# Advancements In Diagnostics, Treatments and Precision Medicines of Lyme Diseases – A Review

Md Shamsuddin Sultan Khan [1*], John Anthony Catanzaro [1]

## Abstract

The incidence of Lyme disease, which is caused by the bacteria Borrelia burgdorferi and is transmitted by ticks in 77% of cases, has significantly increased. Skin rashes, neurological, dermatological, cardiovascular, and musculoskeletal problems are all brought on by the illness. Ten to twenty percent of individuals with post-treatment Lyme disease syndrome (PTLDS) do not improve after receiving treatment. It is essential to comprehend the traits of Borrelia burgdorferi in order to create Lyme disease diagnostic equipment and treatments. Since North America has the highest prevalence of infected black-legged ticks, the disease is spread by their bite. Preventing health issues requires early detection and treatment. Lyme disease is diagnosed using diagnostic methods such as PCR, qPCR, RT-PCR, NAATs, NGS, and multiplex PCR panels. Lyme arthritis treatment, longer courses of oral antibiotics, intravenous antibiotics, and post-treatment Lyme disease syndrome are among the treatments available. Precision medicine, also known as customized medicine, tries to modify medical judgments and treatments for specific patients in light of their distinctive genetic makeup, way of life, and environment. The future treatment of Lyme disease will comprise better diagnostic equipment, sophisticated imaging methods, precision medicine, individualized vaccination plans, and patient-centered research.

**Keywords:** Lyme disease, Complications, Treatment, PTLD, Precision medicine.

***Significance*** | Lyme disease's rising incidence, varied symptoms, diagnostic challenges, economic burden, and limited treatments necessitate multifaceted precision medicine-driven approaches for effective management.

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Editor Md Asaduzzaman Shishir. And accepted by the Editorial Board Dec 13, 2023 (received for review Oct 18, 2023)

## Introduction

### Incidence

Lyme disease is a vector-borne disease that has been rapidly on the rise, despite an established treatment plan. The failure to contain this disease is multifactorial. Due to variables like climate, tick populations, and human behavior, the incidence of Lyme disease varies by region and can alter over time (Dumic & Severnini, 2018). While Europe is prominent in central and Eastern Europe, with significant instances documented in Germany, Austria, and Scandinavian countries, North America is most frequently reported in the northeastern and north-central regions of the United States (Sood et al., 2011). Rural and forested areas of Asia, including China and Japan, also experience LD incidents that can have implications on tourism (Donohoe et al., 2015). While increased knowledge and reporting can have an impact on the perceived incidence, climate change has the potential to increase the geographic range of ticks that transmit the disease (Gilbert, 2021). A CDC report presented the geographical distribution of LD in the US (Figure 1).

### Signs and symptoms

The presentation and severity of the symptoms of Lyme disease can vary from person to person. Early localized, early diffused and late stages are the three stages of Lyme disease (Bratton et al.,

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**Please cite this article:**
Md Shamsuddin Sultan Khan, John Anthony Catanzaro, (2023), Advancements In Diagnostics, Treatments and Precision Medicines of Lyme Diseases – A Review, Microbial Bioactives, 6(1), 1-8, 9391

2008). In the early stages patients may have fever, chills, headache, fatigue, muscle and joint aches, and swollen lymph nodes may occur in the absence of rash. Erythema migrans (EM) rash occurs in approximately 70 to 80 percent of infected persons. Later clinical progression in affected individuals can impact the brain system, dizziness, memory issues, and facial paralysis (Bell's palsy). Meningitis or encephalitis can occur in severe situations (Signs and Symptoms of Untreated Lyme Disease | Lyme Disease | CDC, n.d.). Some patients suffer from Chronic Lyme Disease, also called Post-Treatment Lyme Disease Syndrome, PTLDS having symptoms of pain, fatigue, or difficulty thinking that lasts for more than 6 months after they finish treatment (Bratton et al., 2008). The specific cause of PTLDS is unknown and is the topic of ongoing investigation. Lyme disease can lead to myocarditis, inflammation of the Joints (Lyme Arthritis) (Bennett, 2019). If left untreated, it can progress to chronic disease and cause permanent joint damage (Bush & Vazquez-Pertejo, 2018). Ticks can carry pathogens other than Borrelia burgdorferi, resulting in co-infections. These co-infections might make the clinical picture more complicated and necessitate further therapy (Cutler et al., 2021). Moreover, inflammatory reactions and immunological activation in the body can cause tissue damage in a variety of organs and systems, including the skin, joints, and nervous system. It can result in despair, anxiety, and a lower quality of life (Cox, 2020).

