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Emerging role of eHealth in the identification of very early inflammatory rheumatic diseases

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A B S T R A C T

Digital health or eHealth technologies, notably pervasive computing, robotics, big-data, wearable devices, machine learning, and artificial intelligence (AI), have opened unprecedented opportunities as to how the diseases are diagnosed and managed with active patient engagement. Patient-related data have provided insights (real world data) into understanding the disease processes. Advanced analytics have refined these insights further to draw dynamic algorithms aiding clinicians in making more accurate diagnosis with the help of machine learning. AI is another tool, which, although is still in the evolution stage, has the potential to help identify early signs even before the clinical features are apparent. The evolving digital developments pose challenges on allowing access to health-related data for further research but, at the same time, protecting each patient's privacy. This review focuses on the recent technological advances and their applications and highlights the immense potential to enable early diagnosis of rheumatological diseases.

Introduction

Digital age dawns before us and threatens to disrupt the traditional model of health care and the relationship between a clinician and patient. Rheumatology as a specialty is also not immune to these

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advancements with tremendous but vast untapped potential [1]. On the other hand, the adoption of electronic health records (EHRs) has aptly demonstrated that the health care industry has a record of tepid response to adopting new technologies and for its inability to maximize efficiency gains by harnessing them. It is among the last industries to adopt the digitization process, which have somehow implemented digital systems that hinder productivity of health care professionals and their support staff. It is therefore important to understand, embrace, and apply technology as a facilitator for achieving better patient outcomes. In this review, we intend to discuss opportunities and challenges for eHealth in a case finding of very early inflammatory rheumatic diseases and discuss strategies to apply eHealth for optimizing early diagnosis in our current practice.

Disruption in healthcare

A recent survey by CB Insights – a global tech market intelligence company – provided us a few indicators on the way healthcare technology is heading. It is apparent that the impact of technology-driven disruption will be felt by almost all stakeholders in the health care system (Fig. 1) and that technologies such as artificial intelligence (AI) are likely to create the maximum impact (Fig. 2). AI is the simulation of human intelligence processes by machines, especially computer systems. These processes include learning (the acquisition of information and rules for using the information), reasoning (using rules to reach approximate or definite conclusions), and self-correction.

As the end user of modern technology, millennials and the Generation Z are challenging the traditional model of primary care, referral processes, and the traditional healthcare delivery. This generation is also molding the way healthcare is accessed by their older family members. According to a recent digital health consumer survey conducted by Accenture [2] in the US, the younger generations have little interest in the healthcare status quo and they are open to different forms of health care delivery. Younger consumers are more inclined than any other generation to choose medical providers offering digital capabilities, such as easy access to test results through mobile or online and requesting prescription refills electronically [2].

According to the Rock Health's 4th annual digital health consumer adoption survey of 4-year duration [3], Americans are increasingly using digital tools to manage diagnoses, connect with providers, and make healthcare decisions. In this survey, growing willingness to adopt telemedicine (34% in 2018 *vs.* 19% in 2017) and wearables (33% in 2018 *vs.* 24% in 2017) and accessing online health information (80% in 2018) were some of the key findings [3].

Based on these two surveys, it can be inferred that with increasing digitization, self-tracking of health parameters by patients, and availability of patient data from multiple sources, coupled with inputs from general practitioners, eHealth offers chances for earlier diagnosis of inflammatory rheumatologic diseases and may lead to quicker referrals.

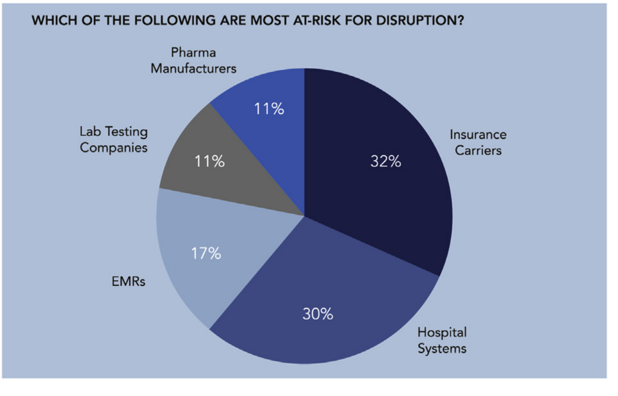

Fig. 1. Technology-led disruption impact on healthcare industry players (Source CB Insights (www.cbinsights.com). Research 2019, with permission).

