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AI and Lyme Disease: Pioneering Advances in Diagnostic Accuracy

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Abstract

Introduction and Purpose: Accurate diagnosis of Lyme disease remains challenging due to its varied manifestations and the limitations of current diagnostic tests. This review examines the emerging role of artificial intelligence (AI) in enhancing the diagnostic accuracy for Lyme disease, aiming to understand how these technologies can be integrated into clinical practice.

State of Knowledge: AI and machine learning techniques are increasingly applied to improve diagnostic processes. In Lyme disease, AI models have been developed to identify patterns in clinical data, enhancing early detection and accuracy. Studies have focused on using AI to interpret complex serological results and clinical symptoms more effectively than traditional methods. Additionally, AI has been utilized to analyze geographical and epidemiological data to predict Lyme disease risk areas, aiding in preventive strategies.

Summary: AI holds significant promise in transforming Lyme disease diagnostics by increasing the speed and accuracy of detection. These technologies not only help in overcoming the limitations of current serological testing but also provide a framework for predictive analytics in epidemiology. As AI models continue to evolve, their integration into healthcare systems requires careful consideration of ethical implications and validation on broader scales. Future research should focus on refining AI algorithms, improving data inclusivity, and enhancing interoperability with existing medical systems to fully realize AI's potential in battling Lyme disease.

Keywords: Artificial Intelligence; Lyme Disease; Machine Learning

I. Introduction and purpose

In recent years, there has been a dynamic surge of interest in the potential applications of machine learning (ML) methods across various medical domains. Enabled by programmed algorithms, this innovative realm of artificial intelligence possesses the capability for automatic self-improvement of complex mathematical models through experiential learning and data analysis, aiming to diminish reliance on human involvement. Machine learning algorithms find utility in diverse fields of science where traditional algorithmic design for specific tasks becomes problematic or even unfeasible. Presently, ML systems are being integrated into medicine, generating mathematical models capable of autonomous decision-making such as autonomous disease diagnosis, clinical analysis, therapy effectiveness assessment, and outcome forecasting. The dynamically evolving field of ML, a crucial pillar of AI-focused computer science, continually unveils novel practical applications in medicine. Its vast potential for diverse implementations suggests that in the future, nearly every medical discipline will incorporate aspects of machine learning algorithms, potentially significantly enhancing the efficiency and efficacy of medical procedures while simultaneously streamlining financial investments and reducing the incidence of erroneous diagnoses.

According to the report by Ross em Boyce et al. from 2020, in a review of 1146 referrals of American patients potentially associated with tick-borne diseases, it was found that statistically, in as many as 23 out of 35 cases, at least one error in test ordering or interpretation was identified. As the authors mention, potential errors could stem from a lack of familiarity with current diagnostic and treatment guidelines, leading to misinterpretation of test results, as well as the frequent trivialization of accompanying symptoms in patients due to their early stage [1].

In the review analysis by Berner E. and Graber M. from 2008, the main emphasis was placed on identifying factors leading to diagnostic errors in various medical fields. The authors point out several factors influencing this state, including overestimation of diagnostic accuracy by physicians due to overconfidence and overrated skills, limited access to effective diagnostic methods, prolonged waiting times for medical procedures due to insufficient numbers of specialists, and high costs[2].

Considering the works cited above, it seems necessary to search for effective solutions that can streamline the diagnostic process of diseases. ML and the application of modern tools and techniques that assist specialists in their work may contribute to increasing the efficiency of the healthcare system. A search of the PUBMED database using the keywords "machine learning medicine" in the title or abstract reveals nearly 40,000 scientific publications related to this topic in the last 10 years, with over 30,000 of them appearing between 2020 and 2023, suggesting that interest in ML techniques in medicine is growing at an almost exponential rate. This chapter aims to discuss diagnostic methods for Lyme disease and present the latest publications related to the application of machine learning methods in analyzing the results of these methods.

Lyme disease - general information, symptoms, diagnosis and treatment

Lyme disease is a tick-borne bacterial infection caused by Borrelia burgdorferi. As a systemic disease, it affects many organs, significantly impacting the heart by causing myocarditis and conduction disturbances. Additionally, it affects the musculoskeletal system by inducing joint inflammation and the visual system by contributing to uveitis and keratitis. The involvement of Borrelia spirochetes in the development of skin disorders such as lymphoma or chronic cutaneous atrophy has also been documented [3].

Lyme disease (LD) was first identified in the United States in 1975, in Lyme, Connecticut, in children with inflammatory non-arthritic joint swelling [4], becoming the most common tick-borne infection in the USA. At that time, 28000 cases were reported annually, with an estimated 300,000 cases per year in 2015 by the Centers for Disease Control and Prevention (CDC). Despite the fairly recognizable rash of erythema migrans, it is assumed that the number of unreported cases is significant. Currently, in Europe, approximately 35000 cases are reported annually, and the perspective of time reveals that the disease existed for over a hundred years before the first reports from the USA emerged.

