We thank members of the infectious diseases, neurology and rheumatology community as well as the general public for their comments on our Lyme disease guideline project plan. In general, the comments could be categorized into two main themes: guideline panel composition and guideline content/Patient, Intervention, Comparison and Outcomes (PICO) questions.

The following is a summary of the changes that will be made as a result of the public input:

- Three patients treated for Lyme disease and one parent of a pediatric patient treated for Lyme disease have been added to the guideline panel.
- Expanded discussion on whether Lyme disease can be acquired by means other than tick bites.
- Incorporation of the following into the PICO:
  - Evaluation of 1) psychiatric and 2) pediatric behavioral / developmental disorders as presentations of Lyme disease.
  - Consideration of 1) the diagnosis of Lyme disease in those suspected of immunodeficiency, and 2) rationale for an immunodeficiency evaluation in patients suspected of having Lyme disease.
  - Evaluation of laboratory evidence of clearance vs persistence of infection.
  - Evaluation of whether the proposed biologically persistent forms of *B. burgdorferi* (e.g. cysts and biofilms) require specific treatment.

Specific suggestions and concerns submitted to the panel are addressed below:

**Guideline Panel Composition**

- Have the panelists been sufficiently screened for conflicts of interest?
  The process by which panelists were evaluated for conflicts of interest is detailed on pp 8 and 9 of the *project plan*. A separate conflict of interest review group was formed to review and approve the panel members, in adherence with Section 7 of the Council of Medical Specialty Societies’ Code for Interactions with Companies. The four guideline co-chairs do not have relationships that constitute conflicts of interest, and the majority of the remainder of the panel have no relevant conflicts of interest. Full disclosure of financial relationships is listed in Table 1 of the *project plan*.

- Inclusion of a patient representative on the panel.
  We have added three patients treated for Lyme disease and one parent of a pediatric patient treated for Lyme disease to the guideline panel. All were reviewed for possible conflicts of interest and found to have no conflicts.

- Should a psychiatrist be included on the guideline panel?
  We have added two PICO to address Lyme disease as a diagnostic consideration among patients with 1) psychiatric illness and 2) pediatric behavioral and developmental disorders. The specific management of psychiatric, behavioral, and developmental diseases falls within the expertise of several specialties (adult psychiatry, child psychiatry, developmental and behavioral pediatrics, geriatrics, and clinical psychology) and their management is beyond the guideline scope.
Guideline Content/PICO Questions

**Geography, transmission, and prevention of Lyme disease**

- Can Lyme disease be acquired by means other than tick bites?
  We will include discussion of this topic in the text of the guideline.

- How should the public be educated about Lyme disease recognition and prevention?
  The method of education is beyond the scope of this guideline, but the guideline is partly intended to serve as a resource for education of the public.

- Under what circumstances is prophylaxis appropriate after a tick bite? Is the need for prophylaxis affected by geography?
  Current PICOs address the indications for antimicrobial prophylaxis following a tick bite. Geography informs the abundance of questing, infected *Ixodes* ticks; this is addressed within the section on Prevention and Prophylaxis.

- Can areas that are not endemic for Lyme disease become classified as endemic?
  Surveillance classifications are beyond the scope of this guideline. The CDC has clinical and entomologic criteria for endemicity at the county level.

**Clinical and Laboratory Diagnosis of Lyme disease**

- What is the utility of currently recommended 2-tier testing, including the sensitivity of ELISA?
  We will comprehensively review the performance characteristics of the currently recommended 2-tier testing algorithm and evaluate its utility in light of current evidence. This includes the individual performance of ELISA, IgM Western blots, IgG Western blots; their performance when used sequentially; and the evidence behind currently recommended band counts. These will be addressed for specific manifestations of Lyme disease. The reporting and clinical interpretation of these tests also will be addressed.

- What are the roles of alternative serologic testing algorithms, including C6 peptide testing, and the use of alternative antibody bands for Western blot testing?
  We will review the utility of C6 test, both alone and as part of a testing panel and will also include an evaluation of the utility of alternative bands for the serologic diagnosis of Lyme disease.

- What is the role of molecular testing (polymerase chain reaction, PCR) in the diagnosis of Lyme disease?
  We will comprehensively evaluate the utility of PCR, both of blood and of select tissues (cerebrospinal fluid, synovial fluid and tissue, and skin biopsy specimens).

- What is the proper role and interpretation of molecular and antibody tests from cerebrospinal fluid specimens?
The laboratory diagnosis of nervous system Lyme disease, including this question, will be addressed.

- Is there a role for immunologic, host-based diagnostics for Lyme disease including CD57?
  We will evaluate the utility of CD57 testing, as well as other alternative diagnostic tests.

- Under what circumstances should Lyme disease be considered in seronegative individuals?
  This question will be directly addressed. In addition, the syndrome-specific sensitivity of serology also will be addressed.

- Should Lyme testing be done routinely regardless of clinical symptoms?
  We will evaluate the diagnostic value of positive Lyme disease tests in patients who are either asymptomatic or who lack the better-established manifestations of infection.

- Should seronegative patients be tested for immunodeficiency?
  This will be incorporated into the Diagnosis section.

- How does strain variability affect the performance of diagnostic testing? Is *Borrelia miyamotoi* identified by current Lyme disease tests?
  The section on Diagnosis will address how test sensitivity and specificity are affected by strain variability, differences between European and North American genospecies, including the newly emergent Lyme-associated *Borrelia mayonii* and other pathogenic non-Lyme *Borrelia* species such as *B. miyamoti*. The clinical features of *Borrelia mayonii* and those of *B. miyamoti* coinfection in patients with Lyme disease also will be evaluated.

- Should a history of Lyme disease vaccination affect subsequent diagnosis or treatment?
  This will be addressed in the guideline.

*Treatment of Lyme disease*

- Are there sufficient data to support 28 or fewer days of treatment? Do data justify longer treatment in some situations?
  Treatment durations and the evidence basis behind recommendations will be addressed throughout the guideline.

- How should Lyme disease be treated in pregnant patients?
  Pregnant patients are a specifically named patient population within each treatment PICO in the guideline.

*Persistent symptoms and persistent infection*

- Can prolonged symptoms be caused by persistent infections with other tick-borne pathogens?
  This will be formally addressed.

- What tests can document clearance vs persistence of Lyme disease following treatment, including suspected central nervous system infection?
This will be addressed and will include several diagnostic modalities, including serologic testing, PCR, culture, and xenodiagnoses.

- What are the long term cognitive effects of Lyme disease?
  The section on neurologic Lyme will address the neurologic syndromes that are known to be associated with Lyme disease. The outcomes of treatment for neurologic Lyme disease also will be addressed.

- How should “cyst” forms of *B. burgdorferi* be treated?
  Incorporated into the guideline will be the assessment of whether *B. burgdorferi* is known to have a fastidious or treatment-resistant biology in vivo and whether this requires a dedicated treatment approach.

In conclusion, the panel thanks the medical community and the general public for their comments on the Lyme disease guideline project plan. After a draft of the full guideline is developed, it will be posted on the IDSA website for a 45-day public comment period. Additional information on the timing and availability of this draft will be posted to the [IDSA website](https://www.idsa.org) as it becomes available.