In Vivo
Pharma intelligence | informa

While conventional treatment with antibiotics is generally successful, there is a rising cohort of patients with unexplained post-treatment symptoms that are debilitating or even life-threatening. Addressing their needs is compounded by the absence of an accurate diagnostic test to guide treatment decisions.

Big pharma has largely abandoned R&D on Lyme disease, but some progress is being made among smaller biotechs. Work is focused on diagnostics that can be applied beyond Lyme to other infectious indications as well as a next-generation vaccine to replace one that was withdrawn 15 years ago due to pressure from anti-jab activists.

So what? Diseases like Lyme with a mash of biological markers represent a challenge to the traditional RCT protocol. Changes involving greater flexibility around test populations, data requirements and performance metrics are needed to foster private-sector commitments to diagnosis, treatment and cure for what is estimated to be a billion-dollar market in the US alone.

LYME DISEASE: Has Big Pharma Stopped The Clock On A Cure?

Though vastly underreported, new cases of Lyme in the US total more than 300,000 a year; its incidence now exceeds infections for far more visible conditions like HIV. A higher profile for Lyme is hobbled by a slow and distorted institutional response, especially among clinicians who disagree on whether Lyme is one disease or a complex constellation of many – much like cancer, but without the commitment.

BY WILLIAM LOONEY

The fight against infectious disease presents a revealing truth to medical practice: as hard as it is to understand the intricate variations in the life cycle of a single pathogen, it is harder still to understand the larger effects from that pathogen's relationship to its even more complex human hosts. Ultimate success in finding new treatments depends on how well researchers relate to the environmental factors that shape – and often distort – interactions between the pathogen and the patient. These include the mode of transmission, the distinctiveness of symptoms and the capacity to identify and diagnose the illness in normal clinical practice. Remove these from the physician playbook and you have the makings of a crisis in the administration of care – one where a transmissible condition is known to exist but for which there is no accompanying consensus on a single source of contagion or on the various ways it presents in the human population.

Medical practice now has that crisis – and it's happening in real time. The culprit is Lyme disease, which since its origins in small-town coastal Connecticut in the mid-1970s now ranks as the most common and fastest growing vector-borne disease in the US. More than half of all US counties have the *Borrelia burgdorferi* tick that is the main cause of human infections, but there are other pathogens in the tick population that produce similar symptoms of the disease. Infection is growing rapidly in areas of the country such as California and the Pacific Northwest, which until recently had a low incidence of disease.

The result is, despite years of effort, researchers, clinicians and patients still lack a focused, consistent strategy to combat the disease. Instead, we see a distracting intramural war among the physicians who treat its victims over what Lyme disease actually is – and isn't. Or who has it – and who doesn't.

In the following feature, *In Vivo* takes a closer look at what many of the experts we talked to describe as "the single most controversial disease of the past 50 years." Institutional disarray in managing the response to Lyme disease remains a barrier to productive private sector work in biopharma enterprise on diagnostics, medicines and vaccines to treat or cure it. Progress is taking place – and the pace is accelerating. Nevertheless, Lyme's checkered history underscores the importance of a strong, aligned health care ecosystem in fostering the innovation that society now expects from biopharma.

Ecology Of Contagion

As with most other infectious diseases, interest in Lyme disease coincides with its growing prominence as a threat to public health. Lyme disease extends well beyond the US epicenter, with documented cases in more than 80 countries. The number of reported cases in the US is rising fast, putting significant pressure on scarce health care resources. This is

largely because accurate diagnosis of Lyme disease is an elusive, difficult and time-consuming process. Researchers are discovering just how complex is the etiology of the disease, with variations of the spirochete *B. burgdorferi,* carried by the black-legged tick, appearing as Lyme's geographic range expands beyond its original core in the northeastern states.

Like most infectious diseases, Lyme disease is of indefinite origins, though researchers have detected it in the DNA of skeletal remains dating back to the stone age – 5,000 years. The condition was formally designated as Lyme disease after the town in Connecticut where epidemiological studies determined a tick-borne vector was the cause of an outbreak of an arthritis-like condition among children in 1975. In 1981, the *Borrelia* pathogen carried by the black-legged tick was identified as the source of disease by William Burgdorfer, PhD, a scientist at the **National Institutes of Health**'s **National Institute of Allergy and Infectious Diseases** (NIAID).

Overall, ticks have been shown to be highly effective transmitters of diseases that, in addition to Lyme, include babesiosis, with symptoms similar to malaria; and Powassan virus, which can cause brain damage and is sometimes fatal. Tick-borne encephalitis is found in Europe and Asia, but not North America. In the last decade, researchers at the **Centers for Disease Control and Prevention** (CDC) have discovered five new tick-borne pathogens in the US, two of which are directly related to Lyme and its symptoms. Anaplasmosis and ehrlichiosis, borne by the black-legged tick (*Ixodes scapularis*) and the so-called lone star tick, respectively, are related to the *Rickettsia* bacterium, and have symptoms similar to Lyme.

