LymeDisease.org and the national Lyme Disease Association Comments on Behalf of 67 Patient Groups
Submitted April 9, 2015

LymeDisease.org and the national Lyme Disease Association are submitting these comments on behalf of 67 Lyme disease patient groups across the nation in response to the Public Comment Period for the IDSA/AAN/ACR Lyme Disease Guideline Project Plan announced on March 9, 2015. LymeDisease.org also launched a patient survey on March 28 to solicit patient views on healthcare outcomes they deem important. This survey drew more than 5,500 responses in less than two weeks. Some of the findings from the survey are included in these comments.

Organizational Sponsorship
Page 1, lines 6-9

The Project Plan (Plan) lists the following groups as organizational sponsors of the Lyme guidelines development process: the Infectious Diseases Society of America (IDSA), the American Academy of Neurology (AAN), and American College of Rheumatology (ACR). This gives the impression of a broad base of support from independent organizations. Yet with respect to Lyme disease, these organizations are hardly independent. All were implicated by an antitrust investigation by the Connecticut Attorney General in connection with the development of the 2006 IDSA Lyme guidelines.[1, 2] Key members from all three organizations who sat on the panel of the 2006 IDSA Lyme guidelines as well as two of the organizations, the AAN and IDSA, were subject to the investigation by the Attorney General.

Antitrust law is concerned with abuses of power. Ultimately, antitrust laws focus on actions by 'dominant' organizations that constrain consumer choice and employ 'exclusionary conduct' to suppress the views of competitors. The Attorney General's findings in connection with the 2006 IDSA Lyme guidelines development process included the fact that the panel that formulated those guidelines was hand-picked by Dr. Gary Wormser and excluded participation by those with divergent viewpoints.[3]

In its report on how guideline development groups (GDGs) can formulate trustworthy guidelines, the Institute of Medicine (IOM) singled out the IDSA for its flawed development process for the 2006 IDSA Lyme Clinical Practice Guidelines (CPGs): "The 2006 lawsuit by Connecticut's Attorney General against the Infectious Diseases Society of America's Lyme Disease Guidelines highlights the need for standardization and transparency in all aspects of systemic data collection and review, committee administration, and guideline development, so that questions about these issues do not detract from the science. GDGs must be aware of the many, varied observers who will consider their development processes, particularly when their recommendations are likely to be controversial."[4]

Developers of CPGs become 'promoters and defenders' of the guidelines produced under their auspices, particularly when their own guidelines have been legally challenged and criticized publicly.[5] Validation of prior recommendations enables these societies to support their key opinion leaders, maintain their sphere of influence, suppress opposing viewpoints, and reduce potential litigation risk based on the guidelines.

As mentioned above, members of IDSA/AAN/ACR sat on the IDSA 2006 CPG panel. The IDSA and AAN created overlapping panels to develop their last set of Lyme CPGs and were subject to the antitrust investigation. The Attorney General's findings stated that the IDSA portrayed the AAN and IDSA guidelines as "independent" corroboration even though the panels in fact contained overlapping members and were controlled by a small group of overlapping members, including chairs. [2] Hence, the sponsors do not reflect a broad base of support at all. Rather their interests arise as promoters and defenders of guidelines that were legally challenged, increased their legal exposure, and sullied their reputations.

The IOM highlights the need for guideline panels to guard against organizational conflicts of interest (COIs): "The committee believes potential for COIs are great when funding for CPG development or for the supporting organization comes from stakeholders, particularly … specialty societies, which might benefit or whose members

might gain from guideline recommendations."[4] The sponsorship of this guideline development process by three organizations connected with the prior anti-trust action constitutes a classic COI where organizational interests may supersede the ethical mandate in medicine to hold patient interests paramount.[6]

The COI disclosure form for the current IDSA/AAN/ACR panel highlights the conflicts of interest this panel faces. It explicitly states "panel chair and member should act in the best interest of the IDSA, AAN, and ACR, its membership and the public." What happens when those interests conflict? Moreover, the ethical mandate of those in medicine is to hold the interests of patients paramount.[6] The interests of patients who actually suffer from a disease are quite different from those who do not.

The IOM stresses the importance of assessing institutional conflicts of interest. It states they should "be evaluated for the likelihood of undue influence and the seriousness of potential harms. . . , the extent of institutional accountability as well as the degree to which discretion is involved."[7] For treatment guidelines, there is considerable discretion to fill evidence gaps with judgment. For example, a research study by Lee and Vielemeyer, published in an IDSA journal, found low quality evidence supporting recommendations in more than half of the IDSA guidelines examined.[8] This finding was subsequently confirmed by Khan and colleagues.[9] The evidence base of the 2006 Lyme CPGs had similarly low levels of evidentiary support.[2] When the evidence base is weak, the opinions of those on the panel play a stronger role and the ability of COI to influence outcomes and to harm patients increases.

