December 20th 2018

VIRAS opinion on the IDSI Statement to the Oireachtas Joint Committee on Health

Last updated 24th December 2018

On November 28th, 2018, the Oireachtas Joint Committee on Health, heard evidence from patients, patient advocates and professionals about Lyme disease. The Infectious Disease Society of Ireland (IDSI), submitted a statement authored by twenty eight of its members. A copy had not been provided to Dr John Lambert, who gave evidence in person at the hearing, even though he is a member of the IDSI. Dr Lambert is knowledgeable and experienced regarding Lyme borreliosis and its coinfections, having had years of first-hand experience in diagnosing and treating patients. This exclusion was discourteous - to put it mildly.

Before reading from sections of the IDSI statement during the hearing, Senator Colm Burke remarked, "Other than the Chairperson, none of us are qualified medical practitioners, so we have to rely on advice given to us by medical practitioners."
(Video: https://www.oireachtas.ie/en/oireachtas-tv/video-archive/committees/2131/?fbclid=IwAR2FzW3-pqsCL_Jkzytcv_fA_abMfIG9RpXO8IIl_xriwfvRAt90NlwLwGc at 1:49:30)

This statement had implications for those providing evidence to the committee, especially those who are 'qualified medical practitioners'. Evidence should provide government committees with information which they can weigh to inform policy and professional witnesses have an obligation to give evidence which is reliable and balanced.

The IDSI statement showed that the authors had adopted wholesale, the Infectious Disease Society of America (IDSA) position on Lyme disease. The IDSI statement endorsed the outdated IDSA guidelines and repeated IDSA opinions on important aspects of the disease and patient care.

When second-hand opinions are submitted as evidence, the onus to verify the reliability of those opinions rests with the witnesses. As Senator Burke's comment made clear, it was not for the committee to discern the veracity of the evidence because, "we have to rely on advice given to us by medical practitioners". Therefore the twenty eight authors of the IDSI statement were severally responsible for verifying the opinions which they submitted as evidence to the committee.

The following quotes are from the IDSI Statement to the Health Committee which were presented as bullet-points in the Introduction section of the document.

"We seek to ensure that all patients under our care, including those with Lyme disease, receive the highest quality of evidence based care"

"Evidence based care" does not exist for Lyme borreliosis. The National Institute for Clinical and Care Excellence (NICE – England) guideline for Lyme disease was published on April 11th 2018. The development of the guideline included a comprehensive literature review. Published research was rated according to its quality and risk of bias. NICE found that almost every piece of evidence was of 'low' or 'very low quality' or at 'high' or 'very high' risk of bias. NICE found no good quality evidence to inform any aspect of patient care. See Table 1 for the source and ratings of evidence used for various sections of the guideline.

Table 1
Sources and Quality of the 'Evidence' used in the NICE Guideline for Lyme disease. Adapted from: (The British Medical Journal, 2018; 361 doi: https://doi.org/10.1136/bmj.k1261)

1. Incidence and distribution of ticks: Based on the experience and opinion of the Guideline Committee (GC) and informed by an evidence review on Lyme disease incidence in the UK
2. Infection rates of ticks: Based on the experience and opinion of the GC
3. Prevention advice: Based on the experience and opinion of the GC
4. EM rash: Based on the experience and opinion of the GC
5. Non-focal presenting symptoms: Based on the experience and opinion of the GC
6. Focal presenting symptoms: Based on very low quality evidence from observational studies and the experience and opinion of the GC
7. Other risk factors for getting the infection: Based on the experience and opinion of the GC
8. Diagnosing: Based on very low quality evidence from observational studies and the experience and opinion of the GC
9. Laboratory testing: Based on the experience and opinion of the GC
10. Treatment: Based on the experience and opinion of the GC
11. Second treatment: Based on the experience and opinion of the GC
12. Referral of patients who do not recover: Based on moderate to very low quality evidence from randomised controlled trials and the experience and opinion of the GC
13. Explain to patients uncertainties about testing: Based on very low quality evidence from observational studies and the experience and opinion of the GC
14. Explain why test results might be wrong: Based on the experience and opinion of the GC
15. Explain to patients about ongoing symptoms: Based on the experience and opinion of the GC

It is misleading for the authors of the IDSI statement to claim that they provide, "the highest quality of evidence based care", because there is no good quality evidence available - not that NICE with all their resources could discover.