The CDC also discovered a regional variation of Lyme centered in the southern states, which it designated as southern tick-associated rash illness (STARI). Last year, researchers at the **Mayo Clinic** uncovered an additional pathogenic variation to the *B. burgdorferi* bacterium, *Borrelia mayonii*, which is distinctive to the upper Midwestern states. Each of these discoveries has the potential to better define the characteristics of tick transmission and infection, which in turn enhances the prospects for accurate diagnosis of Lyme disease. "There is a growing consensus that Lyme, much like cancer, is a series of different diseases. Geographic variations in how the disease expresses in patients tend to confirm this thinking," says Wendy Adams, research grant director for the Bay Area Lyme Foundation, a California-based philanthropic enterprise devoted to promoting new approaches to research, treatment and prevention of the disease.

It also reinforces the importance of large-scale ecological factors – climate change, suburbanization, biodiversity and habitat disruption, among others – in setting the script on how humans, animals like deer and mice, and disease-bearing pathogens interact. Population pressures and land use practices that lead to more contact between people and tick-borne pathogens adds a big measure of uncertainty in predicting the future course of all vector-based infectious diseases. Many experts contend that communities are likely to see what were once very rare tick infections become more common, and Lyme is no exception.

> *"Lyme disease today is where cancer was 40 years ago. No practicing oncologist today looks at every breast cancer as the same disease. Treatments are tailored to the individual based on the molecular profile of their tumor. I think this is what is going to happen with Lyme."*
>
> *– Neil Spector, MD*

All this presents a stiff challenge to researchers seeking better diagnostics and treatment. "What we've discovered is that ticks are capable of transmitting multiple different infections in a single bite," Adams tells *In Vivo*. She also notes that in California a greater variety of small mammals are carriers of the black-legged tick, which renders the *Borrelia* bacterium more genetically diverse than elsewhere in the country. "The result is that the immune response to our local strains of *Borrelia* are even less detectable using the standard antibody-based diagnostic test for the disease."

Contributing to its complexity, the way Lyme disease presents initially in patients can vary significantly. Less than 70% of patients experience a rash – and even fewer experience the circular red rash – *erythema migrans* – at the site of tick bite. Other symptoms may include fever, headaches, joint pain and fatigue. The standard treatment has not changed since the 1980s, and consists largely of a two- to four-week cycle of antibiotics such as doxycycline and amoxicillin.

Most victims recover rapidly with drug therapy, but success depends heavily on early administration of the antibiotic. If treatment is delayed, there is risk of more serious infections like meningitis along with severe joint pain, chronic arthritis and additional neurological and cardiovascular complications. The diversity of symptoms and a poor diagnostic armamentarium means that Lyme is frequently mistaken for a range of inflammatory and neurological disorders, including multiple sclerosis, fibromyalgia, Epstein-Barr disease, chronic fatigue syndrome and bipolar depression.

A complicating factor in addressing this disease is the clinical split between patients who recover under the standard treatment protocol and the small – but

growing – minority of patients who don't get better, with truly debilitating and life-altering symptoms that can persist for years. Studies have shown that 10% to 20% of patients experience lingering symptoms following treatment. Clinicians call this condition post-treatment Lyme disease syndrome (PTLDS) and debate why this occurs. Some clinicians postulate a possible autoimmune response triggered by the original Lyme bacterial infection. But numerous studies *in vitro* and in animals show that the pathogen can survive the normal short course of antibiotics, leading some physicians to argue that PTLDS should be more aptly called chronic Lyme disease. (*See sidebar, "Post-Treatment Lyme Disease: The Forgotten Fifth*.")

Neil Spector, MD, associate professor at **Duke University School of Medicine**, a victim of Lyme disease himself who received a heart transplant after being misdiagnosed for several years before his Lyme infection was identified, a delay that caused irreparable damage to his heart, empathizes with the chronic Lyme disease community. "Most medical professionals fail to understand there is a clinical difference between patients who are diagnosed and treated early, recovering without long-term consequences, and those who aren't treated quickly and fail to respond to standard antibiotic treatment. He continues, "Patients can have long-term debilitating symptoms that not only affect quality of life but can actually be life-threatening. A number of deaths have been reported as a consequence of Lyme carditis, which is an inflammation of the heart related to the infection."

Spector, a cancer clinician and researcher, is convinced that some percentage of patients with Lyme have a "constellation" of infectious diseases, in a pattern that is similar to many cancers. A standardized one size fits all approach to treatment isn't enough to confront the creative ways that *Borrelia* finds safe refuge in the joints, nerves and muscles or in key organs like the brain and heart.

"Lyme disease today is where cancer was 40 years ago. No practicing oncologist today looks at every breast cancer as the same disease, but rather subsets that are distinguished by their molecular signature. Treatments are tailored to the individual based on the molecular profile of their tumor. I think this is what is going to happen with Lyme," says Spector. As a survivor of Lyme, he tells *In Vivo* his key message is the importance of incorporating lessons learned from other disciplines in science and medicine, most notably cancer biology, to address Lyme disease and its various co-infections. "Why are we always starting from scratch?," he wonders. "Scientists from adjacent disciplines like cancer biology and immunology should be brought under the tent. They discovered how to take the brakes off the immune system to confront the cancerous cells that overcome normal immune response. This has transformed outcomes for many cancer patients and the same approach could allow us to understand how *Borrelia* evades the host immune response as well as develop a similar strategy that would recognize and eliminate the pathogen."