Moreover, as the IOM notes, the opportunity for harm in treatment guidelines is enormous because they "set standards of care and criteria for insurance coverage [and] may affect millions of patients."[7] The consequence of "getting it wrong," particularly when treatment options (and patient autonomy) are restricted as the IDSA Lyme CPGs have done in the past, may have devastating effects on the patient's quality of life. Further, there is no institutional accountability for CPGs and no regulatory oversight of the process. These factors heighten the need to control COIs.

The Plan does not contain any information regarding sponsorship COIs, which appear not to have been considered. The IOM recommends that institutions have separate committees with members from outside the organization to recognize and manage institutional COIs.[7] The Plan lacks the transparency required by the IOM in Standard 1, by failing to disclose the antitrust context in which this CPG development process arises and its connection with these sponsors. In addition, the Plan should disclose whether there is any other source of funding for these guidelines.

Sponsoring Organization Recommendation

The oversight committee should require that institutional COIs be disclosed and that they be managed by a separate independent committee. IDSA/AAN/ACR have substantial COIs in promoting organizational interests over patient interests and should not be developing joint guidelines for this very reason. Panel members should be advised of the ethical duty to hold the interest of the patient paramount.[6] All sources of funding for the guidelines should be disclosed. The Plan should disclose the antitrust context which plagued past Lyme CPG efforts.

Panel Constitution
Page 2 lines 14-48
Pages 8-9, lines 116-126: Conflicts of Interest

The IOM states that "[t]o be trustworthy, clinical practice guidelines should:

- Be developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups;
- Consider important patient subgroups and patient preferences, as appropriate;
- Be based on an explicit and transparent process that minimizes distortions, biases, and conflicts of interest."[10]

The IOM explains that the ability of the GDG to perform seemingly technical assessments, "depends on the composition of the group (whether the right participants have been brought to the table) and group processes

(whether the process allows all participants to be involved in a constructive way)." As the IOM notes, "the aim is to ensure that group processes fundamentally encourage inclusion of all opinions and grant adequate hearing to all arguments."[4]

As the IOM observes, guideline panel membership is a main determinant of the trustworthiness of guidelines.[4] This is because guideline recommendations are largely determined by the constitution of the guideline panel. As the Agency for Healthcare Research and Quality (AHRQ) explains "the key questions generated, literature search strategy, inclusion and exclusion criteria, study selection, definition of outcomes, analysis strategies, or interpretation of results may contribute to the report being biased towards his/her preconceived notion."[11]

This IDSA/AAN/ACR guidelines panel falls short of accomplishing the IOM panel constitution criteria on all fronts. The panel constitution process lacks transparency, excludes those most deeply affected, includes members with financial and intellectual biases, and creates process distortion through minority influence and group-think.

Lack of Transparency Regarding Panel Selection

There is no transparency as to how either the guidelines authors or members of the panel were selected. In the 2006 antitrust investigation, the Connecticut Attorney General found that the panel was "hand-picked" by Dr. Wormser to include viewpoints that aligned with his. This panel appears to have been selected by the same invisible hand. It appears to have been designed to achieve consensus by including those who agree and excluding those who do not. It appears poised to achieve predetermined conclusions that promote organizational interests over those of the patient.

Exclusion of Those Affected—Lyme Patients

The IOM notes that in addition to representing the interests of those affected by a disease or condition, a patient representative ensures process integrity by a) providing a window into the process and some assurance that guidelines were not developed "behind closed doors" to suit special interests, b) providing sensitivity to what matters most to those living with disease, c) acting as a safeguard against COIs that may skew judgment of clinical and scientific experts, and d) identifying evidence gaps and weighing in on the balance of benefits and harms from the viewpoint of the patient.[4]

Unfortunately, this panel does not have any representation of the interests of patients with chronic Lyme disease—a key affected population. Instead, the panel has selected a consumer reviewer who works on a cancer research panel at the University of Nebraska Medical School—a state which reports just 10 cases of Lyme disease per year.

When contacted, this consumer stated that she has never had Lyme disease and knows nothing about it or the issues facing the community. She stated that she thought this lack of knowledge was why she was chosen—so that she could be "impartial." But representation is the opposite of impartiality. A patient representative should have personal experience with and knowledge of the disease. She should be known and trusted by the Lyme community, and empowered to effectively represent their interests. A token patient on the panel is worse than no patient at all. It gives the illusion of process integrity where there is none.

The exclusion of Lyme patients and their advocates appears to be deliberate. LymeDisease.org applied to represent patient interests, but was rejected. Furthermore, IDSA/AAN/ACR approached Consumers United for Evidence Based Healthcare (CUE), a highly regarded national organization that educates and refers patients trained in evidence-based medicine, and requested a patient for their Lyme guidelines panel. CUE recommended the Executive Director of LymeDisease.org. The sponsors rejected this person, who is widely known and well regarded as a representative of the Lyme community. They also stated that they did not want a Lyme patient.