B. afzelii and B. garinii are the dominant causes of borreliosis in Europe, but there have also been cases caused by B. burgdorferi and two less common species, B. speilmanii and B. bavariensis [5].

Infection occurs through the transfer of B. burgdorferi to humans as a result of the bite of an infected tick, Ixodes. This tick undergoes a two-year life cycle consisting of three stages, feeding only once during each stage. Larvae hatch in the summer and are rarely infected with B. burgdorferi because transovarial transmission of the spirochete is uncommon. However, the tick can become infected at any stage of its life while feeding on a host, typically a small mammal such as the white-footed mouse, Peromyscus leucopus, which serves as a natural reservoir for B. burgdorferi. Subsequently, in the following spring, larvae emerge as nymphs. It is likely that it is during this developmental stage that the tick most commonly transmits the infection, possibly due to its small size, which makes it difficult to identify the bite and remove it in a timely manner. Additionally, due to their small size, they engorge more rapidly than adult ticks, requiring time for pathogen transmission. Nymphs are prevalent in the spring and summer when people often frequent tick habitats. They molt in the fall, transforming into adult ticks, while females lay eggs in the spring before dying, initiating a new two-year life cycle [6,7].

To initiate infection in mammals, Borrelia must evade the host's immune response. To achieve this, the spirochetes employ various sophisticated mechanisms, such as active immune suppression, induction of immune tolerance, antigenic variation, hiding the spirochete in specialized tissues resistant to immune reaction, and forming morphologically and physiologically altered forms that may be resistant to antimicrobial treatment. When faced with a hostile environment, such as the presence of antimicrobial agents, a biphasic killing is observed, in which a portion of the bacterial population dies, while persisting subpopulations with pleomorphic phenotypes emerge as looped or ring-shaped bacteria, vesicles, round bodies, spirochetal colonies, or biofilm aggregates. Hence, short antibiotic therapy carries the risk of developing long-lasting subpopulations of B. burgdorferi, capable of cyclically transitioning between dormant and active forms, leading to disease relapses. Furthermore, there is evidence of persistent B. burgdorferi infection in various mammalian species, including mice, rats, hamsters, guinea pigs, voles, dogs, monkeys, and baboons, with clinical studies demonstrating persistent B. burgdorferi infection in humans as well [8,9].

Lyme disease can manifest in three commonly defined stages: early localized stage (associated with erythema migrans on the skin, sometimes accompanied by fever, headache, muscle, and joint pain), early disseminated stage (characterized by multiple erythema migrans, cranial nerve palsy, heart inflammation, or meningitis), and late stage (typically non-arthritic joint inflammation). Early localized and disseminated stages typically present symptoms within a few weeks after tick bite, while later Lyme disease symptoms may occur several months after infection. After completing antibiotic therapy, most infected individuals return to their baseline health. However, a small percentage of patients may still experience extracutaneous symptoms, such as Lyme arthritis [10].

The gold standard treatment for erythema migrans is oral doxycycline at a dose of (100 mg) twice daily for 10 days. Alternative treatment methods for Lyme disease include oral amoxicillin (500 mg) three times daily for 14 days, oral cefuroxime axetil (500 mg) three times daily for 14 days, or oral phenoxymethylpenicillin (500 mg) four times daily. For patients unable to take a β-lactam antibiotic, an acceptable alternative is oral azithromycin (500 mg) once daily for 5–7 days [11-13].

Selected diagnostic methods for Lyme disease are described in the following section.

Available diagnostics

To establish a proper diagnosis of Lyme disease, objective laboratory tests are necessary, as diagnosing it based solely on symptoms is impossible [14].

The currently accepted and widely used diagnostic standard for Lyme disease is a two-tier serological test identifying the presence of antibodies against, among others: B. burgdorferi, B. garinii, B. afzelii. Conventional two-tier tests involve performing a first-tier quantitative test, often an enzyme-linked immunosorbent assay (ELISA), followed by a more specific second-tier test - Western immunoblot. The test result can be considered positive only when both tests - both ELISA and Western blot - show a positive result because ELISA alone may yield an ambiguous result. FDA-approved in 2019 [15], modified two-tier tests include a series of different ELISA tests conducted at each of the two levels.

It should be noted that in the early stage of infection, patients often show negative results in serological tests because the sensitivity of these tests to the presence of antibodies is low (30-40%), so when interpreting the test result, the stage of Lyme disease should be taken into account. Additionally, early antibiotic treatment may cause patients with early-stage Lyme disease to also show negative results. However, in later stages of Lyme disease, antibody tests show excellent sensitivity.

