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Machine Learning for Early Diagnosis of Rare Diseases: A Review

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Abstract:
Diseases with a lot in common but differ a lot in symptoms, age of onset, translation, and more are rare diseases. But they affect 3.5% to 5.9% of the population at some point in life. A lot of rare diseases can cause life-threatening or severely debilitating diseases without timely treatment, so the early diagnosis of these diseases is vital for better outcomes in patients. Most rare diseases take more than three months before being diagnosed. More than half of patients wait a year or more. Patients undergo a barrage of tests, many of which may be of little help due to high false-negative rates. Even when correctly diagnosed, the treatment pathways remain unknown. A major hurdle is the unawareness of general practitioners, who hence send patients to specialized centers. However, these centers can only take on a limited number of cases, delaying treatment. To increase accuracy and efficiency, diagnostic processes must be automated. Machine learning (ML) can help us model vast amounts of data to identify complex correlations. This paper outlines an approach based on machine learning that combines patient and test data with the help of an expert system to improve diagnostic decision-making with minimum delay and better patient satisfaction.

INTRODUCTION

Rare diseases, also known as rare disorders, are medical conditions that affect a relatively small percentage of the population (Sequeira *et al.*, 2021). Although the specific description of rare diseases varies between countries, they are usually defined as being in the lower range of prevalence, often between a range of 1 in 1,000 to 1 in 150,000 (Somanadhan *et al.*, 2023). There are estimated to be between 6,000 and 8,000 rare diseases, which are complex and associated with diagnostic difficulties, as well as challenges in prognosis and management (Chung *et al.*, 2022). Together with therapy development, rare diseases are prioritized through advocacy organizations and state and scientific bodies, since although each one is rare, as a group rare diseases are relatively common: an estimated 400 million individuals live with a rare disease globally (Chung *et al.*, 2023).

Rare diseases can lead to feelings of stigmatization, isolation, discrimination, and loss of self-consciousness (Newman-Toker *et al.*, 2021). Mental health disorders such as anxiety and depression are more prevalent among these patients (Dong *et al.*, 2020). Furthermore, due to the rarity and variety of rare diseases, individuals often face a lack of awareness of their condition and possible consequences when dealing with healthcare providers (Kwok *et al.*, 2021). It is important to remain vigilant for potential symptoms and/or signs of the disease, as this can lead to improved or extended life (Fusar-Poli *et al.*, 2022; Iqbal and Ashraf, 2020). Many patients only get a diagnosis after several misdiagnoses and years after the first symptoms appear (Suzuki *et al.*, 2022). Over time, there is a critical need to increase public and healthcare provider awareness of rare diseases and to prioritize the call for advancement in preventative intervention, early diagnosis, and intervention in the fight against rare diseases (Cleghorn, 2022; Iqbal, 2021a; Iqbal, 2021b; Iqbal, 2023; Iqbal *et al.*, 2021b). Even though they are at low prevalence, collective forces can make significant impacts (Wong *et al.*, 2021).

Definition and Prevalence of Rare Diseases

One of the most important characteristics of rare diseases is, of course, their rarity (Nguengang Wakap *et al.*, 2020). So, what is a rare disease? This seemingly straightforward question has several answers, with different jurisdictional areas of the world defining rare diseases differently (Maher *et al.*, 2021). The defining piece of legislation surrounding rare diseases sets the prevalence threshold to approximately 8% (Hanany *et al.*, 2020). Depending on the number of inhabitants of the predefined area, rare diseases can vary in prevalence (Schaefer *et al.*, 2020). However, absent an official definition, a range from zero to eight individuals per 10,000 inhabitants is taken into account (Arnold *et al.*, 2020). In Japan, a rare disease is anything with a prevalence at or below 4.64 individuals per 10,000 inhabitants (Roessler *et al.*, 2021). Indonesia defines rare diseases to be anything with less than 1 in 50,000 prevalence (Richard *et al.*, 2022).