A detached consumer might be adequate for representing the needs of consumers in acute illnesses like the common cold, where disease advocacy organizations are not needed. However, it would be ludicrous to think that the interests of HIV/AIDS patients could be represented by someone with no knowledge of their disease. This panel also calls for a legitimate representative of Lyme patients. In healthcare, in particular, because the interests of stakeholders conflict, when someone else speaks for you, "there is a high chance that individuals will be prevented from realizing their interests or their interest will be sacrificed to someone else's interest."[12]

Moreover, patients have complained that the strict format requirements of the IDSA for filing comments using page and line number is too complex and has detoured patients from making comments.

The complete disregard shown by the IDSA/AAN/ACR panel for the interests of those affected by these guidelines is unacceptable. It fails to comply with IOM Standard 3, which specifies that the guidelines process must include "populations expected to be affected by the guidelines."[4] In addition, the IDSA/AAN/ACR further fails to comply with this standard which calls for two patient representatives, including one from a patient organization.

Exclusion of Those Affected—Physicians who Treat Chronic Lyme Disease

The IOM notes that in evidence-based medicine "clinical expertise and patient preferences remain vital to clinical decision making".[4] Yet, the IDSA/AAN/ACR panel does not include physicians who treat chronic Lyme disease – another population that will be deeply affected by these guidelines. Clinicians who do not comply with the guidelines are targeted by medical boards. Members of the IDSA testify against them.[13] Essentially, this allows the IDSA/AAN/ACR to develop the rules and standard of care and use them as a sword against their competitors who are not permitted in the room.

This situation has created a crisis in patient access to care. Patients with Lyme disease face substantial barriers to accessing care, with the majority traveling over 50 miles to receive care.[14] A number of states have adopted legislation protecting physicians who treat chronic Lyme disease. This situation bears a striking parallel to the legislation passed by fourteen states in the 1980s to ensure that women with breast cancer were provided with treatment options.[15]

The IDSA members on this panel are academic researchers. While researchers may set the evidence bar quite high for research purposes, clinicians deal with decision making in the face of uncertainty every day. They recognize that treatment decisions are context specific—how severe is this person's illness, how functionally impaired are they, what is their risk tolerance, how well do they tolerate treatment, and how beneficial has treatment been to them in the past. These clinicians also recognize that for Lyme patients, there are no treatment alternatives to antibiotics and that this lack of treatment alternatives matters.

As Deborah Zarin, Director of ClinicalTrials.gov, points out:

> Clinical decisions are driven by the current reality. You can't say to someone who has a medical need right then and there, 'hold on we'll do more clinical trials and get back to you in two years. You have to make decisions based on the best information available.[16]

The exclusion of clinicians who treat the majority of patients with chronic Lyme disease means that their experience and perspective on treating these patients will not be heard or discussed. In addition, the International Lyme and Associated Diseases Society (ILADS) has recently published the first Lyme guidelines using the GRADE assessment scheme, which included weighing risks and benefits and determining the role of the patient in participatory medical decision making. Even beyond ILADS physicians, however, there are members of the IDSA who disagree with the IDSA treatment guidelines. These physicians are also not included and, as the Attorney General noted, were systematically excluded from the prior IDSA guidelines process.

Exclusion of Those affected—Researchers with Divergent Viewpoints

The very nature of science depends upon the free market of ideas to ensure scientific integrity. The exclusion of researchers who do not follow the IDSA viewpoint precludes the type of robust discussion of the issues as contemplated by the IOM. Instead, panel deliberations will be confined to a narrow viewpoint reflecting the bias of one side of this debate.

Researchers excluded from this IDSA/AAN/ACR panel are also affected by this guideline development process. Their research is easily dismissed and the research of those on the panel is elevated. The public is harmed when the state of science in guidelines is prematurely presented as closed and settled. Essential research simply does not get put on the public agenda when patient needs go unidentified and are not addressed.

The inclusion of diverse researchers encourages a broad discussion of the issues. It also helps discourage self-promotional practices, such as self-citation of articles written by panel members to further their career goals. [17] In the 2006 Lyme guidelines, 40% of the citations were to research published by those on the panel.

Inclusion of Those with Known Biases and Conflicts of Interest

Key Panel Members--Financial Conflicts of Interest

Key questions for the IDSA/AAN/ACR panel include the sensitivity of Lyme disease laboratory tests, when they should be used, what type of band reporting is recommended, and which tests should be used. Six of the panel members report financial COI related to Lyme diagnostic tests, having either received grants or commercial funding for Lyme tests. Four of the members of the panel have financial COI with Immunetics, the developer of the C6 Lyme test. One of the members, Dr. Wormser has financial COI with six diagnostic test companies.