In serological studies of patients with disseminated cutaneous Lyme borreliosis, the sensitivity of tests ranges from 70-95%, and in cases of late-stage Lyme disease, this sensitivity approaches 100%, while after the infection resolves, patients may remain seropositive indefinitely. Within 30 days of infection in untreated individuals, the IgG test result is typically positive. However, if a patient's IgG result is negative, and the IgM result becomes positive after 4–6 weeks, it is likely a false-positive IgM result. Serological tests, however, are not adequate for determining cure because both IgG and IgM antibodies usually persist for a long time after the treatment and resolution of the infection. Furthermore, positive test results may result from a previous B. burgdorferi infection that was asymptomatic, so seropositivity does not always indicate an active infection [10].

At the Second National Conference on Serologic Diagnosis of Lyme Disease convened by the Association of State and Territorial Public Health Laboratory Directors, CDC, FDA, National Institutes of Health, Council of State and Territorial Epidemiologists, and the National Committee for Clinical Laboratory Standards in 1994, the use of a sensitive, quantitative enzyme immunoassay (EIA) or immunofluorescence assay (IFA) as the initial test was recommended. According to the guidelines, Western blot testing should be performed as a second-tier test in cases of positive or equivocal results on the first tier, based on evidence confirming the specificity improvement of immunoblots [16].

Endorsed by the FDA, professional society guidelines approved STTT as a diagnostic tool for Lyme disease in patients exhibiting objective symptoms other than acute EM.

The first stage of STTT functions as a screening test detecting antibodies using a highly sensitive EIA or IFA, assessing blood for the presence of IgM and IgG antibodies (separately or together) reacting to B. burgdorferi antigens. Initially, the basis of the first stage used in FDA-approved tests was sonication of B. burgdorferi culture cells. Although still in use, amendments have been introduced to enhance the accuracy of the WCS approach, including adsorption stages limiting antibody cross-reactions, antibody detection techniques, cell fractionation, and the use of synthetically produced antigens such as surface lipoprotein VlsE, C6, or C10. Studies have shown that C6 or VlsE epitope-based EIA tests are more specific than WCS-based EIAs. IFA is currently rarely used due to specialized technical knowledge requirements, while automated EIA approaches are the preferred, modern choice. If first-tier test results are below a clinically confirmed threshold, the serum is considered negative for antibodies against B. burgdorferi, and further testing is unnecessary. In the case of a positive or indeterminate result, the second stage, including separate IgM and IgG immunoblotting, is conducted [16].

The second stage of the test detects antibodies against B. burgdorferi, focusing on selected standard antigens. This process involves separating proteins from B. burgdorferi in a porous gel through an electric field. These proteins are identified based on their molecular weight, and then transferred onto the surface of a membrane onto which serum containing antibodies against the antigens of this bacterium is applied. Binding of antibody-antigen leads to the identification of specific bands in immunoblots.

For IgM immunoblot, the result is positive if at least 2 out of 3 bands show greater intensity than control sera. This criterion is applied only for symptoms lasting 4 weeks or less, due to the high rate of false-positive results in patients with prolonged symptoms. IgG immunoblot is considered positive if 5 or more out of 10 pre-defined bands are detected. These tests are approved for B. burgdorferi sensu stricto in Lyme disease in North America, however, their effectiveness in diagnosing other Borrelia genotypes in Europe, such as B. afzelii and B. garinii, is limited [16].

Early localized cases of Lyme disease are usually diagnosed based solely on clinical symptoms, especially when a characteristic EM rash appears, and its imitations occur in a patient who lives in or recently traveled to a high-risk area for infection. Testing for early Lyme disease in the first week may yield a low result, as low as around 20% with STTT, because a full immune response takes several weeks. If Lyme disease is suspected but there is no visible rash or the skin lesion is atypical, and initial tests are negative, it is worth repeating the tests about 3-4 weeks later, as immunoblots may then show a positive result. In later stages of Lyme disease, test sensitivity ranges from 70% to 100%, with specificity greater than 95%, including with current FDA-approved test kits. Late-stage Lyme disease symptoms, such as arthritis, typically result in a virtually uniform positive IgG class result according to two-tier criteria, demonstrating similar serological reactivity in late neuroborreliosis. Conversely, in individuals with prolonged symptoms, negative serological test results exclude the presence of Lyme disease [16].

Material and methods

On February 14, 2024, the research team reviewed the literature using the PUBMED database and key phrases such as: (i) “diagnosing borreliosis machine learning”, (ii) “machine learning in the diagnosis of Lyme disease”, (iii) “diagnosing patent borreliosis machine learning”. The work was assessed according to the simplified version of PRISMA guidelines for systematic reviews [17] (see Figure 1). 22, 14 and 15 publications related to each key phrase were identified, eliminating 19 duplicate articles.