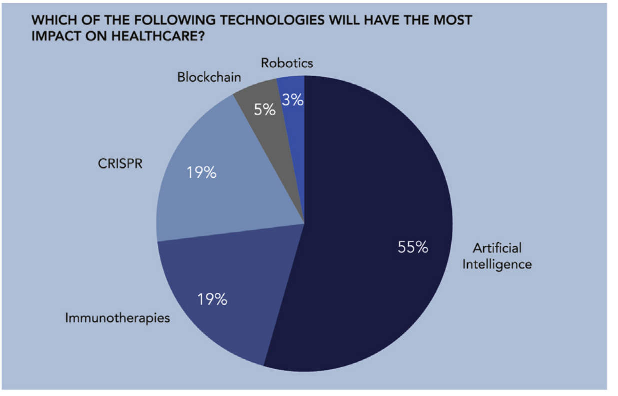

Fig. 2. Technologies impacting healthcare (Source CB Insights (www.cbinsights.com). Research 2019, with permission).

Enabling early diagnosis: properties and key features of technology

For technology to be an enabler in early diagnosis, it needs to embody the following key elements [4]:

- *Intelligence*: the capability to sense or predict and act on those insights. This goes beyond the available or known facts or repetitive learning. Eventually, it is the capability to "make associative sense" of different closely or remotely related things.
- *Natural interface*: the capability to assist the activity, uniqueness, and elements of the human thought process in the natural environment. It encompasses the voice, gestures, and other biomechanical attributes in fulfilling various digital tasks.
- *Ubiquity*: the ability to be universal in interactions, engagements, objects, machines, and individuals. The technologies should have the capabilities to be embedded within everyday objects and simple to use.

One of the biggest opportunities for a clinician in digital health is the availability of data in myriad forms, which was not previously available. Patients spend only a small proportion of time with the healthcare providers in the outpatient clinics or during the inpatient stay. The data for the >99% of the remaining time were not previously accessible but are now being enabled by the digital technologies. The insights from these data can address key issues that clinicians grapple with, such as clues for early diagnosis before the clinical signs and symptoms are apparent, and patient adherence to treatment after the diagnosis. However, skepticism with data-driven prediction models widely prevails among health care providers [5].

In this context, the following discussion outlines important technologies (Fig. 3) that are already playing an important role or are slated to create tremendous impact in different permutations and combinations. We envisage that their utility in rheumatology will grow manifold in the near future. With the amalgamation of various technologies, the emerging newer technologies will play an important role for clinicians to harness their unique properties at various stages of patient management. For example, Amazon Web Services is creating Comprehend Medical. This specialized outfit will mine unstructured medical text from electronic medical records (EMRs) and other patient data by deploying natural language processing [6]. The data outcomes would help the clinicians and patients in various decision-making processes.

Pervasive computing: embedded, proactive, networked digital processors

Pervasive computing (omnipresent computational power enabled by various devices like wearable, smartphone, tablet, or laptop etc.) provides information, media, context, and processing power to the

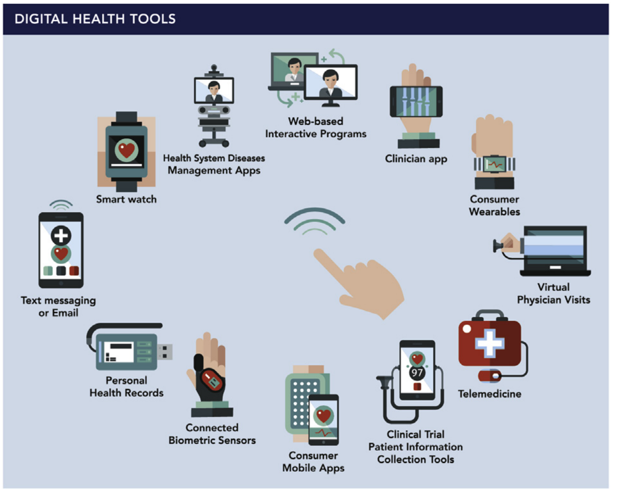

Fig. 3. Digital health tools.

individuals regardless of the situation. This category comprises massive networks of connected microprocessors embedded in everyday objects. The information is shared across the devices with embedded data continuously reconciled in public networks. It is the technology driving the Internet of things (IoT), and unlike conventional computing platforms, its networks are unseen, omnipresent, and available all the time [7]. The information exchange and collaborative potential are not restricted to a single device or a fixed location. Instead, they are distributed all around us. The devices can be mobile, wearable, or implantable [8].

Pervasive computing has the potential to recalibrate the established norms of the clinician–patient interaction. To tap into the opportunities of pervasive computing, the clinicians and the hospital systems need to consider how connected digital devices, networks, and vast data outputs could be embedded in wearable and implantable devices for establishing an early diagnosis, assisting the clinical decision-making process, care pathways, and monitoring the results of interventions.