In the absence of any good evidence, the NICE guideline committee made recommendations "Based on the experience and opinion of the Guideline

Committee". One problem with opinions is that they could be swayed by the influence of vested interests. These interests could include associations with patent holders, vaccine developers, test-kit manufacturers and investors, research sponsors and funding, medical insurance and reinsurance companies. The value to interested groups in controlling the narrative and perceptions around Lyme borreliosis, could run into billions of dollars over time. In view of the interests involved, uncritical adoption of opinions which could be influenced by these sources would be a dereliction of the duty that doctors owe to their patients.

The low number of cases of Lyme borreliosis reported in Ireland suggests that the number seen and diagnosed by clinicians and members of IDSI is very small and those seen by a given doctor may not reflect the diverse and complex nature of a disease that can affect every organ and tissue of the body.

Perhaps the authors of the IDSI Statement would provide the numbers of Lyme borreliosis patients that each of them have treated each year. Then in the absence of good evidence, the Health Committee could factor for the extent of the physicians' first-hand experience.

It seems likely that most of them cannot realistically claim to base their opinions about the care of Lyme borreliosis patients on 'experience', any more than they can claim to base their opinions on 'evidence'.

"We recognise that there are a minority of patients who may experience persistent symptoms following appropriate and adequate antibiotic treatment for Lyme infection"

It was established by the NICE literature search, that there is no proven or established treatment protocol for Lyme borreliosis, let alone one which could be designated: "appropriate and adequate antibiotic treatment for Lyme infection". That is why NICE contrived their own treatment protocols which actually diverge from any and every existing treatment recommendations made in the past 30+ years. If a treatment fails to eradicate the infection then it is not by definition, "appropriate and adequate". As there are literally hundreds of peer-reviewed studies which have shown persistence of the infection following 'adequate treatment' – the IDSI statement is not just misleading, it is meaningless.

"We recognise that there are patients who experience symptoms for which there are no readily available explanation and that these symptoms can have profound effect on quality of life"

"We sympathise with patients and families who are affected. Our sincere goal is that all patients can have the best possible outcome However, in clinical trials prolonged courses of either oral or intravenous antibiotics have not been shown to have an appreciable effect in these cases and have been associated with increased risk of serious, unintentional harm in some cases"

It is misleading to claim that there is "no readily available explanation" for Lyme borreliosis patients who have persistent symptoms. A simple explanation would be that the patient remains infected with the Lyme bacteria. Embers et al showed that the infection persisted following four weeks of doxycycline treatment in rhesus macaques.[1]

Furthermore, Middleveen et al stated:[2]

> "We present evidence of persistent Borrelia infection despite antibiotic therapy in patients with ongoing Lyme disease symptoms. Methods: In this pilot study, culture of body fluids and tissues was performed in a randomly selected group of 12 patients with persistent Lyme disease symptoms who had been treated or who were being treated with antibiotics. Cultures were also performed on a group of ten control subjects without Lyme disease. The cultures were subjected to corroborative microscopic, histopathological and molecular testing for Borrelia organisms in four independent laboratories in a blinded manner. Results: Motile spirochetes identified histopathologically as Borrelia were detected in culture specimens, and these spirochetes were genetically identified as Borrelia burgdorferi by three distinct polymerase chain reaction (PCR)-based approaches. Spirochetes identified as Borrelia burgdorferi were cultured from the blood of seven subjects, from the genital secretions of ten subjects, and from a skin lesion of one subject. Cultures from control subjects without Lyme disease were negative for Borrelia using these methods. **Conclusions: Using multiple corroborative detection methods, we showed that patients with persistent Lyme disease symptoms may have ongoing spirochetal infection despite antibiotic treatment, similar to findings in non-human primates. The optimal treatment for persistent Borrelia infection remains to be determined."**