Inclusion criteria for the review included: a. original research, literature reviews and case reports; b. papers on the use of machine learning methods in the diagnosis of Lyme disease; c. papers published in English, Chinese or Polish. Publications were rejected according to exclusion criteria such as: d. letters to the editor and conference abstracts; e. studies older than 10 years; f. studies performed in animal models.

Titles and abstracts of 32 selected publications were independently evaluated by two researchers. As a result of the selection based on established criteria, x scientific papers published in English, Chinese or Polish were qualified for further analysis.

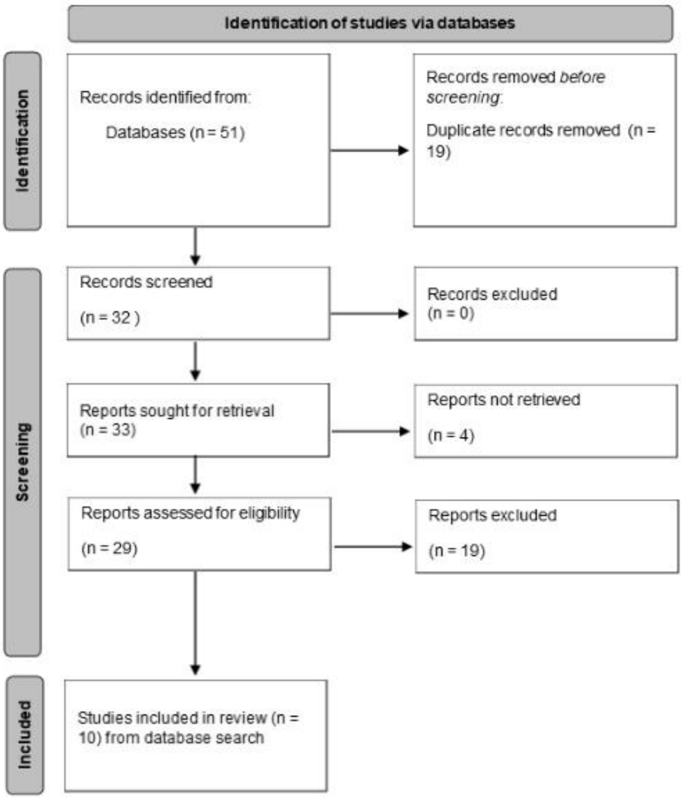

Figure 1. PRISMA 2020 flow diagram [17]

Throughout the chapter, a total of (n=21) references were included to ensure a sufficient scientific background for the presented topics, with section "Results" containing (n=10) substantive references from the citation review, not further considered as review results.

II. State of Knowledge

Results

Authors and year	Study population	Results
Forresta I. S. et al. [18] 2023	1069504 patients with electronic medical records from a large healthcare system	The application of machine learning models significantly increased the effectiveness of predicting Lyme disease compared to conventional analysis techniques.
Boligarla S. et. al. [19] 2023	419 000 unprocessed tweets from the Twitter platform	The study found a correlation between the number of tweets about Lyme disease and the incidence of the disease, but certain differences were observed, as a large number of tweets was not always correlated with the number of Lyme disease cases.
Elkhadrawi M. et al. [21] 2023	2755 samples collected from pediatric patients for screening tests for Lyme	For the rule-based approach, it was established that the frequency threshold was identical to the machine learning classifier in the case of confirming a negative result. Researchers anticipate that the machine learning classifier may

	disease	prove to be more effective in other patient groups than the final rule-based algorithm.
Ichikawa O. et. al [23]. 2019	3639 combinations of samples from patients with Lyme disease and coexisting conditions	The algorithm developed by researchers enables the differentiation of Lyme disease and achieves similar results to infectious disease specialists, using the findings of researchers regarding coexisting conditions. These findings may be useful for personalizing treatment regimens, which could benefit in terms of improving clinical outcomes for patients.
Bobe R. J. et al. [26] 2019	1834 photographs of patients with erythema migrans, including 1718 online images from unidentified individuals with erythema migrans, fungal and infections of the body	After conducting the analysis, the algorithm yielded an accuracy of 86.53%, an ROCAUC of 0.9510, and a Kappa coefficient of 0.7143 in recognizing erythema migrans. The machine almost always achieved better specificity and had the potential to operate with higher sensitivity compared to the machine with evaluation by a non-medical person.
Laison E. K. E. et. al. [28] 2023	20000 tweets collected worldwide from a database containing over 1.3 million tweets about Lyme disease	The study found that among all classification models, BERTweet achieved the highest performance, with an average F1 score of 89.3%, classification accuracy of 90.0%, and precision of 97.1%. The analysis results indicated the effectiveness of BERTweet and DistilBERT classifiers in identifying potential cases of Lyme disease based on user-reported data.
Joung H-A et. al. [30] 2020	50 human serum samples (25 early-stage LD samples and 25 endemic controls), obtained from the Lyme Disease Biobank	Improving the POC test increased its specificity to 96.3%, with a minimal reduction in sensitivity to 85.7% compared to typical two-step serological tests. The results suggest that xVFA tests are more effective in detecting Lyme disease in the early stage compared to conventional serological tests, which typically have low sensitivity (<50%).
Servellita V et. Al. [31] 2022	63 samples of peripheral blood mononuclear cells from patients	Testing the Lyme Disease Classifier panel showed an overall sensitivity of 90.0%, specificity of 100%, and accuracy of 95.2%. The LDC test yielded positive results in 85.7% of patients who were seronegative and persisted for at least 3 weeks in 75% of the 12 patients tested.