One good example is VitalConnect's VitalPatch (Fig. 4), which is a single-use and fully disposable biosensor worn on the upper left chest; it monitors 8 vital signs (heart rate with its variability, respiratory rate, skin temperature, body activity, posture, fall detection, and ECG) and delivers in real time to the hospital servers, computers, and mobile devices of health care professionals [9]. It uses an interface called Vista Solution™, which provides easy-to-interpret and actionable patient data visualization (Fig. 5). This interface helps to detect changes in patient physiology earlier than ever and provides physicians and hospital staff a continuous data stream to monitor and safeguard the health of patients in addition to predicting possible events. The uninterrupted stream of data prevents unnecessary readmissions and helps in remote monitoring when the patient is at home.

Wireless mesh networks: high-bandwidth, dynamic, wireless, smart connectivity for telemedicine

The traditional model of connectivity has been the hub and spoke model (akin to a bicycle tyre that has a central pivot and various spokes centered around and moving in harmony) where the devices are connected through fixed points. Now the devices can form their networks, opening-up new possibilities with more efficient collaboration between machines, individuals, and products. Wireless mesh networks (WMNs) are makeshift loops of wireless connectivity where a single device needs to be connected to the Internet. Since WMNs are created from the bottom-up by connections between devices (versus top-down, inflexible network infrastructures), their self-creating and self-repairing properties ensure robust and reliable communication anywhere, at low cost, and without fixed

Fig. 4. VitalPatch (with permission from VitalConnect, Inc., USA, reference [9]).

Fig. 5. Vista Solution™ interface: All patients on a single screen (with permission from VitalConnect, Inc., USA, reference [9]).

infrastructure [10]. One example of WMN is using a smartphone that enables creating a hotspot around it, and all devices connected through it can extract Internet connection to be run in real time.

Despite its huge promise, telemedicine remains underutilized in remote diagnosis and patient management, especially in chronic diseases. This underutilization is primarily due to low-bandwidth connections, which are unable to transmit complex images and video chats. WMN technology is an effective solution to this problem owing to high-speed networks that can handle telemedicine by seamlessly providing data, voice, and video communications.

According to Pew Research Center's consumer senior survey data, the year 2019 found that nearly 24.85 million seniors (~52% of older adults) in the US were open to using telehealth for accessing care. American Telemedicine Company – American Well – is partnering with technology giant Cisco Systems to deliver care through home television sets. This would be particularly useful for seniors who are not so well versed with using tablets or smartphone for availing telehealth services remotely. Comcast is developing an at-home health monitoring device that is capable of detecting falls and potentially paving the path to early interventions in addition to keeping constant vigil over individuals with disabilities [11].

Robotics: precise, agile, intelligent mechanical systems

Robotics blends together mechanical engineering, electrical engineering, and computer science in a manner by which the device operates autonomously or semi-autonomously. Modern robotics embodies three essential traits:

- Accuracy: the ability to carry out arduous and skillful tasks precisely.
- Astuteness: the ability to execute a diverse set of tasks in a quick and easy manner.
- Acumen: the ability to imbibe and apply new learning and competencies.

Robots are becoming our companions, helpers, and tutors in various ways. For example, a programmable robotic dog, called "MiRo," has optical navigating skills, a wide array of smart sensors to detect its surroundings, face recognition technology, etc. Within the realm of health care, robotics is revolutionizing surgery. Another example is the da Vinci Surgical System, which allows physicians to translate their hand movements into precise movements of small instruments inside the patient's body. For the patient, a da Vinci procedure may offer all the potential benefits of a minimally invasive procedure, including less pain and blood loss [12]. We envisage that Robotics shall be applicable in Rheumatology mainly for the rehabilitation process. In addition, as the machine learns more about the diseases, the insights/learning may catch the subtle signs and symptoms earlier before they become apparent for the treating rheumatologists, and it has the potential implications for early diagnosis too.

Intelligent interfaces: wearables, smart sensors, voice assistants

Compared to the traditional keyboards and touchscreens, voice commands are providing more integrated and natural methods of interaction. Images and video feeds can be used to track patient identity, individual movements, gait, gestures, and understanding the context. Advanced voice capabilities, intuiting human gestures responses by the AI system, allow interaction with the complex system in a simplified manner. Intelligent interfaces blend the human centric design techniques with cutting-edge technologies such as virtual reality, augmented reality, computer vision, individual voice interpretations, and auditory analytics. Working in isolation or in various combinations, these advances have the potential of empowering rheumatologists in early diagnosis. For example, a rheumatologist can track and obtain body movements and gaze behavior and different responses to external stimulus with the help of cameras, sensors, and computer vision. Smartwatches and wearables can detect the patient's heart rates, ECG abnormalities, physical movements, sleep rhythms, etc., while transmitting biofeedback in real time to the health care system. Affective computing, which is emotion-sensing software, adds another dimension to the intelligent interfaces. Before the clinical signs and symptoms become apparent, there are several digital footprints the patients start generating depending on their technology savviness. Some of the digital imprints are voluntary (recording symptoms in an app or portal), and the rest are involuntary (search history, location, movement tracker, etc.).

