



A Global Update

Lyme disease research from around the world

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- Significant uncertainties in diagnosis, treatment and the scale of the problem
- Current serology tests have limitations
- No gold standard test
- No reliable biomarker of disease activity or cure
- Need better tests and treatments
- Need increased awareness - raising the profile of Lyme and Tick-Borne Diseases through reliably sourced information
- Urgent need for UK expertise and UK research



Lyme Disease Action

Lyme disease: Uncertainties



James
Lind
Alliance

Priority Setting Partnerships

<http://www.jla.nihr.ac.uk/>

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Lyme Disease Top 10

1. How effective are the current UK tests in detecting infections due to the genospecies and strains of *B burgdorferi* s.l in the UK and which single test and what combination of tests performs best in diagnosing or ruling out active Lyme disease. Should stage of the disease and patient age be taken into account when interpreting these tests?
2. What key questions (clinical and epidemiological) should be considered to help make a diagnosis of Lyme disease in children and adults in the UK and would a weighting table be useful?
3. What is the best treatment for children and adults presenting with a) early Lyme disease without neurological involvement and not including erythema migrans and b) late Lyme disease of any manifestation? To include consideration of drug(s), dose, duration.
4. What is the optimal course of action if symptoms relapse after a treatment course is finished?

Results: 78 studies evaluating an ELISA or immunoblot against a reference standard of clinical criteria were included.

None of the studies had low risk of bias.

Sensitivity was highly variable:

- Erythema migrans 50% (40 - 61%)
- Neuroborreliosis 77% (67 - 85 %)
- Acrodermatitis chronica atrophicans 97 % (94 - 99%)
- Unspecified Lyme borreliosis 73% (53 - 87%)

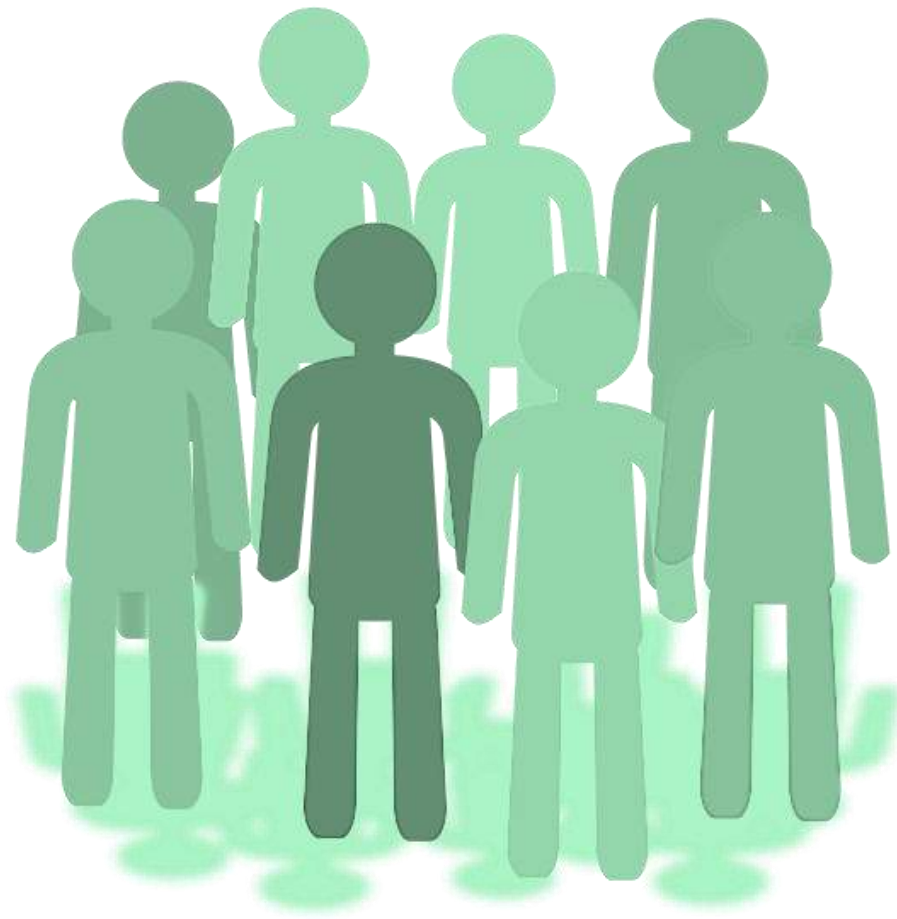
Specificity was around 95% in studies with healthy controls, but around 80% in cross-sectional studies.

