To: The Infectious Diseases Society of America (IDSA), the American Academy of Neurology (AAN) and the American College of Rheumatology (ACR)
From: The International Lyme & Associated Diseases Society (ILADS)

Re: IDSA/AAN/ACR Lyme Disease Guideline Project Plan

Dear IDSA/AAN/ACR Lyme Disease Clinical Practice Guideline Development Panel:

The IDSA/AAN/ACR Lyme Disease Clinical Practice Guideline (CPG) Development Panel has requested public comments in order to "fine-tune" its plan to revise the outdated 2006 IDSA Lyme guidelines. The International Lyme & Associated Diseases Society (ILADS) appreciates having the opportunity to weigh-in on this topic. ILADS is a professional medical society that promotes scientific knowledge, clinical expertise and healthcare policy related to Lyme and associated tick-borne diseases. ILADS healthcare providers currently serve more than 100,000 patients with Lyme and associated tick-borne diseases in the USA and around the world. Based on the collective work of its members, the organization has a wealth of clinical expertise in treating complex and advanced cases of Lyme disease.

ILADS has profound reservations regarding the panel's proposed project plan because it consistently violates fundamental principles established by the Institute of Medicine (IOM) for the formulation of high-quality and trustworthy guidelines.[1] The specific violations that ILADS would like the panel to address and our remedial recommendations for your Lyme disease guideline development plan are outlined below:

1. Page 4, lines 23 -40. The IDSA/AAN/ACR CPG development panel does not include physicians with substantial experience in using antibiotic therapies to treat chronic manifestations of Lyme disease. We specifically note that there are no ILADS members on the panel.[2] Given that the IOM concluded that any failure to include stakeholders in CPG deliberations undermines the quality and trustworthiness of the CPG, this omission is unacceptable.[1]

> ILADS recommends that the IDSA/AAN/ACR CPG development panel include ILADS physicians with experience in treating chronic manifestations of Lyme disease in its CPG formulation process.

2. Page 6, line 63-65; pages 9-16, lines 130-281. The IDSA/AAN/ACR CPG development plan lists 81 questions which are characterized by the CPG development panel as satisfying the Population/Patient, Interventions/Treatments, Comparator, and Outcomes format. The plan states these questions will frame the guidelines development process, guide the literature searches and the formal recommendations. Given the overall importance of the questions we think it is important to point out that they were generated via a flawed process and have several inadequacies.

Not only did the CPG development panel fail to include ILADS members, it also made no effort to include patient stakeholders or their advocates when formulating its clinical questions.[2] This

decision directly conflicts with IOM position 3.2 regarding guideline development groups in which the IOM clearly states that patients should be involved in formulating clinical questions.[1] Additionally, many of the questions do not align with the PICO format and many exhibit framing bias (i.e., "should we use unvalidated tests for Lyme disease?").

> ILADS recommends that the IDSA/AAN/ACR CPG development panel be expanded to include patient stakeholders and that the proposed list of questions be reviewed (and necessary revisions made) following the addition of patient stakeholders. ILADS also recommends that all questions follow a PICO format and that the IDSA/AAN/ACR CPG development panel frame questions in an unbiased manner

3. Page 6, lines 70-80; page 3, lines 16-22. The IDSA/AAN/ACR CPG development panel proposes to use "well-performed existing systematic reviews" to establish its evidence base without defining what constitutes a "well-performed" review. And, while the plan's wording suggests that the IOM recommends using existing reviews, this is only true when the systematic review and the CPG activities "are independent of one another".[1] Clearly this is not the case given that many of the CPG development panel members have conducted systematic reviews on Lyme disease, some of which appear to have been done as a prelude to the current CPG development panel (i.e., the paper by panel members Lantos and Wormser, Am J Med 2014; 127: 1105-1110.[3]) We could not help but note that while the background section mentions the existence of several different guidelines on Lyme disease, it failed to include ILADS' GRADE-based guidelines which were published in 2014.[4]

The use of existing reviews poses many problems. The reviews may not include the most recent studies or basic science information. Reviews authored by current CPG development panel members may unduly bias the group's findings regarding the quality of the review itself or the implications of its findings.[1] Many of the existing reviews on the treatment of Lyme disease are based on poor-quality studies some of which were authored by the reviewers themselves, setting up situations where the quality of the evidence and the strength of its findings were overstated. For example, ILADS' GRADE-based analysis of the clinical trial evidence regarding the management of known tick bites, the treatment of erythema migrans and the usefulness of antibiotic retreatment consistently found that the evidence was of very low quality.[4] Hayes and Mead of the CDC came to a similar conclusion regarding the literature on late neurologic Lyme disease[5] yet the 2006 IDSA CPG development panel often assigned the highest possible rating to the trial evidence.[6] Given that 20% of the current CPG development panel, including co-chair Bockenstedt, co-authored the 2006 IDSA guidelines,[2,6] this apparent inability to objectively assess the evidence is especially concerning.