Häupl et al reported the case of a woman with Lyme disease who had received six weeks treatment of 200mg per day of doxycycline. Four weeks later, cardiac and musculoskeletal symptoms occurred. She was given intravenous ceftriaxone at 2g per day for 14 days. After another two months symptoms returned and she was given another two weeks of an antibiotic protocol which had been described as effective in 'advanced Lyme borreliosis'. The patient developed a 'trigger finger'. A biopsy of ligamentous tissue was obtained and cultured positive for *Borrelia burgdorferi* spirochaetes, the bacteria which cause Lyme disease. It was even possible to identify how the spirochaetes were located within the tissue by microscopy.[3] Unfortunately, the patient had lost 70% of vision in one eye before her failed "adequate treatment" was finally successful.

There have never been any clinical trials of "prolonged courses of either oral or intravenous antibiotics" for chronic Lyme borreliosis. Sixteen weeks is the longest that we know of and most are shorter. This is a moderate term of treatment for an established infection which has multiple strategies to evade immune clearance and survive antibiotic treatment – e.g., biofilm formation, cystic or 'round-body' (adverse condition) dormant forms, invasion of deep tissue and 'privileged sites'.

Infectious disease doctors treat chronic infections with individualised care. Bone infections need 6 weeks of intravenous antibiotics, but if the patient is a diabetic this can sometimes increase to 12 weeks followed by oral doxycycline plus co-trimoxazole for months, based on the patient's clinical response. Clinical guidance for dermatology is to treat for a 3 to 6 month period for 'bad acne' with doxycycline or sometimes co trimoxazole, as precedent to considering the more toxic and more expensive acne drugs like roaccutane. Recommended treatment for Tuberculosis is for 6 to 9 months with high dose combination antibiotics. If a 14 day or longer break in treatment occurs, the whole protocol starts again from scratch. Chronic Q fever can require up to four years of treatment with doxycycline and quinolones or doxycycline with hydroxychloroquine.

The many hundreds and possibly thousands of chronically infected patients in Ireland, will draw little comfort from the sympathy and sincere wishes of the IDSI authors. Especially if, by the time that those people finally discover that they have been ill for years or decades with a treatable infection, they realise that their suffering and the wasted years of their lives, were unnecessarily prolonged because of some IDSI members felt qualified to air opinions about borreliosis, but who apparently, have not troubled to evaluate the literature for themselves but instead, uncritically adopted the outdated opinions of other groups.

Emphasising the known risks of taking long-term antibiotics is an old ploy of those IDSA members responsible for their outdated guideline. One might have hoped that the IDSI would consider presenting figures for the actual risk of harms and balance these against the irrefutable risks of non-treatment, delayed treatment and inadequate treatment. That is what doctors are required to do when getting a patient's Informed Consent. They provide information about the potential risks and benefits of a treatment, so that patients are properly involved in their healthcare and able to make an informed choice. As the IDSI seem more interested in pandering to the IDSA than in dealing with the problems of Lyme borreliosis and associated infections in Ireland, it seems that patients will have little or no choices regarding their healthcare. Their options will be dictated by the opinions of an unaccountable American group.

"IDSI is very concerned that the use of tests, that are not validated as clinical diagnostic tests to diagnose Lyme infection, can result in the over-diagnosis of Lyme disease and often of other infections"

And so they should be 'very concerned', because the only, "diagnostic tests to diagnose Lyme infection", are *direct detection tests* which locate and identify the infective organism, and which are hardly ever offered to patients except by private laboratories. E.g., microscopy with appropriate staining such as immuno-fluorescence or fluorescence in-situ hybridisation (FISH), with or without bacteria culture. These laboratory procedures can directly detect and identify the presence of an organism in patient tissues and can therefore be used to: "diagnose Lyme infection". However, even these methods cannot be used to *exclude* an infection.

