

**CENTER FOR HEALTH  
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**MANDATED BENEFIT REVIEW OF H.B. 989: AN  
ACT RELATIVE TO LYME DISEASE TREATMENT COVERAGE**

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## Benefit Mandate Overview: H.B. 989: Chronic Lyme Disease

### HISTORY OF THE BILL

The Joint Committee on Financial Services referred House Bill (H.B.) 989, “An Act relative to Lyme disease treatment coverage,” sponsored by Rep. Speliotis of Danvers, to the Center for Health Information and Analysis (CHIA) for review. Massachusetts General Laws, chapter 3, section 38C requires CHIA to review and evaluate the potential fiscal impact of each mandated benefit bill referred to the agency by a legislative committee.

### WHAT DOES THE BILL PROPOSE?

H.B. 989 requires that health insurance plans defined in the bill “provide coverage for diagnostic testing and long-term antibiotic treatment of chronic Lyme disease when determined to be medically necessary and ordered by a physician after making a thorough evaluation of the patient’s symptoms, diagnostic test results and response to treatment.”

### MEDICAL EFFICACY OF CHRONIC LYME DISEASE TREATMENT

Lyme disease is the most common vector-borne illness<sup>i</sup> in the United States and Europe,<sup>ii,iii</sup> and is transmitted to humans through tick bites.<sup>iv</sup> While the majority of Lyme disease patients are successfully treated with a single or double course of antibiotics, an estimated 10 to 20 percent of patients have symptoms that last months or years after antibiotic treatment, including fatigue and sleep disturbances, muscle and joint pain, and cognitive deficits.<sup>v</sup>

The proposed mandate refers to chronic Lyme disease (CLD) and is intended to provide insurance coverage for long-term antibiotic treatment for this subset of patients. A consensus definition of CLD currently does not exist, and the means of detecting the presence of the disease in an atypical case, in which symptoms last months or years after a single or double course of antibiotics, is not clearly defined. Symptoms vary in type and severity.

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- i Vector-borne disease: “[B]acteria, viruses, or parasites transmitted to people by mosquitoes, ticks, and fleas.” Vectorborne Diseases: The Centers for Disease Control and Prevention (CDC) joins the World Health Organization (WHO) and other public health partners in recognizing World Health Day, which this year spotlights vectorborne diseases; accessed 22 April 2014: <http://www.infectioncontrolday.com/galleries/2014/04/vectorborne-diseases.aspx?pg=3#gallery>.
  - ii U.S. Centers for Disease Control (CDC): Lyme Disease Diagnosis and Testing. Updated 10 January 2013; accessed 30 January 2014: <http://www.cdc.gov/lyme/diagnosis/testing/>.
  - iii Wormser GP, Dattwyler RJ, Shapiro ED, et. al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America (IDSA Lyme Guidelines). *Clin Infect Dis*. 2006 Nov 1;43(9):1089-134. Epub 2 Oct 2006; accessed 3 February 2014: <http://cid.oxfordjournals.org/content/43/9/1089.full>.
  - iv *Ibid*. Species *Ixodes scapularis* and *Ixodes pacificus*.
  - v U.S. CDC: Post-Treatment Lyme Disease Syndrome. Updated 24 February 2014; accessed 21 February 2014: <http://www.cdc.gov/lyme/postLDS/index.html>.