Another disruptive issue among Lyme researchers is the question of whether the disease can be spread through sexual contact and, during pregnancy, to unborn children. While there is scant evidence of the former, *Borrelia* placental transmission in untreated mothers has been shown in several published cases, with negative outcomes for the fetus – including miscarriage and death shortly after birth. Two other spirochetes, *Treponema palladium*, the causal agent of syphilis, and *Jeptospira*, are also known to be transmitted during pregnancy. In 2016, the CDC issued an information notice to pregnant women about the risk of infection. It's fair warning that further evidence on reproductive risks would dramatically refocus attention on the disease, putting Lyme on a par with the Zika virus as a high-visibility public health threat.

How Big Is The Threat? A Look At The Numbers

There is a consensus among researchers and Lyme disease advocates that the infection rate for *B. burgdorferi* is woefully underreported. This is acknowledged by the CDC itself.

According to the CDC, there were 33,461 officially reported cases of Lyme disease in the US in 2014, making it the fifth most common notifiable infectious disease, after the three top sexually transmitted diseases – gonorrhea, chancroid and syphilis – and salmonella. Lyme ranks first in incidence among vector-borne conditions. CDC statistics for 2015 indicate the number of cases is close to 40,000, on par with new cases of HIV, which the CDC tracks separately.

An August 2015 CDC survey found that the number of "high-incidence" US counties with Lyme rose from 69 in 1993 to 260 in 2012, resulting in a "relatively constant rate of geographic expansion in all directions." (see "Geographic Distribution and Expansion of Human Lyme Disease, United States," *Emerging Infectious Diseases*, volume 21/number 8, pp. 1455–57). These high incidence counties are now found in 17 states, compared with only four in 1993. Hawaii is the only state with no reported cases of Lyme disease to date.

The CDC relies on an official reporting system for infectious diseases it classifies as "notifiable." The system is cumbersome, requiring a physician to contact the local county board of health and document each patient diagnosis in writing or, in some cases, by telephone as well. Many physicians either don't know about the procedure or are reluctant to take the time to do it. The absence of an accurate diagnostic and the frequency of co-morbidities among patients who present with Lyme symptoms pose an additional challenge to the physician's judgment in deciding whether to report.

A September 2015 paper published by CDC staff in the CDC journal *Emerging Infectious Diseases* documented the underreporting by using a nationwide health insurance claims database to conclude that the actual number of cases where patients present with Lyme disease is around 329,000 annually – 10 times the number derived from official county board of health reports. Use of insurance claims reporting also enabled the authors to conclude that Lyme disease is a significant financial burden on the health system due to the inadequacy of preventive measures, the variability of symptoms and co-morbidities as well as the potential for physician misdiagnosis. "Lyme disease is a considerable public health problem, both in terms of number of cases and overall health care use," the paper concludes.

Filling The Knowledge Gap

Advocates seeking a higher profile for Lyme disease point to the CDC's statistical approach to case reporting and surveillance as a barrier to progress. In January, the CDC adopted a new definition of exposure to Lyme that reduces the prospect that counties and states can be classified as having a "high incidence" of cases. The exposure language also discounts the fact that, in addition to the most common bacterium, *B. burgdorferi*, other tick-borne pathogens suspected as causing or contributing to Lyme are appearing in the southeast, California and the Pacific Northwest.

For Lyme patients in these regions, where the incidence of the disease is growing, the implications of the higher definitional hurdle are obvious: less public attention means fewer resources provided by key stakeholders such as clinicians, legislators and insurers. "Three quarters of the counties in California – home to 32 million people – now harbor the *B. burgdorferi* spirochete in ticks," Adams tells *In Vivo*. "We are concerned the narrowing of the CDC criteria on exposure will limit options for our state to address the public health and welfare consequences of this disease."

The CDC's conservative approach to registering cases may also explain the persistently low funding for Lyme disease research by federal agencies like the National Institutes of Health (NIH). The current NIH 2017 fiscal-year budget allocates only $29 million for Lyme research – about one half of one percent of the overall NIH spend for research on infectious diseases. This is despite the fact that Lyme ranks in the top five among CDC-reported cases of all infectious diseases. NIH also spent $3 billion in the current fiscal year on HIV/AIDS, even though the reported incidence of Lyme is now significantly more than new cases of HIV. "From a public health point of view, it's surprising there is this hundred-fold differential in funding for these two devastating diseases," Adams says.

The CDC's budgetary contribution for Lyme disease is equally modest. It is proposing a budget of $49.5 million in fiscal-year 2018 for all vector-borne conditions, but Lyme must share this sum with other diseases linked to tick bites as well as top-of-the-news infections like Zika and West Nile virus.