Serology is the most commonly used test for suspected Lyme borreliosis. It is an *indirect* detection method which cannot be used to "diagnose Lyme infection". This

is because instead of identifying the infective organism, it looks for the presence of antibodies produced by the immune system. Serology for Lyme disease has repeatedly been shown to be inefficient and fraught with problems such as, a weak, absent or declining immune response, morphological changes of the bacteria resulting in the 'wrong' antibodies,[4] the bacteria employing multiple strategies to evade and conceal itself from the immune system. Lingering antibodies from past infections and an inability to demonstrate clearance of the bacteria. All of these problems have been documented. Please also see the quotes below from the Tick-Borne Disease Working Group 2018 Report to Congress.

Therefore there is no serology test or combination of tests (e.g. ELISA + Western Blot) which has ever been validated for, or claims to, "diagnose Lyme infection". Even the manufacturers of the laboratory test kits and laboratories providing the tests, state that diagnosis is a clinical decision, that these tests cannot exclude the infection and should only be used to 'support a clinical diagnosis'.

Furthermore, no ELISA or Western Blot or combination of the two has ever been validated, even for the purposes of supporting a clinical diagnosis, for patients in Ireland, just as they have never been validated for England and most other countries.

Of note, is that in a study of 90 patients comparing test methodologies, Tylewska-Wierzbanowska and Chmielewski concluded that:[5]

> "There is no correlation between the level of antibodies (ELISA), the number of protein bands (Western blot) and the presence of spirochetes in body fluids (culture and PCR), indicating that in addition to serological testing the use of PCR and cultivation in the diagnosis of Lyme borreliosis should be recommended."
>
> "Moreover, Lyme borreliosis patients who have live spirochetes in body fluids have low or negative levels of borrelial antibodies in their sera. This indicates that an efficient diagnosis of Lyme borreliosis has to be based on a combination of various techniques such as serology, PCR and culture, not solely on serology."

Remarkably, the approach of Tylewska-Wierzbanowska and Chmielewski echoed research and diagnostics recommendations made almost a decade earlier in the Report of a World Health Organisation Workshop on Lyme borreliosis.[6] The report recommended development and standardization of seven distinct methods for detecting the infection. The fact that so few experiments have ever adopted this simple and logical approach of testing patients by multiple methodologies, is most likely due to the fact that such experiments are quite expensive, would likely undermine the credibility and the profits of serological test kit manufacturers, patent holders and laboratory service providers, and also cause embarrassment to those who claim that diagnosis can depend upon serology.

The unreliability of standard testing for Lyme borreliosis is why a purely clinical diagnosis is sometimes necessary. This might require considerable knowledge and

experience. It is incredible that the Statement submitted to the Joint Committee on Health, suggests that the authors are not conversant with some of the most basic facts about diagnosis.

The IDSI and others believe that patients who remain ill following "adequate treatment" are no longer infected with Lyme bacteria and that further treatment is unnecessary and potentially harmful. VIRAS invite the IDSI to conduct a simple experiment using multiple test methods which could provide compelling evidence to support their view. We provide a simple draft protocol for an experiment in Appendix 1 included below.

"IDSI is particularly concerned that vulnerable individuals with non-specific, chronic symptoms are being encouraged to access non-accredited diagnostics related to tick-borne infections offered by commercial laboratories overseas, often at considerable personal expense. Use of these unvalidated, exploratory diagnostics can result in public mis-information, undue anxiety to individuals and their families, and unnecessary personal financial burden. Additionally, in the worst cases, there is the potential for mis-directed referral, inappropriate treatment and missed opportunities for formal medical assessment to outrule significant alternative pathology as explanation for the chronic symptoms, as a result of use of these unaccredited diagnostic tests."