**Detection of Lyme disease**

Lyme disease is diagnosed using a combination of clinical assessment, patient history, and laboratory testing. It might be difficult because symptoms can be vague and overlap with other illnesses. Initially blood tests are done to confirm a diagnosis by Enzyme Immunoassay (EIA) or Immunofluorescence Assay (IFA), to check for antibodies. However, testing in the early stages may lead to false negative results (Bratton et al., 2008). Western blot is conducted to confirm the diagnosis targeting Borrelia burgdorferi proteins (Bennett, 2019). Serological tests, therefore, can be time consuming. Therefore, detection of Borrelia burgdorferi sensu lato (Bbsl) DNA using polymerase chain reaction (PCR) may be a useful adjunct to serologic testing for the detection of acute disease. The DNA target of PCR is a conserved region of plasminogen-binding protein gene (OppA2) (PBORB - Overview: Lyme Disease, Molecular Detection, PCR, Blood, n.d.). Besides, qPCR, RT-PCR and NAATs can be carried out with a patient's synovial fluid or seropositive tissues. These are very sensitive and specific tests that are frequently used to confirm Lyme disease diagnoses. Multiplex PCR panels can detect and differentiate tick-borne infections and co-infections (Yagupsky et al., 2019).

**Psych-economic impact**

Patients have to bear increased costs for probable cases that might result from higher healthcare use for diseases unrelated to Lyme disease due to misdiagnosis (Rebman & Aucott, 2020). The delayed treatment can lead to more serious health concerns. People with persistent symptoms even after treatment, can have difficulty to manage and may necessitate additional medical attention (Schoen, 2020). Also, living with Lyme disease, particularly if symptoms are chronic, can have a substantial psychosocial impact (Rebman & Aucott, 2020). A study done in High-Incidence Areas in the United States, finds that Lyme disease puts a substantial economic burden to individual patients and US society. The aggregate cost of diagnosed Lyme disease could be nearly $1 billion annually, not including suspected, undiagnosed, or non-acute cases. These findings emphasize the importance of early and accurate diagnosis to reduce both illness and its associated personal and societal costs (Hook et al., 2022).

**Available Lyme disease treatments and their shortcomings.**

**Antibiotic**

Current medical care is based on antibiotic administration either orally or intravenously, depending on the disease severity. Factors such as the patient's age, allergies, and other medical conditions may influence the antibiotic used. The standard treatment for early-stage Lyme disease is oral antibiotics, especially when there is an erythema migrans (EM) rash but no other symptoms. If the infection has spread beyond the skin, the treatment usually consists of a longer course of antibiotics that are taken orally. In severe cases of Lyme disease, such as those involving the nervous system or the heart, intravenous (IV) antibiotics may be required. This treatment is typically administered in a hospital setting. The overall Lyme disease prescriptions used are shown in the table 1 below, taken from previous studies (Sanchez et al., 2016). Antibiotic dosages are usually different from those applied to adults as shown in Table 2. The concern with antibiotic treatment being the sole treatment strategy is that, they are moderately effective when the total patient population is considered. These antibiotics also come with several adverse effects, thus posing risk to patient health and prognosis. The side effects are summarized below in table 3.

**Vaccine against Lyme disease**

LYMErix, the first Lyme disease vaccine, was authorized in the United States in 1998 and showed efficacy of approximately 76% after completing a recommended three-dose series. However, some adverse health concerns like hypersensitivity reactions were soon reported (Lathrop et al., 2002). Finally, due to lack of public demand the rOspA-based Lyme vaccine was voluntarily removed