Two-tiered algorithms or antibody indices did not outperform single test approaches.

Significant Research Challenges

- Resources: funding, human resources
- 'Red-tape'
- Methodological challenges: sample size, diagnostics
- Technology: frontiers of biomedical research
'Omics revolution': genomics, proteomics or metabolomics etc.
- Borrelia-related factors
- Human factors: Lyme disease as a 'Wicked problem'
 - incomplete/contradictory knowledge
 - number of people/opinions involved
 - economic burden
 - interconnected with other problems





Individual Host-Pathogen Interaction

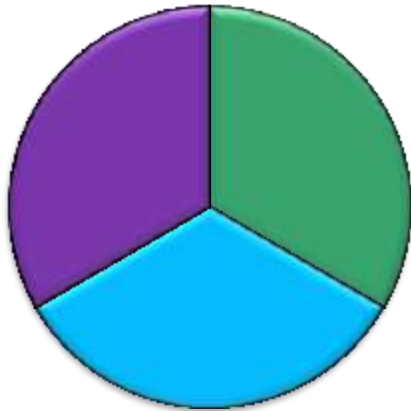
Bouquet J, Soloski MJ, Swei A, et al. *MBio* 2016; 7: 1–11

Strle K, Jones KL, Drouin EE, et al. *Am J Pathol* 2011; 178: 2726–39

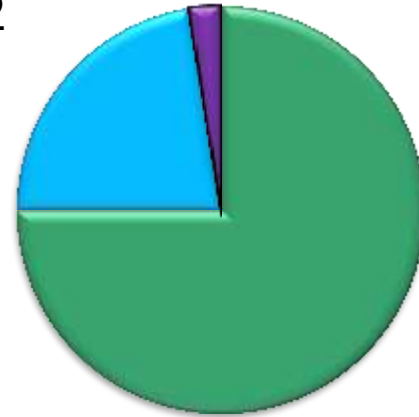
Lyme disease

What are we treating?