We can assuage the IDSI's concerns about "non-accredited diagnostics" because there is no such thing. It is laboratories which gain accreditation to perform a test, if they have demonstrated that they can manage the test materials and protocol properly. This does not validate or make any judgement about the quality or accuracy of a test – only the competency of the laboratory to follow procedures.

On the topic of "unvalidated, exploratory diagnostics", it appears that the authors of the IDSI statement are unaware that the two-tier (ELISA, Western Blot) test is not a validated diagnostic protocol and was not designed to be used as such. The two tier test is hopelessly insensitive. E.g., Cook and Puri (2017) report that two-tier Lyme borreliosis testing produces around 500 times more false-negative results than test protocols for HIV.[7] The company which supplies test kits to the Lyme borreliosis Reference Laboratory for England, published figures showing that Two-tier testing had only 55.3% sensitivity for 'all Lyme disease patients' and it detected only 41% of culture-positive patients.[8]

The U.S. Department of Health and Human Services (HHS) established the Tick-Borne Disease Working Group to report on key aspects of Lyme disease in the USA. The Tick-Borne Disease Working Group 2018 Report to the Secretary of the Department of Health and Human Services and to Congress identified serious issues relating to Lyme borreliosis patients and their medical care.[9] They state: (https://www.hhs.gov/ash/advisory-committees/tickbornedisease/reports/index.html)

> **Lyme disease is a clinical diagnosis**
> "Demonstration of active infection is not feasible as a matter of routine, given the insensitivity of the PCR test, the impracticality of culture tests, and

the drawbacks of antibody detection methods. Conversely, the current state of diagnostic testing cannot demonstrate the eradication of B. burgdorferi (because negative test results do not mean an absence of infection). Due to weaknesses in laboratory tests, the diagnosis of Lyme disease remains primarily clinical, with the focus on vector exposure and symptoms that reflect the multisystemic nature of the disease, with laboratory tests playing a supporting role [205].

"The CDC, US Food and Drug Administration (FDA), and NIAID have all expressed concern regarding the over-reliance on laboratory tests for diagnosing Lyme disease [21,47,205], with the FDA stating that tests 'should never be the primary basis for making diagnostic or treatment decisions. Diagnosis should be based on a patient history, including symptoms and exposure to the tick vector and physical findings' [21]. In accordance with these recommendations, most practitioners use a clinical definition of Lyme disease that includes a combination of symptoms and clinical signs with or without positive serological support [45], although some clinicians maintain that diagnosis should be supported by positive serology [46]."

"Misuse of the CDC surveillance criteria for diagnosis

"The Lyme disease surveillance case definition is frequently misunderstood and misused throughout the medical community. According to CDC, a surveillance case definition is "a set of uniform criteria used to define a disease for public health surveillance… [and is] not intended to be used by health care providers for making a clinical diagnosis or determining how to meet an individual patient's health needs" (Centers for Disease Control and Prevention, 2017). However, treating practitioners routinely use the Lyme disease case definition to diagnose patients, and insurance companies often require that patients meet the surveillance criteria before agreeing to cover their care. Compounding the issue is the broad misunderstanding in the medical community that patients who do not meet the case definition cannot have Lyme disease. Those patients who have tick-borne disease-related chronic illness yet do not meet the surveillance criteria often face difficulties obtaining diagnosis, treatment, and medical insurance reimbursement" (pp 20-21)

It appears that the authors of the IDSI statement have misplaced concerns. If they were sincere about ensuring the best possible outcome for patients, then they would educate themselves and not simply parrot outdated opinions from groups which cannot be held to account for how their views affect patients in Ireland.

It also seems that the authors of the IDSI Statement are prepared to portray patients as 'vulnerable' and susceptible to 'undue anxiety' as though patients are just neurotic and gullible. Our opinion is that it is the authors of the IDSI statement, who are vulnerable to exploitation and who proved their gullibility by endorsing IDSA opinions, replete with anti-science and anti-patient prejudices.

