Defining post-treatment Lyme disease syndrome: A systematic scoping review

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Abstract

Background

Lyme disease is an illness caused by borrelia bacteria that is generally transmitted to humans through the bite of an infected tick. It is reported that anywhere from 5-20% of patients continue to experience symptoms after completing the standard treatment for Lyme disease which is referred to as post-treatment Lyme disease syndrome (PTLDS). Clinicians do not have a standard definition, symptomatology, or diagnostic procedure for PTLDS which is why this review examined how different studies define post-treatment Lyme disease syndrome.

Methods

PubMed was searched on February 16 2025 for scientific studies that discuss PTLDS. Eligible studies were conducted in the United States, stated a clear definition of PTLDS, and included symptomatology and diagnostic procedures. All studies were either randomized control trials, observational studies, or clinicians' guidelines. Results were narratively synthesized by symptomatology, and grouped by diagnostic procedures.

Results

Nine studies were included, eight of which were patient facing, which resulted in 1,671 participants being represented. Of the included participants, 1,558 were classified as cases with PTLDS and 113 did not have PTLDS. Of studies that reported demographic information, the majority of participants (greater than 90%) across all studies were white individuals with an average age in the 50s. There was a relatively equal representation of gender across studies.

Four terms were commonly included across the nine studies, however there was no consensus about what PTLDS actually entails for patients. The same six studies stated that fatigue, musculoskeletal pain/myalgia, and cognitive dysfunction were primary symptoms. Five studies cited subjective non-specific symptoms as the main indicator of PTLDS. One study did not have any of the aforementioned key words and defined PTLDS as patient-reported symptoms after treatment for Borrelia burgdorferi infection.

Discussion

The literature is not representative of all people at risk for developing PTLDS. More research is needed with a more diverse cohort of patients. There was no standard of duration or intensity for symptoms experienced by patients which limits understanding of the disease. Clinicians should work with researchers to develop a concrete definition for PTLDS to design treatment protocols.

Introduction

Defining Lyme Disease

Lyme disease is an illness caused by borrelia bacteria that is generally transmitted to humans through the bite of an infected tick[1]. The symptoms of Lyme disease vary and typically show up in stages which depends on the length of time from infection to treatment. Stage 1 usually happens within 3 to 30 days after a tick bite, stage 2 symptoms often show up within 3 to 10 weeks after a tick bite, and stage 3 symptoms usually begin 2 to 12 months after a tick bite. In 2023 there were over 89,000 cases of Lyme disease reported to the Center for Disease Control (CDC) however other methods estimate that approximately 476,000 people may be diagnosed and treated for Lyme disease each year in the United States[2].

Prolonged Symptoms in People who have had Lyme Disease

Across studies it is reported that anywhere from 5-20% of patients with Lyme disease continue to experience symptoms after treatment 1-3. The CDC does not have a definition for post-treatment Lyme disease, a recommended treatment plan, or any diagnostic criteria listed for clinicians[3]. The CDC does recommend and encourage using Post-Treatment Lyme Disease Syndrome (PTLDS) to reference the condition where patients experience prolonged symptoms due to Lyme disease and discourages the use of Chronic Lyme Disease. The CDC emphasizes the need for further research into prolonged symptoms as they can “have devastating effects on a person’s life. There is a critical need to better understand the causes of prolonged symptoms in people who have had Lyme disease and best approaches to treatment and care.” [3].

Lyme Disease and Social Equity

Post-treatment Lyme disease syndrome comes with significant barriers in access to care due to the stigma surrounding PTLDS. Patients struggle with finding clinicians to treat them, having insurance cover their care, and facing discrimination, disrespect, or general difficulties when obtaining care[4]. These barriers are further emphasized within marginalized groups. One primary issue for marginalized populations is the diagnostic

criteria associated with Lyme disease. There is a clear under-recognition of identifying erythema migrans rashes (EM) in people of color. EM rashes are one of the most utilized diagnostic criteria for identifying and treating Lyme disease, and the lack of imagery depicting EM rashes on people of color contributes to the diagnostic delays experienced by people of color. These delays are further associated with persistent symptoms and developing PTLDS.