These challenges result in treatment regimens in which length of treatment is often based on a patient's symptoms rather than on a concretely pre-determined time period. While this approach is recommended by the International Lyme and Associated Diseases Society (ILADS)<sup>vi</sup>, the U.S. Centers for Disease Control and Prevention (CDC), the National Institute for Allergy and Infectious Disease (NIAID), and the Infectious Disease Society of America (IDSA) have stated that the use of long-term antibiotic treatment for Lyme disease or CLD, specifically beyond one or two 10- to 28-day treatment regimens, is not effective and may result in serious complications; these agencies hold that reported cases in which CLD has been successfully treated are more likely the result of the “placebo effect” rather than of the antibiotic treatment itself.<sup>vii,viii,ix</sup>

## CURRENT COVERAGE

In a recent survey of eight of the largest insurance carriers in Massachusetts, all carriers note that at least one round of intravenous antibiotic therapy, lasting between two and four weeks, is covered by their policies, as are oral antibiotics. Some plans allow an additional course, following the guidelines of the Infectious Disease Society of America (IDSA).<sup>x</sup> Carriers are more likely to restrict the length of treatment with intravenous than with oral antibiotics.

## COST OF IMPLEMENTING THE BILL

Requiring coverage for this benefit by fully-insured health plans would result in an average annual increase, over five years, to the typical member's monthly health insurance premiums of between a negligible amount (0.00%) and \$0.11 (0.02%) per year.

## PLANS AFFECTED BY THE PROPOSED BENEFIT MANDATE

Individual and group accident and sickness insurance policies, corporate group insurance policies, and HMO policies issued pursuant to Massachusetts General Laws, as well as the Group Insurance Commission (GIC) covering public employees and their dependents, would be subject to this proposed mandate. The proposed benefit mandate would apply to members covered under the relevant plans, regardless of whether they reside within the Commonwealth or merely have their principal place of employment in the Commonwealth.

vi International Lyme and Associated Diseases Society (ILADS): Evidence-based guidelines for the management of Lyme disease. Released 2004; accessed 27 February 2014: [http://www.ilads.org/files/ILADS\\_Guidelines.pdf](http://www.ilads.org/files/ILADS_Guidelines.pdf).

vii CDC: Post-Treatment Lyme Disease Syndrome. Updated 7 February 2014; accessed 21 February 2014: <http://www.cdc.gov/lyme/postLDS/index.html>.

viii NIAID: “Chronic Lyme Disease”. Updated 27 September 2013; accessed 21 February 2014: <http://www.niaid.nih.gov/topics/LymeDisease/understanding/Pages/chronic.aspx>.

ix *Op. cit.* Wormser GP, Dattwyler RJ, Shapiro ED, et. al.

x *Ibid.*

## PLANS NOT AFFECTED BY THE PROPOSED BENEFIT MANDATE

Self-insured plans (i.e., where the employer policyholder retains the risk for medical expenses and uses an insurer to provide administrative functions) are subject to federal law and not to state-level health insurance benefit mandates.

State health benefit mandates do not apply to Medicare and Medicare Advantage plans whose benefits are qualified by Medicare. Consequently this analysis excludes any members of commercial fully-insured plans over 64 years of age. These mandates also do not apply to federally-funded plans including TRICARE (covering military personnel and dependents), Veterans Administration, and the Federal Employee's Health Benefit Plan. Finally, this bill does not apply to Medicaid/MassHealth.

## PRELIMINARY ESTIMATE OF POTENTIAL MASSACHUSETTS LIABILITY UNDER THE ACA

Analysis of the cost associated with proposed state benefit mandates is important in light of new requirements introduced by the Affordable Care Act (ACA). In accordance with the ACA, all states must set an Essential Health Benefits (EHB) benchmark that all qualified health plans (QHPs), and those plans sold in the individual and small-group markets, must cover, at a minimum. Section 1311(d)(3)(B) of the ACA, as codified in 45 C.F.R. § 155.170, explicitly permits a state to require QHPs to offer benefits in addition to EHB, provided that the state is liable to defray the cost of additional mandated benefits by making payments to or on behalf of individuals enrolled in QHPs. The state is not financially responsible for the costs of state-required benefits that are considered part of the EHB benchmark plan. State-required benefits enacted on or before December 31, 2011 (even if effective after that date) are not considered "in addition" to EHB and therefore will not be the financial obligation of the state. The policy regarding state-required benefits is effective as of January 1, 2014 and is intended to apply for at least plan years 2014 and 2015.