The impact of these differences potentially has important implications, especially for the allocation of resources for treatments and for policy around rare diseases (Nguengang Wakap *et al.*, 2020). Although each rare disease is rare, the aggregate number of individuals affected by at least one of the 7,000 rare diseases is very large (Turro *et al.*, 2020). Reports estimate the prevalence of rare diseases somewhere between 1 in 1,500 and 1 in 5,000 according to definitions in the United States and Europe (Tambuyzer *et al.*, 2020). However, these diseases disproportionately affect specific geographic, racial, gender, and age populations, with limited to no treatment available (Marwaha *et al.*, 2022). In addition, people with rare diseases are often undiagnosed, with most disease-tracking databases only accounting for diagnosed cases, showing only a fraction of the true prevalence of these diseases (Munro *et al.*, 2022). It is for this reason that better diagnostic classification is sought, with many in the rare diseases world seeking a uniform definition of a rare disease (Haendel *et al.*, 2020).

Challenges in Early Diagnosis

Its early diagnosis becomes a complicated task due to numerous factors, among them misdiagnosis due to lack of knowledge about the disease and delayed recognition, as it often occurs when symptoms mimic more prevalent diseases (Dong *et al.*, 2020). Such diseases are mostly caused by the defect of a single gene, and their symptoms affect various body systems at different ages, leading to more confounding symptoms (Isono *et al.*, 2022). As rare diseases are multifaceted and cause not only healthcare-related concerns but also societal and ethical issues, the importance of understanding them early becomes crucial in terms of disrupting the health of patients and their families (Merker *et al.*, 2022). Another roadblock in the early detection of rare diseases is a lack of exposure to healthcare professionals, which usually leads patients to be misdiagnosed by general practitioners who do not have enough information about the disease, as they commonly do not have any experience or education with it (Yan *et al.*, 2020). The required specialized testing and expert consultation are hindered by financial barriers, which also prevent patients from receiving an accurate diagnosis (Llubes-Arrià *et al.*, 2022). Nevertheless, rare disease diagnosis can often be misrepresented, even though the relevant specialist is involved, in spite of the fact that in order to nail the right etiologic diagnosis, thorough details about the patient's clinical history, pedigree, and requirements are necessary (Faviez *et al.*, 2020). It is a time-consuming procedure that often yields no results (Walkowiak and Domaradzki, 2021). Drug makers are not willing to fund investment in novel medication for a cohort of a few thousand patients in general (Zhou *et al.*, 2022). The rare diagnosis is lengthy due to a lack of diagnostic training and awareness among specialists (Kenny *et al.*, 2022).

The early diagnosis of the disease needs upscaled and cross-functional interventions at consistent advancements to accomplish symptomatic care, regulatory implications, and laboratory diagnostics (Exuzides *et al.*, 2022). This personalized treatment stream incorporates varied specialisms promoting early diagnosis of diseases to function together and pushes for effective treatment and prevention responses (Chengang *et al.*, 2024). For some sets of rare disorders, a genome-wide diagnostic range should be reconciled with a medical and hereditary counseling appointment that documents clinical sequence details and estimates the choices of relatives (Elliott, 2020). Its particularly pressing goal is the effective development of a treatment that might avoid irreversible health issues and be accessible to accommodate (Rose *et al.*, 2020). Many individuals residing with a rare illness may die easily, particularly in the meantime when the earliest symptoms become evident (Brown *et al.*, 2024). Preventive initiatives need to be planned and implemented rapidly for rare diseases (Dolla *et al.*, 2023).