Disparities in Lyme disease can be explained by the Health Belief Model. The Health Belief Model is a theoretical model that explains an individual's perceptions around their risk of disease and their subsequent health-related behaviors[5]. Lyme disease surveillance and interventions have produced a homogeneous group as the most at-risk group for developing Lyme disease and subsequently developing PTLDS[4]. This group is primarily white, middle to upper middle class individuals, and completely discounts the larger Lyme disease population. The discounting of minority groups leads to an at risk population being unaware of their true risk. One study showed that in Maryland and Virginia, minority groups were less familiar with the transmission and symptoms of Lyme disease, despite the minority groups working in high-risk occupations like landscaping-related services[4]. Already marginalized populations are at a higher risk for contracting Lyme disease due to their higher-risk occupations, facing delays in diagnosis and treatment due to the unrepresentative diagnostic criteria and not understanding their risk for the disease. The delay in treatment can lead to more serious complications and poor outcomes including PTLDS[8]. If at-risk populations are unaware of the risk that Lyme disease poses, the signs to look for with Lyme disease, and the way to treat Lyme disease, they are less likely to take action in pursuing treatment, checking for ticks, and taking preventative measures. The minimized perceived risk of Lyme disease in marginalized populations is what is contributing to the delay in treatment and complications associated with Lyme disease.

Rationale

Patients who develop PTLDS have significantly lower life functioning compared to patients without PTLDS 6. In addition to the physical and mental effects of PTLDS, the underdiagnosis and inadequate treatment can lead to depression and anxiety in patients[7]. The lack of awareness among healthcare providers, overlapping symptoms, and limited treatment options further complicate reaching a diagnosis and finding relief from PTLDS. Spreading awareness about the different challenges associated with PTLDS, identifying the range of possible definitions, and providing support for further research into PTLDS will help patients moving forward be able to advocate for themselves, understand what their clinicians mean, and will aid clinicians in best treating their patients. Identifying the different definitions of PTLDS, where they are similar and where they are different, could lead to creating a standard definition that

patients and clinicians alike can use to improve the quality of life for patients and promote their general health and wellbeing.

Review question

How do different studies define post-treatment Lyme disease syndrome?

Methods

I pre-specified my methods in advance.

Inclusion Criteria

To be included, studies must:

- Clearly define chronic Lyme disease
- Include diagnostic criteria for chronic Lyme disease
- Indicate diagnostic tools used to diagnose chronic Lyme disease
- Be conducted in the United States
- Be either Randomized Clinical Trials, Observational Studies, or Practical Guidelines

Chronic Lyme disease may be substituted by “post-treatment Lyme disease syndrome”, “post-treatment Lyme disease disorder”, and/or “post-treatment Lyme disease”.

Searching

I began my search using the PubMed database. I ran my preliminary search on February 16th, 2025. I utilized the following search terms: “chronic Lyme disease” OR “post-treatment lyme disease” AND diagnos* AND defin*. This search yielded 54 results. I displayed all of my searches as abstracts and saved a PubMed file to later upload for screening.

Screening

I uploaded my PubMed search results to the web application Rayyan. Rayyan is designed to help streamline the search process by assisting with screening. I screened studies by title and for key terms in the abstract, then again by reading the full abstract, and then at the full text stage.

Data Extraction

I extracted information on the following variables:

- Methods (study setting and study design)
- Year study was conducted and year study was published

- Diagnostic steps taken
- Diagnostic tools used
- Key words in definition (ex. “lethargy” “arthritis” “swelling” etc.)
- Number of participants and participants demographics
- Participant recruitment strategies
- Funding and authors’ background

Data Synthesis

I narratively synthesized the definitions in the studies and grouped them by the key words describing PTLDS symptomatology and then grouped definitions based on the tools used by professionals to assess case’s symptoms.

Critical Appraisal

I did not use a formal tool to assess risk of bias across studies, however when reviewing studies I considered the funding source and the publisher credentials as measures of study quality and validity. Studies that reported no funding or funding from an independent source (e.g. government) were considered more reliable than studies that noted funding that could be from an organization that had vested interest in the outcome. Studies that were conducted by “Lyme literate” professionals, or not professionals, who tend to advocate for specific chronic Lyme disease diagnoses without having high-quality research to support them will be considered unreliable as well. Study authors with verified credentials in their respective fields will be considered more reliable. Reliable fields include medicine, epidemiology, and clinical research.

Results

Results of the search

Initial searches returned 54 articles, there were no duplicates so all 54 were screened for titles and abstracts (Figure 1.). I retrieved and screened 29 full text articles, excluding 20 due to: wrong study design (11 articles); no definition of chronic Lyme disease (5 articles); wrong country (1 article); wrong outcome (1 article); too old (1 article); and redacted articles (1 article). I included nine studies in my review.