To provide additional information about the potential state liability under the ACA associated with mandating this benefit, CHIA generated a preliminary estimate of the incremental annual premium costs to QHPs associated with this benefit mandate; incremental premium costs exclude the cost of services already provided absent the mandate or already required by other federal or state laws. CHIA's review of the proposed health benefit mandate is not intended to determine whether or not this mandate is subject to state liability under the ACA. CHIA generated this estimate to provide neutral, reliable information to stakeholders who make decisions that impact health care access and costs in the Commonwealth.

CHIA applied the mid-range PMPM (per-member per-month) actuarial projection for 2015 cost (\$0.03) to an estimated 800,000 potential QHP members.<sup>xi</sup> This results in an estimated potential incremental premium increase to QHPs of approximately \$21,000 per month or \$255,000 per year. If fewer (or more) enrollees join QHPs in the merged market than expected, the potential incremental premium cost may be less (or more) than this estimate. A final determination of the Commonwealth's liability will require a detailed analysis by the appropriate state agencies.

<sup>xi</sup> Estimated QHP membership provided by the Massachusetts Division of Insurance.

## H.B. 989 Medical Efficacy Assessment: Chronic Lyme Disease

Massachusetts House Bill (H.B.) 989 requires health insurance plans to cover the costs of “diagnostic testing and long-term antibiotic treatment of chronic Lyme disease when determined to be medically necessary and ordered by a physician after making a thorough evaluation of the patient’s symptoms, diagnostic test results and response to treatment.”<sup>1</sup> The bill further states that treatment shall not be denied because it may be characterized as unproven, experimental, or investigational in nature.<sup>2</sup> M.G.L. c. 3 § 38C charges the Massachusetts Center for Health Information and Analysis (CHIA) with reviewing the medical efficacy of proposed mandated health insurance benefits.<sup>3</sup> Medical efficacy reviews summarize current literature on the effectiveness and use of the mandated treatment or service, often compared to alternative treatments, and describe the potential impact of a mandated benefit on the quality of patient care and the health status of the population.

A recent report from a National Institute of Medicine workshop on Lyme disease noted that “a significant impasse has developed in the world of Lyme disease. There are conflicts within and among the science; policy; politics; medicine; and professional, public, and patient views pertaining to the subject...”<sup>4</sup> Reflecting this controversy in Massachusetts, a law was enacted in 2010 explicitly permitting physicians to “prescribe, administer or dispense long-term antibiotic therapy for a therapeutic purpose to eliminate infection or to control a patient’s symptoms upon making a clinical diagnosis that the patient has Lyme disease or displays symptoms consistent with a clinical diagnosis of Lyme disease, if such clinical diagnosis and treatment are documented in the patient’s medical record by the prescribing licensed physician,” which would, in effect, protect physicians from medical board discipline for prescribing or dispensing long-term antibiotic treatment for Lyme disease.<sup>5</sup>

This review will attempt to summarize current widely-supported positions, including those reflected in guidelines of the U.S. Centers for Disease Control and Prevention (CDC), the National Institute for Allergy and Infectious Disease (NIAID), and the Infectious Disease Society of America (IDSA). It also describes some of the arguments supporting different disease definitions and treatment guidelines, especially pertaining to chronic Lyme disease (CLD), including those made by the International Lyme and Associated Diseases Society (ILADS).

