Introduction

This paper will outline the concept behind an image classifier-based method for identifying structures in blood. The paper will begin with a description of the methodology, used here in the context of screening for Lyme disease. It will then describe Lyme disease as a Business Problem and how this method provides the Business Solution. The paper then delves into the science behind Lyme disease, giving a detailed overview of what Lyme disease is and the methods currently employed by doctors to identify it. It will also highlight the problems and limitations with these current identification methods.

Methodology

What follows is a description of the methodology proposed by SYSCOM to automate the identification of various organic objects found in live blood samples, including bacteria. While used in the context of screening for Lyme disease in this research paper, the methodology could potentially be used to identify multiple blood-borne pathogens through visual identification. The reading will generate a probabilistic determination from an automated reading of a live blood sample. The determination will come in the form of a numerical value which represents the confidence level that certain organic structures are present in the blood. In the case of pathogens, the reading will estimate the severity of infection based on the volume of pathogens found in the sample. The overall goal of this method is a technology-based solution for discovering information about blood, particularly, structures or objects found within blood. A Machine Learning model, used to classify images, is at the center of this approach. The computer model uses algorithms to generate a visual understanding of organic structures seen in blood under a microscope. The computer model learns to recognize specific objects and structures in blood through training data. Similar to how a human can learn to recognize faces, or letters, or patterns through observation and repetition, so the model learns how to identify certain objects by seeing examples, a subset of Artificial Intelligence called Machine Learning.

The necessary components of this method consist of:

1. Medical equipment to extract blood specimens from patients' fingertips;
2. Blood stain slide for placing specimen on;
3. Digital, computer-controlled microscope able to examine live blood samples at high magnification;
4. Video camera that records microscopic images in real-time and stores the video into a digital repository such as a cloud-based database;
5. Software program that converts video into still images, then delivers still images to image classifier software;
6. Image classifier software.

To obtain information about a person's blood, doctors using this method will obtain a live blood sample by pricking the patient's finger and putting the drop of blood on a slide. The slide will then be put under a digital, computer-controlled microscope equipped with a camera. The

computer will mechanically adjust the position of the slide and alter the magnification levels of the microscope in order to obtain a complete three-dimensional layout of the sample. The microscopic view of the blood specimen will be recorded, and the live video will be automatically stored and processed. The processing will consist of breaking the video into still images at a given frame rate. The frame rate will be adjustable and will be determined by the desired outcome and the given conditions. Most video is recorded at around 30 frames per second, so there is a wide range of frame rates available in this situation. A higher frame rate will result in a greater potential volume of images. It may be useful, under certain circumstances, to have a large number of still images generated from a video clip. However, too many images can slow computer processing time and result in unnecessarily large data sets to work with. The right balance must be found which will generate a comprehensive view of the blood sample without heavily taxing computer processing speeds. These still images are then analyzed by the image classifier to identify microorganisms or other structures found in the blood sample. In the case of identifying Lyme disease, the image classifier will scan for the presence of either spirochete or biofilm contained in the blood. The image classifier will have been trained to visually identify both spirochete and biofilm found in Lyme-positive blood samples.

Spirochete is a corkscrew-shaped microorganism that travels through the blood stream and burrows into issue. The particular strain of spirochete which causes Lyme disease is a bacteria called Borrelia burgdorferi. Biofilm is a mucous-like substance that develops around communities of spirochete and which acts as a protective shield for the bacteria to grow and multiply. The presence of these structures in a person's blood can help doctors determine whether someone has Lyme disease. This is done through a probabilistic estimation that the structures seen in the blood are in fact those structures. The computer model takes each individual image generated from the video of the sample and does a series of calculations. Based on previous examples of spirochete and biofilm under the microscope seen in training, the model calculates the probability that either of these objects are contained in the images. The model also measures the density of these objects within a given region in order to help calculate the level of presence in the blood. These readings will provide doctors with information to help them make an informed opinion. While the sample is small, merely a drop of blood on a slide, the volume of information is enormous. To the human eye, a single drop of blood on a slide is simple and two-dimensional, but under the microscope, we see that the reality is complex and multilayered. To capture this, the computer-controlled microscope will make automatic adjustments in position and magnification in order to obtain a complete, three-dimensional layout of the blood. Once blood is removed from the body, the blood cells immediately begin to break down. During this period of blood cells breaking down, certain microorganisms such as spirochete can become easier to detect. As such, it may be beneficial to take readings of the blood sample multiple times to get varying results during this process.

The Image Classifier

How does the image classifier work? The image classifier will deliver a confidence level to each object class in the form of a numerical value, a number between 0.00 and 1.00. A score of 1.00 means that the classifier has a perfect confidence level that the given object (in the case of Lyme disease, a spirochete or biofilm) is present. Images scoring above a certain threshold will be flagged as positive for the presence of Lyme-related structures. In addition to the flagged images,

the image classifier will calculate the number of spirochete and/or volume of biofilm. This will result in a calculation of the severity level of infection. There are a few ways by which the number of spirochete could be calculated. One way is to take the highest number of spirochete identified in a single image. Another way would be to take the number of spirochete identified in each of the Lyme-positive images and average them out, taking the total number of spirochete and dividing that number by the number of images. Other factors in determining severity include the number of images containing spirochete and the confidence level of these images. The presence of biofilm is indicative of Lyme disease in its more advanced stages of development, since biofilm does not appear right away in newly infected hosts. Thus, the presence of biofilm could play a role in determining the severity and maturation of infection. A positive reading for Lyme disease by the image classifier can help doctors to determine next steps, such as additional testing or treatment. While speaking in the context of Lyme disease, this methodology could be used to identify numerous objects found in the blood, giving doctors the information they need to make informed decisions. Results are delivered quickly, giving doctors feedback in near real-time. While some blood screening tests can take weeks to produce results, this method will give results in minutes.