Pressure from congressional delegations from those "high incidence" states is beginning to bear fruit, with the most recent example being the designation of Lyme and other tick-borne diseases as a priority research focus in the 21st Century Cures Act (HR 34) signed by President Obama in December 2016. Section 2062 of the law creates a working group to review federal government activities in this area, including the identification of gaps in research on tick-borne disease covering pathogenesis, prevention, diagnosis and treatment. The working group of 14 members, from key federal agencies, state and local governments, providers, patients, researchers and industry, will make recommendations to the HHS secretary for initiatives relevant to these four activity streams. The report is due within two years, with updates every two years thereafter until the group's sunset date in 2023. August 16 was set as the deadline for member nominations.

State Of Research

NIH's NIAID unit has created a website to encourage researchers to obtain grants for research on Lyme disease. The focus is still on translational efforts to decipher the biology and pathogenesis of *B. burgdorferi*, with emphasis on improving diagnostic tools and explaining the persistence of infection after standard antibiotic treatment. Vaccines are another area of interest. NIAID has forged a partnership with the CDC, FDA, academia and the biopharma industry to increase the use of a CDC serum repository to validate alternative assay and test methodologies to treat Lyme.

In January, the Bay Area Lyme Foundation announced an ongoing project to provide researchers with blood and urine samples from people with early acute disease from multiple sites across the country, including the West Coast and Midwest in addition to the eastern states. The Lyme Disease Biobank cites a 2016 foundation survey that found 95% of researchers active in Lyme had no access to samples from confirmed patients with the disease, making it virtually impossible to clinically validate the most promising approaches to diagnosis and treatment.

So far, samples have been obtained from 400 patients and controls in multiple locations. Researcher access to the data is subject to a screening process to ensure the most qualified proposals receive the samples. A Lyme Biobank Review Board of experts decides which researchers will receive the samples, based on evidence of the relevance and scientific merit of their proposed work and overall alignment with foundation goals.

Clearly, funding from other sources is going to be needed to extend the armamentarium against Lyme and, most importantly, point the way to a cure. But private sector engagement falls way short of need. Formal research commitments from big pharma are scarce, and recently many projects have been abandoned. (*See Exhibit 1.*)

Mission Critical: Replacing That "D" Grade Diagnostic

There is one issue on which the Lyme disease community agrees – the lamentable state of knowledge on diagnosis. Both the CDC and NIAID are unequivocal in stating early and accurate diagnosis to commence with the right treatment is the most effective way to avoid more serious illness and the potential for dangerous long-term complications. Failure to capture the disease early as well as the potential for a misdiagnosis is exacerbated by the widening scope of infection. This is due in part to unanticipated and hard to measure environmental challenges wrapped in the growth of the tick exposure zone. Adds **Johns Hopkins** Lyme disease expert John Aucott, MD, "In many cases, particularly when the physician fails to diagnosis until late in the game, all we can do is ask if the patient is doing better. Physicians frankly don't like diseases that require complicated answers, so they avoid discussing it. It means that detection of the true burden of Lyme disease lags well behind other infectious diseases, including AIDS."

Even simple steps – such as communicating to physicians that the tell-tale bull's-eye rash around the tick bite is atypical in many patients who actually have the disease – are lacking. Leveraging technology with apps that might allow these facts to circulate through the

Exhibit 1

Products Marketed And In Development For Lyme Disease

DRUG NAME	Ceftriaxone	Azithromycin	Borrelia vaccine	Azithromycin
ORIGINATOR	Roche	Teva	Valneva	Ixodes
LICENSEE	Kyorin	Pfizer, Leadiant Biosciences, Chinoin, Gedeon Richter, Almirall	N/A	N/A
OVERVIEW	Long-acting (6–8hr), ß-lactamase resistant, broad-spectrum (including Pseudomonas), injectable cephalosporin. Dosage is once-daily (1–2g/day) for simple infections and twice-daily (2–4g/day) for serious infections	Semisynthetic azalide antibiotic, developed by Pliva (now Teva, previously Barr) as a once-daily formulation for bacterial infections including STDs and Mycobacterium avium	Intramuscular hexavalent, OspA-based protein subunit vaccine, VLA-15 for the prophylaxis of Lyme borreliosis, using Valneva's Antigen Identification Program. The protein based vaccine targets all 3 disease-causing species, which include Borrelia afzelii, Borrelia burgdorferi and Borrelia garinii	Topical formulation of azithromycin, applied after a tick bite for the prevention of Lyme disease
GLOBAL STATUS	Launched	Launched	Phase I	Phase I
MECHANISM OF ACTION	Cell-wall synthesis inhibitor	Protein 50S ribosomal subunit inhibitor	Immunostimulant	Protein 50S ribosomal subunit inhibitor

SOURCE: Pharmaprojects | Pharma Intelligence, 2017

Lyme community remain a work in progress. "Ignorance is a strong contributor to the spread of infection, and there is insufficient hunger for information among the US public and a lack of urgency in the medical field and in government," Aucott contends.