Another problem with using existing systematic reviews as opposed to conducting a new systematic review is that although the current CPG is intended to "focus on patient-important outcomes" the existing reviews are disease- and not patient-centered. This is due to the fact that the reviews were based on trials which typically selected easily measured endpoints rather than the outcomes that mattered most to patients. Hence, patients with persistent and sometimes disabling symptoms were categorized as successfully treated because their rash cleared or their joint swelling diminished.[7,8]

Finally, it should be noted that existing reviews often relied too heavily on the work of certain authors and did not reflect the broad spectrum of clinical evidence in the medical literature.

> ILADS recommends that the IDSA/AAN/ACR panel not using existing systematic reviews as surrogates for carefully constructed analyses of all of the evidence retrieved via properly conducted searches of the medical literature.

4. Pages 5-7, lines 61-94. The IDSA/AAN/ACR CPG development panel does not explicitly include all of the principle elements of evidence-based medicine in their project plan. While the IOM acknowledges that "health professionals increasingly understand that health care must be based on a combination of scientific evidence, knowledge gained from clinical experience, and patient value judgments and preferences"[1] it is unclear whether the panel agrees with this viewpoint. Given that ILADS members with extensive clinical expertise were not invited to participate on the panel, despite the limited quantity of high-quality the trial evidence, we are concerned that the CPG development panel will attribute undue significance to trial evidence while downplaying the importance of clinical expertise.

> ILADS recommends that the IDSA/AAN/ACR panel should appropriately value the relative contributions from clinical trials and clinical experiences.

5. Pages 5-7, lines 61-94: The IDSA/AAN/ACR CPG development plan does not intend to include patient stakeholders or their advocates when analyzing the evidence or conducting risk-benefit analyses and it includes no methodology for identifying which outcomes are most important to patients. This is a critical shortcoming because, as previously mentioned, the IOM recognizes the importance of considering patient values and preferences in the context of providing evidence-based care.

As we learned in developing ILADS' 2014 treatment guidelines, Lyme patients are a very heterogeneous group. The degree of their quality of life impairments and their values with regard to risk-benefit tradeoffs fall along a wide spectrum. Given these variables, it could be difficult for one patient to adequately represent the interests of this group. Yet, despite the obvious need for broad patient representation, the CPG development panel has but a single consumer representative. Furthermore, it is our understanding that this representative lacks any personal or family experience with the medical complications arising from the infection or the problems patients encounter when attempting to secure insurance coverage for treatment-related expenses. Without patient involvement in this phase of the guideline development process, the proposed plan will be unable to fulfill its goal regarding patient-centeredness.

> ILADS recommends that the IDSA/AAN/ACR CPG development panel include patient stakeholders during all phases of evidence analysis, especially when considering the relative merits of various treatment options.

Pages 4-16, lines 23-281. In light of the significant deficiencies in the proposed project plan, ILADS urges the IDSA/AAN/ACR CPG development panel to address these concerns before proceeding further. Moving ahead without taking corrective action can only lead to the production Lyme disease guidelines that will be appropriately viewed as biased, non-inclusive and ultimately detrimental to patient care.

Sincerely,

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[1] Institute of Medicine. Clinical Practice Guidelines We Can Trust. Available at: https://www.iom.edu/Reports/2011/Clinical-Practice-Guidelines-We-Can-Trust.aspx. Accessed March 31, 2015.

[2] Project plan: Guidelines for the prevention, diagnosis, and treatment of Lyme disease by the Infectious Diseases society of America, the American Academy of Neurology, and the American College of Rheumatology. Available at http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/LD%20Project%20Plan%20March%202015%282%29.pdf Accessed March 31, 2015.

[3] Lantos PM, Wormser GP. Chronic coinfections in patients diagnosed with chronic Lyme disease: A systematic review. Am J Med 2014; 127:1105-1110

[4] Cameron DJ, Johnson LB, Maloney EL Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014;12:1103-35

[5] Hayes E, Mead P. Lyme disease. Clin Evid 2003;10:887-99.

[6] 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. Clin Infect Dis. 2006;43:1089-134.

[7]Nadelman RB, Lugar SW, Frank E, et al. Comparison of cefuroxime axetil and doxycycline in the treatment of early Lyme disease. Ann Intern Med 1992:117:273-80.

[8] Dattwyler RJ, Wormser GP, Rush TJ, et al. A comparison of two treatment regimens of ceftriaxone in late Lyme disease. Wien Klin Wochenschr. 2005;117:393-7.