A number of questions posed by the panel relate to diagnostic test interests. One appears to be directed at the use of the C6 Lyme test as a substitute for two-tiered serology. Another appears to be directed at harming the test of an excluded competitor who reports specific antibody bands with the test results. Finally, there is a question regarding the use of "unvalidated" tests. This appears to be aimed at suppressing the development of innovative tests that may compete with the inferior tests in which panel members have conflicting interests.[18] (See questions 75-81, page 15).

The participation by these panel members will ensure that the status quo which favors existing tests remains unchallenged by new entrants pursuing innovation in the market. The ultimate victims of these COIs and their impact on testing are the patients, whose physicians are instructed to use laboratory tests that miss more than 50% of Lyme cases.[18]

In addition, several panel members report receiving fees for consulting in legal cases against their competitors who do not follow the IDSA guidelines.

Key Panel Members—Intellectual Conflicts of Interest

COIs include not only financial conflicts of interest, but also intellectual conflicts of interest. According to the IOM, "A person whose work or professional group fundamentally is jeopardized, or enhanced, by a guideline recommendation is said to have intellectual COI. Intellectual COI includes authoring a publication or acting as an investigator on a peer reviewed grant directly related to recommendations under consideration."[4] In addition, intellectual COIs include "preconceptions and previously stated positions, and the desire for recognition and career advancement"[7] Intellectual conflicts of interest create the potential for an attachment to a specific point of view."[19] In a highly polemic scientific debate such as Lyme disease, the potential for intellectual COI runs high. Indeed, the IOM has identified the "Lyme Wars" as one of the most contentious debates in medicine.[4]

The Agency for Healthcare Research and Quality (AHRQ) explains that intellectual COI are rampant in "topics with intense advocacy, active policy debate, large interspecialty variations, and limited availability of clinical or content expertise." In such controversies, the debate is typically not about evidence, but about values and perspectives of stakeholders. As a result, exclusion of those who hold divergent perspectives undermines the integrity of the process. The AHRQ recommends that panels in contentious areas address the issue of polemic intellectual COI by either excluding those with the COIs or balancing the panel so that all perspectives are represented.

Ten of the thirty panel members were either investigated for antitrust violations by the Connecticut Attorney General in connection with the IDSA 2006 guidelines, testified on behalf of the IDSA at the hearing, or sat on the IDSA hearing panel. In the wake of the antitrust investigation, the chair of the IDSA guidelines panel, Dr. Wormser, co-authored not only defensive guidelines by the AAN, but also a set of guidelines by a broader group published in the New England Journal of Medicine.[1, 20] The key members of the IDSA/AAN/ACR panel (those with an expertise in Lyme disease) primarily are members of the IDSA 2006 guidelines and authors of these two defensive guidelines.

As a backdrop to the IDSA/AAN/ACR guidelines process, the pattern of bias and collusion continues with Dr. Wormser linking arms with Dr. Lantos (who served on the IDSA antitrust review panel and was the lead author on its report) to publish within the last year two systematic reviews to apparently preemptively "front run" this guidelines process.[6, 7] Meanwhile a systematic review, listing Drs. Auwaerter and Rumbaugh as authors, which has been languishing on the back shelf at Cochrane since 2009, has reportedly picked up speed again with a draft expected soon.[21] This gives the appearance of being an orchestrated campaign directed toward gaming the system and ensuring vindication of the IDSA beleaguered 2006 guidelines.

The IOM Standard 2.1 requires disclosure of all intellectual COIs, yet none of the above disclosures were made. Moreover, disclosure alone would be insufficient to overcome these COIs, which suggest that this group has been coordinating moves as a team since before 2006—first to author the 2006 guidelines, then to defend those guidelines with two defensive copycat guidelines, and by sitting on or testifying before the IDSA antitrust panel. In preparation for this newly convened panel, team members have rushed to print two systematic reviews and have another hovering in the wings at Cochrane. The IOM cautions against these types of processes where "evidence is [being] used to confirm preexisting opinions rather than change them." [4]

Guidelines Panel Process Distortion

According to the IOM, the aim of including a broad spectrum of opinions and viewpoints of those affected is to ensure that "group processes fundamentally encourage inclusion of all opinions and grant adequate hearing to all arguments." This panel, however, consists of two groups of people: those who have strongly held polemic viewpoints and biases against the diagnosis and treatment of patients with Lyme disease and those who apparently have no knowledge of Lyme disease. Those who hold opposing viewpoints, have been deliberately excluded from the process—which appears geared toward attaining consensus by exclusion.