The standard diagnostic test for Lyme dates to the early 1980s. The ELISA/Western blot test is a two-stage serological process that indirectly detects the disease by measuring the presence of antibodies that form against the tick-borne pathogen. Because it takes anywhere from two to six weeks for the antibodies to show up in the blood stream, many readings – 60% by some estimates – come back negative for patients who are in fact infected. The test can also create false-positives by detecting remnants of a previous exposure to an infection where a patient has been cured; it has also been shown to be minimally effective in detecting emerging, related strains of the *Borrelia* bacterium, such as STARI, occurring in the south, or *Borrelia miyamotoi*, an emerging and increasingly common pathogen for Lyme-like illness.

Put simply, the current diagnostic test is *least* effective at the very early stage of disease, when treatment with antibiotics is *most* effective. "Today we stand at the threshold of unlocking the secrets of the human genome, yet the so-called gold standard diagnostic for Lyme is a product of 1960s technology," says Neil Spector. "Most of the commercial ELISA/Western blot diagnostic tests utilize one strain of *Borrelia*, a laboratory tool in place since the early 1980s, even though we know there are several tick species and strains that can cause the disease. These variations and the fact that *Borrelia* and other co-infectious pathogens can suppress the host immune system, in ways we cannot understand, makes the reliability of the two-tier ELISA/Western blot less than ideal."

The Bay Area Lyme Foundation has set the development of a more accurate diagnostic as a key priority. One avenue to that end is led by **Ibis Biosciences Inc.**, a division of **Abbott Laboratories Inc.**, which has been exploring a new isothermal/polymerase chain reaction technology to increase test sensitivity in detecting the actual pathogen rather than human antibodies. The diagnostic would also rely on whole blood samples from patients to better expose the *Borrelia* bacterium and its variations. Ibis has been working on this new technology for a decade. Earlier this year, however, Abbott was rumored to be deciding to scale down the Ibis unit in a redeployment of the company's product pipeline. Mark Eshoo, PhD, a prominent infectious disease specialist who has led the Ibis work on a diagnostic, declined comment on Abbott's next steps.

Elsewhere in biotech,**T2 Biosystems Inc.** has data, published in the *Journal of Clinical Microbiology*, showing that its miniaturized magnetic resonance diagnostic technology, developed with **Canon US Life Sciences Inc.**, can detect Lyme disease-causing bacteria in clinical blood samples.The Massachusetts-based biotech hopes to complete preclinical

POST-TREATMENT LYME DISEASE: THE FORGOTTEN FIFTH

The momentum of research has begun to shift toward defining Lyme as an unpredictably dangerous chronic condition whose incidence is increasing due to rampant underdiagnosis. **Johns Hopkins** and **Stanford University**, each of which receive funding from the Bay Area Lyme Foundation, are the leading institutions where researchers are working to raise the profile of PTLDS as a legitimate disease state.

An example of current work around PTLDS is the Study of Lyme Disease Immunology and Clinical Events (SLICE), which is being conducted at Johns Hopkins. The lead investigator for this ongoing project is John Aucott, MD, an internist in infectious diseases and Lyme disease expert who serves as assistant professor at the Medical School and director of the Lyme Disease Clinical Research Center at Hopkins. The SLICE project is focused on discovery of biomarkers for early- and late-stage diagnosis, and long-term implications for the disease, with particular emphasis on how the immune system may affect patient health status after the prescribed course of treatment with antibiotics.

The study protocol consists of 200 patients with acute, untreated Lyme disease who are being evaluated before and after treatment over a two-year period for the progression and severity of various chronic-stage symptoms ranging from "brain fog," fatigue, depression and other cognitive impairments to a wide range of painful conditions such as arthritis, fibromyalgia and neuropathy. "Our goal is to better understand and diagnose the severe disabling symptoms of chronic post-treatment Lyme disease syndrome as a first step toward treatments that serve this growing cohort of patients," Aucott tells *In Vivo*. He notes that a motivating factor for this work is the lack of any FDA-approved medicine to address the need. "We only have old off-patent drugs like doxycycline, long-term use of which can carry adverse effects of their own, nor do we have any biomarker to guide our interventions. It's treatment by anecdote."

Aucott, who is founder and past-president of the independent Lyme Disease Research Foundation, also represents a faction of the clinical community that believes Lyme is a condition that defies categorization and thus requires an inter-disciplinary approach. This group believes – and intends to prove – that in some patients, for reasons not yet clear, the standard immune system response can fail to respond to the initial tick-borne infection, leading to a breakdown in the immune response that controls infection. "SLICE should give us knowledge about disease as a process that involves, in addition to biological factors, the social and psychological underpinnings of the individual patient experience," Aucott states.

Several peer-reviewed papers have already been published using insights from the SLICE survey work. With support from the Bay Area Lyme Foundation and other sources, Johns Hopkins is building a biorepository containing blood, serum, DNA, RNA and other samples from the test population. This has already been supplied to over 20 researchers around the US, with the aim of adding to the evidence base to yield that next-generation diagnostic for Lyme.