The image classifier is trained to recognize spirochete and its associated biofilm through numerous training examples. To train it, the classifier is given images of Lyme-positive blood samples containing spirochete or biofilm and "learns" the morphology of these organisms through Machine Learning algorithms. Rather than explicitly programming the image classifier model to recognize spirochete or biofilm, the model learns by example, taking repeated training images and developing a picture of how these organisms appear. As such, Machine Learning image classifiers can be trained to identify any number of organisms or structures in blood, not just Borrelia burgdorferi or biofilm. This means that the image classifier could potentially be used to identify multiple objects in blood, so long as it has been trained to identify them. By visually classifying objects found in blood, doctors will be able to gain greater insights into a patient's state of health and help them to make informed decisions.

The Machine Learning model is adaptive, benefitting through repeated training and feedback. As it takes in additional images, doctors can send feedback to the image classifier on the images which have been flagged as Lyme positive, as well as images that the classifier might have missed. This allows the image classifier to train and retrain itself in real-time, using the feedback to make more precise and better-informed calculations. The image classifier learns through its cumulative knowledge-base and makes continuous refinements to its accuracy through constant feedback, much like how a trained doctor learns by on-the-job training and real-world experience.

Business Problem

We will now turn to the issue of identifying Lyme disease from a business standpoint, including the challenges facing doctors and the need for alternative solutions. Lyme disease is a public health concern, affecting millions of people in the U.S. and around the world. Doctors are only beginning to understand the far-reaching and devastating long-term effects of this infection. We know that it leads to debilitating chronic health problems, from arthritis, to joint and muscle pain,

to neurological and heart problems, including memory and sleep issues. Many people who suspect that they are suffering from Lyme disease will go from doctor to doctor without a positive diagnosis. Many patients cannot afford the tests – some of which can cost hundreds or even thousands of dollars and are often not covered by insurance companies – and the tests that do exist are severely lacking in terms of accuracy. Many people suffer from what some call "Chronic Lyme Disease", though the term itself is somewhat controversial and has not been formerly recognized by the medical establishment. While around 30,000 new cases are reported to the CDC each year, the actual number of people diagnosed is estimated to be around 10 times higher. And that is only the number of cases clinically *diagnosed.* It does not consider the number of people who have Lyme disease but have not been diagnosed, which, based on the fact that the CDC-recommended two-tier diagnostic method misses about half of those suffering with Lyme, it is safe to assume that the actual number of people infected is even higher than that. Add to this the problem of Lyme disease patients being misdiagnosed with other illnesses such as colitis, Alzheimer's, Chronic Fatigue Syndrome, arthritis, Lupus, and Crohn's disease, and it becomes clear that Lyme disease is a much bigger problem affecting a lot more people than previously believed.

Treating patients with Lyme disease costs the U.S. healthcare system between $712 million to $1.3 billion a year, according to the Disability Benefits Center. While not currently covered by law as a disability, many people with Lyme disease are either unable to work, or experience difficulty working, leading to unemployment and loss of productivity. One study from 2014 conducted by Lymedisease.org found that over 40% of people suffering from Lyme disease were not able to work. In rare cases, Lyme has resulted in death from cardiac arrest. Though statistically uncommon, Lyme disease can be deadly, especially in those with weakened immune systems such as the very young and very old. According to a study from Johns Hopkins Bloomberg School of Public Health, people with Lyme disease cost the healthcare system nearly $3,000 more, go to the doctor 87% more often, and have 71% more visits to the emergency room within a year after diagnosis than those without Lyme disease. It is clear that the personal, financial, and economic impact of Lyme disease is enormous, diminishing quality of life and burdening the healthcare system. The actual human and economic impact of Lyme disease in terms of lost productivity, opportunity cost, and deterioration of health and happiness is difficult to assess because of how little is known about diagnosing and treating this disease.

With that said, what are doctors doing currently to diagnose and treat Lyme disease? Before being diagnosed, a patient may experience a variety of symptoms early on that manifest similarly to the flu. Symptoms like fever, chills, aching muscles or joints, fatigue, and headache. Because symptoms are prone to periodic outbursts and remissions, many people do not even see a doctor because they might think they have the flu or other common illness. In some cases, the symptoms are more characteristic of Lyme disease, such as when the erythema migrans, or bull's eye rash appears. This can happen between 3 and 30 days after the ticket bite, and can sometimes lead to rash on multiple places on the body, not just at the infected site. Those who do not seek immediate medical treatment because they are not aware of what their symptoms could mean or do not show obvious signs may go weeks, months, or even years without suspecting Lyme disease. In later stages, people may start to develop shifting joint pain, temporary paralysis to one side of the face (Bell's palsy), impaired muscle use, and inflammation around the membranes of the brain.

