Testing and Diagnostics:

Report to Tick-Borne Disease Working Group

Presenters:
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Tick-Borne Disease Working Group

Meeting #4

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Disclaimer

Information and opinions are those of the presenter(s) on behalf of the Testing and Diagnostics Subcommittee, and do not necessarily reflect the opinions of the full Working Group or the Department of Health and Human Services.

Background

- Lyme disease is the most commonly reported vector-borne disease, with CDC estimates of over 300,000 infections per year
- Biological and technical challenges to the diagnosis of Lyme disease limit the opportunities for early identification and treatment
- Currently, CDC recommends diagnosis based on presence of either an erythema migrans (EM) “bulls eye” rash or a positive two-tiered serology in an appropriate clinical scenario
- Less than half of all patients have a typical bulls-eye rash, making diagnosis difficult
- Current serology has limitations that can result in negative tests in patients with disease
- With federal support, better diagnostics could be rapidly developed and/or adapted from other diseases

Tick-Borne Disease Working Group

Name	Member type	Stakeholder group	Expertise
Chairs (2)			
Lise E. Nigrovic, MD MPH	Public	Health care provider	Boston Children's Hospital
David Roth, JD	Public	Advocate	

Name	Member type	Stakeholder group	Expertise
Members			
Holly Ahern, MS MT(ASCP)	Public	Advocate	State University of New York
Charles Chiu, MD PhD	Public	Health care provider	UCSF
Roberta DeBiasi, MD MS	Public	Health care provider	Children's National
Noel Gerald, PhD	Federal	Public health	FDA
Deborah Hoadley, MD	Public	Health care provider	New England Institute for Lyme Disease and Tick-Borne Illness
Maliha Ilias, PhD	Federal	Program officer	NIAID
Bobbi Pritt, MD MSc	Public	Health care provider	Mayo Clinic
Steven Schutzer, MD	Public	Health care provider	Rutgers University

Federal staff: Christina Li MPH & Katie Terra BA

Methods

- **Meetings**
  - **Conference calls (11)**
  - **Electronic discussions**
- **Expert speakers (3)**
  - **Maliha Ilias PhD, Tom Slezak MS, Ray Dattwyler MD**
- **Selection of 3 priority areas**
  - **Assignment of members to sub-groups**

Priority Areas

- **Existing gaps in current diagnostic approaches**
- **Identification of technologies that could improve the state of diagnostic testing**
- **Inclusion of special populations in clinical studies**

Methods

- How was the report to the working group developed?
  - Active discussion
  - Electronic comments
  - Consensus methods
  - No minority report: final report vote
    - Approve without additional comment 10
    - Approve with additional comment 0
    - Disapprove – n/a

Results - Gaps in Current Diagnostics

- **Improved Lyme disease tests are needed**
  - **Two-tiered serology can lead to missed diagnosis or incorrect diagnosis of Lyme disease**
  - **Diagnostic test performance may vary between laboratories or among different test kits**
  - **Test performance in patients without a bulls-eye rash has not been rigorously evaluated**
  - **Gaps in provider education may lead to delays in diagnosis of Lyme disease in patients**

Results and Recommendations

- **Congress can increase appropriations to the National Institutes of Health (NIH) and other federal organizations to fund research that will advance the development of better performing diagnostic tests. NIH and other federal organizations may then take advantage of current and existing peer-review processes to evaluate the feasibility and impact of proposed research projects, including projects that will:**

  1. **Support translational research leading to the development of improved diagnostic tests**
  2. **Rapidly translate new diagnostics into test platforms that can be submitted for evaluation by the FDA for clearance or approval**
  3. **Encourage scientists to repurpose existing technologies available for diagnosis of other diseases such as cancer and non-Lyme infectious diseases**

New Technology — Challenges in testing

- **Direct testing - Pathogen detection**
  - **Low levels of *Borrelia* in clinical samples**
  - **Culture requires large blood volumes as well as special media and laboratory expertise**
  - **Polymerase chain reaction (PCR) may have limited detection ability in blood samples**

New Technology — Challenges in testing

- **Indirect testing - Host response**
  - **The development of detectable levels of antibodies to *B. burgdorferi* by conventional methods takes time, which makes it difficult to diagnose infection during the first few weeks**
  - **Subjective interpretation of the results of the Western blot introduces variability**
  - **Indirect testing ultimately depends on the ability of the host's immune system to respond to infection, as well as the composition of the test itself.**

Types of Lyme Disease Tests

Category	Type	Target
Proteomics	Direct	Bacterial Proteins
Multiplex next-generation DNA/RNA sequencing	Direct	Bacterial DNA or RNA
Metagenomic next-generation DNA/RNA sequencing	Direct	Bacterial DNA or RNA
Culture-based methods	Direct	Living bacterial cells
Nanopore sequencing	Direct Indirect	Bacterial DNA or RNA Host RNA
Metabolomics	Indirect	Host Metabolites
Transcriptomics	Indirect	Host RNA
Next-generation serologic assays	Indirect	Host antibodies
Microfluidics	Indirect	Host antibodies
Cytokine release assays	Indirect	Host cellular responses

Results and Recommendations

- **Need for new technology**
  1. **Increased funding for discovery and development of diagnostics for Lyme disease**
  2. **Development of new (or support for existing) bio-sample repositories for the purposes of supporting basic research and test validation**
  3. **Foster public-private partnerships, open source data-sharing and support prize-based competitions for the development of diagnostics for Lyme disease**

Results

- **Include understudied special populations in clinical research studies**
  - **Children**
  - **Under-represented minorities**
  - **Patients from geographical areas considered non-endemic for Lyme disease**
  - **Immunocompromised patients**
  - **Pregnant women**
  - **Neonates born to women who were infected during pregnancy**

Results and Recommendations

- **Special populations**
  1. **Encourage inclusion of special populations in future federally-funded Lyme disease research**
  2. **Provide federal funds for the development of high-quality Lyme disease biobanks that include special populations, especially children**
  3. **Develop and disseminate high-quality online provider education modules that address the diagnosis of tick-borne illness in general, and special populations more specifically.**

Discussion

- **Challenges to Report**
  - **Limited time and resources**

Summary

- **Important gaps in current diagnostic tests**
  - Delays or failure in diagnosis
- **New approaches needed**
  - Repurposing of existing technologies
  - Novel or improved technologies
- **Under-represented special populations**
  - Improved diagnostic methods in special populations will decrease missed diagnoses and allow timely treatment
  - Study of special populations may reveal new insights into pathogenesis

Author's Concluding Statement

- Lyme disease tests with improved performance could decrease the personal and societal disease burden and associated health care costs of Lyme disease by:
  - Decreasing the number of missed Lyme disease diagnoses
  - Decreasing the number of people with short- and long-term negative health impacts of Lyme disease
  - Decreasing the potential for false positive results and reduce unnecessary treatments
  - Providing a way to "test for cure"
- Improvements in diagnostics are possible within the next few years with federal assistance in funding and infrastructure.
- Why hasn't it happened before now? The bacterium that causes Lyme disease has unusual biological properties that are only now being recognized and investigated
- Federal assistance can enable other infectious disease testing methods to quickly be adapted to Lyme disease to decrease the number of adverse health outcomes
- Funding these endeavors will ensure that a next generation of trained scientists and physicians will be available