Another promising project to address PTLDS is creating an armamentarium to destroy selected defense mechanisms that the *Borrelia* bacterium use against antibiotics. One such defense is a "biofilm" that bacterial colonies generate as cover to divert and diminish the antibody effects of these drugs. **Agile Sciences Inc.**, a North Carolina biotech that specializes in treatments for biofilm and other types of antibiotic resistance, is assisting the foundation in investigating a library of proprietary compounds that hold promise in penetrating the biofilm barrier to enhance the potency of antibiotic therapy,

studies in 2017, followed by a clinical trial for FDA submission in 2018. And in 2014 **Oxford Immunotec Global PLC**acquired the assets of Boulder Diagnostics Inc., whose preclinical *SpiroFind* test is designed to detect Lyme disease in both early- and late-presenting forms.

"Enhanced diagnostics are essential to disease awareness – the two are interrelated. Without an accurate way to detect Lyme disease, the public health community will never address the true scope of contagion. Researchers will focus on other conditions that attract better financing from private-sector players like the biopharma industry," says Bay Area Lyme Foundation research grant director Adams. Adds Neil Spector from Duke, "When the scientific consensus around a solid diagnostic finally arrives, I expect a public relations tsunami from patients and politicians to get clinicians to take this chronic condition seriously."

Future States

One way to describe the state of Lyme disease today is contentious neglect. Yet in research laboratories that employ the latest IT tools and systems, there is a palpable air of confidence that a breakthrough in diagnostics is at hand. Pardis Sabeti, DPhil, MD, a geneticist and bioinformatics expert who runs her own Sabeti Lab as part of the FAS Center for Systems Biology at **Harvard University** as well as serving as a lead in the Infectious Disease and Microbiome Program at Harvard/**Massachusetts Institute of Technology**'s **Broad Institute**, tells *In Vivo* that technology is progressing to the point that tick pathogens are detectable today at "incredibly low concentrations." She explains, "We are in a place right now where the technology exists to transform infectious disease research and clinical care – it is close to being deployed. By combining new genomic and computational techniques with advanced computer processing, we can mine vast volumes of data to find out how these pathogens invade and then hide in the human body."

To that end, the Bay Area Lyme Foundation is partnering with Sabeti Lab on

particularly for those patients for whom the initial round of therapy has proved ineffective against Lyme.

One project where the foundation has put its funding on the line is a partnership with Stanford University's Biomaterials and Advanced Drug Delivery Lab to develop a new combination therapy designed to make the standard, clinically accepted antibiotic regimen more effective. Again, the focus is on the PTLDS community and the failure so far of researchers to come up with a solution to the multiple crippling disorders that often follow the failure of conventional antibiotic therapy. The Stanford team has discovered that a common FDA-approved over the counter (OTC) drug, loratadine, when used in combination with antibiotics, can block essential protein synthesis in the *Borrelia* spirochete. More important, loratadine has the surprising effect of reducing antibiotic toxicity in humans while accentuating its toxicity against the Lyme bacterium.

Stanford and the Bay Area Lyme Foundation are now developing a protocol for what will be the foundation's first sponsored clinical trial on a new treatment for Lyme disease. The foundation has organized a panel of experts to design the investigation criteria, establish relevant endpoints as well as conditions for patient recruitment. If successful, the process should lead to initiation of the trial in early 2018. About $1 million has been raised so far by the foundation to fund this research.

An approved medicine like this one could be very important in addressing clinical concerns about the medical ethics of physicians who believe in PTLDS and ignore current treatment guidelines by giving patients higher doses of antibiotics, on a long-term basis. Physicians who oppose this approach believe it is a causative factor in making PTLDS patients even sicker by promoting antimicrobial resistance. High doses of these drugs over time can raise the possibility of septic shock – an emergency, life-threatening condition.

Unfortunately, the failure of some in the medical community to address the concerns of patients with persistent symptoms of Lyme disease has contributed to it being tagged as a condition that the providers want to avoid – a divisive chapter in the annals of medical care. "This disease is a complex condition or even a messy set of diseases. It does not offer the simple answers that physicians like to give to their patients," Duke's Neil Spector, MD, observes. The Infectious Disease Society of America (IDSA), the group that establishes treatment guidelines for infectious diseases, has avoided formal recognition of chronic Lyme disease due to the absence of a medical consensus on whether symptoms in people who have completed initial therapy with antibiotics are caused by the persistency of the pathogen, or some other process, for example, autoimmunity. More important, IDSA, as a general principle, opposes long-term use of antibiotics as inherently dangerous.

The controversy spurred when parts of mainstream clinical practice refer to PTLDS symptoms as "psychosomatic" or the "aches and pains of daily living" has led to political action. Several state legislatures – including Connecticut, Rhode Island, Massachusetts, Vermont, New York, Maryland and California – have passed laws that bar local medical boards from taking disciplinary action against physicians who treat Lyme patients with unconventional remedies, including long-term prescribing of antibiotics.

Some countries outside the US even insist that Lyme disease does not exist there. Australia's national health system will not treat Lyme disease because the tick species that transmit the *Borrelia* pathogen are not represented in the local microbiome, resulting in a media circus profiling angry patients forced to travel to the US and Europe for care.