The IDSI statement shows a lack of balance and an unwillingness to acknowledge, let alone strive to understand the complexities of Lyme borreliosis. The authors appear to have omitted to undertake a critical analysis of the available literature. It is unfortunate that they did not consult with an expert patient group before submitting such an unworthy statement to a government committee. The TBDWG Report to the Congress, is vastly more authoritative and balanced. If the IDSI wished to simply adopt another group's opinions in the absence of sufficient domestic research or first-hand experience, this would have been a much better choice. The TBDWG report is up to date and balanced, and it could serve Lyme borreliosis patients in Ireland just as well as it promises to serve the 300,000+ patients in the USA each year, and do so without any whiff of sycophancy or snobbery.

Senator Burke's comment was not an invitation for witnesses to submit unsubstantiated and biased opinions as evidence to the committee. Rather, his modest remark made it clear that medical practitioners have a duty to provide information which the committee can rely upon. For the reasons detailed above, it is the opinion of VIRAS that the IDSI Statement did not meet this requirement.

Peter Kemp MA
On behalf of VIRAS
(http://counsellingme.com/VIRAS/VIRAS.html)

Appendix 1
VIRAS proposal to the Infectious Diseases Society of Ireland for an Experiment

By performing the simple experiment outlined in the draft protocol below, the IDSI could verify their opinions and do so using the best possible evidence. This could satisfy the concerns of many patients, protect them from exploitation and help them to save their financial resources, and save them unnecessary and possibly harmful treatment, which the IDSI have indicated as being of concern to them. In the process, Ireland and members of the IDSI would gain a worldwide reputation for Lyme borreliosis research and medicine.

With sufficient participants and the use of the participant symptom measures as recommended in the VIRAS proposal, the experiment would produce data which could be used to develop selection criteria for, 'Post-Treatment Lyme Disease Syndrome' for future research, potentially leading to the development of treatment and management protocols.

This simple idea would strengthen relations between doctors, patients and advocacy groups who are in disagreement, putting Ireland at the forefront of settling the long-standing and disruptive disputes which affect so many people. Patients, patients families, healthcare providers, members of the IDSI and Ireland as a whole could all benefit from this initiative. VIRAS would be glad to support the IDSI in undertaking this essential and long-overdue investigation.

An ongoing study to verify by gold-standard methods, the absence or presence of *Borrelia spirochaetes* in patients who have been treated for Lyme borreliosis but who experience chronic symptoms

Rationale

The Tick-Borne Disease Working Group 2018 Report to Congress states that "While most Lyme disease patients who are diagnosed and treated early can fully recover, 10 to 20% of patients suffer from persistent symptoms, which for some are chronic and disabling."

Some doctors believe that recommended treatments for Lyme disease (borreliosis) fail to eradicate the infection in a significant number of patients, leaving them infected and suffering chronic and relapsing symptoms. This group generally describe the ongoing illness as 'Chronic Lyme Disease'. Patients that believe that they have chronic Lyme disease sometimes spend time and money investigating their illness, paying for their own laboratory tests and even travelling abroad for treatment.

Other doctors believe that ongoing symptoms do not arise from an ongoing infection. They observe that recovery from the illness can be slow and may take many months. This group sometimes describe ongoing symptoms as 'Post-Treatment Lyme Disease Syndrome' (PTLDS) and do not believe that further antibiotic treatment is necessary and might involve unjustified risks.

Gold-standard identification of bacterial infections requires direct detection of the organism in patient tissues and often uses culture methods to grow the bacteria for identification. With Lyme borreliosis bacteria, the sensitivity of these methods is quite low. These methods are also relatively time consuming and quite expensive to carry out, so they are rarely used for routine testing. However, they have been shown to be sufficiently sensitive to make their gold-standard specificity ideal for high-quality research purposes. We propose that an investigation employing these methods could determine infection status and resolve some of the uncertainty regarding Lyme borreliosis patients who suffer with ongoing symptoms.