The IOM warns against dysfunctional group processes, which include "minority influence (a single member or minority of group members sway the majority, often by capitalizing on small divisions in the group), group polarization (group dynamic leads to more extreme decisions than members would make individually), and 'groupthink' (members' desire for unanimity trumps objective appraisal of the evidence)". They caution that multidisciplinary groups are particularly at risk because members vary in "professional status, in the nature or depth of their specialist knowledge, and in their appreciation of roles and modus operandi of professional colleagues."[4]

Key panel members (those with Lyme expertise) routinely publish with each other and sit on grant peer review study groups together. They support each other's careers, which are predicated on the view that Lyme disease is "hard to catch and easy to diagnose and cure". This group holds laboratory interests in Lyme diagnostic tests. The tests are highly insensitive, but the group bands together to support these tests, require them for diagnosis, and works to oppose competing tests.[18] These COIs are both commercial and intellectual, as outlined above.

Based on coordinated group actions related to the publications and defense of the IDSA 2006 guidelines and the "front running" by this group of systematic reviews for the IDSA/AAN/ACR guidelines process, it is clear that the key members of the panel do not speak with individual unique voices – they speak as a single unified voice. That they have systematically excluded anyone from the panel who might hold them accountable for their actions ensures that their unified voice will not be opposed.

The remainder of the group may be expected to play "follow the leader" as they defer to the expertise of the only experts permitted in the room—those with strong intellectual and financial COIs. By excluding those with divergent viewpoints, the Process ensures that a robust discussion of the issues will not occur. Instead, the process will be dominated by the type of "groupthink" and minority influence that the IOM specifically warns guidelines panels to avoid.[5]

Recommendation Regarding Panel Constitution

In this process, all of those with an expertise in Lyme disease have either a financial or an intellectual COI. Many have been operating as a coordinated team for over a decade, preparing and defending the IDSA 2006 guidelines. Now the team bands together once again as a single unified voice on the new IDSA/AAN/ACR guidelines panel.

Other researchers or patients and their treating physicians who might counteract these process irregularities, criticize the preemptive systematic reviews, or limit self-citation practices are excluded. This means that there are no checks and balances on the pursuit of these self-interested activities. Even though some members of the panel are from other disciplines, their relative lack of expertise in Lyme disease coupled with the exclusion of all opposing viewpoints permits minority group distortion to dominate the process.

The IOM states that "whenever possible [guidelines panels] should not have COIs" and that guidelines panels should include "those affected," including clinicians and patients. The guidelines panel should be reconstituted to include a balance of those affected by the guidelines, including representation from patients with Lyme disease and the organizations representing them, physicians who treat chronic Lyme disease, and researchers representing the spectrum of scientific viewpoints regarding Lyme disease. Panel members who hold strong biases against patients, (including those associated with the Connecticut Attorney General antitrust investigation) and those with financial COIs (particularly those related to diagnostic tests) should be removed from the panel.

All six members with financial COI related to diagnostic tests should be removed from the panel. If it is determined that any of these members is needed for expertise, the number should be limited to those few who are absolutely essential. Testing expertise outside those on the panel exists and drawing from this pool is the ideal. The current state of diagnostic tests is poor. Requiring a positive test result when tests are insensitive harms patients by leaving many undiagnosed and untreated. This issue has been contentious and at the IDSA antitrust panel, there was a split vote on testing. Hence, managing COIs here is critically important. Dr. Wormser, who has financial COIs with six diagnostic companies and has extensive intellectual COI, heads the list of those who should be removed.

Panel Constitution – Authorship and Leadership
Page 2, lines 4-11: Guidelines Authors, Panel Leadership.
Page 8-9, lines 116-126: Conflicts of Interest

The Plan lists as guidelines authors and panel leadership, Linda Bockenstedt, MD (ACR), Paul Lantos, MD (IDSA and ACP), and Jeffrey Rumbaugh, MD (AAN). Bockenstedt has considerable financial COIs related to lab testing and all three have considerable intellectual COI as outlined above under panel constitution. Both Lantos and Rumbaugh, representing two organizations that were subject to an antitrust investigation in connection with the 2006 guidelines, appear to be championing systematic reviews that the new panel can cite as support for their recommendations.

Recommendation Regarding Authorship and Leadership

The IOM recommends that members of the panel leadership be entirely free of COIs. Lack of COIs on the leadership team is critical as the leadership team is responsible for conducting the literature search and other tasks which require that issues be framed in a manner that does not lead to a predetermined result. Furthermore, those on the leadership team apparently would be responsible for reviewing their own work, which is unacceptable. Accordingly, Bockenstedt, Lantos, and Rumbaugh should be removed from leadership of this panel.