The key to combating Lyme disease is early identification and treatment. If identified early, Lyme disease can usually be effectively treated with a regiment of antibiotics. However, if left untreated, Lyme disease can become chronic and lead to an array of long-term health problems that are very difficult to treat. Doctors need to diagnose Lyme disease early on to treat it effectively and avoid long-term damage. The next section will talk about how this method of computer image classification will solve that problem.

Business Solution

The previous sections described the theory behind SYSCOM's concept and the business problem posed by Lyme disease. Now, we will look at how the concept can be implemented to solve that specific business problem. Some of the basic architecture for implementing this solution will likely already exist, and the missing components should not be difficult to add. Some of the basic components are things such as medical equipment for drawing blood in a safe, sterile environment, and blood slides for placing the blood samples on. The personnel carrying out these tasks will need to be trained phlebotomists who can safely draw samples from patients, namely at the fingertips, and transfer these samples to a microscope. This procedure could take place in a variety of circumstances, including when a patient is suspected of having Lyme disease due to a recent tick-bite, and/or is showing signs of being infected by Lyme disease, or as part of a routine screening procedure in high-risk regions. Once the sample has been transferred to the slide, it is placed under a computer-controlled digital microscope capable of viewing the sample at a high enough resolution that microscopic structures are plainly visible. Specifically, the image classifier will be looking for spirochete and biofilm, both of which indicate the presence of Lyme disease in an infected host. Once the slide is placed under the microscope, a computer program will direct the microscope to make tiny adjustments up, down, left, and right to view the width and height of the sample. While making bidirectional adjustments, the computer will also change the zoom of the microscope, viewing the sample at various depths. Combined, these adjustments in placement and magnification will render a three-dimensional picture of the sample. The entire episode will be recorded, and the video will be uploaded in real-time to a digital repository. The best candidate for such a repository will be a cloud-based environment with secure access. The video will only need to be a few seconds long, just long enough to get a full view of the sample. As soon as the video is uploaded to the repository, the video will be sliced into still frames with a video-to-picture conversion software program. There is a wide range of possibilities in terms of video length, frame rate, and number of images, and all parameters will be adjustable depending on conditions.

The image classifier is a computer model, consisting of algorithms that have been modified to identify specific objects in images. Such image classifiers can be trained to recognize anything from plants and animals, to the make and model of vehicles, to human faces, to handwritten numbers and letters. The image classifier used in this use-case will have been trained to identify both spirochete and biofilm in microscopic images of blood samples. The computer will pass the images created from the video of the sample to the image classifier, which will analyze the images. The image classifier will assign a numerical value to each object class per image. The object classes are *spirochete* and *biofilm.* Each object class will receive a number between 0.00

and 1.00. The higher the value, the greater the confidence level that the image contains that object. Images that score above a certain threshold in either object class will be flagged. Along with the confidence value, the image classifier will count the number of spirochete and/or the volume of biofilm contained in each image. These two values, the confidence level and number of spirochete/volume of biofilm in each image will be used to calculate an overall score for the entire sample. The overall score for the sample will be an evaluation of whether Lyme bacteria is present in the sample, and if so, how much. The threshold for how high the confidence value must be is adjustable. The overall confidence level will be presented as a number between 0.00 and 1.00, while the spirochete count and biofilm volume will be represented as ratios, taking into account the density of spirochete and relative volume of biofilm found in the sample. A high ratio of biofilm to spirochete can be indicative of a Lyme disease infection that is more advanced, since biofilm does not develop immediately upon infecting the host.

The image classifier's results will be presented to the doctor who will be able to decide next steps, whether further testing is required, or whether treatment options are appropriate. One of the powerful things about the image classifier is that it can be continuously trained to improve its accuracy. Each time it analyzes a new sample, doctors will be able to view all the images generated from the microscope's video. The doctor can examine the confidence and density scores for each image and provide feedback to the image classifier on how accurately it classified each image. The doctor can confirm the image classifier's scores or correct it for false positives or false negatives. This will allow the image classifier to adjust its algorithms, learning to classify more accurately through direct, expert feedback. This process is called Machine Learning, a process for teaching computers specific domain-knowledge to assist humans. And, doctors do not need specialized technical training in order to use it. The retraining cycle is a simple matter of viewing the images on a computer screen and agreeing or disagreeing with the image classifier's readings. Any feedback given to the image classifier will affect future calculations, so it may be good practice to use version control to revert to previous versions if performance degrades. Feedback could also be disabled as an optional way to preserve the "out-of-the-box" state of the image classifier. In the long term, continuous retraining through feedback is in the best interests of both doctors and patients, since good feedback will allow the image classifier to make better informed calculations, resulting in more accurate readings.

Since all the results are digital, they can be sent electronically to other medical offices or laboratories for further evaluation, or to the patient for their records. Because the calculations are done with a computer program purely through visual identification, there is no specialized processing of the blood sample required. The end goal is to have a reliable, affordable option for people to be screened for Lyme disease so that they can receive the treatment they need. The following section will describe in more detail why this is not currently happening due to the challenges of diagnosing Lyme disease and the limitations of common testing methods.