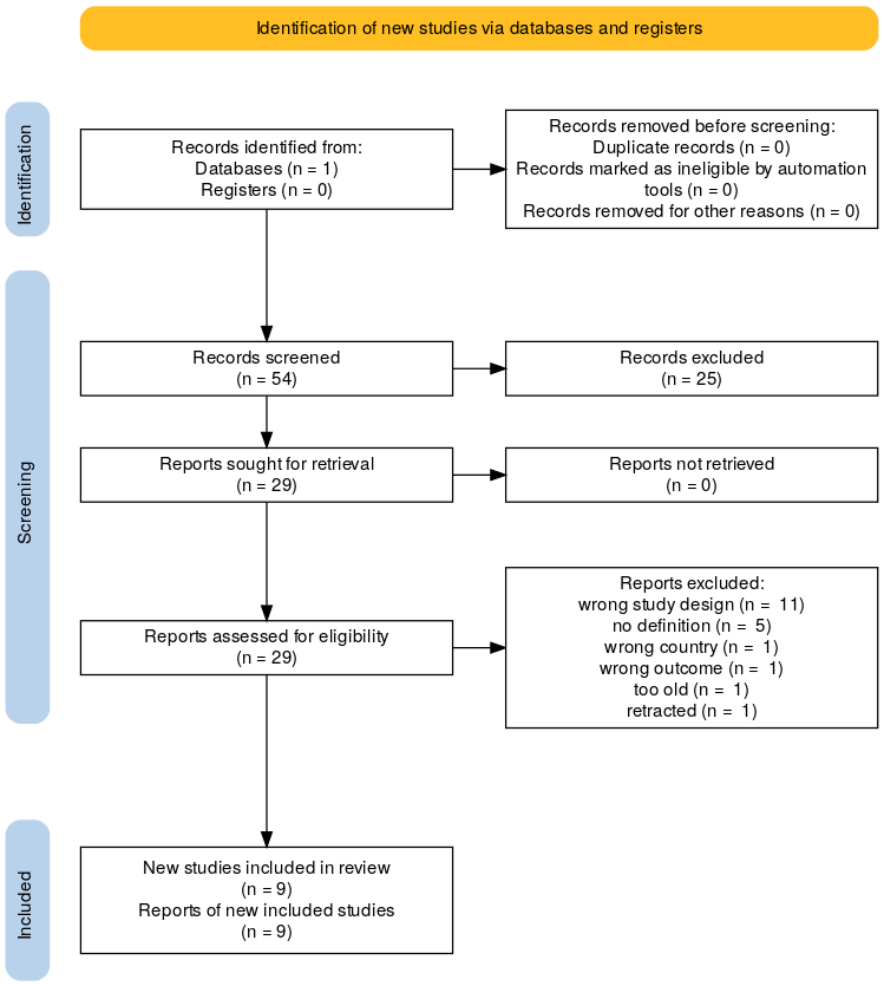

Figure 1. PRISMA diagram of study flow

Characteristics of Included Studies

Table 1 includes details of the nine included studies. Across the eight studies that were patient facing, 1,671 individuals were represented. 1,558 of these individuals were considered cases with some form of post-treatment Lyme disease syndrome, 113 did not have post-treatment Lyme disease. Five studies were cross sectional, two were prospective cohorts, one was a retrospective cohort, and one report was a practical guideline for practicing epidemiologists developed without patients. Five studies used patient surveys, three studies used serologic testing, and three studies used patient history to identify symptoms and markers or signs of post-treatment Lyme disease. Four studies recruited patients from clinical settings, one study used archived samples, two studies did not report how participants were recruited and one report did not recruit participants. All studies listed diagnostic criteria and a definition for post-treatment Lyme disease.