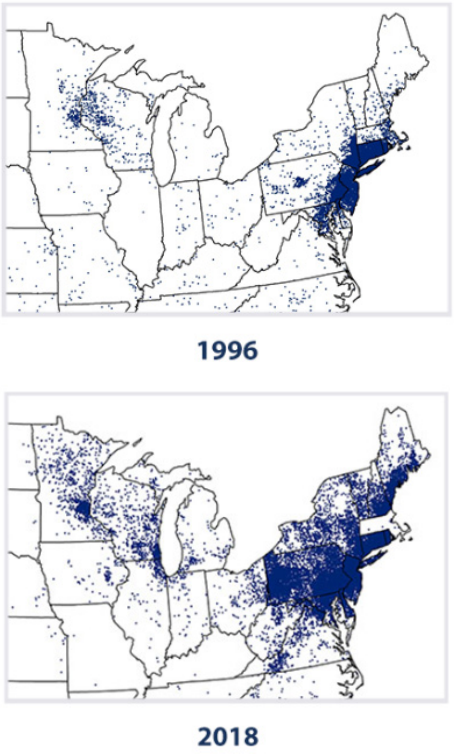


Figure 1: These maps show the distribution of Lyme disease cases reported to CDC in 1996 and 2018. Each dot represents an individual case placed according to the patient's county of residence, which may be different from the county of exposure. The year 1996 was chosen as a reasonable starting point for comparison with recent years. These maps focus on the parts of the United States where Lyme disease is most common. The lack of dots in Massachusetts in 2018 is due to a difference in reporting standards, not an absence of Lyme disease. (*Climate Change Indicators: Lyme Disease | US EPA*, n.d.)

**Table 1.** Available antibiotic treatment (Sanchez et al., 2016)

| Manifestation | Antibiotic | Duration* | Grade* |
|---|---|---|---|
| **Erythema migrans** | Doxycycline 100 mg orally twice daily | 10 days | I-A |
| | Amoxicillin 500 mg orally three times daily | 14 days | IIa-C |
| | Cefuroxime axetil 500 mg orally twice daily | 14 days | IIa-C |
| **Erythema migrans in a patient unable to take beta lactams or tetracyclines** | Azithromycin 500 mg orally once daily | 7-10 days | IIa-A |
| **Lyme meningitis** Ambulatory | Doxycycline 100 mg orally twice daily or 200 mg once daily | 14 days | IIa-C |
| Hospitalized | Ceftriaxone 2 grams intravenously once daily | 14 days | I-B |
| **Lyme cranial neuropathy or radiculopathy** | Doxycycline 100 mg orally twice daily or 200 mg once daily | 14 days | IIa-B |
| **Lyme cranial neuropathy or radiculopathy in a patient unable to take tetracyclines** | Amoxicillin 500 mg orally three times daily | 14 days | IIa-B |
| | Cefuroxime axetil 500 mg orally twice daily | 14 days | IIa-B |
| **Cardiac Lyme disease** Ambulatory | Same as for erythema migrans | 14 days (range 14-21 days) | IIa-C |
| Hospitalized | Ceftriaxone 2 grams intravenously once daily until stabilized or discharged.<br><br>Complete course with oral antibiotic recommended for erythema migrans | 14 days (range 14-21 days) | IIa-C<br><br>IIa-C |
| **Lyme arthritis:** Initial | Doxycycline 100 mg orally twice daily | 28 days | IIa-B |
| | Amoxicillin 500 mg orally three times daily | 28 days | IIa-B |
| | Cefuroxime axetil 500 mg orally twice daily | 28 days | IIa-C |
| Persistent Lyme arthritis after 1st course of oral therapy | Re-treat using one of the above oral regimens | 28 days | IIb-C |
| | Ceftriaxone 2 grams intravenously once daily | 14-28 days | IIb-C |

*Detailed information can be found in the reference source (*Table - PMC*, n.d.)

**Table 2.** Lyme disease antibiotic dosages in children (*Treatment | Tufts Lyme Disease Initiative*, n.d.)

| Antibiotic | Dosage | Maximum | Days |
|---|---|---|---|
| Doxycycline | 50 mg/kg orally, divided into 3 doses | 500 mg per dose | 14-21 |
| Amoxicillin | 4.4 mg/kg orally, divided into 2 doses | 100 mg per dose | 10-21* |
| Cefuroxime axetil | 50 mg/kg orally, divided into 2 doses | 500 mg per dose | 14-21 |

**Table 3.** Side effects of antibiotics used (Choo-Kang et al., 2010)

| Antibiotic | Side effects |
|---|---|
| Doxycycline | Common:<br>Gastrointestinal (GI) disturbances, dermatologic manifestations, cause fetal harm<br><br>Rare:<br>Esophageal ulceration, esophagitis, exfoliative dermatitis, hepatotoxicity |
| Amoxicillin, Clavulanic acid<br>Penicillin G | GI side effects.<br>Rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which are life-threatening |
| Cefuroxime axetil | GI disturbances are common.<br>Rare:<br>Pseudomembranous colitis, SJS, TEN and stomach cramps |
| Ceftriaxone | Common:<br>Injection-site pain and tenderness, rash and diarrhea<br><br>Rare:<br>Pseudomembranous colitis, SJS and TEN |
| Azithromycin (Macrolide) | Common:<br>Nausea, vomiting, diarrhea and rash<br><br>Rare:<br>SJS, TEN, hearing loss or pseudomembranous colitis or arrythmias<br><br>*among macrolides, Azithromycin and Erythromycin are pregnancy category B, but Clarithromycin is category C having adverse fetal effect |