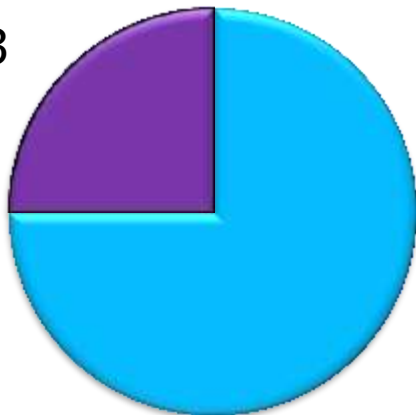
Patient 1



Patient 2



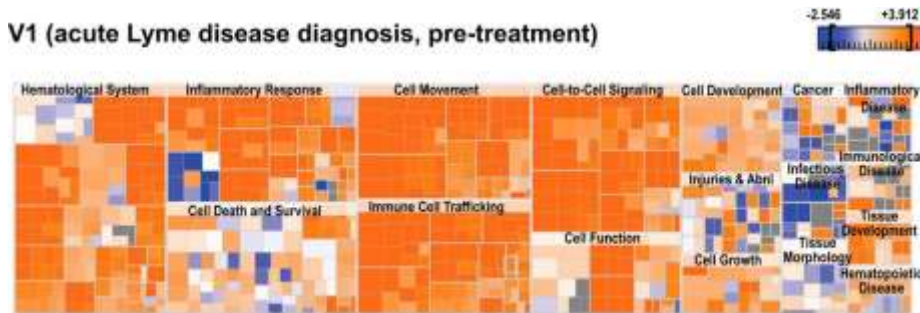
Patient 3



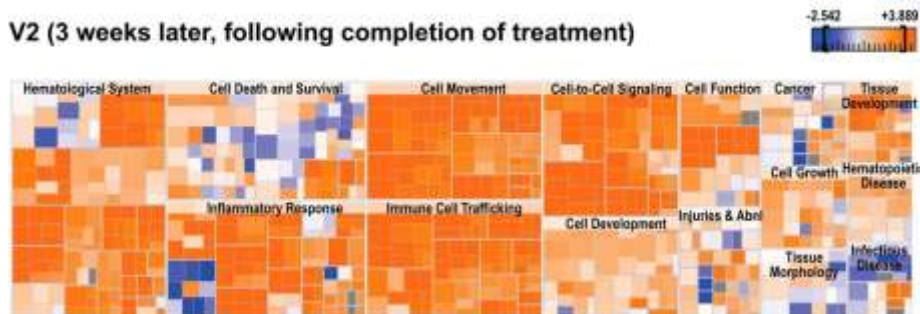
Green: Infection
Blue: Autoimmunity
Purple: Tissue Damage

Heat maps of disease and functional categories predicted to be involved in Lyme disease

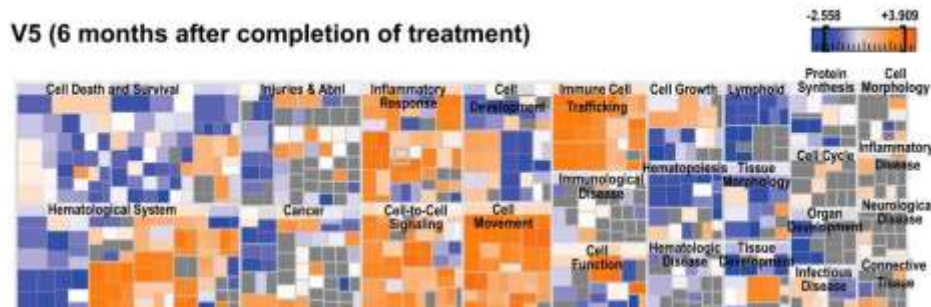
V1 (acute Lyme disease diagnosis, pre-treatment)



V2 (3 weeks later, following completion of treatment)



V5 (6 months after completion of treatment)



Jerome Bouquet et al. mBio 2016; doi:10.1128/mBio.00100-16

Novel Next Generation Tests

- T cell tests (I =Indirect test):
 - ❖ Inatoss: Netherlands
 - ❖ Oxford Immunotec: NCT03201042 - 'LyTIC study' - USA
- Advanced serology (I)
- Metabolomics (I)
- Advanced PCR techniques (D = Direct)
- Urine antigen detection (D)
- Xenodiagnosis (D)
- Advanced culture techniques (D)
- T2MRI assay(D)



- **A Five-Antigen Fluorescent Bead-based Assay**

Embers ME, Hasenkampf NR, Barnes MB, et al. *Clin Vaccine Immunol* 2016

- **Multiantigen panel for improved detection early Lyme disease**

Lahey et al. *J Clin Microbiol* 2015

- **Global Lyme Diagnostics**

- Novel chimeritope (chimeric proteins) technology. IgG and IgM
- Recombinant proteins
- Screens for multiple US strains and species of Borrelia
- Designed for use as a vaccine or as diagnostic antigens
- Derived from multiple diverse OspC variants, strains and species
- Diversity of targets allows for reduced false negatives

<https://glymedx.com/clinicians/>

<https://glymedx.com/patients/>

http://glymedx.com/wp-content/uploads/2017/06/GLD_Publications.pdf

What on earth are recombinant chimeric proteins?!