Importance of Early Diagnosis

Early diagnosis is critical in rare diseases to improve prognosis and care (Marwaha *et al.*, 2022). Early detection can prevent disease progression, and timely treatment can spare organs from further damage (Schaefer *et al.*, 2020). Additionally, patients with a confirmed diagnosis have reported improvements in their quality of life (Stranneheim *et al.*, 2021). Late diagnosis can worsen the psychological condition of both patients and their families (Roessler *et al.*, 2021). Patients often move from specialist to specialist, blindly hoping for an answer, in denial that something is wrong, questioning whether the pain is real, or feeling guilty (Stranneheim *et al.*, 2021). Delays in diagnosis can increase costs for public health systems due to ancillary care caused by the complications of the disease that often develop before the diagnosis (Germain *et al.*, 2021). Patients with ultra-rare diseases usually report more misdiagnoses and longer delays in diagnosis than patients with more common rare diseases (Garred *et al.*, 2021). In many cases, timely diagnosis and supportive care can prevent complications and improve prognosis, as in the case of Pompe disease: the delay in diagnosis has been associated with an accelerated deterioration of patients' walking ability (Berger *et al.*, 2021).

Healthcare systems that strengthen early diagnostic capabilities, therefore, are referred to as knowledge-based (Wright *et al.*, 2023). The shift towards this approach should benefit society as a whole through technological and scientific innovation, from increased research and development investments, as well as encouraging autonomy, infrastructural development, and competence in the development and use of artificially intelligent systems in their countries (Abdallah *et al.*, 2023). Providing better training and educational programs on pediatric rare diseases among healthcare professionals should lead to an earlier and correct diagnosis, useful not only to the patient but also to society by reducing healthcare costs (Marwaha *et al.*, 2022). An earlier diagnosis could reduce the economic and social costs in terms of healthcare resources (Stranneheim *et al.*, 2021). Early diagnosis and early treatment initiation have always been a priority for policymakers and patient organizations; the economic framework in which healthcare systems find themselves today requires a comprehensive approach to rare diseases and their early diagnosis (Ramalle-Gómara *et al.*, 2020).

Impact on Patient Outcomes

For many diseases, it has become widely accepted that the earlier we diagnose and intervene, the better the subsequent clinical course for the patient. For rare diseases, this assumption is no different (Limongelli *et al.*, 2022). In rare diseases, delayed diagnosis and management are associated with a range of adverse clinical and psychosocial impacts (Forny *et al.*, 2021). Early diagnosis allows healthcare professionals to provide patients with accurate and reliable prognostic information, effective tailored management, access to new targeted treatments, and the possibility of participating in clinical trials in which they may not have had the opportunity to participate following symptom progression or onset of disability (Schmidt *et al.*, 2021). In addition, many rare diseases result in profound impairments and disabilities that may be ameliorated or amenable to preventive measures if addressed with early intervention prior to irreversible organ damage (Trang *et al.*, 2020). Furthermore, therapeutic outcomes may be substantially improved by preemptive and patient-specific tailored treatments and the reduction of diagnostic 'odysseys' (Luppi *et al.*, 2021).

In relation to the impact of diagnosis on social functioning, earlier diagnosis would also reduce the 'stigmatization' and neglect of patients with unknown disorders due to diagnostic delay (McDaniels *et al.*, 2023). While patients and professionals report that rare diseases are often mismanaged, and there is no doubt that timely diagnosis is essential, modern medical care is not well arranged to expedite it (Da Silva *et al.*, 2020). There is often a focus on technical aspects of medical assessment to define the diagnosis, rather than listening to patients' stories and caring for their concerns (Bielenberg *et al.*, 2021). Patient advocacy and support groups, as well as rare disease collaborations, have been instrumental in raising the profile of rare conditions, securing funding for research, and developing recommendations, and care pathways for their management from the patient's perspective which has led to an increasing engagement at a governmental level (Deng *et al.*, 2022).