Table 1. Characteristics of Included Studies

Study ID	Study Design	Diagnostic Steps	Recruitment	Participants
Aucott2013[9]	Prospective Cohort	PT Surveys	Adults being evaluated for skin lesions or primary care offices, referred and screened, eligible cases had a diagnosed EM and evidence of systemic disease	Cases (n=71) Controls (n=14)
Aucott2022[10]	Prospective Cohort	Serologic Testing	Adult PTs with early LD self-referred or were recruited from primary or urgent care settings Cases(n=234) Controls (n=49).	Cases (n=234) Controls (n=49)
Fitzgerald2021[11]	Case-Control	Serologic Testing	Study samples were obtained from 2 separate cohorts. Cohort 1 consisted of archived serum samples from PTLDS and non-PTLDS patients with LD obtained at New York Medical College from 1991 to 2011. Cohort 2 consisted of retrospective serum samples from PTLDS and non-PTLDS patients with LD obtained at Johns Hopkins University between 2008 and 2012	$Cases_1$ (n=11) $Controls_1$ (n=10) $Cases_2$ (n=13) $Controls_2$ (n=13)
Hirsch2020[8]	Cross-Sectional	PT History & PT Surveys	Mailed questionnaires to > 5K individuals with an LD diagnosis in PA health system records. Cases reported treatment, a rash, and a positive blood test.	Cases (n=778)
Horowitz2018[12]	Retrospective Cohort	Serologic Testing & PT Surveys	Adults recruited from a specialized LD medical practice using email and phone calls.	Cases (n=200)
Monaghan2024[13]	Cross-Sectional	PT Survey & PT History	Children with confirmed LD diagnosed 6M-10Y prior to enrollment; data extracted from electronic health records.	Cases (n=102)
Touradji2019[14]	Cross-Sectional	PT History & Serologic Testing	NR	Cases (n=124)
Turk2019[15]	Cross-Sectional	PT Surveys & PT History	NR	$Cases_D$ (n=15) $Controls_D$ (n=14) $Cases_V$ (n=10) $Controls_V$ (n=13)
Wong2021[16]	Practical Guidelines	N/A	N/A	N/A

PT: Patient; LD: Lyme Disease; EM: Erythema Migrans Rash; NR: Not Reported; IDSA: Infectious Diseases Society of America

Critical Appraisal

Three studies reported statements of potential conflicting relationships that were considered to be relevant (Fitzgerald 2021, Aucott 2022, and Monhangan 2024). Fitzgerald 2021 reports that a contributing author received research grants from the NIH and is an unpaid board member of the American Lyme Disease Foundation. Aucott 2022 reports that contributing authors have received grants for work on Lyme disease and Monaghan 2024 reports being currently employed by the National Institutes of Health however all information was collected prior to their employment.

Another appraisal element that was originally being considered was the groups who authored the studies and their credibility. All studies were conducted by credible groups with appropriate qualifications.

Synthesis of Findings

Across all nine studies, there were several commonalities amongst the definitions of PTLDS, however there was no consensus about what PTLDS actually entails for patients. Definitions will be synthesized based on the symptomatology they associate with PTLDS and within that, grouped based on the tools used by professionals to assess case's symptoms.

Fatigue

Six studies (Aucott 2013, Fitzgerald 2021, Hirsch 2020, Horowitz 2018, Touradji 2019, and Wong 2021) cite fatigue as one of the primary symptoms associated with PTLDS. Aucott 2013, Wong 2021, and Fitzgerald 2021 state that fatigue must be present for at least six months post treatment and do not indicate a threshold of severity while Aucott 2013 states that levels of fatigue post treatment must be higher than pre infection. No study defines what fatigue means for patients nor did studies indicate how their tool or method was utilized to measure fatigue.

Table 2. Fatigue Measures

Study ID	**Tool/Method Used to Measure**	**Timescale required to meet diagnostic criteria**	**Severity required to meet diagnostic criteria**
Aucott 2013[9]	Patient Surveys	≥ 6 months	Level of fatigue must be higher post treatment than pre infection
Fitzgerald 2021[11]	Serologic Testing [a]	≥6 months	NR
Hirsch 2020[8]	Patient Surveys & Patient History	NR	NR
Horowitz 2018[12]	Patient Surveys & Serologic Testing	NR	NR
Tourajid 2019[14]	Patient History & Serologic Testing	NR	NR
Wong 2021[16]	Patient History	≥6 months	NR

Musculoskeletal Pain/Myalgia

Six studies (Aucott 2013, Fitzgerald 2021 Hirsch 2020, Horowitz 2018, Touradji 2019, and Wong 2021) include musculoskeletal pain as a symptom associated with PTLDS. Wong 2021 does not use the language of musculoskeletal pain rather uses the term

myalgia which is a medical term for muscle pain and Hirsch 2020 says muscle pain. Aucott 2013, Hirsch 2020, Horowitz 2018, Wong 2021, and Fitzgerald 2021 indicate that this pain must be occurring for at least six months post treatment while Aucott 2013 includes an additional threshold that at least three areas of the body are affected by musculoskeletal pain.