Specific Panel Member Objections

Page 2, Line 4-5: Linda Bockenstedt MD, Co-Chair representing ACR (and page 17): Financial COI in Lyme disease diagnostics and vaccines as well as Babesia therapeutics; Intellectual COI: author of IDSA 2006 Lyme guidelines, subject to antitrust investigation, author of NEJM Lyme defense article.[1, 20]

Page 2, Line 8-9: Paul Lantos, Co-Chair representing IDSA and ACP: Intellectual COI: IDSA Lyme spokesperson, member of IDSA antitrust review panel, lead author of IDSA review panel report, author of two preemptive systematic review articles.[22-24]

Page 2, Line 10: Jeffrey Rumbaugh, representing the AAN, one of the organizations investigated for antitrust violations in connection with the 2006 guidelines and co-author with Auwaerter of a Cochrane protocol timed to permit self-citation and inclusion of evidence generated in contemplation of this guideline process.[21]

Page 2, Line 14: Paul G. Auwaerter, MD, representing IDSA (and page17), Financial COI: testifies and consults on Lyme legal cases; Intellectual COI: Reviewer of IDSA 2006 guidelines, IDSA Lyme spokesperson, author of strongly biased viewpoints. [1, 20, 25, 26]

Page 2, Line 18: Maria E. Aguero-Rosenfeld, MD (and page 17): Financial COI: consultant on legal cases in Lyme disease; Intellectual COI: consultant for IDSA 2006 Lyme guidelines.[1]

Page 2, Line 19: John A. Branda (and page 18) Financial COI: Lyme diagnostic tests and Immunetics

Page 2, Line 24: John J. Halperin, MD (and page20) Financial COI: collects samples for Lyme diagnostics. Intellectual COI: represents AAN which was subject to antitrust investigation; author of IDSA 2006 Lyme guidelines, subject to antitrust investigation, author of NEJM Lyme defense article, author of AAN defense article.[1, 20, 27]

Page 2, Line 25: Peter J. Krause, MD, representing IDSA (and page 20-21) Financial COI: Lyme tests and Immunetics; Intellectual COI: author of IDSA 2006 Lyme guidelines, subject to antitrust investigation, author of NEJM Lyme defense article.[1, 20]

Page 2, Line 28: Lise E. Nigrovic, MD, MPH, representing AAP-EM (and page 21-22). Financial COI regarding Lyme diagnostic tests.

Page 2, Line 31: Jane Rips, consumer representative: This person is not a Lyme patient, has no knowledge of the disease and does not represent patients with Lyme disease.

Page 2, line 34: Sunil Sood, MD, representing IDSA. Intellectual COI: testified at IDSA hearing, author of NEJM Lyme defense article.[20]

Page 2, Line 35: Allen C. Steere, Jr., MD, representing ACR (and page 23-24) Financial COI: Lyme tests, Immunetics, Baxter Lyme vaccine. Intellectual COI: author of IDSA 2006 Lyme guidelines, subject to antitrust investigation, testified at IDSA antitrust hearing, author of NEJM Lyme defense article.[1, 20]

Page 2, Line 36: Frank Strle MD, PhD, representing ESCMID (and page24) author of IDSA 2006 Lyme guidelines, subject to antitrust investigation.[1]

Page 2, Line 39: Gary Wormser, MD, representing IDSA (and page 24-25): Financial COI Immunetics (developer of C6 Lyme test), BioMerieux, Biorad, DioSorin, Rarecyte, Institute for Systems Biology. Intellectual COI. Chair and lead author of IDSA 2006 Lyme guidelines, subject to antitrust investigation, found to have "hand-picked" the 2006 panel and intentionally excluded opposing scientific viewpoints, testifier at IDSA antitrust hearing, author of NEJM Lyme defense article, author of AAN defense article; author of two recent preemptive systematic Lyme reviews.[1, 20, 22, 24, 27]

Page 2, Line 40: Lawrence Zemel, MD representing ACR. Intellectual COI author of NEJM Lyme defense article[20]

Background

Page 3, lines 16-22:

The background needs to reflect the fact that the CDC increased its estimate of annual Lyme disease cases from 30,000 to 300,000.[28] Otherwise, it leaves the impression that Lyme is a rare disease, when it is actually quite common. The burden of illness of this disease on patients, their families, and communities is substantial. The healthcare utilization rates of those with Lyme disease are sizeable.[29, 30] Improving the quality of life and functional impairment for this population is a pressing unaddressed need.

The process lists the guidelines of other medical societies. Conspicuous in its absence is any mention of the ILADS 2014 guidelines, which are the only Lyme guidelines to employ a rigorous GRADE assessment evaluation of the evidence. It also included participation by a chronic Lyme disease patient who heads one of the most influential national advocacy organizations, LymeDisease.org. The ILADS guidelines delineated evidence gaps and clearly explained the role of patient values and preferences in weighing treatment risks and benefits, as the IOM recommends.