Overview of Lyme Disease

Up to this point, we have considered Lyme disease from a business standpoint as a public health issue, examining the financial and economic costs of diagnosing and treating the disease, as well as the human toll inflicted on those suffering from it. The previous sections serve to highlight the

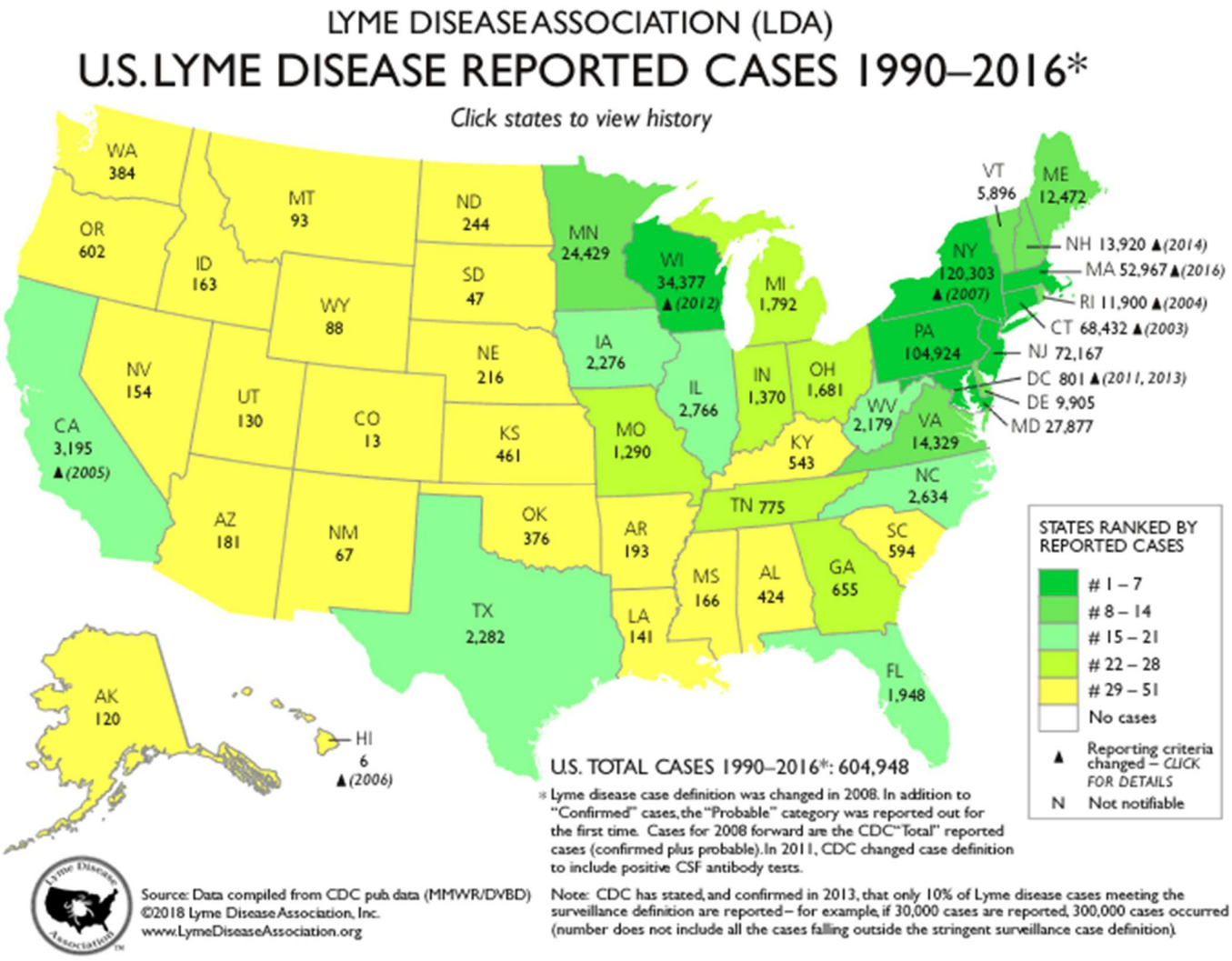
need for better methods of screening for Lyme disease and how the SYSCOM image classifier concept can be implemented. They were meant to function as the backdrop for putting the methodology to a specific use-case. What follows is a closer examination of Lyme disease itself from a scientific and clinical standpoint, exploring what Lyme disease is, how it is diagnosed, and why it is so difficult to identify and treat. The remainder of the paper will focus on Lyme disease from this standpoint, however, it is only meant to enhance our scientific understanding of the disease itself; it is not necessary to read this section in order to grasp the methodology. Nevertheless, it is important that the image classifier methodology be grounded in valid science. In the spirit of making informed opinions about this complex issue, efforts have been made to validate and source the research done here.