Table 3. Musculoskeletal Pain/Myalgia Measures

Study ID	**Tool/Method Used to Measure**	**Timescale required to meet diagnostic criteria**	**Severity required to meet diagnostic criteria**	**Language Used**
Aucott 2013[9]	Patient Surveys	≥ 6 months	Affects ≥ 3 areas of the body	Musculoskeletal Pain
Fitzgerald 2021[11]	Serologic Testing	≥6 months	NR	Musculoskeletal Pain
Hirsch 2020[8]	Patient Surveys & Patient History	≥6 months	NR	Muscle Pain
Horowitz 2018[12]	Patient Surveys & Serologic Testing	≥6 months	NR	Musculoskeletal Pain
Tourajid 2019[17]	Patient History & Serologic Testing	NR	NR	Musculoskeletal Pain
Wong 2021[16]	Patient History	≥6 months	NR	Myalgia

Cognitive Dysfunction

Six studies (Aucott 2013, Fitzgerald 2021, Hirsch 2020, Horowitz 2018, Touradji 2019, and Wong 2021) include some elements of cognitive dysfunction as a symptom associated with PTLDS. Horowitz 2018, Wong 2021, Touradji 2019, and Fitzgerald 2021 specifically use the language or cognitive difficulties, dysfunction, or complaints when discussing this element of the symptomology. Aucott 2013 and Hirsch 2020 cite PTLDS patients will experience memory changes, difficulty finding words, difficulty focusing or concentrating. Aucott 2013, Hirsch 2020, Horowitz 2018, Wong 2021, and Fitzgerald 2021 indicate that cognitive dysfunction must be occurring for at least six months post treatment without including a threshold for what cognitive dysfunction indicates. Studies did not indicate how their tool or method was used to measure cognitive dysfunction.

Table 4. Cognitive dysfunction measures

Study ID	**Tool/Method Used to Measure**	**Timescale required to meet**	**Severity required to meet**	**Language Used**

		diagnostic criteria	diagnostic criteria	
Aucott 2013[9]	Patient Surveys	≥ 6 months	≥6 months post treatment	PTLDS patients will experience memory changes, difficulty finding words, difficulty focusing or concentrating
Fitzgerald 2021[11]	Serologic Testing	≥6 months	≥6 months post treatment	PTLDS patients will experience memory changes, difficulty finding words, difficulty focusing or concentrating
Hirsch 2020[8]	Patient Surveys & Patient History	≥6 months	≥6 months post treatment	Muscle Pain
Horowitz 2018[12]	Patient Surveys & Serologic Testing	≥6 months	≥6 months post treatment	Cognitive difficulties, dysfunction, or complaints
Tourajid 2019[14]	Patient History & Serologic Testing	NR	NR	Cognitive difficulties, dysfunction, or complaints
Wong 2021[16]	Patient History	≥6 months	≥6 months post treatment	Cognitive difficulties, dysfunction, or complaints

Subjective Non-Specific Symptoms

Five studies (Aucott 2013, Turk 2019, Monaghan 2024, Wong 2021, and Fitzgerald 2021) begin their definitions by emphasizing that the symptoms associated with PTLDS are either subjective, nonspecific, or both subjective and nonspecific.

Table 5. Measures of Subjective Non-Specific Symptoms

Study ID	Tool/Method Used to Measure	Language Used
Aucott 2013[9]	Patient Surveys	Subjective symptoms
Fitzgerald 2021[11]	Serologic Testing	Persistent subjective symptoms
Monaghan 2024[13]	Patient Surveys & Patient	Relapsing nonspecific symptoms

Study ID	Tool/Method Used to Measure	Language Used
	History	
Turk 2019[15]	Patient Surveys & Patient History	Residual nonspecific symptoms
Wong 2021[16]	Patient History	Accompanying nonspecific symptoms

Subjective symptoms are “arising out of or identified by means of one’s perception of one’s own states and processes and not observable by an examiner.”[17] meaning that subjective symptoms cannot be measured by clinicians and cannot accurately be observed. Defining a symptom as nonspecific could indicate that it is either not caused by a specific agent, not restricted to a particular category, region, or group, and/or it has a general effect[18]. No paper clarifies what is meant by subjective nonspecific symptoms nor did studies report how their respective tools/methods were used to measure subjective nonspecific symptoms.