Healthcare Cost Reduction

The timely diagnosis of a rare disease is expected to save costs for the healthcare system because patients are often operated on more complex and costly procedures in a later phase (Chung *et al.*, 2020). For many rare ear pathologies, it is expected that timely interventions may prevent conditions from deteriorating to the extent that cochlear implant surgery is indicated (Adachi *et al.*, 2023). As surgery is usually more complex and time-consuming, such partial intervention can be expected to result in a reduction in costs (Willmen *et al.*, 2021). Another important argument in favor of investing in early diagnosis of patients with a rare disease is that it may reduce the use of regular care (Simpson *et al.*, 2021). Long diagnosis often results in a long period of uncertainty about the cause of the physical complaints and results in more frequent

visits to the GP or the hospital (Yan *et al.*, 2020). More frequent use of caregivers can eventually lead to higher healthcare expenditure. In addition, early diagnosis, especially in the group of adults, may also save other healthcare costs due to comorbidity. Adults, for example, often have a paid job (Simpson *et al.*, 2021). They may be completely or partially incapacitated due to rare diseases. This will result in a loss of income for the sick person, but may also result in an extra economic loss for companies. At an early stage, preventive measures can be taken so that people with a rare disease do not have to go on sick leave (Willmen *et al.*, 2023). This may lead to lower direct healthcare costs in the long term but is also beneficial to society (Simpson *et al.*, 2021).

Finally, early diagnosis can cure or stop the progression of chronic symptoms, and this can result in lower long-term care costs. It is increasingly recognized that, next to improving health, investments in timely diagnostics can pay off due to cost savings in healthcare and health benefits to society (Willmen *et al.*, 2021). The cost savings are more than compensating for the health gains and investments in diagnostic technology (Chung *et al.*, 2020). In conclusion, there are many problems in the provision of healthcare in the field of rare diseases (Adachi *et al.*, 2023). Patients visit a large number of care providers before the correct diagnosis is made (Deng *et al.*, 2022). In the meantime, the health of many young patients deteriorates, leading to uncertainty for parents and a heavy economic burden for society (Adachi *et al.*, 2023).

Machine Learning Basics

Machine learning brings predictability to decision-making. Most entities can be formulated as data: food, languages, music, and even diseases (Battineni *et al.*, 2020). This data can then be partitioned into two groups: input features and outcomes (Milad *et al.*, 2022). The first set refers to the independent variables of the dataset being analyzed, and the latter holds the dependent (or output) variables of that data (Navarro *et al.*, 2021). Together, these parameters are utilized for prognosis, diagnosis, decision-making, and many other purposes (Zhang *et al.*, 2020). In summary, machine learning is incorporated within predictive modeling and data analysis (Ramesh *et al.*, 2022).

There are two types of machine learning: unsupervised and supervised learning (Rasool *et al.*, 2023). In unsupervised learning, often reserved for exploratory purposes, the model generates no intrinsic expectations or preconceptions and identifies raw or hidden structures and/or patterns metrically or through visualization, without regard for an initial response. In contrast, supervised learning is very much concerned with outcomes (Khandakar *et al.*, 2024). A regression algorithm is responsible for mapping continuous inputs to a numeric output. In contrast, classification algorithms group together continuous or discrete inputs according to a predetermined class (Gupta and Katarya, 2020). Healthcare professionals are expected to one day work closely with machine learning techniques, whether they are statisticians, software engineers, applied mathematicians, philosophers, or doctors. As modern medicine becomes more data-centric and individualized, large healthcare systems direct more focus toward improving care specific to a given patient (Ahmed *et al.*, 2020). Combining such technologies with medical surveillance leads to earlier diagnoses, which is especially important for rare diseases (Iqbal *et al.*, 2021a).

Supervised vs Unsupervised Learning

Machine learning can be applied using two fundamentally different learning methods: one can train algorithms using labeled data in so-called supervised learning settings and make predictions or diagnoses based on the obtained model; or one can rely on unsupervised learning to identify patterns in data across continuous variables or time-series data to allow for unseen groups of patients, representing new rare diseases or drug-response subtypes. Supervised learning is practical in a diagnostic context for diseases where historical data are available (Banerjee *et al.*, 2023). Unsupervised learning, on the other hand, can reveal patterns

across continuous and multimodal variables that otherwise may be hidden in a complex phenotypic space. In practice, some approaches combine both data-driven and supervised learning by deriving a reduced representation after uncovering hidden or complementary patterns in the data through unsupervised methods (Dingemans *et al.*, 2023).