### LYME DISEASE

Lyme disease is the most common vector-borne illness<sup>6</sup> in the United States and Europe,<sup>7,8</sup> and is transmitted to humans through bites of ticks<sup>9</sup> infected with spirochete bacteria,<sup>10</sup> specifically *Borrelia burgdorferi* in North America.<sup>11</sup> The incidence of CDC-confirmed cases of Lyme disease in Massachusetts has been somewhat erratic over time, with the most recent estimates of 51.1 cases per 100,000 residents in the state in 2012.<sup>12</sup> However, this number is based on 3,396 confirmed cases in the state; the CDC reports another 1,742 probable cases of Lyme disease in Massachusetts in 2012.<sup>13</sup> Including these probable cases would raise the incidence rate of Lyme disease to 77.3 per 100,000 residents in the most recent year measured. This number also may be understated, as additional cases may not be reported to the CDC and not included in its statistics. In 2012, Massachusetts had the fifth highest confirmed-case incidence rate of Lyme disease in the U.S.<sup>14</sup>

Common early symptoms of Lyme disease, which can mimic the flu, are fatigue, headache, fever, and joint aches.<sup>15</sup> When undiagnosed or untreated, the disease can affect the circulatory, muscular, nervous, and skeletal systems in the body,<sup>16</sup> sometimes causing arthritis, meningitis, cardiac problems, eye inflammation, Bell’s palsy, and hepatitis, among other illnesses.<sup>17</sup>



Often indicative of Lyme disease is a “bull’s-eye” skin rash – appearing most often as a red center surrounded by a clear area and outlined by a red ring – clinically called erythema migrans (EM), and unique to Lyme disease.<sup>18,19</sup> When a patient presents with an EM rash, a diagnosis of Lyme disease is fairly straightforward, and may be more easily correctly identified and treated in earlier stages of the disease.<sup>20</sup> However, estimates of the portion of patients who develop the EM rash vary from less than fifty percent<sup>21</sup> to seventy to eighty percent.<sup>22</sup>

In the absence of an EM rash, a diagnosis of Lyme disease is sometimes difficult to make, given that the disease’s symptoms are often similar to those of other diseases.<sup>23</sup> The NIAID states that diagnosis should be made based on clinical judgment of the signs and symptoms of the disease, specifically on a patient’s detailed medical history and symptoms, the patient’s exposure in an area where Lyme disease exists, and the time of year.<sup>24</sup> Later-stage diagnosis of the disease is often made based on the presence of Lyme arthritis, or neurologic symptoms such as Bell’s palsy.<sup>25</sup> Laboratory testing may be supportive of the diagnosis, but has been found to be problematic in its sensitivity for identifying the disease in its early stages.<sup>26,27</sup> Moreover, while these tests are more likely to accurately identify Lyme disease in its second or third phases, treatment is generally more effective when prescribed in an earlier disease stage<sup>28</sup>, resulting in the paradox that early treatment makes laboratory testing less accurate in later Lyme disease stages. And while often used by clinicians in community settings, the CDC’s diagnostic criteria was developed for use in defining cases for surveillance purposes in reporting Lyme disease nationally; the agency explicitly states that their definition “is not intended to be used in clinical diagnosis.”<sup>29</sup>

The challenges in making a correct Lyme disease diagnosis can be further complicated by infections by other tick-transmitted organisms; these co-infections may cause additional symptoms or co-morbidities and prevent the successful treatment of Lyme disease.<sup>30</sup> Likewise, the presence in the patient of autoimmune disorders or previously undiagnosed diseases also makes diagnosis and treatment of Lyme disease difficult.<sup>31</sup> These difficulties in making a clear diagnosis, and the heterogeneity of symptom presentation, can make early successful treatment difficult, and may in part explain the progress of the disease to a post-treatment or chronic phase.