To begin, let us consider the following description of Lyme disease from the Center for Disease Control and Prevention (CDC) website:

"Lyme disease is caused by the bacterium Borrelia burgdorferi and is transmitted to humans through the bite of infected black-legged ticks. Typical symptoms include fever, headache, fatigue, and a characteristic skin rash called erythema migrans. If left untreated, infection can spread to joints, the heart, and the nervous system. Lyme disease is diagnosed based on symptoms, physical findings (e.g., rash), and the possibility of exposure to infected ticks. Laboratory testing is helpful if used correctly and performed with validated methods. Most cases of Lyme disease can be treated successfully with a few weeks of antibiotics. Steps to prevent Lyme disease include using insect repellent, removing ticks promptly, applying pesticides, and reducing tick habitat. The ticks that transmit Lyme disease can occasionally transmit other tick-borne diseases as well."

Lyme disease is a growing problem in the United States, with a reported 80% increase of infections between 2004 and 2016, according to one study from the Center for Disease Control and Prevention (CDC). As of 2015, there are about 30,000 cases of Lyme disease reported each year to the CDC, though the actual number of cases is closer to 300,000. A big part of the problem with Lyme disease is how difficult it is to definitively diagnose, due to its similarity to several other diseases and a lack of effective diagnostic methods. Many of the commonly reported symptoms of Lyme disease such as chills, fever, headache, joint pain, muscle pain, and stiff neck are also associated with other illnesses such as fibromyalgia, Rheumatoid arthritis, and chronic fatigue syndrome. As a result, it is very difficult to diagnose Lyme disease based solely on the symptoms. The characteristic "bulls eye" rash (erythema migrans) sometimes found at the infected point of the tick bite is only reported by a small number of people, and many don't even recall being bitten by a tick in the first place, which adds to the uncertainty in diagnosis. The majority of reported Lyme disease cases are concentrated in the northeast, mid-Atlantic, and mid-west, as is seen in the below map.

Graphic 1:



Diagnosing Lyme Disease - *Indirect vs Direct*

Indirect

The current CDC-recommended laboratory method for diagnosing Lyme disease is an *indirect,* two-tier process. It is called indirect because the method does not test for the presence of Lyme disease itself, but rather your body's expected *response* to the infection. The first tier is a screening test called the enzyme-linked immunosorbent assay, or EIA/ELISA. It is a blood test that looks for antibodies produced by an infected individual to combat Borrelia burgdorferi, the Lyme disease bacteria. If the result from the ELISA test is negative, the CDC deems that no further testing is necessary. The problem is, the ELISA gives false negatives nearly 50% of the time. If the person tests positively on the ELISA test, the second step in the two-tier process is to

get a confirmatory test, called the Western Blot. The Western Blot test is designed to rule out false positives created by the ELISA test, and is considered to be more reliable than the ELISA test. The Western Blot has a fairly high specificity rate, meaning that it does not give many false positives. On the other hand, the ELISA test, which is a screening test, has a low sensitivity rate, meaning that it gives many false negatives. It is important in diagnosis to have both a high sensitivity as well as high specificity. If your diagnosis is highly sensitive, you will most likely not get many false negatives, because the more sensitive the test, the more it will return positive. However, you can have *false positives,* which is why it is important to balance this out with having a high specificity to confirm that your positives are true positives.

To illustrate this, imagine a fisherman fishing for salmon. He wants to throw out his net and gather as many salmon and as few of everything else as possible so that he is not wasting time sorting through the salmon among the unwanted things like shoes, trout, crabs, and jellyfish. If his net is highly sensitive, it is a wide net that will bring back a large number of salmon (and maybe some shoes and other things as well). However, he may have many false positives in the form of crabs, trout, shoes, and jellyfish. If his net is 100% sensitive, he will not miss any salmon in the water, but if the net is not highly specific, he may have many false positives alongside the true positives. On the flip side, let's say he has a net that has a very low sensitivity. This means that he will miss many of the salmon because the net only picks up the fish that he is confident are indeed salmon. So he misses many true positives, or to put it another way, the net produces many false negatives. Meanwhile, the specificity of the net measures how many of the fish are actually salmon, i.e. how many positives are true positives. Ideally, you want your net to have both high sensitivity, so that it doesn't miss any salmon, but also high specificity, so that it doesn't bring back false positives in the form of crabs, trout, etc. If that distinction is clear, we will now move onto the second tier in the two-tier diagnosis: the Western Blot.

The Western Blot test is accurate an estimated 80% of the time, though many Lyme-positive individuals never even receive the Western Blot because they received negative results from the ELISA test. Like the ELISA screening test, the Western Blot test looks for antibodies in the blood in response to the Lyme disease bacteria. Namely, the IgM and IgG antibodies used to combat Borrelia burgdorferi. If the patient reports that symptoms began within the last 30 days, doctors look for IgM antibodies since they typically disappear a few weeks after infection. If symptoms first appeared more than 30 days ago, Doctors look for IgG antibodies. The problem with IgG antibodies is that they stay in the blood stream for a very long time, perhaps indefinitely. So the presence of these antibodies is not enough to determine that has a person has Lyme disease *now,* only that the person *has had or has been* exposed to Lyme disease at some point in the past.