Discussion

Summary of Main Results

There was no consensus across the nine included studies on a definition for post-treatment Lyme disease syndrome. There were similarities of what researchers identified as the symptomatology of post-treatment Lyme disease syndrome including experiences of fatigue, musculoskeletal pain, cognitive dysfunction, and subjective non-specific symptoms [8-16]. Subjective non-specific symptoms are symptoms that clinicians classify as not observable, are not caused by a specific agent, and/or are not restricted to a particular category, region, or group [17-18]. Across the nine studies, there was some consistency with certain studies citing that certain symptoms needed to persist for at least six months post treatment. However only one study, Aucott 2013, indicated the level of severity required to meet diagnostic criteria for symptoms. There were few consistencies across the literature to define post-treatment Lyme disease syndrome.

Strengths and Limitations of the Literature

All studies were authored by credible groups with appropriate qualifications. Three studies did report statements of potential conflicting relationships, however these conflicting relationships did not prove to sway the findings of their respective studies. Of the studies that reported cases and controls, the population was not diverse or representative. Studies that reported race reported majority white participants, 73.5% -

100% of participants in studies were white. Across all studies but one, participants' average age was in the fifties. The literature proved to be from reliable sources but the patients did not prove to be representative.

Strengths and Limitations of the Review Process

The support from professors and librarians helped guide the review process in selecting and screening studies. Being able to follow a guided structure for the review allowed me to screen studies for the key elements that would contribute most to understanding the different definitions of post-treatment Lyme disease syndrome. The review process was limited by only reviewing one database and the lack of dedicated literature to post-treatment Lyme disease syndrome. The original search was limited in results making screening more difficult to acquire an appropriate sample size for the review. Screening and data extraction were not done in duplicate, which means relevant studies could have been missed and/or some data could have been incorrectly extracted.

The Broader Literature

There was no additional literature found that reviewed different definitions of post-treatment Lyme disease syndrome. There was no comparison of studies found that would solidify a definition for post-treatment Lyme disease syndrome. Some editorials were found that argued against a definition for post-treatment Lyme disease syndrome that claimed it was not a legitimate diagnosis such as Paul Lantos' 'Chronic Lyme disease' stating that "data do not support the proposition that chronic, treatment-refractory infection with Borrelia burgdorferi is responsible for the many conditions that get labeled as chronic Lyme disease" and that chronic Lyme disease is a poorly defined diagnosis given to patients with "prolonged, unexplained symptoms or with alternative medical diagnosis."[19].

Context

Patients experiencing post-treatment Lyme disease syndrome experience many barriers related to accessing care. One of the key factors accounting for health disparities for patients with PTLDS is the inability to afford treatment and care. Clinicians reported 75% of patients had an inability to pay out-of-pocket costs and 50% of patients reported their insurance will not cover their care[20]. Insurance companies may deny further care for Lyme disease related symptoms because the standard protocol, as determined by the Centers for Disease Control and Prevention, is a 10-14 day antibiotic treatment course and insurers predicate their coverage on the CDC definition[21]. Without a standard CDC definition for PTLDS, insurers will continue to deny care for PTLDS and patients' ability to receive care and treatment will be determined by their socioeconomic status and their ability to afford out-of-pocket care. For patients with confirmed

disseminated Lyme disease, the average out-of-pocket cost was $1,692, with some patients reporting costs as high as $30,628[22]. The cost per patient represents the sum of their medical costs, nonmedical costs and cost of productivity losses and other related costs. The lack of a standard definition for PTLDS continues to allow for insurers to deny claims to cover treatment and further perpetuates socioeconomically disadvantaged patients to have poorer health outcomes.

Next Steps

More research needs to be conducted with larger cohorts of diverse patients of all races, ethnicities, ages and genders. Researchers and clinicians should work together to develop a concrete definition for post-treatment Lyme disease syndrome with definitive symptomatology to treat patients. Furthermore, a concrete definition and definitive symptomatology will allow researchers and clinicians to begin developing appropriate treatment protocols for patients with post-treatment Lyme disease syndrome. Researchers and clinicians need to advocate for patients who are experiencing debilitating symptoms relating to a previous diagnosis of Lyme disease through further research and investigation into post-treatment Lyme disease syndrome.

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