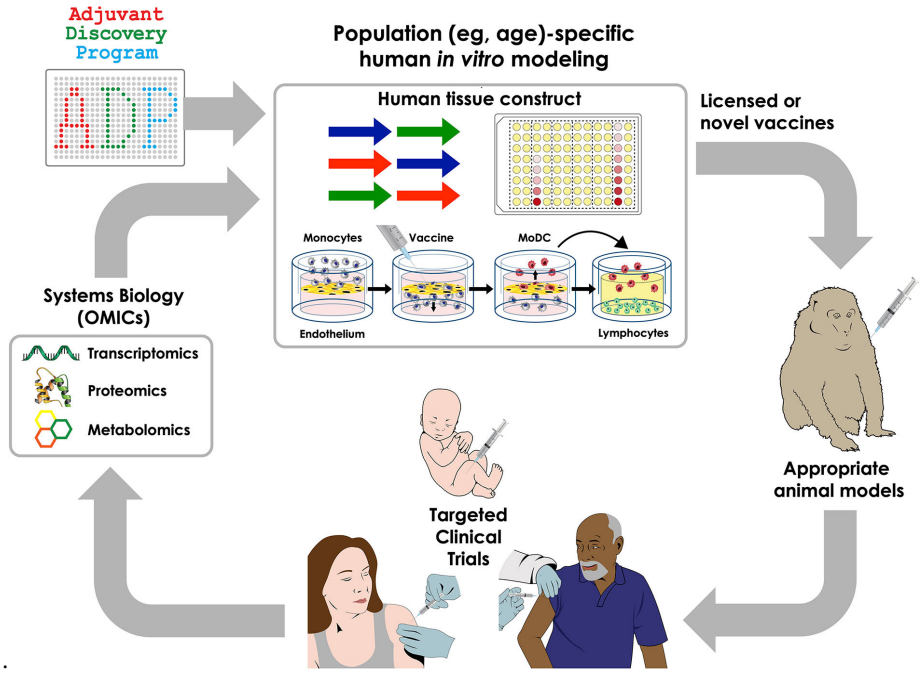


**Figure 2.** Integrated approaches to precision vaccinology (Soni et al., 2020)

from the market in 2002, leaving a vacuum in Lyme disease prevention measures (Stricker & Johnson, 2014).

**Troubleshooting the challenges**

Future therapeutics need to be available at an affordable price, have higher precision, lower treatment duration and be safe for use. Understanding the biology and genetics of Borrelia burgdorferi is critical for developing Lyme disease diagnostic tests, therapies, and prevention measures. The processes by which this bacterium infects and interacts with its hosts are still being studied. The NIH has thus far made a limited annual commitment to LD research compared to many other infectious diseases, and the research community has mainly lacked the essential resources to adequately develop a scientific and clinical understanding of LD and its sequels (Lyme Disease Diagnostics Research | NIH: National Institute of Allergy and Infectious Diseases, n.d.). More research dedicated to Lyme disease eradication is imperative. The primary issues that led to the LYMErix's withdrawal were a combination of vaccine safety concerns, where the vaccine antigen acted as an autoantigen and hence was arthritogenic, vaccine cost, schedule, low public demand, which acts as a guideline for the new vaccine development strategy (Poland, 2011). Other outer surface proteins (Osps), such as OspA, OspC, and Vmps, are important in host interactions. Antigenic variation in variable main proteins allows the bacteria to modify its surface proteins and evade the host's immunological response. Borrelia burgdorferi has a limited range of critical metabolic pathways, making it dependent on resources derived from the host. Such knowledge can be taken into account for the development of diagnostic tools and treatments (Lynch et al., 2023). Due to the ability of this bacterium to mutate, there is an urgent need for precision medicine in the form of single or combination interventions (The Unmet Need for Precision Medicine in Lyme Disease - Clarivate, n.d.). The development of safe vaccines that give broader and longer-lasting protection is crucial for public demand. As chronic Lyme incidence and complications in patients increase, clinical studies have doubled in the past three years. Current trials are focused on both antibiotics (85%) and vaccine candidates (15%), However, despite routine antibiotic therapy, a real-world study by Johnson et al reported that only half of the treated patients showed improvements (Johnson et al., 2018).