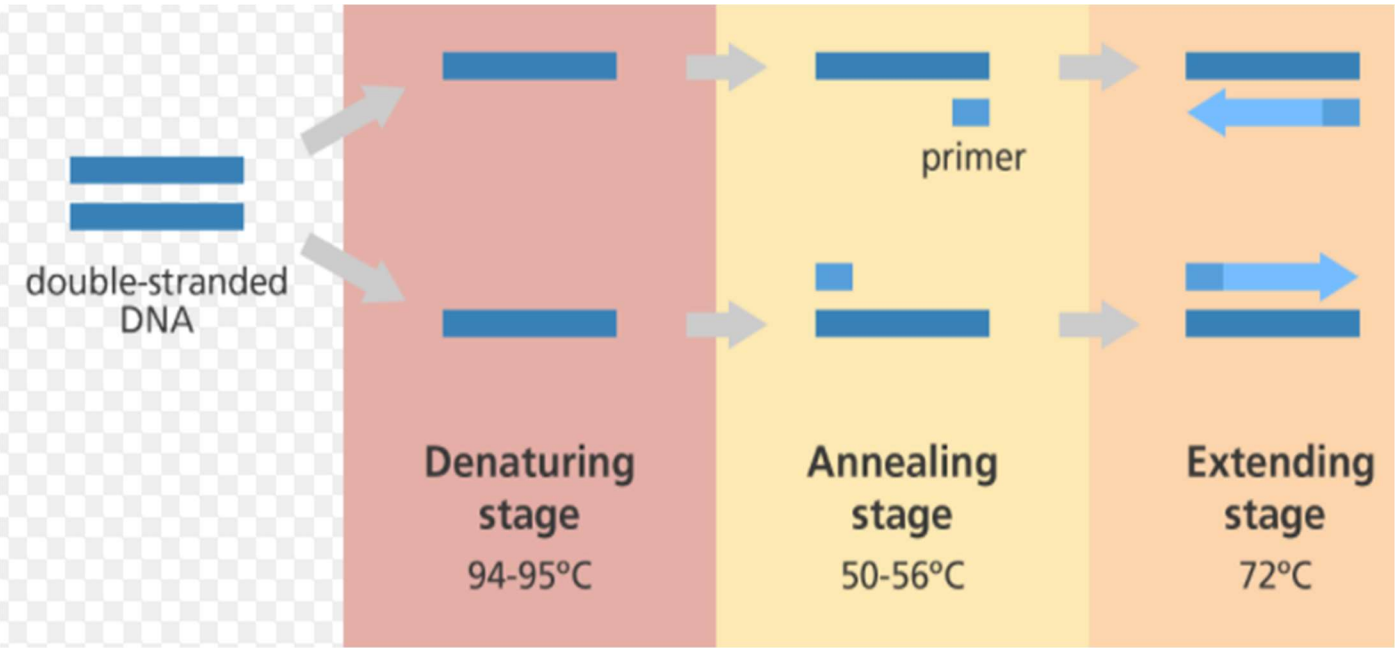
Together, the two-tiered process recommended by the CDC misses an estimated 54% of Lyme-positive patients. To go back to the fishing example, these tests have a low-sensitivity (ELISA) and moderate specificity (Western Blot). So when we cast our net, we miss many of the salmon (true positives) but we don't get many crabs or jellyfish (false positives). Both the ELISA and Western Blot tests are "indirect", measuring the body's response to possible infection of Borrelia burgdorferi, rather than testing for the presence of the bacteria itself. The problem with this method is that many people are slow to produce antibodies in response to the infection, so it can

be difficult to detect their presence. As a result, the current CDC-recommended two-tier diagnostic method is woefully inadequate in identifying Lyme disease.

Direct

Unlike indirect methods of diagnosis, direct methods of diagnosis identify the presence of the bacteria itself. One such method is called the Polymerase Chain Reaction (PCR) test, which copies segments of DNA strands which are then analyzed to determine if Borrelia burgdorferi DNA is present. While complex to fully appreciate, PCR is fairly easy to grasp as a concept. The DNA is first put into test tubes and heated in order to separate the two strands, a process called *denaturation.* Next, the DNA strands are cooled down and set with "primers" which act as markers for the beginning and ending points for the sequence to be copied, a process called *annealing*. Third, an enzyme called polymerase attaches to the primers and makes copies of the missing sequences, a process known as *extension*. The end result is that you end up with two pairs of the DNA sequence where you started with just one. This process can be repeated over and over again within a test tube, doubling the resulting copies at each cycle and allowing for thousands or even millions of copies of the DNA sequence to be made in a short time. Whereas old methods of cloning could take weeks to perform, PCR allows for over a billion copies to be made in a few hours. PCR testing for Lyme disease is extremely accurate when the Lyme DNA is detected, but in practice the test also produces many false negatives because the bacteria is not always readily present in the sample being tested.

Graphic 2:



One strain of Borrelia that can be detected by the PCR test is Borrelia mayonii, an organism that has been observed in the mid-west and which is genetically distinct from Borrelia burgdorferi. While different from its burgdorferi cousin, this strain of Borrelia also causes Lyme disease, and has been successfully treated with antibiotics just like a Borrelia burgdorferi infection.

According to Mayo Clinic Laboratories, PCR sensitivity has yet to be quantified. The National Institute of Health (NIH) has stated that although PCR testing has proven to be highly specific, giving few false positives, it has low sensitivity and is prone to contamination which skews the results. While not universally adopted as an optimal diagnosis technique, PCR testing has showed potential in detecting newer strains of Borrelia, such as Borrelia miyamotoi and Borrelia mayonii.