Voice assistant devices are leaving their mark in patient care. Hospitals are examining opportunities to use them in intensive care units and surgical recovery rooms. Also, looking to make the voice assistant an integral part of the care provider team by monitoring doctor—patient interactions, suggesting treatment methodologies and alerting care providers to voice changes that could be an early indicator of a possible health emergency. Northwell Health in New York is in the process to install Alexa in the rooms (in-patient and even their own homes) to enable patients to tap into their medical records. Mayo Clinic is putting voice assistants to use for providing wound care instructions for surgical patients. It is also investigating the ability of technology to diagnose cardiovascular disease and other conditions. Various companies are developing diagnostic tools based on alterations in an individual's voice in an expectation that analyzing subtle variations in tone, clarity, and modulation may help in predicting the onset of psychotic event, stroke, or other health emergencies. Voice assistants in rheumatology could be used for counseling, fixing appointments with rheumatologists, placing request for medications for the elderly or patients with rheumatoid diseases led disability, etc. [13]. To address the burgeoning problem of medication non-adherence a Finnish digital health company, Popit, has started the trial run to improve medication adherence and treatment outcomes for rheumatoid arthritis patients. Popit's solution will monitor chosen patients' pill-taking with a smart device and alerts users through an app if they forget to take their medication. In the initial stage, this is being implemented among 1000 patients in Finland, Sweden, and Norway. Subsequently, this may be expanded to other Central European countries.

The new technologies, when applied in rheumatology, create possibilities of detecting comorbidities and behavioral changes and identifying subtle changes in addition to the known disease features, which may help in early disease diagnosis and remote monitoring.

Cloud computing, big data, and artificial intelligence

Three currently available technologies, namely, cloud computing, big data, and AI (augmented intelligence); when combined together, they unlock key potential of each individual technology's role:

- *Cloud computing* offers access to computing assets, which include software programs, data storage, Internet, and other allied services. The advantage that cloud computing provides is the bifurcation of storage and processing from the device, resulting in singular access to software and data.
- *Big data* is the formation and aggregation of huge volumes of structured and unstructured data derived to obtain new insights.
- AI is the programming and algorithms that enable digital devices to utilize, blend, and dispense data to establish, demonstrate, and predict phenomenon, mechanisms, episodes, and future course.

Although each of the above is very distinct, they all co-exist and combine in myriad forms to create a vast impact. This is because (1) data are available in different forms from multiple sources; (2) the capacity to avail them in many locations and from many devices; and (3) the ability to systematically analyze data and apply them to maximum benefit.

Machine learning: augmented, automated data analysis

The health care system in the US generates around one trillion gigabytes of data every year [14]. In addition to the availability of a huge amount of such data, there is an exponential growth in large-scale computing power. Big data coupled with cheap large-scale computing power potentially creates interesting opportunities for application of deep machine learning and AI [15]. The obtained insights should be able to bring forth new dimensions in diagnostics and render health care more effective. Although in the various stages of evolution machine learning offers transformative potential to not only clinicians but also the entire health care system, machine learning includes a large span of technologies and competencies while being a type of AI. An algorithm is meant to accomplish a specific task, subsequently trained on data, and refined further. The algorithms are repeatedly trained from data sets, with or without extensive guidance, to better the predictions or classifications of available data (involving pattern recognition, statistical modeling, and analytics for decision-making). The process is repeated until the algorithm achieves optimal predictive performance in the data sets used for training. The machine (computer) generates the algorithm on its own rather than being dependent on external human coding (guidance) to execute the algorithm's design or process task. Deep learning is again a type of machine learning that utilizes multiple layers of neural networks with large quantities of data sets to optimize a group of algorithms for performing a specific task.

Machine learning has immense potential for drug discovery and to clinicians in assisting with diagnosis and decision making. The evolution of machine learning promises a paradigm shift in treatment and diagnosis strategies. Instead of waiting for symptoms to appear, clinicians can continuously monitor the key health markers of patients much earlier. This would enable preventive measures and more timely interventions. The advancement and application of big data and augmented intelligence herald a move toward more evidence-based strategies derived from aggregation and analysis of a patient's data, clinical trials, and all other available data sources. The eventual outcome is a personalized plan of action for the patients, which takes into consideration individual differences, salient features, genetic factors, lifestyle, biomarkers with potential threats, and issues that have occurred in patients with the same condition. Data modeling and analytics facilitate these possibilities, and therefore, therapies could be individually tailored for the best possible outcomes.