Objectives and Scope
Page 5, line 49

The document is filled with framing biases that beg preselected answers. For example, the objective "evidence-based recognition of Lyme disease clinical presentations" implies that the use of "objective findings" will be elevated and patient symptoms will be disregarded as "not evidence." This demonstrates researcher bias in these guidelines. While objective indicators of disease are convenient for researchers, patient-centered guidelines consider patient reported outcomes to be the primary indicators of wellness.[31]

There are many reasons for this, including the fact that for many conditions that affect quality of life or ability to function, information must come directly from the patient. In addition, studies have shown that researchers and physicians tend to underestimate the severity of symptoms and their assessments have low reliability.[32] Hence, while the 2006 IDSA guidelines dismiss patient symptoms as no more than the "aches and pains of daily living", a survey of Lyme patients using the Centers for Disease Control and Prevention Health Related Quality of Life survey found that the majority reported poor or fair quality of life and significant functional impairment.[30] They also reported many symptoms as severe or very severe.[30]

Methodology
Page 5, lines 61-65

The Plan states that it will use Population, Intervention, Comparator, Outcomes (PICO) as the method for determining questions to be asked by the IDSA/AAN/ACR panel. However, most of these questions are not reflective of PICO, failing to indicate population, intervention, comparator, or outcome. For example, questions 90 and 91 regarding positive and negative predictive values of Lyme laboratory testing do not specify the population contemplated. These appear to be written from the perspective of screening the general population. However, patients who go to their doctors' offices with symptoms compatible with Lyme disease are not a screening population. The questions need to be rewritten in proper PICO format.

Methods of Summarizing
Page 8-9, lines 66-90

Under GRADE, PICO determinations are supposed to be delineated into those important to *patients* (less important, important and critically important). This panel has no one who can represent patient interests. A recent commentary in the Journal of the American Medical Association points to the connection between evidence-based medicine and shared medical decision-making. The authors observe that: "Evidence-based medicine should begin and end with the patient: after finding and appraising the evidence and integrating its inferences with their expertise, clinicians attempt a decision that reflects their patient's values and circumstances."[33]

One of the reasons guideline panels need patient representation is that numerous studies have reported the discrepancies between the clinician's judgment of patient perception and the patient's actual view or experience. Because "most health care decisions are made either without optimal evidence or with evidence of both benefits and harms that must be balanced. . . the interplay between the evidence and patient priorities drives shared decision making and ultimately determines the value of the intervention."[34]

Moreover, at every turn, the key opinion leaders on this panel have opposed patient interests and outcomes deemed important by patients, from representation on legislative councils to selection of a "not Lyme" consumer for the panel. We want to make it clear that the IDSA/AAN/ACR panel viewpoints cannot act as surrogates for the interests and outcomes that Lyme patients deem to be important.

The Plan fails to disclose the search criteria that will be employed in the evidence assessment and is not transparent about how it will review evidence. It is critical that this panel consider the full body of scientific evidence, including animal model research and observational trials, because the evidence base in Lyme disease treatment is scant. Moreover, systematic reviews cannot overcome the limitations of underlying randomized controlled trials. Hence, any treatment trials must be reviewed directly together with criticism of such trials. In addition, the AHRQ

admonishes those involved in systematic reviews to not rely on interpretation of data by study authors because of the risk that authors may put "spin" on the results.[35]

In Lyme disease, there are only four randomized treatment trials. These have suffered from small sample sizes (the largest has only 74 patients in the treatment arm). They have also been criticized for not being generalizable to the clinical population and for using treatment effects that were far higher than would be clinically meaningful to patients.[36, 37] In addition, the trials suffered from poor recruitment and employed differing selection and outcome measurements as well as varying treatment follow up durations, all of which make comparisons difficult.

The recently published ILADS Lyme guidelines feature rigorous evidence evaluation using GRADE. These guidelines provide a careful analysis of the roles of patient preferences and outcomes that patients deem important. These guidelines should be a key review article for the IDSA/AAN/ACR panel.[38] The ILADS guidelines are patient-centered, included a patient on the working team, and have been endorsed by a major Lyme disease organization, LymeDisease.org. Reconciling the IDSA/AAN/ACR panel's views with those reflected in the ILADS guidelines should be a fundamental task of the IDSA/AAN/ACR guidelines panel.

In addition, the Plan needs to acknowledge that a) there is a divergence of opinion in both the physician and researcher communities regarding chronic Lyme disease, b) conflicting guidelines exist, and c) patient viewpoints when properly represented play a substantial role in guideline recommendations. The process and ultimate guidelines should acknowledge these facts as a fundamental tenet of transparency.

The panel should also consider the GRADE assessment by Hayes and Mead of the CDC regarding the treatment of late neurologic Lyme disease, which rated the quality of the evidence as very low.[39]

The panel has gone to great lengths to exclude meaningful voices in the guidelines process. As the ultimate stakeholders, patients should have a role in determining whether potential individual risks outweigh benefits of any treatment approach. These decisions should be made in the context of patient circumstances, including severity of disease, functional impairment, as well as values and preferences. As the IOM recognizes: "Informed choice under uncertainty is an ideal to strive for, especially because it enhances the exercise of the patient's right of self-determination, which is a cornerstone of medical ethics."[4] Many guidelines authors also recognize that: "As a rule, good practice guidelines make strong recommendations only when there is strong evidence to support them. . . Good guidelines acknowledge situations where clinical decisions are not clear-cut, and offer flexibility in these situations."[40] A primary concern of patients regarding the IDSA 2006 guidelines has been the use of strong recommendations in the face of weak evidence.