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several projects: a study to characterize bacterial microbes present in a diverse cohort of patients with various tick-borne infections, followed by a gene sequencing protocol for the *Borrelia* bacterium as well as other organisms that can cause Lyme disease and related co-infections. A priority is to uncover the genomes of individuals with PTLDS: are there indicators or patterns that suggest a genetic predisposition to this condition? What is that host effect that could lead to increased susceptibility to a chronic, unresolved case of disease? Sabeti adds, "Multiple infections are the big hidden challenge in addressing Lyme. The goal is to classify all these pathogenic drivers to the point where we know how to deliver the right diagnosis for each patient."

Both studies are slated for completion in 2018, after which Sabeti's group will apply the learnings to develop a next-gen diagnostic with the increased sensitivity to improve clinical practice. The endpoint? An FDA-approved diagnostic by 2023 – and not just for Lyme disease but for other tick-borne infections as well.

Further out in research agenda are techniques like the CRISPR gene-editing platform. A colleague of Sabeti, James Collins, PhD, of the **Wyss Institute** of Harvard University and professor of biological engineering at MIT, is working with Lyme researchers to examine how an alteration to the DNA sequence in the *Borrelia* bacterium might make it more detectable in the human system – or even render the tick harmless as a vector for infection.

Biopharma Research: Ready For Prime Time?

Biopharma companies have not been major players in the search for new treatments on Lyme disease – for obvious reasons that include poor understanding of the etiology of infection, inadequate tools for diagnosis and disarray in medical practice on how to address patients with unresolved symptoms. Together, these have prevented companies from accurately assessing risk and the prospective financial return on investment in drug development for Lyme. "The

private-sector likes to come in when a lot of the intensive, basic work in linking a therapy to disease state has been done," says Pardis Sabeti. "Until we have a strong case definition of Lyme; a sound methodology for characterizing who has it, and who does not; and the ability to test for efficacy based on measurable, non-subjective criteria, then I think the drug industry will stay on the sidelines."

Nevertheless, two companies – both small biotechs – are forging ahead to build a viable business from detecting and treating the disease. **Ceres Nanosciences**, a Virginia-based diagnostics platform company, is leveraging private investment and grant funding from the NIH, the state of Virginia, the US Department of Defense (DoD) and the Bill and Melinda Gates Foundation to develop a novel nano-particle platform, called the *Nanotrap* particle, to detect diseases at the earliest states and with the highest degree of accuracy. This technology was originally developed at **George Mason University** under NIH funding to capture cancer biomarkers for early detection. It has since been applied to detect many other conditions in the infectious disease space, including Lyme. Specifically, in 2008 Ceres partnered with George Mason to apply the nano-technology to many diseases where improved sensitivity is required to define, detect and measure a pathogen at very low levels.

"Our location in the DC suburbs is in the middle of the Lyme epidemic, so our investors and scientists helped us make the connection to the disease early on," Ceres founder and CEO Ross Dunlap tells *In Vivo*.

Ceres researchers, in collaboration with George Mason scientists, responded with development of a new direct diagnostic test known as the *Nanotrap Lyme Antigen Test*. In contrast to the test currently in uses, the Ceres antigen test uses a urine sample rather than a blood draw, directly detecting Lyme disease by measuring the bacterial antigen from the infection. This is a significant advance over the current serology test that only measures the presence of antibodies in the bloodstream produced by the immune system in response to infection. This serology test has serious limitations as not all people have immune responses that product enough detectable antibodies in time for detection and treatment.

In a 2014 clinical trial of more than 250 patients, the Nanotrap Lyme Antigen Test was used to detect the *B. burgdorferi* Lyme antigen with close to 100% accuracy in acute patient samples, in contrast to the serology test, which is known to detect infection in only about 40% to 60% of acute Lyme disease cases. Results of this study were peer reviewed and published in 2013, in the *Journal of Translational Medicine*.

Ceres has already released this test in a clinical reference lab as a Laboratory Developed Test (LDT) and is testing patient urine samples from all over the US. Ceres uses collection kits that it ships directly to physician offices or to patient's homes that allow patients to self-collect and send a sample back to Ceres' clinical lab in northern Virginia. Also, Ceres is partnering with a clinical lab in the Netherlands to release this test into the EU later this autumn. In addition, Dunlap says Ceres has begun to work on the development of a "point-of-care" version of the Lyme antigen test that could be performed in the physician's office.

This point-of-care test requires formal FDA approval. Dunlap says that process will take place next year, in time for a US market launch of the test kit in 2019. Ceres is raising $9 million as part of a Series A financing round and will use the funds to support the FDA approval process.