Machine learning and diagnosis

Medicine practice is an amalgamation of art and science to make diagnoses and render appropriate care by utilizing the waiting time at the emergency room with help of AI systems, which may provide “augmented care.” AI-based methods have evolved as robust tools to revolutionize medical care. Notwithstanding the fact that machine learning has already established strong performance in image-based diagnoses, evaluation of diverse and vast EHR data poses big challenges. In a recent study from southern China, researchers demonstrated that machine learning can interrogate EHRs in a manner akin to the hypothetico-deductive logic used by physicians and uncover interconnections that earlier statistical methods could not do [16]. This study contributes to a growing proof of concept of putting into practice an AI-based system as a mechanism to help physicians in managing large amounts of data, augmenting diagnostic evaluations, and obtaining clinical decision support in an event of diagnostic uncertainty or complexity.

It is an established fact that machine learning techniques improve as the amount of input data increases [17–19]; hence, large volume of data sets and harmonized inputs contribute to the strong diagnostic system. Harmonized inputs describe the data in a consistent manner and enhance the quality of the data using machine learning capabilities.

In terms of adoption and execution, this type of AI-assisted diagnostic system can be integrated in various ways.

- When patients present at the emergency department, their basic history, vital signs, and physical examination findings recorded by a triage nurse could be fed into the framework, allowing the algorithm to generate a predicted diagnosis. The predicted diagnoses prioritize the patients to be seen earlier by a physician. This diagnostic prediction would help to ensure that physicians' time is dedicated to the patients with the highest and/or most urgent needs.
- Assisting physicians with the diagnosis of patients with connective tissue disorders that are quite complex and rare as well. This AI-based diagnostic framework harnesses the power generated by data from millions of patients and would be less prone to the individual biases of physicians. A physician may use the AI-generated diagnosis to broaden diagnostic possibilities, which may not have been obvious at the outset.

In a nutshell, this model is a potential AI framework that extracts clinically relevant information from EHR to accurately predict a patient's diagnosis.

Prediction models have been attempted in two rheumatic diseases. The model for SLE had a sensitivity of 34% and a specificity of 90% [20]. This implies that 66% of the cases remained unidentified. In granulomatosis with polyangiitis, it was reported that in 5 years before diagnosis, there is increased health care activity when compared with those without diagnosis. However, there were no specific symptoms – either solitary or in combination – with sufficient differentiation to build models [21].

In recent years, we have witnessed various FDA-approved AI systems. Some notable ones have been Apple for atrial fibrillation detection, Aidoc for CT brain bleed diagnosis, iCAD for bone density by mammography, Zebra medical – coronary calcium scoring, etc.

Keys to unlocking machine leaning's potential: pitfalls and overcoming inherent challenges

We would like to emphasize here that health care, specifically the understanding of diseases and treatments, is fundamentally different from other areas where machine learning has been used. Despite significant gains in the understanding of disease, the common health conditions remain poorly understood multifactorial processes. Despite its enormous potential, the data-driven technology has yet to make a meaningful impact in the health care system. One of the reasons for this is that this huge volume of health care data remains by and large hidden or otherwise inaccessible to researchers.

Therefore, it is unlikely that administrative data will offer truly meaningful insights when compared with richer clinical data.

Health represents a peculiar challenge for machine learning because of our limited understanding of disease processes, the impact of interventions on different individuals, and the apparent lack of integrated data, which effectively captures the complex information at a meaningful scale. Science has an understanding about only miniscule proportions of proteins, RNAs, mediators, pathways, and their mechanisms. Given these challenges (please see below) with analytical environment, at this stage, we need to be more circumspect about the deployment of machine learning in health and healthcare.