LymeDisease.org has conducted a survey to identify outcomes of that patient regard as important. For example, the outcome of most interest to patients with early Lyme disease is improving the treatment success rates to prevent chronic Lyme disease. Patients also want to be promptly diagnosed and treated, even if the incidence of Lyme disease in their area is not high. The results of this survey, which drew over 5,500 patient responses in less than two weeks, will be posted on the LymeDisease.org website. This high rate of response indicates how suppressed the patient voice has been. We encourage panel members to review the survey results carefully and consider them in their deliberations.

Conclusion

The current Plan fails to provide the type of process integrity essential to creating trustworthy guidelines. We believe that the Plan to should be revised to achieve the following goals.

1. The IDSA/AAN/ACR panels should be balanced and represent scientists and physicians from both opposing Lyme paradigms.
2. Robust patient representation (2 or more) is important and should not be token. Patients should be empowered and prepared patients who represent the population affected by Lyme disease.
3. Consensus should not be obtained by excluding people who disagree.
4. Controversies and disagreement should be acknowledged. Minority viewpoints should be published with the guidelines.

5. A public docket of all comments should be maintained and be publicly posted on the IDSA website.
6. The IDSA/AAN/ACR guidelines should be reconciled with the guidelines of ILADS.
7. All value judgments by the panel, particularly those pertaining to the patient's role in risk/benefit assessment, should be carefully delineated together with the basis for such judgment.
8. Guidelines should undergo rigorous external peer review by all interested parties. Responses to comments should be made public.

These comments are submitted by LymeDisease.org and the national Lyme Disease Association on behalf of the following 67 Lyme disease organizations across the nation:

Lyme Disease.org
Lyme Disease Association, Inc. NJ
Indiana Lyme Connect, IN
WA Lyme Fighters, WA
Gear Up for Lyme, VT
The Lyme Association of Greater Kansas City, KS
Kentuckiana Lyme Disease Support Group, KY
Greater Manchester Lyme Disease Support Group, NH
Bedford Lyme Disease Council, NH
MissouriLyme, MO
Illinois Lyme Group, IL
Journey Through Challenge, PA
Brookfield/Wolfeboro Lyme Support Group, NH
Greater St Louis Lyme-Masters Disease Support Group, MO
Mid-Shore Lyme Disease Association, Inc, MD
Lyme Disease Eugene Oregon, OR
Military Lyme, CO
Cfsfmld, CO
Lyme Action Network, NY
TXLDA, TX
Hudson Valley Lyme Disease Association, NY
Lyme Connection/RLDTF, CT
Lyme Alliance of the Berkshires, NY
Mid Missouri Lyme Support Group, MO
United Lyme Action, CA
New York City Lyme Disease Support Group, NY
Missouri Lyme, MO
MN Lyme Association, MN
Lyme Disease Association of Southeastern Pennsylvania, Inc., PA
LYME411, NH
Lyme Disease Seattle WA Organization, WA
Oregon Lyme Disease Network, OR
Central Mass Lyme Foundation, MA
Massachusetts Lyme Legislative Task Force, MA
Lyme Disease Education & Support Groups of Maryland, MD
Harford County Lyme Disease Support Group, Inc., MD
Central Maryland Lyme Disease Support Group, MD
National Tick-Borne Disease Advocates, TX
Michigan Lyme Disease Association, MI
LDA RI Chapter, RI
Madison Lyme Support Group, WI

Arizona Lyme Disease Association (AzLDA), AZ
Bergen Bowmen, NJ
Iowa Lyme, IA
Wisconsin Lyme Yahoo, WI
Newtown Lyme Disease Task Force, CT
Lyme Disease Support Group of Southwestern Vermont, VT
Professional Research Center of Naples, FL
Arklatex Lyme Disease Prevention & Support, TX
Clarksville Lyme Support, TN
Lyme Disease Support, WY
Greater Boston Area Metro West Lyme Disease Support Group, MA
Ticked Off On Lyme WA, WA
National Capital Lyme Disease Association, VA
Greater Danbury Lyme Disease Support Group, CT
Kentucky Lyme Disease Association (KyLDA), KY
Sturbridge Lyme Awareness of MA (S.L.A.M.), MA
Utah Lyme Disease Alliance, UT
New Hampshire Lyme Alliance, NH
MaineLyme, ME
Mid Missouri Lyme support group, MO
IGeneX, Inc., CA
PALRN (PA Lyme Resource Network) Delco Region, PA
Massachusetts Lyme Coalition, MA
The Charles E. Holman Morgellons Disease Foundation, Nursing Advisory Panel, TN
Eastern Ct Chapter, Lyme Disease Association, CT
Florida Lyme Disease Association, FL

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