## CHRONIC LYME DISEASE

While the majority of Lyme disease patients are successfully treated with a single or double course of antibiotics, especially if treatment begins in the early disease stage, an estimated 10 to 20 percent of patients have symptoms that last months or years after antibiotic treatment, including fatigue and sleep disturbances, muscle and joint pain, and cognitive deficits.<sup>32</sup> The NIAID reports that studies have “reinforced the evidence that patients reporting [post-treatment Lyme disease syndrome] symptoms have a severe impairment in overall physical health and quality of life.”<sup>33</sup>

A variety of terms have been used to group these cases, including “post-treatment Lyme disease syndrome,”<sup>34</sup> “post-Lyme disease syndrome,”<sup>35</sup> and “chronic Lyme disease” (CLD). This report uses “CLD” following the language in the proposed mandate, H.B. 989. ILADS further classifies CLD into persistent, recurrent, and refractory Lyme disease.<sup>36</sup>

Views on the definition and very existence of CLD vary significantly. In addition to continuing symptoms, some patients may have another tick-borne infection<sup>37</sup> which may complicate treatment of Lyme disease. For other patients, Lyme disease may have coincided with autoimmune diseases or chronic syndromes, including fibromyalgia, Gulf War syndrome, and chronic fatigue, or Lyme disease may exacerbate the symptoms of these conditions. Still others may continue to experience symptoms after treatment and during recovery of the disease, given that healing of the neurological or cardiac system or joints, for example, often occurs after elimination of the bacteria from the body. According to IDSA, “[t]here is no well-accepted definition... This has contributed to confusion and controversy and to a lack of firm data on its incidence, prevalence, and pathogenesis.”<sup>38</sup>

While there is widespread agreement on the existence of cases with post-treatment symptoms (10 to 20 percent, as noted previously), a consensus definition of these cases does not currently exist, and the means of detecting the presence of the disease in an atypical case, in which symptoms last months or years after a single or double course of antibiotics, is not clearly defined. Some patients with persistent symptoms have been documented as having previously tested positive for Lyme disease using a commercially-approved blood test and have followed the recommended antibiotic course without symptom abatement.<sup>39</sup> Others cannot or did not confirm Lyme disease with a blood test, but had a diagnosis based on medical history and symptoms.

The exact cause of continuing symptoms is a point of disagreement, and according to the CDC, unknown.<sup>40</sup> The CDC states that the cause of ongoing symptoms is not due to continuing infection with the Lyme disease bacteria, and mentions a possible autoimmune response by the patient.<sup>41</sup> The IDSA states in its proposed definition for post-Lyme disease syndrome that “having once had objective evidence of *B. burgdorferi* infection must be a condition sine qua non.”<sup>42</sup>

Another perspective suggests that CLD could be residual symptoms of an episode of active Lyme disease, or that it could be a persistent form of the disease not recognizable by current testing.<sup>43,44</sup> Proponents of the latter position hold that because no approved commercially-available test detects the presence of the bacteria, but only typical antibody response, and because those tests that measure antibody response have limitations, the absence of the Lyme disease bacteria in people with ongoing symptoms cannot be unequivocally proven.<sup>45</sup>

Results from some basic science (non-clinical) studies appear to provide information that may contradict clinical research.<sup>46</sup> The NIAID has sponsored research that concluded that *B. burgdorferi* persisted in animals (including mice and non-human primates) after antibiotic treatment, and has indicated that additional research is needed to understand the potential implication of these findings on human disease.<sup>47</sup> Moreover, there are published peer-reviewed studies that show that CLD may be caused by persistent infection with *B. burgdorferi*,<sup>48</sup> may not trigger the expected immune response in some patients,<sup>49</sup> or that certain types or courses of antibiotics may not be sufficient to eradicate the disease.<sup>50</sup>

## TREATMENT FOR CHRONIC LYME DISEASE

Accompanying the divergence of opinion on the existence or definition of CLD is significant disagreement on how to treat these patients, including the length of treatment and types of antibiotics. Based on the results of several published double-blind, placebo-controlled studies, the CDC, NIAID, and IDSA have stated that the use of long-term antibiotic treatment for Lyme disease or CLD, specifically beyond one or two 10- to 28-day treatment regimens, is not effective; these agencies hold that reported cases in which CLD has been successfully treated are more likely the result of the “placebo effect” rather than of the antibiotic treatment itself.<sup>51,52,53</sup> These agencies underscore rare but serious complications from long-term antibiotic treatment, most often associated with intravenous treatment, as well as an increased risk for infection with other harmful bacteria (*c. difficile*) from increased antibiotic use.<sup>54</sup>