1. *Representative data and appropriate sample size*: Data quality is critical because statistical techniques depend on it to be able to generate insights. Poor-quality data will not yield meaningful insights, and regardless of its sophistication, no analytical method can overcome shortfalls in data sufficiency, representation, or scale. For example, the omission of clinical practice guidelines produced a machine learning algorithm, suggesting that respiratory infections are a leading cause of chest pain, completely omitting cardiac causes. Equally important is to ensure that data inputs are representative. Data pooled from selectively chosen population groups carry the risk of not only lacking generalizability but also generating incorrect conclusions. For instance, an algorithm developed to help detect melanoma should be derived from an appropriate diverse sample; when these data are not used or aren't available, algorithms run the risk of overlooking disease in underrepresented patient populations. Robust and clinically important variables and endpoints should be present. However, this is always a challenge in many data resources.
   In addition, machine learning cannot overcome the analytic constraints posed by the small sample size [22] Dependence on a small sample with fewoutcomes is not possible to overcome with an algorithm, which feeds in additional data elements. This also translates into the difficulty of developing robust prediction models for rare rheumatic diseases such as systemic lupus erythematosus (SLE) and granulomatosis with polyangiitis (GPA) [20,21]. Machine learning will not be able to overcome the limitations in data availability, quality, or generalizability. Appropriate data engineering, data set curation, deployment of rigorous epidemiological methods to eliminate bias, and well-integrated domain expertise are needed to ensure the validity of data, and consideration of Bayesian modeling techniques can reduce data-related challenges.
2. *Validation and reproducibility:* As compared to the conventional statistical approach machine learning algorithms perform well as or better with the data set used to develop them. The evident gain in performance and the resultant insights may be artifacts of the sample and not essentially indicative of truly underlying causal processes. This is always the risk associated with machine learning; to overcome this problem, testing is required in a different population, without recalibration or retraining. In an ideal scenario, this validation is done prospectively or using unified data models, which support validation between different data sources. This method differentiates between algorithm features that are robust across settings (hence truly insightful) and those that contribute marginally ensuring that the vital components of the algorithm are truly informative and continue to remain so that additional insights are generated. Most critical is demonstrating consistent results across settings, which validate the algorithm's utility.
3. *Transparency in algorithms:* The most common criticism of machine learning is that there is no clear understanding of how insights are generated. As no algorithm “understands” its inputs or outputs, key healthcare stakeholders are unlikely to accept machine learning algorithms lacking transparency, as there is a lot at stake during the decision-making process. The users are not aware which part of the algorithm provided a gain over conventional approaches, and hence, the absence of transparency restricts the impact of machine learning [23]. Greater attention to explainable AI is the correct approach to overcome these issues [24]. Clarifying the elements of an algorithm and their unique impact will be increasingly important if machine learning is to establish its credibility with all the health care stakeholders.
4. *Consistency of the insights rooted in science*: Machine learning algorithms must offer credible insights and need to be aligned with the scientific or clinical rationale. Any algorithm failing to replicate established findings or countering the established evidence perhaps indicates either a

methodological oversight or a data artifact than a truly novel insight. An appropriate context with foundation in domain-specific expertise is extremely important. An absence of these would result in decisions which may be analytically logical, but the produced algorithms are not likely to find any takers. For instance, “lack of data” was included as a key risk factor in a recent machine learning algorithm meant to predict cardiovascular events [25]. The unmonitored clusters in real sense may end up generating clinically incomprehensible or irrelevant combinations. Therefore, ensuring that domain expertise guides the structure of an algorithm and provides feedback during its generation minimizes the risk and channelizes the algorithm toward a credible and relevant outcome.

5. *Demonstratable impact and quantification of gain*: The fundamental “Does this machine learning algorithm do something better than we do now, and in doing so, *does this materially change outcomes?*” The impact of a machine learning algorithm needs to be tested and verified like any other healthcare intervention. To detect macular degeneration automatically, Verily has developed an algorithm with an ability to identify lesions that currently providers miss. However, it remains unclear whether the algorithms produce meaningfully better outcomes than screening by ophthalmologists. Combined approaches (artificial and human intelligence) where machine learning algorithms enhance or amplify (augmented intelligence) existing processes instead of replacing them entirely will find greater acceptance at all levels.
6. *Factoring in the clinical and social context:* Without recognizing the context and relevance of data, advanced analytical methods may unknowingly perpetuate systemic problems. In scenarios where the demarcating lines are delicate, the use of specific data may come with important trade-offs. For example, using a patient's socioeconomic status as a representative for external resources may enhance prediction and unintentionally “ignore” low-quality care provided to hapless patient populations. Even typical characteristics (for example, age or sex) need to be carefully considered to prevent generating algorithms, which unknowingly preserve or aggravate unevenness. These possibilities are far reaching, especially when it comes to individual health and health care system per se. To reduce these risks, machine learning methods would be required to recognize data context and deploy approaches that adhere to and safeguard important social values [26].

Software-as-a-Medical-Device (SaMD)

Software is the core of any technology transformation. Software-as-a-Medical-Device (SaMD) permits patients to play a proactive role in self-care [27]. This software program is embedded in the hardware and performs one or more medical functions. Aided by AI-enabled algorithms, SaMD has outperformed the accuracy of diagnoses by trained clinicians. For instance, Google's DeepMind algorithm analyzes 3-D retinal scans, which may soon be able to detect early signs of eye disease six months ahead of clinicians [28]. As SaMD technology evolves further, it can play a transformative role in health care delivery, personalized medicine, and medical research (Fig. 6).