Description
Sequential and retrospective patients attending participating GP surgeries or outpatient clinics for infectious diseases, neurology and rheumatology who meet the criteria for participation, will be invited to join the trial. Those who give Informed Consent will be tested for the presence Lyme borreliosis spirochaetes in tissue samples by multiple laboratory methods.

Participant criteria
Participants will have been previously diagnosed with Lyme borreliosis with supporting positive two-tier serology. They will have received at least the minimum recommended treatment with suitable antibiotics at an appropriate dosage. A minimum of one year after completion of their treatment, they will be experiencing intrusive but unexplained symptoms which do not predate their Lyme borreliosis infection.

Primary Measures
Laboratories meeting international standards for accreditation will perform the following tests:

1. Culture positive/negative (see note A)
2. PCR detection and species identification (see note B)
3. Western Blot (see note C)

Note A): As described in: Gomes-solecki MJC, Wormser GP, Schriefer M, et al. Recombinant Assay for Serodiagnosis of Lyme Disease Regardless of OspA Vaccination Status. J Clin Microbiol. 2002;40(1):193-197. doi:10.1128/JCM.40.1.193.
Note B): Using serum samples and speciation for major US and European borrelia.
Note C): Using test kits that will detect US and European species.

Secondary Measures
Hospital short form 36 (SF-36)
Hospital anxiety and depression scale
Horowitz Lyme Questionnaire

Analysis and Report
Laboratory results will provide evidence for the presence or absence of a borreliosis infection per participant.
Secondary measure data will be evaluated for generalisability of the data.

Spreadsheet tables will present correlations if any exist, between Primary and Secondary Measures.

References

1 Embers ME, Barthold SW, Borda JT, Bowers L, Doyle L, Hodzic E, et al. (2012) Persistence of Borrelia burgdorferi in Rhesus Macaques following Antibiotic Treatment of Disseminated Infection. PLoS ONE 7(1): e29914. https://doi.org/10.1371/journal.pone.0029914

2 Middelveen, M.J.; Sapi, E.; Burke, J.; Filush, K.R.; Franco, A.; Fesler, M.C.; Stricker, R.B. Persistent Borrelia Infection in Patients with Ongoing Symptoms of Lyme Disease. Healthcare 2018, 6, 33.

3 Häupl, T. , Hahn, G. , Rittig, M. , Krause, A. , Schoerner, C. , Schönherr, U. , Kalden, J. R. and Burmester, G. R. (1993), Persistence of borrelia burgdorferi in ligamentous tissue from a patient with chronic lyme borreliosis. Arthritis & Rheumatism, 36: 1621-1626. doi:10.1002/art.1780361118

4 Garg K, Meriläinen L, Franz O, et al. Evaluating polymicrobial immune responses in patients suffering from tick-borne diseases.*Sci Rep*. 2018;8(1):15932. Published 2018 Oct 29. doi:10.1038/s41598-018-34393-9

5 Tylewska-Wierzbanowska S., Chmielewski T. Limitation of serological testing for Lyme borreliosis: evaluation of ELISA and western blot in comparison with PCR and culture methods. Wiener Klinische Wochenschrift. 2002;114(13–14):601–605.

6 Report of a WHO Workshop on Lyme borreliosis. Slovakia. 6th October 1993. Online: http://apps.who.int/iris/bitstream/handle/10665/62025/WHO_CDS_VPH_93.132.pdf

7 Cook MJ, Puri BK. Application of Bayesian decision-making to laboratory testing for Lyme disease and comparison with testing for HIV. Int J Gen Med. 2017;10:113-123. Published 2017 Apr 10. doi:10.2147/IJGM.S131909. Online: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5391870/

8 Immunetics. C6 Lyme ELISA Kit. Online: http://www.oxfordimmunotec.com/international/wp-content/uploads/sites/3/CF-E601-807_Manual.pdf

9 USA Department of Health and Human Services. Working Group Report to Congress. Online: https://www.hhs.gov/sites/default/files/tbdwg-report-to-congress-2018.pdf