**Scope of precision or personalized therapeutics development against Lyme disease (borreliosis)**

Clinicians need information that reflects their patient population to provide individualized care. Today, the ability to analyze large data bases, including patient registries, enables examining treatment variation within the sample and identifying groups of patients that are most responsive to treatment (Johnson et al., 2018). Some notable precision medicine including innovative recombinant protein vaccines and DNA-based vaccinations have been discussed. Fine tuning these related investigations can increase the likelihood of creating better precision medicine. In 2018, evaluated the efficacy of dapsone (diaminodiphenyl sulfone, i.e., DDS) combined with other antibiotics and agents that disrupt biofilms for the treatment of chronic Lyme disease/post-treatment Lyme disease syndrome (PTLDS). DDS combination therapy decreased eight major Lyme symptoms severity and improved treatment outcomes among patients with chronic Lyme disease/PTLDS and associated coinfections (Horowitz & Freeman, 2019).

Another interesting finding was the rediscovery of a neglected antibiotic, hygromycin A, which was potent at killing B. burgdorferi but did not kill most bacteria, including many beneficial gut microbes. It is fascinating that hygromycin A works by blocking the cellular machinery that makes proteins, which is highly conserved across all bacteria. Upon further investigation it was found that B. burgdorferi took up the drug much more easily than other bacteria. B. burgdorferi use a specific protein on their surfaces to take in certain essential nutrients from the environment. This protein allowed hygromycin A to enter the cell (Leimer et al., 2021). If the clinical trials go well, this antibiotic can be a promising alternative to the ones used currently.

Personalized vaccinations could target specific antigens or epitopes relevant to an individual's immunological profile, taking into account characteristics such as genetic vulnerability, immune response, and history of exposure (Castiblanco & Anaya, 2015). These vaccinations may provide various benefits, including improved vaccine efficacy and personalized preventative tactics. To boost protection against different strains of bacteria, personalized vaccinations could target a greater spectrum of antigen variations (Soni et al., 2020). Co-infection factors could be considered since ticks in some areas carry multiple pathogens. Personalized vaccines may be able to target numerous tick-borne infections at the same time, and also help patients with treatment-resistant or recurring Lyme disease (Kullberg et al., 2020). Addressing regional variability in Borrelia strains and tick populations could lead to global adaptability. Second-generation polyvalent outer surface protein (Osp)C vaccines may overcome some of these concerns but the precise antigenic components required for efficacy are uncertain (Hanson & Edelman, 2003). In 2012, Horowitz described a multifactorial model for chronic disease known as MSIDS, or Multiple Systemic Infectious Disease Syndrome (Suvarna, 2012), where the individual patient's risks are evaluated during the initial evaluation. The model recognizes that a "one size fits all" approach using general medical guidelines may not account for individual differences and risk factors. The 16-

point MSIDS model can efficiently screen through multifactorial etiologies contributing to chronic illness and focus on prevention (epigenetics), thus personalizing treatment (Horowitz & Freeman, 2018).

Clinical trials of new vaccines for Lyme disease are currently ongoing. Valneva and Pfizer have developed a Lyme disease vaccine candidate VLA15, which is currently in Phase 3 human trials (Pfizer and Valneva Initiate Phase 3 Study of Lyme Disease Vaccine Candidate VLA15 | Pfizer, n.d.). VLA15 is a multivalent, protein subunit vaccine that targets the outer surface protein A (OspA) of Borrelia. This vaccine is designed to protect people against North American and European strains of the Lyme disease bacterium (Lyme Disease | Lyme Disease | CDC, n.d.). The University of Massachusetts Medical School's MassBiologics has developed a human monoclonal antibody designed to be used as pre-exposure prophylaxis (PrEP) for Lyme disease (Wang et al., 2019). Human trials are expected to begin soon. This approach would provide seasonal protection against Lyme disease. People visiting endemic areas during tick season can get a shot at the beginning of tick season as protection (Lyme Disease | Lyme Disease | CDC, n.d.).