Digital biomarkers: new paradigm

Connected devices such as blood pressure cuffs, ECG monitors, etc. provide parameter-specific measurements, which are clinical indicators about human health. However, the data collected from activity trackers and other consumer wearables should be able to capture variations in these digital measurements (e.g., rotation, GPS movement through space, etc.) and track the health status with outcomes. The data points need to be deciphered using algorithms such as “digital biomarkers, “which can help the clinician identify the right patient and the right time for intervention like a pill or a device and in parallel monitor the disease status.” This opens new avenues for precision medicine.

Various areas have been preliminary targets for the development of digital biomarkers that may affect disease tracking and treatment. Determinants of mobility/motion sleep and sleep disturbances (tracked by wearables) have been used as indicators of disease intensity or impact in almost every major disease. Measuring the progression of diseases in a real-world setting with digital biomarkers bundled with predictive analytics can enable physicians to offer help to the patients whenever it is needed. Likely uses of digital biomarkers in the real-world scenario include the following:

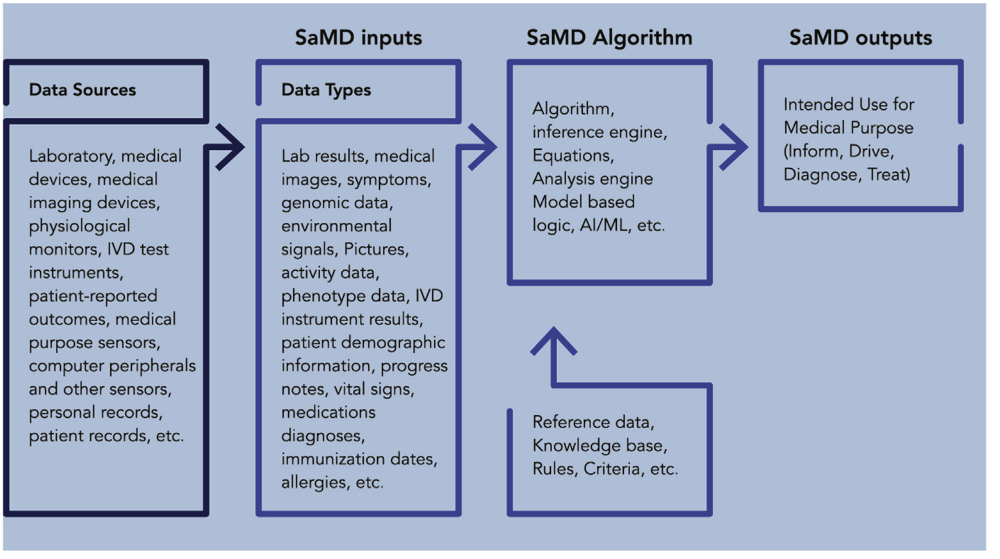

Fig. 6. FDA's description of SaMD components including data sources (Drawn from the information available in Ref. [27]).

- Identifying patients for treatment, using targeted drug, or for inclusion in clinical trials using digital biomarkers in addition to biological biomarkers (e.g., blood tests).
- Ascertaining the drug's efficacy using digital biomarkers to track severity in Phase IV studies.
- Obtaining a better understanding of patient experience while on the chosen therapy.
- Engaging patients for drug adherence and essential lifestyle modifications.

Digital biomarkers are obtained through connected sensors, wearables, and mobile devices by capturing the biomarker data (any substance, structure, or process of the body; its actions; or products) to forecast the incidence of disease or health conditions while tracking the salient aspects or evaluate the outcomes and utility of treatments or interventions. These include both user-generated physiological and behavioral data collected with the built-in sensors, health apps, etc. The value of digital biomarkers is the inherent ability to passively track in real time and utilize the user-generated data to explain, mold, or predict health outcomes. Table 1 lists examples of the digital biomarkers [29–37].

Sunovion is using the Empatica Embrace wearable in a Phase IV clinical study of the seizure drug Aptiom, and Poole Hospital in the United Kingdom is using the Microsoft Band. Devices can send alerts to the patient's kin or caregivers [38].

Early diagnosis with utilization of technology: key strategies

Utilizing patient data

Biomarkers are the cornerstone of rheumatology diagnosis and monitoring of disease progression. Biological biomarkers, digital biomarkers coupled with clinical information in EMRs, and patient data from various sources discussed earlier would identify complex genetic signatures linked to patient responses. Eventually, bigger sample sizes will produce phase IV-quality data and enable algorithms to be trained in different rheumatology disorders in various patient-care settings.

Rigorous, pragmatic, and real data sets would be needed from diverse settings to define and standardize the collection, analysis, and reporting of such real-world evidence. Furthermore, recommended decisions should be subjected to robust analytics to confirm that data methods eliminate biases, are controlled for quality, and allowed for the appropriate incorporation of disparate data sources. Additionally, patient data collection, storage, and usage should comply with increasingly

Table 1
Digital biomarkers.