Table 1. Results of the Literature Review

Forresta I. S. et al., recognizing the significant burden of Lyme disease infections on the healthcare sector in the United States, developed an ML algorithm in 2023 for diagnosing Lyme disease using routine lipid panel measurements and laboratory tests. The authors focused on studying patients of various ethnic backgrounds enrolled in ambulatory centers of the Mount Sinai healthcare system in New York, with diagnosed Lyme disease and without diagnosis. Researchers applied algorithms to analyze data from anonymous electronic health records (EHR) from the Mount Sinai Data Warehouse (MSDW), covering over 2 million patients within the Mount Sinai healthcare system. They also utilized a method called

Random Forest-based machine learning system, which enabled the prediction of Lyme disease based on lipid measurements, metabolites, and blood cell counts from EHR. The authors presented high accuracy (ACC) of the algorithm, achieving higher scores in receiver operating characteristic curve (AUROC) indicators and performance compared to simple Bayesian models, logistic regression, and support vector machine-based models.

In the validation dataset from MSDW, the model achieved an AUROC score of 0.80 (95% CI: 0.79–0.80), with sensitivity of 0.75 (95% CI: 0.74–0.77) and specificity of 0.74 (95% CI: 0.73–0.75). Meanwhile, in the Bio Me control dataset, the model identified Lyme disease with an AUROC of 0.80 (95% CI: 0.79–0.80), achieving sensitivity of 0.73 (95% CI: 0.72–0.73) and specificity of 0.77 (95% CI: 0.76–0.78).

The use of machine learning model significantly improved the effectiveness of automated Lyme disease prognosis compared to traditional analysis methods. Forresta I. S. et al. emphasize that the model has the potential for clinical application, allowing for preliminary diagnosis without the need for specialized diagnostic tests, thereby enabling positive cases to be referred to specialized hospitals for effective therapy implementation [18].

Recognizing the high frequency of Lyme disease infections, constituting over 90% of all vector-borne diseases in North America, Boligarla S. et al. in 2023 decided to conduct a study to assess the effectiveness of using machine learning techniques to analyze their own posts on the Twitter platform to forecast potential Lyme disease cases and accurately assess morbidity rates in the United States.

In creating the algorithm, the authors utilized the Twitter Application Programming Interfaces (APIs) and the Python library GeoPy to enhance the geolocation of counties and states from the collected tweet database. The team thus analyzed the relationship between spatial and temporal data based on the number of tweets obtained through the best classification algorithm and morbidity indicators for diseases reported to the Centers for Disease Control and Prevention (CDC). Due to its classification accuracy, BERTweet was chosen as the model to classify the set of 419000 unprocessed tweets to assess correlations or forecast Lyme disease cases. Further exploratory data analysis was conducted for additional research purposes.

The study revealed a clear and significant relationship between the volume of secret tweets and the number of Lyme disease cases. Noticeable analogous trends were observed in both cases, although some exceptions were noted. In many of the counties studied, high

Twitter activity was observed, but a lack of reflection of the same trend in CDC data was noted, leading to the conclusion that a large number of tweets does not always correlate with the number of Lyme disease cases. The aim of this study was to demonstrate that using a more extensive, carefully curated dataset can yield significant results, as confirmed by the initial results of Experiment I, where the BERTweet model achieved the highest classification accuracy, with an F1 score of 90%. The current goal of the researchers is to improve the classification of tweets by identifying and labeling truly confirmed Lyme disease-related tweets, which is expected to result in more accurate correlations across all counties in the USA and the creation of an early warning system for this disease in the country [19].