Vaccine Revival

Private enterprise is also making a splash with a vaccine to prevent the *Borrelia* pathogen from infecting humans. Surprisingly, industry was once quite active on this front, with a licensed Lyme vaccine, *LYMERix*, introduced by SmithKline Beecham (now **GlaxoSmithKline PLC**) in the US and Europe in 1998. Although the vaccine was very effective in clinical testing, the FDA limited its use to patients living in high contagion areas of the country, a move that confused physicians. After marketing approval LYMERix was the subject of complaints from patients about side effects, including highly publicized claims that the vaccine caused arthritis. Class action litigation in pursuit of this claim persuaded SmithKline Beecham to withdraw LYMERix from sale in 2002. *(Also see "GSK Lymerix Withdrawn: Production Stopped, Inventory To Be Discarded" - Pink Sheet, March 4, 2002.)*

Fifteen years later, a small French biotech, **Valneva SE**, is positioning a new vaccine candidate, VLA15, for FDA "fast track" approval as a preventive against Lyme disease. The company is already established in the business of travelers' vaccines, distinguished by their higher price points. It looks at a Lyme vaccine as offering a similar commercial selling proposition.

According to Valneva CEO Thomas Lingelbach, VLA15 is the only active Lyme vaccine candidate in clinical development, a situation the FDA cited as an unmet medical need when it awarded the compound a fast track designation in July. A Phase I trial on VLA15 is now underway, involving 180 subjects at three sites in the US and Belgium. The trial will evaluate VLA15's toxicity and side-effect profile as well as the immunogenicity response to six strains of the *Borrelia* spirochete prevalent in the US and Europe.

Initial results of the trial are expected to be available by the end of the first quarter of 2018, and the company is committed to following that promptly with a larger Phase II study, assuming the first trial meets its endpoints. With the confusingly narrow indication for the defunct LYMERix in mind, Valneva is seeking a broad designation for VLA15 as an "active prophylactic" against Lyme for both children and adults. It estimates the potential market size for the two regions as around €800 million annually.

More Industry Engagement: What Will It Take?

R&D experts contacted by *In Vivo*, none of whom were willing to speak on the record, set out a series of daunting challenges, the resolution of which is a prerequisite for increased investment by the big pharma majors in treatments for Lyme. A first step is a significant increase in public pressure – as the argument goes, what other condition could be infecting more than 300,000 people a year yet still receive only a tiny fraction of government funding for basic research in the already undersubscribed field of communicable diseases?

Lyme disease advocates also have common cause with environmental factors that engage the larger public in a visceral way. Evidence is clear that population

pressures, land use and habitat changes are putting more people in contact with disease-bearing vectors. It's a trend, induced by consumer economics, that is destined to make what is already a serious spike in transmissions significantly worse. In some ways, Lyme is a lifestyle disease, but one where its victims bear no direct responsibility. Unless the human desire for decent housing, accessible to semi-rural pockets of outdoor recreation, and shared with small mammals and insects, can be viewed as a selfish aberration.

The takeaway? If *community* pressures combined with patient advocacy, convinces legislators to authorize a more visible role for government laboratories in the search for new Lyme treatments that work, then precedent suggests more biopharma players in the private sector will step up to the plate. Money does talk.

Another critical step is addressing the constraints that current regulatory standards for clinical trials pose for a disease with symptoms as complex as Lyme. It's not an issue confined to this condition alone: top-of-mind ailments for patients such as fibromyalgia/nerve pain, irritable bowel disease and chronic fatigue syndrome are a mash as well. From a practical standpoint, this makes it harder for R&D organizations to check the box around the essential questions required for a conclusive program of research. What is the basic mechanism of disease? How to define the population to be tested? What are the measurable endpoints and relevant controls against placebo? Do we focus on immune targets or something else?

Failure to resolve these basic procedural questions triggers the default mechanism in budgeted R&D programs: the avoidance of risk linked to uncertainty. It leads many experts interviewed by *In Vivo* to the same question: the best path is prevention, based on a two-phase approach, starting with consensus approval of an improved, high-vector sensitivity diagnostic that can be extended for use in the PTLDS population; followed by a next-generation vaccine designed to manage the spread of infection in vulnerable populations and geographies.

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Lyme Disease: THE SAD FACTS

HIGH PREVALENCE

THE CDC REPORTED 40,000 "official" cases of Lyme in the US in 2015. But CDC researchers using health insurance data concluded that the actual number was close to 330,000

Top 5 infectious diseases in the US

1. Gonorrhea
2. Chancroid
3. Syphillis
4. Salmonella
5. Lyme disease

LACK OF FUNDING

- **NIH 2017 BUDGET** for Lyme research: $29 million. That's ½ of 1% of the total NIH spend for infectious disease research
- **THE CDC IS REQUESTING** $49.5 million for infectious disease research for FY 2018. That includes ALL vector-borne conditions, including Lyme, Zika and West Nile

BAD DIAGNOSTICS

STANDARD WESTERN BLOT test that measures ant-Lyme antibodies developed in the 1980s. It takes 2-6 weeks for antibodies to show up in the bloodstream

60%: NUMBER OF false negative readings from the Western blot test

INADEQUATE TREATMENT

MOST PATIENTS ARE prescribed 2 weeks of antibiotics But up to one-fifth of patients experience lingering, serious symptoms following treatment

SOURCES: *In Vivo* research; Centers for Disease Control and Prevention; National Institutes of Health; lymedisease.org

Gayle Rembold Furbert