Vaccines aimed at animal reservoirs affect the natural enzootic cycle and reduce hazard by decreasing the number of infected vectors (Gomes-Solecki et al., 2020). A research group explored vaccine options against LD in canines, where they focused on the analysis of immune responses elicited by outer surface proteins OspA and OspC, and examined the lysates of 2 laboratory-cultivated LD spirochete strains for vaccine strategy. They found a dominant conserved antigen in OspC to be an effective vaccine candidate in canines. Whereas, the bacterin (cell lysate) vaccine counterpart stimulated weaker immune response (Izac & Marconi, 2019). Similarly for human vaccines, OspC and live mutant vaccines are being investigated (Gomes-Solecki et al., 2020). Different bioinformatics tools can also be utilized for vaccine development strategies, as illustrated below (Figure 2). Systems vaccinology alludes to the application of systems biology to study vaccine discovery, development, and immunogenicity. Immune signatures measured prior to and after vaccination enable predicting modulated targets and inform optimized vaccination strategies (Tsang et al., 2020). Internalizing the understanding of the signaling pathways involved in vaccine-induced immunity will allow for rational vaccine design and formulation (Pulendran & Ahmed, 2011).

In a recent study, the similarity between tumor cells and Borrelia burgdorferi, sharing an unusual feature about the way they grow, was noted. They found out that cancer cells and Borrelia both rely solely on glycolysis for their metabolism. Thus, Lactate dehydrogenase (LDH) inhibitors, which are used as drug therapies to target certain cancers, might also be an effective strategy against Lyme disease (Research Points to Potential New Medical Therapy for Lyme Disease | ScienceDaily, n.d.). Since earlier time, many DNA vaccine studies have ongoing with OspC a promising vaccine candidate, namely research done with OspC encoding plasmid DNA (Scheiblhofer et al., 2003) and employing OspC DNA tattooing (Wagemakers et al., 2014), a novel vaccination method. In a recent study OspA was also targeted in the making of synthetically engineered DNA vaccines against Lyme disease (Guibinga et al., 2020). All these studies are showing promise in the animal models, and require more examination before going for clinical trials.

**Future directions**

Lyme disease treatment in the future is projected to take numerous viable paths targeted at enhancing diagnosis, treatment, and prevention. Improved diagnostic tools, advanced imaging techniques, precision medicine and treatment personalization, vaccine strategies, co-infection management, tick control measures, treatment alternatives, public awareness and education, global surveillance, and patient-centered research are key areas of future development. PET and MRI scans, for example, can aid in the visualization of Lyme disease-related alterations in tissues and organs. Novel antimicrobial medicines or immunomodulatory therapy, for example, may provide new alternatives for treating Lyme disease. Precision medicine and treatment personalization entail the investigation of genetic and molecular elements that influence therapy responses, resulting in more tailored treatment approaches. Immunological profiling could be used to develop adaptive vaccine schedules in response to a person's changing immune state or anticipated exposure risk. An individual's risk factors, such as geographic location, outdoor activity, and previous tick exposures, could be considered in risk assessment. Attention to personalized vaccine development can help individuals, particularly with specific risk factors or those who may not respond well to traditional vaccine techniques.

Besides clinical approaches, nonclinical interventions are also necessary to combat Lyme disease. Tick management strategies, such as the creation of new repellents or eco-friendly ways, can aid in the prevention of Lyme disease. Lyme disease prevention requires public awareness and education. Global surveillance initiatives are crucial for tracking the development of tick-borne infections, particularly in developing countries.

**Conclusion**

Given the rapidly rising prevalence of LD and the potential for serious long-term health effects in those who contract it, a multifaceted approach is required to improve prevention methods, diagnostic procedures, and therapeutic approaches, as well as to

advance basic research on ticks, tick-borne pathogens, and the pathophysiology of LD. Advanced imaging techniques, precision medicine and treatment personalization, vaccine strategies, co-infection management, tick control measures, treatment alternatives, public awareness and education, global surveillance, and patient-centered research are all viable options for future Lyme disease treatment. A multidisciplinary strategy to improve preventative strategies, diagnostic processes, and therapy approaches is required. Precision medicine is gaining popularity and studies for developing effective personalized therapeutics are underway. Research in this field has started to gain traction and continuing interest will soon lead to advancing therapy development and providing this patient population with adequate care.

## Author Contributions

MSSK drafted the manuscript and made substantial contributions to the design of the study. J.A.C. reviewed and drafted the paper.

## Acknowledgment

The authors are thankful to Neo7bioscience to support this study.

## Competing financial interests

The author has no conflict of interest.

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