The diagnosis of Lyme disease is currently a significant challenge due to its variable clinical presentation and the lack of widely available molecular methods with sufficient sensitivity. Current routine laboratory tests, based on serological examinations, assess patients' immune response to infection; however, direct detection using molecular methods is hindered due to the biological specificity of the infection [20]. Recognizing the limitations of the currently used two-tiered diagnostic method for Lyme disease, Elkhadrawi M. et al. developed an algorithm in 2023 aimed at improving the effectiveness of early detection of this disease entity by utilizing deep-learning models (DL). Based on confirmed infection results using the Western blot (WB) method, computational models were developed, suggesting the introduction of automated, specialized second-tier tests. These tests, based on recombination, would enable faster and more specific diagnostic procedures. Researchers utilized a cohort of pediatric Lyme disease tests with confirmed WB to assess the most appropriate second-tier antigens for use in confirmatory serological tests. The study constituted a retrospective analysis of all Lyme disease tests conducted between June 2018 and June 2019 at UPMC Children's Hospital in Pittsburgh. It included 2755 samples that underwent serological evaluation for Lyme disease diagnosis. After determining the optimal EIA threshold and frequency selection thresholds at the second diagnostic level, using a rule-based approach with 100 new variants of the dataset, Elkhadrawi M. et al. examined whether the machine learning classifier improved its classifications. The aim of the experiment was to assess the sensitivity, specificity, and accuracy of such an approach, in which all selected proteins in the second test had to show a positive result to consider the test result positive. It was found that for the rule-based approach, in the case of a confirmatory negative result, the frequency threshold (65%) was the same as for the machine learning classifier. Sensitivity, specificity, and accuracy of 83.14%, 87.64%, and 87.5%, respectively, were achieved.

The use of a Support Vector Machine (SVM) machine learning model instead of the traditional rule-based approach yielded similar accuracy of the examined dataset (92%) compared to the currently recognized gold standard, Western Blot IgG method. Therefore, researchers predict that the use of a machine learning classifier as part of the testing algorithm may be more effective if tested on other patient groups compared to the final rule-based algorithm. Because in this case, the rule-based algorithm depends on the initial machine learning classifier, experts suggest continuing research on both solutions [21].

Accurate diagnosis of Lyme disease, which is becoming a major healthcare challenge in the USA, still remains a difficult task and is associated with many difficulties, so it is extremely important to improve clinical therapy for Lyme disease by thoroughly examining this disease and precisely defining patient groups.To address this issue, Osamu I. et al. decided to investigate it in 2019 when they developed a machine learning algorithm, based on in-depth analysis of electronic medical records, to more accurately describe the diversity of Lyme disease, aiming to create models predicting the identification of drugs associated with the risk of developing additional comorbidities [22,23].

The authors utilized an adaptive LASSO estimator, a feature selection method aiding in identifying variables of highest significance associated with comorbidities post Lyme disease diagnosis, to analyze results and classify patients based on disease variables encoded in single-level CCS categories and medication variables mapped to RxNorm ingredient codes. Researchers identified respectively 3, 16, and 17 cases of comorbidities within broader disease categories occurring at intervals of 2, 5, and 10 years post-diagnosis. In the case of more detailed ICD-9 codes, they also discovered associations already known with Lyme disease, such as chronic pain or cognitive impairments, as well as specific comorbidities occurring at time intervals corresponding to Post-Treatment Lyme Disease Syndrome (PTLDS) symptoms. Their work also resulted in the identification of 7, 30, and 35 drugs associated with the risk of these comorbidities within 2, 5, and 10 years. It demonstrated that doxycycline, as a first-line antibiotic, consistently showed benefit in typical Parkinson's disease symptoms, such as back pain. The methodology and results presented in the experiment may suggest new concepts for tailored treatment regimens for individuals with Lyme disease. The findings of this analysis are directed towards medical organizations dealing with comorbidities and may be useful in crafting therapeutic plans. The researchers' discoveries suggest that the use of steroid drugs may increase the risk of developing characteristic post-treatment Lyme disease symptoms. Additionally, the algorithm developed by the researchers differentiates the aforementioned diagnosis, achieving comparable results to infectious disease specialists using the remaining research team's findings regarding comorbidities, as they can facilitate treatment regimen customization, leading to improved clinical outcomes for patients [23].

Untreated Lyme disease can result in neurological, cardiac, and rheumatologic complications, making its prompt diagnosis crucial [24,25]. Considering the limitations of currently used two-tiered tests by physicians, and the fact that they are not recommended for diagnosing infections in the early stage when the risk of erythema migrans (EM) is highest, as they have low sensitivity (below or equal to 40%), it can be concluded that this method is not perfect. In the proper treatment of Lyme disease, it is essential to promptly identify erythema migrans in the acute stage of this disease by both patients and physicians, as this is crucial for rapid diagnosis and commencement of treatment. Despite the crucial importance of early Lyme disease diagnosis, identifying disease changes remains challenging, mainly due to the diversity of forms that erythema migrans often takes.