Classification and Regression Algorithms

A key element of machine learning is to take an algorithm as a template that is automatically adapted to the properties of the data for the problem at hand (Sarker, 2021). The purpose of the algorithms for digital diagnostics is either to classify the input data into predefined classes, categories, or ranges, or to learn associations between input data and an outcome, measure, or diagnostic score. The measures to be generated are, for example, a patient's diagnosis or disease severity (Jo, 2021). For both types of tasks, we may use algorithms that are simply based on values of input variables that have definite numerical meanings, but they could also be based on combinations of data that have a temporal structure. Predictive algorithms that use time-structured data are, of course, able to predict the future course of the associated measure (Siddalingappa and Kanagaraj, 2023). If the outcome measure has either a binary or an ordinal grading, we talk about classification learning; for all other outcome measures, such as those for the melanoma images or diagnostic abilities, we talk about regression learning (Hiran *et al.*, 2021).

Applications of Machine Learning in Healthcare

There are several applications in healthcare where machine learning can help in the diagnosis or prediction. Moreover, when talking about rare diseases, both less data and the disease's characteristics confirm this difficulty (Myszczynska *et al.*, 2020). Rare diseases are diseases that affect a small population. However, in recent years, data recording has improved, as the digitalization of healthcare has increased (Vasey *et al.*, 2021). Machine learning technologies could offer a huge improvement to clinicians in the diagnosis, treatment, and monitoring of their patients, potentially leading to useful personalized medicine (Alowais *et al.*, 2023; Din *et al.*, 2016).

Artificial intelligence has the potential to revolutionize healthcare. By integrating with electronic patient records, AI-powered systems can help verify information, analyze complex data, and derive insights that can be used to guide clinical practice as well as to manage and improve healthcare services (Alowais *et al.*, 2023). There are countless examples of AI and ML being used in healthcare settings, such as predictive analytics, which allow us to anticipate future outcomes for patients on a given treatment or to anticipate future breakdowns of pieces of medical equipment. AI and ML are also used in conjunction with apps and wearable healthcare devices to help patients manage their own conditions, such as diabetics doing blood glucose measurements at home (Nadella *et al.*, 2023). Some of these AI systems are already fully implemented and operational, but in other cases, ongoing studies or trials are investigating the benefits of AI and ML systems before or after their implementation (Yang, 2022).

Conducting trials to assess whether these systems yield the expected outcomes is particularly important in the medical and healthcare sectors given the high risks involved. If trialed successfully, these technologies could have a huge impact on improving patients' outcomes and making the healthcare system financially more sustainable by improving efficiency and identifying cost-saving opportunities (Khan and Alotaibi, 2020). However, given the depth and complexity of these medical and healthcare tools, they remain of limited availability and are still confined to selected national and international institutions (Nadella *et al.*, 2023). In addition, for these technologies to be rolled out, data is required, both in terms of quantity and quality (Alowais *et al.*, 2023). Being able to access this data can be an obstacle to initiating them. For this to happen there needs to be greater collaboration between technologists and healthcare professionals (Ajegbile *et al.*, 2024).

Diagnostic Imaging

Diagnostic imaging is the field of medicine where both the anatomy and function of the human body can be assessed using a range of non-invasive techniques (Liu *et al.*, 2021). The technique is classified based on the principles behind the acquisition and formation, such as anatomic and molecular imaging. The primary classification includes X-ray and computed tomography, magnetic resonance imaging, single-photon emission computed tomography, and positron emission tomography (Kaur *et al.*, 2020). All these imaging modalities effectively diagnose defects in the body, but due to human error, some information may be missed, which in advanced stages can lead to the death of patients. Machine learning and AI algorithms have shown progressive performance in medical imaging, such as image processing, accuracy of results, and completion of data reading in less time (Varoquaux and Cheplygina, 2022). A study using machine learning-unassisted PA reading showed that the correct diagnosis of pneumonia was 92.7% in two projects, which is better than the interpretations of registered radiologists (Rehouma *et al.*, 2021).

