitoring [79]. Additional ML applications have been developed in other fields but could be translated for RD usage. For example, epigenetic biomarkers have been evaluated for cardiovascular diseases and cancer using omics data [80] and could be developed to study age-related inflammation in autoimmune rheumatic diseases or the reasons behind the different onset in autoinflammatory disorders. To unravel the full potential of these technologies, the poor ability to simultaneously incorporate multimodal data (i.e. omics, images and clinical data) should be overcome in the next few years. It will be important to collect these multimodal data on larger and more representative samples in rigorously designed studies for discovery and validation [67]. Newly ML methodologies have to be developed capable to handle this integrated information. The chatbot, as chatGPT, is headed in this direction. It can currently be considered a tool capable of detecting anomalies in laboratory parameters and understanding of laboratory medicine test results [81]. A soon-to-come improvement will be the use of chatbot for helping in trustworthy diagnosis of complex diseases (i.e. RD) from general symptoms and serological results.

7. Conclusions

The use of AI analytics for advances in RD research using laboratory data is in rapid expansion and implementation. Disease classification and subtyping and gene signature identification with ML might give an insight into the most appropriate treatment for each patient, improving personalized medicine. Care must be taken not to amplify potential biases, especially if dealing with rare RD. The combination of AI technique and laboratory medicine can be used to better integrate evidence into practices. There are several challenges, but having good and diverse experts is essential to apply ML properly.

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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.

Data availability

No data was used for the research described in the article.

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