In 2019, Bobe R J. et al. hypothesized that implementing a deep learning system, which would analyze images of erythema migrans of varying quality and acquisition conditions, could assist infectious disease specialists in making accurate diagnoses of acute Lyme disease. The authors prepared an algorithm whose task was to use a deep convolutional neural network for classifying erythema migrans compared to other skin conditions, including body mycosis, shingles, and normal, non-pathogenic skin. In this experiment, a group of scientists used publicly available photos of erythema migrans and other skin lesions unrelated to Lyme disease, and combined them with photos of actual cases of erythema migrans in patients with acute Lyme disease, collected from healthcare facilities from 2016 to 2017. The compiled data set included 1834 photos, including 1718 images selected online by specialists, as well as 116 photos from 63 study participants. The set also included images depicting cases of mycosis, shingles, and healthy skin. Two physicians described each photo, and a panel of 7 individuals without medical experience was used for comparisons with the machine algorithm. After analyzing indicators such as accuracy, Kappa coefficient, ROC curve, and area under the curve, the algorithm's results showed an accuracy of 86.53%, ROCAUC of 0.9510, and Kappa coefficient of 0.7143 in recognizing erythema migrans.

Researchers suggest that the device may be more sensitive than subjective patient assessment and potentially more accurate than a diagnosis made by a primary care physician, who usually handles the initial assessment of rashes such as erythema migrans (EM).

Considering the frequent cases of missed erythema migrans diagnoses, the use of automatic detection could be beneficial, increasing the number of patients referred for further medical evaluation due to EM rash and minimizing the number of undiagnosed cases. This can help prevent serious, long-term complications associated with late-stage Lyme disease. The results of the above studies clearly indicate significant agreement between machine performance and clinician assessment. Comparing the machine to assessment by a non-medical person showed that the machine almost always had better specificity and could operate with greater sensitivity. Such a situation may bring benefits in the context of screening studies, allowing for early recognition, early treatment, and reduced risk of infection [26].

Early and accurate diagnosis of Lyme disease is currently a significant diagnostic challenge for infectious disease specialists, thus Garcia-Marti I. et al. aimed to present a novel solution that could represent a breakthrough in modeling infection risk. In recent decades, the development of residential areas on the outskirts of cities in Europe has become the norm. This process, called uncontrolled urban development, carries negative consequences for the climate, landscape, and ecosystems, as well as bringing city dwellers closer to nature and rural areas. Certain species of birds and mammals have adapted to life on the outskirts of urban and forested areas, increasing the risk of tick-borne disease transmission. Changes in society's lifestyle, encouraging greater outdoor activity, may increase the risk of tick-borne infections. In 2019, a team of researchers proposed a method for predicting the risk of tick bites based on human exposure factors to bites and the threat posed by these parasites. By utilizing tick bite reports collected as part of two Dutch projects, they were able to compare the commonly used machine learning technique, Random Forest, with four count data models from the Poisson family (accounting for zero inflation). Unlike standard machine learning models, the technique applied by the researchers allowed for the detection of excessive dispersion or zero inflation specific to the data, enabling the prediction of tick bite risk that reflects the original signal reported by volunteers. To create a model that strikes a balance between error and the ability to predict tick bites within a realistic range of data values, various model configurations were tested. By examining indicators such as standard deviation, root-mean-square deviation (RMSD), and correlation coefficient, experts found that zero-inflated Poisson (ZIP) and zero-inflated negative binomial regression (ZINB) models showed better results. High correlation coefficient values and lower RMSD allow for effective detection of excessive dispersion or zero inflation phenomena, opening up the possibility of broad application in ecological modeling and public health. The maps presented in this study demonstrate the use of a new approach to estimate tick bite risk. NB and ZINB models effectively identify areas with low risk, especially in the absence of data. ZIP models are effective for scattered data, allowing for a wide range of estimates. The results indicate areas of low risk according to NB and ZINB maps, while ZIP maps expand the range of estimates, facilitating the location of risk areas in the country. ZIP and ZINB models identify both popular recreational areas with high risk and less frequented areas, which may contribute to public health efforts to reduce the number of tick bites.

Currently, scientists are continuously expanding the current knowledge about tick bite risk modeling by developing and integrating various threat and exposure indicators, thus creating tick bite risk maps for the Netherlands that take into account population exposure analysis [28].

There is ample evidence suggesting that artificial intelligence can be a useful tool in the education process of future infectious disease specialists by identifying the most prevalent infections, such as Lyme disease, nowadays. A team of researchers led by Zhang Y. et al. in 2013 developed a machine learning algorithm (particle swarm optimization with kernel support vector machine, PSO-KSVM) that learns all stages of the model simultaneously from the input phase to the final outcome, rather than sequentially, to recognize Borrelia infection with simultaneous visualization of the damage area [27].