Genomic Sequencing

Rare diseases are traditionally diagnosed based on physical, symptom-based examinations performed by expert physicians. These methods yield limited results and suffering for rare disease patients tend to persist or worsen because healthcare sources are not able to diagnose and treat their disorders. Hence, there is a compelling need to develop diagnostic tests based on objective findings in order to provide earlier treatment (Francomano *et al.*, 2023). Oftentimes, the genetic variations associated with these patients have not been discovered. Consequently, the diagnosis of rare diseases depends on multiple laboratory tests for which results are usually inconsistent and can be influenced by a wide range of patient variables, including diet and current medications (Bedirhan *et al.*, 2023).

Newer breakthroughs in the rapid development of sequencing technologies allow physicians to request a genetic examination on patients to uncover detailed information about rare or common genomic variations that affect their health (Ashraf *et al.*, 2018; Kingsmore *et al.*, 2024; Satam *et al.*, 2023). Sequencing refers to the direct analysis of the genetic composition of an individual on a chromosomal level and/or an individual's expressed genes. The human genomic sequence contains several billion units of DNA called nucleotides (Galla *et al.*, 2023). Consequently, a human genome should be represented as a sequence of approximately 3 billion nucleotides. Despite the small size of genes, whole genomic sequencing can generate petabytes of data when sequencing large patient populations (Abdullah and Ahmet, 2020). Digital examination of such large amounts of genomic data in a rare disease population allows the development of machine-learning tools for several diagnostic applications (Shah, 2023).

Case Studies and Success Stories

The tremendous potential of machine learning for the early diagnosis of rare diseases can best be illustrated by real-world application examples. The following list of case studies and ideas of sustainability combines expert opinions from patients, patient advocates, developers, technologists, data experts, researchers, clinicians, and social scientists (Faviez *et al.*, 2024). In combining their insights and experiences, patients, data experts, and developers managed to overcome one of the most pressing problems in the realm of rare diseases: the lack of data suitable for the development of machine learning algorithms. By combining multiple sources of biological data with questionnaire data from patients, researchers could train a machine-learning model to identify previously unknown disease subtypes (Visibelli *et al.*, 2023). To achieve this, they first pre-processed the data, harmonizing multiple types of biological measurements with measurements from questionnaires. Following this step, they selected cut-off values for patient inclusion based on the year of onset of symptoms. They fed the resulting data into a random forest algorithm, which then learned to classify patients into two groups. Additionally, the algorithm suggested the molecules that

might be involved in the presence of disease (Al-Hussaini *et al.*, 2024).

The machine learning model provided an anonymized list of questionnaire-based symptoms, blood values, gene expression values, and microRNA expression values that make it possible to sort a previously unknown patient population into two subtypes. These subtypes were associated with different times before the onset of symptoms, suggesting corresponding disease processes that may occur during the pre-patient phase of the disease. Finally, the analysis pointed to a number of genes as potential markers that could be interrogated for the presence of one of the subtypes (Moon *et al.*, 2023). The latter would need to be followed up in detail in further laboratory and clinical studies. If the initial subtyping generated by machine learning turns out to relate to actual biological differences, the information will be taken into account in the planned data analysis. For this reason, the machine learning model of the disease subtype has served as an inspiration for the preparation of the analysis that takes potential disease course differences into account (Dingemans *et al.*, 2023).

CONCLUSION

Research into the use of machine learning for early diagnosis in the context of rare diseases has consistently demonstrated both past and ongoing applications of computational technologies to facilitate healthcare. An example is the emergence of collaborations between healthcare providers, machine learning experts, and data providers to tackle a previously underserved field. This is of particular importance, given the role of medical imaging in modern healthcare systems and the limited availability of trained specialists to interpret such images. Other studies on computational diagnostics address the more general problems of rare disease recognition and genetic testing, hinting at the potential of machine learning to mitigate global uncertainties faced by patients with undiagnosed disorders.

CONFLICT OF INTEREST

Authors hereby declare that they have no conflict of interest.

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