On the other hand, ILADS guidelines state that “[t]he management of chronic Lyme disease must be individualized, since patients will vary according to severity of presentation and response to previous treatment,” and that, “the patient’s clinical response should guide duration of [antibiotic] therapy.”<sup>55</sup> For CLD specifically, ILADS also considers the use of intramuscular antibiotics when oral or intravenous treatments fail. The group cautions against routinely combining oral and intravenous treatments as it “raises the risk of adverse reactions,” but does consider sequential treatment of CLD, first with intravenous treatment followed by an oral therapy, as a possible alternative.<sup>56</sup>

Finally, in the absence of a consensus “standard” CLD treatment regimen, other treatments have been proposed, including alternative antibiotics, indefinite and possibly lifelong antibiotic treatment, and hyperbaric oxygen therapy. This review has uncovered no widely-recognized sources of support for routine use of these treatments.<sup>57</sup>

Again, widespread agreement exists that the symptoms of a certain portion of patients with Lyme disease are not ameliorated through short-course treatments of antibiotic. The disagreement on whether this population continues to be ill due to some form of Lyme disease, or whether their symptoms result from other causes, produces further differences on recommended treatments. The dilemma for clinicians is avoiding inappropriate or over-treatment while effectively managing their patients’ ailments. The NIAID itself states that “[t]o help combat these problems, researchers are trying to find out how long a person should take antibiotics for the various symptoms that may follow a bout with Lyme disease.”<sup>58</sup>