Antigen detection tests look for a unique Lyme disease protein in urine. The method was developed by a diagnostic company in Virginia called Ceres Nanosciences and is currently seeking FDA approval. This direct method tests for the antigen OspA (Outer source protein A) in urine produced by the Borrelia burgdorferi microbe. The test is non-invasive, requiring only a urine sample from the patient and promises accurate results within two weeks. The CDC does not recommend antigen testing at the moment because its accuracy and usefulness has not been adequately determined.

Culture testing is another direct method for diagnosing Lyme disease. This is done by taking samples of blood or other fluid and incubating the cultures in a petri dish. If Borrelia burgdorferi spirochete are present in the sample, they will multiply during the period of incubation and become detectable. One study from 2014 was able to positively identify Lyme disease spirochete in cultures taken from vaginal and seminal secretions. This finding has added weight to the hypothesis that Lyme disease could be transmitted from person to person through sexual contact, though this has not yet been confirmed. Because culture testing is labor intensive and plagued by low sensitivity, it is generally not recommended other than for research purposes or corroboration of diagnosis with other methods.

Co-infections - Adding to the Problem

There is another issue that adds to the problem of diagnosing and treating Lyme disease, and that is the presence of co-infections. Lyme disease is often referred to as the "great imitator" because the symptoms are shared closely with many other medical conditions such as Rheumatoid arthritis, fibromyalgia, multiple sclerosis, and even depression. According to Dr. Richard Horowitz, there are several other tick-borne infections that are often found alongside Lyme disease, and which often have overlapping symptoms. Not only does this make diagnosis increasingly difficult, it makes treatment equally challenging because treating one infection may not cause the symptoms to go away. For example, a patient may test positive for Lyme disease and begin treatment, usually in the form of several rounds of antibiotics over a few weeks. Even if the treatment helps combat the Lyme disease, the patient could also have one or more additional tick-borne infections such as Bartonella, Babesia, Ehrlichia, or Anaplasma, all of which have similar symptoms to Lyme disease. People with one of these infections often complain about symptoms that come and go. Among them are: periods of lethargy and tiredness, memory problems, frequently getting sick due to a weakened immune system, headaches, flu-like symptoms, aching or stiffness in the joints or muscles, sensitivity to light or sound, vision problems, sleep problems, anxiety, trouble concentrating, neurological issues, chest pain, and heart palpitations. The presence of these co-infections often make symptoms worse than if Lyme disease was the only infection present. It is not only these similar tick-borne infections which can accompany and intensify Lyme disease, it is also other strains of the Borrelia microbe. Borrelia burgdorferi is the spirochete which causes Lyme disease, but according to Dr. Horowitz, there

are about 100 strains of Borrelia in the U.S., and about 300 worldwide. Of note, there is one strain of Borrelia from Japan which has made appearances in New York, California, and Canada called Borrelia miyamotoi which can cause the familiar erythema migrans, or "bulls-eye" rash, bell's palsy, and encephalitis. Although it causes very similar symptoms to Borrelia burgdorferi, Borrelia miyamotoi does not show up on traditional Lyme disease screening tests. One study from 2014 which looked at various Borrelia infections in the south showed that 42% of the patients infected with a strain of Borrelia had some form of Borrelia other than Borrelia burgdorferi. These were not Lyme disease cases, and they do not show up positive in the ELISA or Western Blot tests. This same study noted that screening tests designed to only detect Borrelia burgdorferi and not other strains of Borrelia which may cause Lyme disease may be contributing to the high rates of false negatives produced by these tests. Even the Western Blot test may miss many of these other strains of Borrelia. To understand why, we must look at how the Western Blot test works.

The Western Blot test uses a laboratory technique called immunoblotting, which sends electrical currents through the blood sample to separate specific proteins found in the cells. These proteins are then tested to see how they react to antibodies found in the patient's blood. If the patient has an antibody specific to the protein, a "band" will appear on the sample. The resulting bands look similar to that of a bar-code, and doctors are able to read these biological bar-codes and where they show up on the immunoblot to determine if the patient is positive for Lyme disease. Each strain of Borrelia has its own unique bands that will show up distinct from Borrelia burgdorferi. If any of these bands show up, it means that the patient probably is positive for some Lyme-related infection, but it is not always easy to determine which one. Borrelia miyamotoi, for example, the Japanese Borrelia strain similar to Lyme disease, has been observed in 4.5% of ticks on deer in Wisconsin, according to a study from 2016. This strain of Borrelia causes similar symptoms as its cousin, Borrelia burgdorferi, but it does not show up in an ELISA test and the Western Blot test is not designed to detect it. According to a lymedisease.org survey, over 50% of patients with chronic Lyme disease had co-infections, with 30% reporting two or more co-infections. The most common were Babesia (32%), Bartonella (28%), Ehrlichia (15%), Mycoplasma (15%), Rocky Mountain Spotted Fever (6%), Anaplasma (5%), and Tularemia (1%). Like Borrelia, which has many different species, these other tick-borne infections also come in many different forms, many of which do not show up in traditional screening tests. This makes diagnosing patients an absolute nightmare, since symptoms alone only suggest that a patient has one of literally dozens of infectious diseases, and even then, narrowing down which strain of infection is extremely difficult.