Laison E. K. E. et al. in 2023 conducted a study aimed at evaluating the effectiveness of using a transformer-based classification system to analyze global Twitter data to understand its potential as a tool for Lyme disease surveillance. Aware of the scale of potential consequences of late Lyme disease diagnosis, they developed a classifier model specifically trained to identify potential Lyme disease cases based on self-reported tweets, which may improve Lyme disease monitoring by utilizing alternative data sources such as web data. The authors validated and tested the performance of all classifiers DistilBERT (Distilled version of BERT), ALBERT (A Lite BERT), and BERTweet (BERT for English tweets) using a labeled set of tweets. The study results clearly showed that among all classification models, BERTweet achieved the highest results (average F1 score of 89.3%, classification accuracy of 90.0%, and precision of 97.1%). The study demonstrated the effectiveness of BERTweet and DistilBERT as classifiers of potential Lyme disease cases based on self-reported data. Furthermore, the results also showed that emojis effectively enrich content, thereby improving tweet analysis accuracy and classifier performance.

The presented data unequivocally suggest that methods based on neural networks analyzing data from the Twitter platform can be an effective way to improve Lyme disease monitoring, which in the future could be a tool in the hands of specialists in case of uncertain diagnoses, making early detection of this disease easier. The Lyme disease detection system suggested by the researchers, based on the classifier, utilizes information from tweets to detect possible cases of this disease. Additionally, they argue that there is potential to adapt this technology to other social media platforms, such as Reddit, which is important for analyzing Lyme disease cases in different languages and regions. Despite limitations, such a model could be a valuable tool for researchers and decision-makers, enabling the analysis of Lyme disease trends on social media, especially in areas with low disease incidence [29].

Aware of the limitations of currently used Lyme disease detection methods such as insufficient sensitivity during early stages of Lyme disease and the high cost and long wait time for serological tests recommended by the Centers for Disease Control and Prevention, the team of Joung H-A et al. in 2020 undertook to develop an algorithm specifically trained to detect Lyme disease at an early stage. The task of this economical and rapid bedside diagnostic test is to identify specific antibodies for seven Borrelia antigens and a synthetic peptide using a paper-based multiplex vertical flow assay (xVFA), which may aid in early detection and treatment of this disease.The diagnostic algorithm trained on 50 human serum samples from the Lyme Disease Biobank was used for automatic diagnosis based on multiple immunological reactions. Human serum samples, analyzed twice for IgM and IgG antibodies, allowed for the activation of 200 xVFA, constituting the training dataset. Using this data for computational selection of antigen subgroups contributed to improving diagnostic accuracy and reducing test costs. After training the diagnostic algorithm on 50 human serum samples, high sensitivity (90.5%) and specificity (87.0%) were achieved in detecting early-stage Lyme disease. Further refinement of the diagnostic test improved its specificity to 96.3%, minimally reducing sensitivity to 85.7% compared to standard two-step serological tests. The results indicate greater effectiveness of xVFA tests in diagnosing early-stage Lyme disease compared to traditional serological tests, which typically have low sensitivity (<50%).

The current lack of FDA-approved point-of-care (POC) tests for Lyme disease requires the development of a rapid and effective alternative test, especially in light of the projected increase in cases. Previous multi-tiered studies in Lyme disease diagnosis use expensive laboratory tools and do not provide higher performance. The proposed diagnostic platform based on deep learning allows for rapid multiplex testing in paper form, representing a significant improvement in early-stage Lyme disease diagnosis in POC settings [30].

The continuous progress in the field of artificial intelligence and machine learning algorithms enables the development of diagnostics for many medical conditions, such as arthritis, facial paralysis, neuroborreliosis, and myocarditis caused by late Lyme disease diagnosis.Aware of this, the team led by Bouquet J. et al. in 2022 undertook the development of a specialized classifier panel based on machine learning. By utilizing 263 samples of peripheral blood mononuclear cells from 218 individuals, including 94 patients with early Lyme disease, 48 uninfected control subjects, and 57 patients with other infections such as influenza, bacteremia, or tuberculosis, the researchers conducted a transcriptome analysis using RNA sequencing (RNA-Seq), targeted RNA sequencing, and machine learning-based classification [31].

III. Summary

Contemporary medical practice faces increasing challenges in diagnosing complex disease entities due to their dynamic nature. In this context, the development of computer science, particularly in the field of artificial intelligence, can serve as a significant tool to support physicians in assessing health status, and methods based on artificial intelligence may contribute to earlier and more precise diagnosis and application of appropriate therapies. The literature review on the diagnosis of Lyme disease highlights the importance of using laboratory techniques such as ELISA and Western blot, but their interpretation requires time-consuming expertise. In the future perspective, the use of machine learning techniques may play an increasingly important role in the diagnosis of infectious diseases. This study examines the potential applications of modern innovations in artificial intelligence to streamline the efforts of physicians dealing with infectious diseases, with particular emphasis on Lyme disease recognition. The literature review conducted by the authors emphasizes that utilizing machine learning algorithms can significantly increase the precision of disease diagnosis, as in the case of congenital heart defects. However, further research into these techniques is necessary to ensure the highest standards of healthcare.

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