## Endnotes

- 1 The 188<sup>th</sup> General Court of the Commonwealth of Massachusetts. Bill H. 989: An Act relative to Lyme Disease treatment coverage. Accessed 26 February 2014: <https://malegislature.gov/Bills/188/House/H989>.
- 2 *Ibid.*
- 3 M.G.L. c. 3, § 38C: Health insurance coverage; mandated health benefit bills; review and evaluation; report. Accessed 14 May 2014: <https://malegislature.gov/Laws/GeneralLaws/Part/Title/Chapter3/Section38C>.
- 4 Institute of Medicine (US) Committee on Lyme Disease and Other Tick-Borne Diseases: The State of the Science. Critical Needs and Gaps in Understanding Prevention, Amelioration, and Resolution of Lyme and Other Tick-Borne Diseases: The Short-Term and Long-Term Outcomes: Workshop Report. Washington (DC): National Academies Press (US); 2011. Accessed 21 February 2014: <http://www.ncbi.nlm.nih.gov/books/NBK57020/>.
- 5 Massachusetts Session Laws 2010 c.131 §67 “A licensed physician may prescribe, administer or dispense long-term antibiotic therapy for a therapeutic purpose to eliminate infection or to control a patient’s symptoms upon making a clinical diagnosis that the patient has Lyme disease or displays symptoms consistent with a clinical diagnosis of Lyme disease, if such clinical diagnosis and treatment are documented in the patient’s medical record by the prescribing licensed physician.” Accessed 27 February 2014: <https://malegislature.gov/Laws/GeneralLaws/Part/TitleXVI/Chapter112/Section12DD>.
- 6 Vector-borne disease: “[B]acteria, viruses, or parasites transmitted to people by mosquitoes, ticks, and fleas.” Vectorborne Diseases: The Centers for Disease Control and Prevention (CDC) joins the World Health Organization (WHO) and other public health partners in recognizing World Health Day, which this year spotlights vectorborne diseases; accessed 22 April 2014: <http://www.infectioncontroltoday.com/galleries/2014/04/vectorborne-diseases.aspx?pg=3#gallery>.
- 7 U.S. Centers for Disease Control (CDC): Lyme Disease Diagnosis and Testing. Updated 10 January 2013; accessed 30 January 2014: <http://www.cdc.gov/lyme/diagnostesting/>.
- 8 Wormser GP, Dattwyler RJ, Shapiro ED, et. al. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America (IDSA Lyme Guidelines). Clin Infect Dis. 2006 Nov 1;43(9):1089-134. Epub 2 Oct 2006; accessed 3 February 2014: <http://cid.oxfordjournals.org/content/43/9/1089.full>.
- 9 *Ibid.* Species *Ixodes scapularis* and *Ixodes pacificus*.
- 10 Spirochete: A type of double-membrane bacteria which is long, slender and tightly-coiled, and moves by rotating in place. Wikipedia: Spirochaete. Accessed 30 January 2014: <http://en.wikipedia.org/wiki/Spirochaete>.
- 11 Hu L, Steere AC, Mitty J. Up To Date: Clinical Manifestations of Lyme disease in adults. Updated 5 February 2013; accessed 30 January 2014: <http://www.uptodate.com/contents/clinical-manifestations-of-lyme-disease-in-adults>. Additional strains of *Borrelia afzelii* and *Borrelia garinii* are found in cases originating in Europe or Asia. This distinction is important as there are patients with Lyme disease in the United States caused by bites from ticks carrying other strains of the bacteria that occurred during travel overseas.
- 12 CDC: Lyme Disease Incidence Rates by State, 2003-2012. Updated 16 September 2013; accessed 21 February 2014: <http://www.cdc.gov/lyme/stats/chartstables/incidencebystate.html>.
- 13 CDC: Reported cases of Lyme disease by state or locality, 2003-2012. Updated 16 September 2013; accessed 21 February 2014: [http://www.cdc.gov/lyme/stats/chartstables/reportedcases\\_statelocality.html](http://www.cdc.gov/lyme/stats/chartstables/reportedcases_statelocality.html).
- 14 *Ibid.*
- 15 CDC: Lyme disease. Updated 15 November 2013; accessed 30 January 2014: <http://www.cdc.gov/lyme/>.
- 16 *Ibid.*
- 17 National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIAID): A History of Lyme Disease, Symptoms, Diagnosis, Treatment, and Prevention. Updated 9 October 2012; accessed 30 January 2014: <http://www.niaid.nih.gov/topics/lymedisease/understanding/Pages/intro.aspx>.
- 18 *Ibid.*
- 19 Meyerhoff JO, Cunha BA, Brent LH, et. al. Medscape: Lyme disease. Updated 19 November 2013; accessed 30 January 2014: <http://emedicine.medscape.com/article/330178-overview#showall>.
- 20 *Op cit.* NIAID: A History of Lyme Disease.
- 21 International Lyme and Associated Diseases Society (ILADS): Basic Information About Lyme Disease. Updated 15 April 2006; accessed 30 January 2014: [http://www.ilads.org/lyme\\_disease/about\\_lyme.html](http://www.ilads.org/lyme_disease/about_lyme.html).
- 22 *Op cit.* CDC: Signs and Symptoms of Lyme Disease.
- 23 *Op cit.* NIAID: A History of Lyme Disease.
- 24 *Ibid.*
- 25 Interview with Samuel Donta, MD, infectious disease specialist, Falmouth Hospital, 10 February 2014.
- 26 Brown SL, Hansen SL, Langone JJ. Role of serology in the diagnosis of Lyme disease. JAMA. 1999 Jul 7;282(1):62-6. Abstract accessed 21 February 2014: <http://www.ncbi.nlm.nih.gov/pubmed/10404913>.