- Global Lyme Diagnostics: Professor Richard Marconi
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- 2-tier serology has low sensitivities (29%-40%) for early infection
- Investigation of metabolic bio-signature for detection of early LD
- Liquid chromatography-mass spectrometry (LC-MS)
- 44 metabolite molecules distinguish early Lyme disease patients from healthy controls
- Sugars, peptides, lipids, amino acids, fatty acids, nucleotides
- Improved sensitivity of 88% (84%-95%), and a specificity of 95% (90%-100%)
- Correctly classified 77%-95% of the of serology negative cases

- Quantification of *Borrelia burgdorferi* Membrane Proteins in Human Serum: A New Concept for Detection of Bacterial Infection
- Collaboration between Johns Hopkins, NIST, Institute for Bioscience and Biotechnology Research/ USA
- Aims to detect membrane proteins from vesicles released by Bb in human serum as a result of innate immune response
- Detects specific Bb proteins eg OspA in very low concentration in early infection
- Proof of concept study

Advanced PCR Techniques

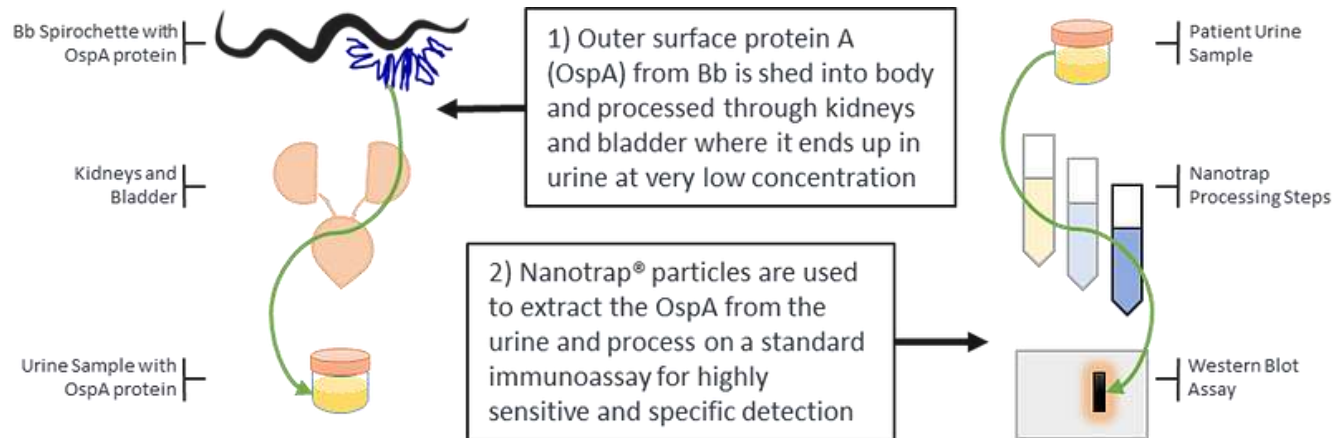
- TGen = Translation Lyme Genomics Institute www.tgen.org
- Working in partnership with 'Focus on Lyme' www.focusonlyme.org
- Currently crowd-funding: <https://www.tgen.org/home/news/2017-media-releases/funding-campaign-launched-for-tgen-lyme-disease-test.aspx#.WVjAOc7rvIV>
- 'LymeSeq' test
- Targeted DNA amplification and sequencing of specific regions Borrelia genome
- Compared to known data-bases: 'BorreliaBase' <http://borreliabase.org/>
- Awaiting Human trials



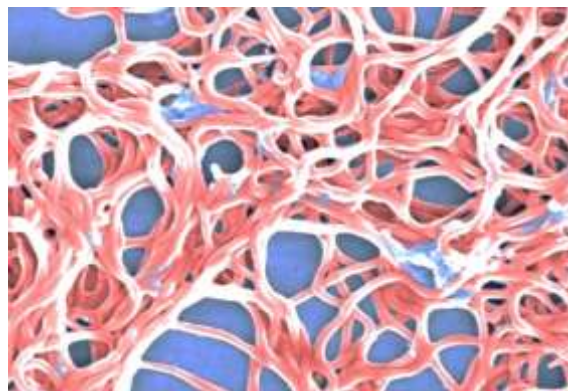
TGen media release 2017

Urine Antigen Detection

- Ceres Nanosciences: Nanotrap Lyme Antigen test
- 'Highly sensitive and specific direct test'
- Non-invasive
- Can be used any time in the infection cycle: before and after treatment