As was previously noted, the two-tier system is highly inadequate, missing about half of all Lyme-positive patients. And this is just for Borrelia burgdorferi, the spirochete which causes Lyme disease. This is not even taking into account the other 100 species of Borrelia or the other co-infections that appear similar to Lyme disease. This is a major problem. As was noted earlier, the key to stopping the spread of Lyme disease and other Lyme-related infections is early identification and treatment. According to Dr. Horowitz, antibiotics can cure Lyme about 75-80% of the time if they are given within 30 days of infection. After 30 days the infection becomes chronic and very difficult to eradicate. The problem is most patients do not seek treatment until long after the infection has become chronic, and symptoms often do not become debilitating for weeks or even years after a person has become infected.

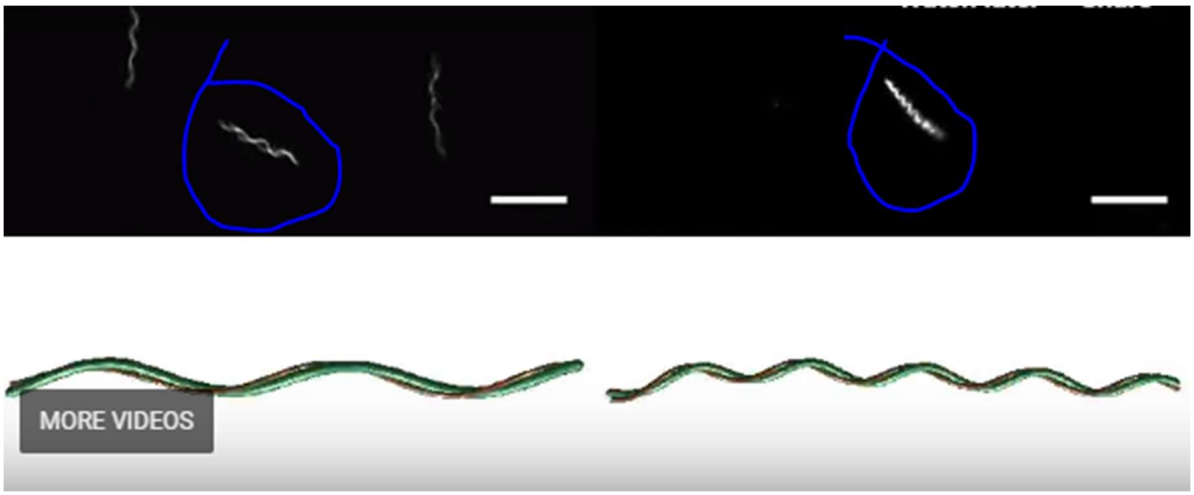
Spirochete

Borrelia burgdorferi is a type of organism called a spirochete, which is a long, thin, spiral bacteria that moves in a corkscrew-like pattern. However, Borrelia burgdorferi is not the only type of spirochete that exists. There is also Treponema pallidum, a spirochete which causes Syphilis and yaws, Leptospira, which leads to Leptospirosis, and Borrelia recurrentis, a bacteria which causes Relapsing fever. Spirochete do not just stay in the blood once they have infected a host. Their corkscrew-like motion allows them to burrow into almost every part of the body, invading issue, muscle, joints, and organs, even drilling into the central nervous system and heart, causing neurological, physiological, and cardiovascular problems. Not all spirochete are actually helical like corkscrews, some are flat with a wave-like pattern, resembling light or radio waves. Spirochetes propel themselves through fluids with a flagellum, a powerful motor that turns at a tremendous speed.

Graphic 3:

While the Lyme and syphilis spirochetes look very similar (Borrelia burgdorferi and Treponema pallidum, respectively), the Lyme spirochete have more flagella, giving them more power to burrow into tissue and cellular membrane:

Graphic 4:



Left: Borrelia burgdorferi (Lyme)
Right: Treponema pallidum (Syphilis)

Biofilm

One of the things that makes Lyme disease more difficult to treat is a mucous-like residue called biofilm. Bacteria everywhere form communities of biofilm which help the bacteria to grow and thrive. Research suggests that biofilm makes treating Lyme disease with antibiotics more difficult because the biofilm acts as a protective shield which hides the spirochete from eradication by both antibodies and antiobiotcs. The biofilm can become more resistant to antibiotics over time. The spirochete bacteria can hide inside biofilm communities, allowing the infection to "fly below the radar" and remain undetected by your body's immune system. This protects the spirochete from antibiotics by essentially becoming invisible inside the biofilm. Biofilm typically does not develop right away, so it may not show up in patients who have been recently infected with Lyme disease. While inside biofilm, spirochete can exchange genetic information, including drug-resistance techniques. This allows spirochete to evolve and develop immunity to antibiotics during the reproduction cycle, making the Lyme bacteria more resilient over time. Biofilm can also make Lyme disease more difficult to detect in screening tests, leading to false negatives. However, it may be possible to use the presence of biofilm itself to help diagnose Lyme disease.

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