- 27 Laboratory testing for Lyme disease in its early stages with serum (blood) diagnostics is not effective, as the test measures a typical patient's antibody response to exposure to the bacteria, and not the presence of the bacteria itself. In the early stage, antibodies in a patient's blood may not have accumulated to a level sufficient for detection; however, the laboratory tests can be an important diagnostic tool for confirming the disease in its second or third stages. HHS (CDC, NIH, FDA) Federal Research Update on Lyme Disease Diagnostics Webinar. Broadcast 24 September 2012; accessed 21 February 2014: <http://www.cdc.gov/lyme/diagnostictesting/index.html>. TRANSCRIPT: HHS Federal Research Update on Lyme Disease Diagnostics Activities September 24, 2012. Accessed 21 February 2014: [http://www.cdc.gov/lyme/resources/webinar/09242012\\_DiagnosticsWebinarTranscript.pdf](http://www.cdc.gov/lyme/resources/webinar/09242012_DiagnosticsWebinarTranscript.pdf).
- 28 *Op cit.* NIAID: A History of Lyme Disease.
- 29 CDC: National Notifiable Diseases Surveillance System, Lyme disease (*Borrelia burgdorferi*), 2011 Case Definition, CSTE Position Statement(s), 10-ID-06. Updated 8 May 2014; accessed 14 May 2014: <http://wwwn.cdc.gov/NNDS/script/casedef.aspx?CondYrID=752&DatePub=1/1/2011%2012:00:00%20AM>.
- 30 *Op cit.* ILADS: Basic Information About Lyme Disease.
- 31 *Op cit.* IDSA Lyme Guidelines.
- 32 CDC: Post-Treatment Lyme Disease Syndrome. Updated 7 February 2014; accessed 21 February 2014: <http://www.cdc.gov/lyme/postLDS/index.html>.
- 33 NIAID: "Chronic Lyme Disease". Updated 27 September 2013; accessed 21 February 2014: <http://www.niaid.nih.gov/topics/lymeDisease/understanding/Pages/chronic.aspx>.
- 34 *Ibid.*
- 35 *Op cit.* IDSA Lyme Guidelines.
- 36 ILADS: Evidence-based guidelines for the management of Lyme disease. Released 2004; accessed 27 February 2014: [http://www.ilads.org/files/ILADS\\_Guidelines.pdf](http://www.ilads.org/files/ILADS_Guidelines.pdf).
- 37 According to the CDC, these may include anaplasmosis, babesiosis, ehrlichiosis, Rocky Mountain Spotted Fever (RMSF), and Southern Tick-Associated Rash Illness (STARI), among others in the United States. CDC: Tickborne Diseases of the U.S. Updated 3 February 2014; accessed 6 March 2014: <http://www.cdc.gov/ticks/diseases/>.
- 38 *Op cit.* IDSA Lyme Guidelines.
- 39 *Op cit.* NIAID: "Chronic Lyme Disease".
- 40 CDC: Signs and Symptoms of Lyme Disease. Updated 11 January 2013; accessed 30 January 2014: [http://www.cdc.gov/lyme/signs\\_symptoms/index.html](http://www.cdc.gov/lyme/signs_symptoms/index.html).
- 41 *Op cit.* CDC: Post-Treatment Lyme Disease Syndrome.
- 42 *Op cit.* IDSA Lyme Guidelines.
- 43 *Op cit.* Interview with Samuel Donta, MD, infectious disease specialist, Falmouth Hospital, 10 February 2014.
- 44 ILADS: Summary of ILADS Guidelines for Lyme Disease. Accessed 28 April 2014: [http://www.ilads.org/lyme\\_disease/treatment\\_guidelines\\_clearing\\_ilads.html](http://www.ilads.org/lyme_disease/treatment_guidelines_clearing_ilads.html).
- 45 *bid.*
- 46 Phillips SE, Harris NS, Horowitz R, et. al. Lyme disease: scratching the surface. *Lancet*. 2005 Nov 19;366(9499):1771. Accessed 27 February 2014: [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(05\)67721-5/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(05)67721-5/fulltext).
- 47 *Op cit.* NIAID: "Chronic Lyme Disease".
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**APPENDIX**

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