- ClinicalTrials.gov Identifier: NCT02741609
- Advanced Laboratory Services www.advanced-lab.com
- Multi-centre study to evaluate a direct Borrelia diagnostic test in subjects with early-stage or late-stage Lyme disease (ALSIBDT)/USA
- Culture of Borrelia spirochetes from human serum in subjects with early or late Lyme disease



?Persistence: Xenodiagnosis

- ClinicalTrials.gov Identifier: NCT02446626
- Previous small pilot study of xenodiagnosis. Bb was positive in 2 participants and indeterminate in 2 participants
[Marques A, Telford SR, Turk S-P, et al. Clin Infect Dis 2014; 1–9](#)
- National Institute of Allergy and Infectious Diseases (NIAID)
- Lead Investigator Dr Adriana Marques
- Currently recruiting n=240
- Aim: To see if ticks can be used to detect *B. burgdorferi* in people who have had Lyme disease and received antibiotic therapy and if it correlates with persistent symptoms
- Estimated primary completion date 01/12/2020
- Estimated study completion date 01/12/2030

Prospective Clinical Studies

- The **S**tudy of **L**yme disease **I**mmunology and **C**linical **E**vents
(**SLICE**)
 - Johns Hopkins University Lyme Disease Research Centre
 - Principal Investigator: Professor John Aucott
 - Aim: To examine risk factors, symptom severity, and immunologic bio-markers in patients diagnosed with Lyme disease over time
 - To develop an extensive biorepository of samples and data
 - Currently recruiting <http://www.slicestudies.org/>
- Similar studies: NIAID, USA: NCT00001539
- Slovenia: NCT02147249

Trials of treatment

- NCT02687165: New York State Psychiatric Institute and Columbia University Medical Centre

Recruiting. Due to complete Feb 2018.

Neural and Immune Mechanisms of Chronic Pain in Post Treatment Lyme Syndrome

Brain imaging, sensory, and immune markers/control group

Response to a combination of SNRI and glutamatergic treatment for chronic pain in PTLS (Milnacipran and D-cycloserine)

- NCT02344537: Meditation and Stretching for Post Treatment Lyme Disease Syndrome

Principal Investigator: Professor Brian Fallon

Borrelia persister cells

- Borrelia persister cells: *In vitro* research only

Zhang Y. Persisters, persistent infections and the Yin–Yang model. *Emerg Microbes Infect* 2014

Feng J, Wang T, Shi W, et al. Identification of novel activity against *Borrelia burgdorferi* persisters using an FDA approved drug library. *Emerg Microbes Infect* 2014

Sharma B, Brown A V, Matluck NE, et al. *Borrelia burgdorferi*, the causative agent of Lyme disease, forms drug-tolerant persister cells. *Antimicrob Agents Chemother* 2015

- Funding for animal studies is required, followed by human studies



- **An effective vaccine?**

- NCT01504347

Phase 1/2 Lyme Vaccine Study, Baxter: Austria and Germany
Completed 2014. Multivalent recombinant OspA

- NCT03010228

Valneva: USA and Belgium

Study Assessing the Safety, Immunogenicity and Dose Response of
VLA15, A New Multivalent Recombinant OspA Vaccine Candidate
Against Lyme Borreliosis, In Healthy Adults Aged Below 40 Years

- **Monoclonal antibodies**

- MassBiologics: University Massachusetts Medical School
Pre-exposure, 6 month seasonal prevention, OspA

Lyme disease: 21st Century Dilemmas





Striving for the prevention and treatment of Lyme disease and associated tick-borne diseases

www.lymediseaseaction.org.uk

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