Disease	Examples of digital biomarkers
Rheumatoid arthritis	Using wrist-worn wearable to measure disease severity (e.g., tracking steps as a measure of activity levels in the period during waking hours)
Parkinson's and Alzheimer's Diseases	Early recognition of disease, associated dementia-related agitation, and disease advancement using motion biomarkers (smartphones for tremors, balance, gait, standing up/sitting down transitions and turns; apps to detect vocal tremors)
Ability to walk during disease conditions	Tracking disease progression – changes in gait or digital biomarker interpretation of the "six-minute walk test" (e.g., in heart failure, multiple sclerosis, pulmonary disease, stroke, spinal cord injury)
Epilepsy	Wearable devices to detect seizures and seizure counting
Migraine	Wearable devices recognizing the patients who have a migraine attack or progress into a migraine attack

stringent data privacy laws, such as the Health Insurance Portability and Accountability Act (HIPAA) in the United States and the General Data Protection Regulation (GDPR) in the European Union [39–41].

Integrating decision support with the EMR

A broad range of competencies would be needed to build a broader analytics platform that integrates rheumatology decision support with EMRs feeding real-time data, as the disease types and prevalence differ in diverse populations [42,43]. Health Level Seven International (HL7)-compliant interfaces and EMR-specific applications would need to be deployed for scrutiny of patient data. Digitization and seamless integration would minimize or eliminate meaningless data entry and provide up-to-date information and insights for the decision-making process.

Currently, different Fast Healthcare Interoperability Resources (FHIR)-enabled tools are linked to EMRs. To visualize genomic information in real time, researchers at the University of Washington [44] and Vanderbilt University [45] are designing applications using the FHIR standard to interface with data in EMRs.

Rheumatologists will also benefit from the insights displayed intuitively through effective visualization in the EMR with the ability to visualize a patient's expected clinical outcome for a certain therapy based on clinical trial RWE data. In addition to enabling clearer interpretation of results, it will also minimize disruption to workflow, avoiding "click fatigue," as clinicians deal with a wealth of information on their screens.

Obtaining meaningful data from patient communications

Portals can be powerful data tools when linked to physician-decision support algorithms. Additionally, well-designed natural language processing (NLP) tools would be needed to extract meaningful data from conversations. Once successful, a range of rich data would be available, including changes in regimen, medication adherence, patient engagement, adverse effects, and qualitative therapeutic benefit.

Linking data-driven systems to patient monitoring

Decision-support systems integrated with EMR shall endeavor to support medical decisions and enable better care when it comes to chronic care in rheumatological disorders. Decision-support solutions could also be linked to quality improvement programs, gathering response to therapeutics, patient compliance, and drug utilization with enhanced sensitivity and accuracy.

Integrating these data-driven measures will unlock a new era in patient outcomes, enabling rheumatologists to effectively analyze and deploy correct strategies in a timely manner.

Summary

Some of the applied strategies for optimizing early diagnosis and preparing for the future would be to keep a close eye on data, sensors, wearables, and various platforms, which will generate the insights needed for personalized, "always-on" decision-making and as a structural backbone in the health ecosystem. Insights providing algorithms are all set to turbo charge the future of health care. Rheumatologists also need to wake up to the numerous possibilities these technologies present [46,47]. Additional capabilities would need to be built around research, developing analytical tools, generating data tools, insights for creating correct algorithms, which will potentially enhance the standards of patient care. Health product development may not only be limited to pharmaceuticals and medical devices but also include software and applications. Patient-centric virtual home and virtual communities housed in highly specialized facilities are places where patients can receive optimal technology-enabled care.

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Conflicts of interest

Suchitra Kataria declares that he has no conflict of interest. Vinod Ravindran declares that he has no conflict of interest.

Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

Practice points

- Voluntary and involuntary digital imprints and data generated by patients through patient apps, patient portal, wearables, etc. provide us real-world information for supporting diagnosis, which was unavailable before.
- Digitization is here to stay, and it may seem daunting initially, but application of technology should be strongly encouraged at all levels in rheumatology practice.
- Artificial intelligence will aid rheumatologists in the process of diagnosis and prognostication by deploying diverse data points for common rheumatological diseases before progressing to include less uncommon ones.
- Digital connectivity provides rheumatologists unique opportunity to crowdsource clinical opinion and, at the same time, to forge real-time multicentric collaborations in enhancing the diagnosis levels with care delivery.

Research agenda

- Research and development of artificial intelligence algorithms for diagnosis of rheumatological disorders without any biases and complete transparency.
- Research into identification of rheumatology-specific digital biomarkers is required.
- eHealth lacks large-scale peer-reviewed digital efficacy studies in diagnosis and patient management. Research groups should focus on creating evidence base for digital health technologies.

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