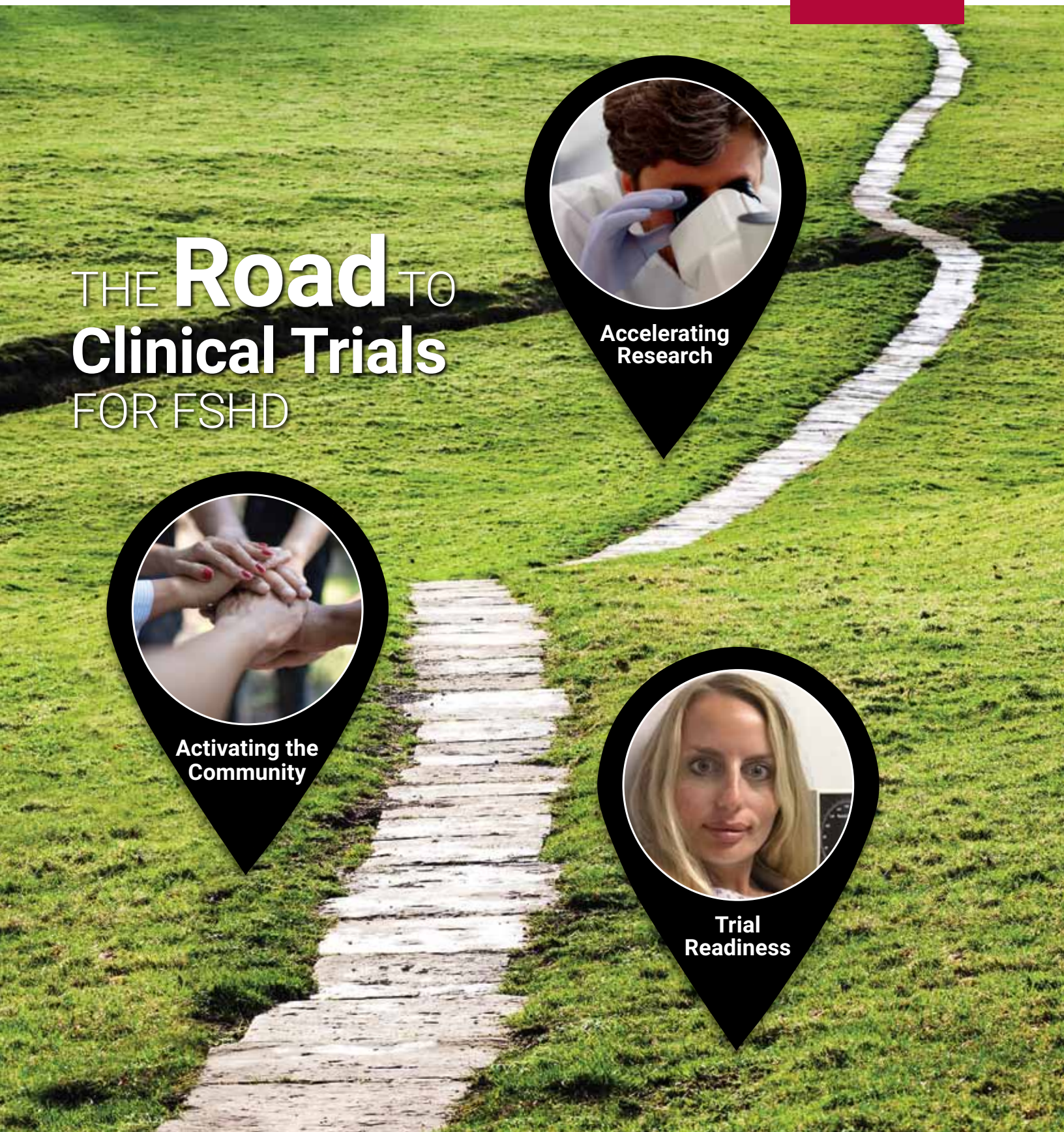
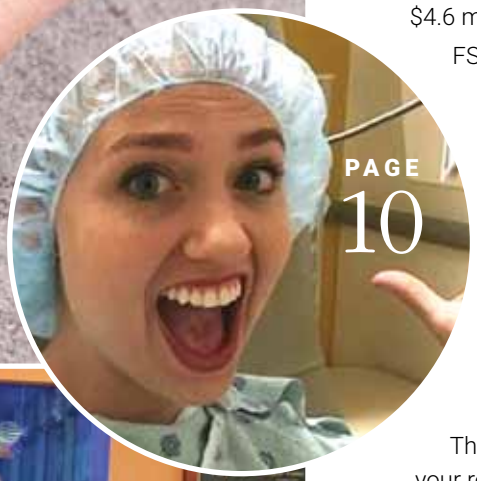
FSHD Advocate

2020 • ISSUE 1

FSHD SOCIETY

THE Road TO Clinical Trials FOR FSHD





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FSHD Advocate

It is our editorial policy to report on developments regarding FSHD, but we do not endorse any of the drugs, procedures, treatments, or products discussed. We urge you to consult with your own physician about any medical interventions.

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CEO Letter

Realizing the dream

Hope and challenge in the new decade

Almost 30 years ago, a few families began working together to seed a global movement to find the cause and ultimately the cure for FSHD. Armed with nothing but a dream, combined with tireless advocacy, strategic funding, and sheer persistence, the FSHD Society became a catalyst to engage families, researchers, governmental agencies, and, when the time was right, the pharmaceutical industry, in pursuit of this goal.

Because of the efforts of the FSHD Society in partnering with key researchers worldwide, the genetic cause of FSHD – the *DUX4* gene – was discovered a decade ago. This discovery has stimulated the research community and industry to search for effective therapies targeting the root cause of the disease, with more than 15 pharmaceutical and biotech companies working on solutions today. Our hopes and dreams seem to be coming true!

But we are not a community that rests on past accomplishments. Instead, we continually renew our commitment to realize the dream and achieve our goal – a cure for FSHD.

As we enter a new decade – one that we believe will see effective therapies become available – the families that form the FSHD Society face new challenges.

This year, we have an unprecedented opportunity to participate in targeted programs designed to accelerate therapies and overcome the obstacles to conducting clinical trials. Additionally, our families around the world will be able to go on record with the FDA through a Voice of the Patient Forum designed to inform and influence the regulatory pathway for promising therapies.

Mark A. Stone

The articles in this issue of *FSHD Advocate* outline many of the activities focused on achieving our collective goal. In these stories, I hope that you will:

- look past the challenges and see the possibilities;
- renew your commitment to our mission;
- allow yourself to dream (again) of a day when FSHD will not limit your life in any way;
- sign up and show up because your voice matters!

Harriet Beecher Stowe once said, "Never give up, for that is just the place and time that the tide will turn." **The. Time. Is. Now.** I'm confident that together, we will do whatever it takes to realize the dream.

Mark

Mark Stone
President and CEO
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THE ROAD TO CLINICAL TRIALS

BY JUNE KINOSHITA, FSHD SOCIETY

Here's what keeps us up at night: Researchers will find a drug that actually works, but they will not have the tools to prove it, and so the FDA will not approve it. You might think it would be easy to prove that a treatment for FSHD works. Can't you just show that a person gets stronger or grows back lost muscles after taking a pink pill? In a word, no. Here's why.

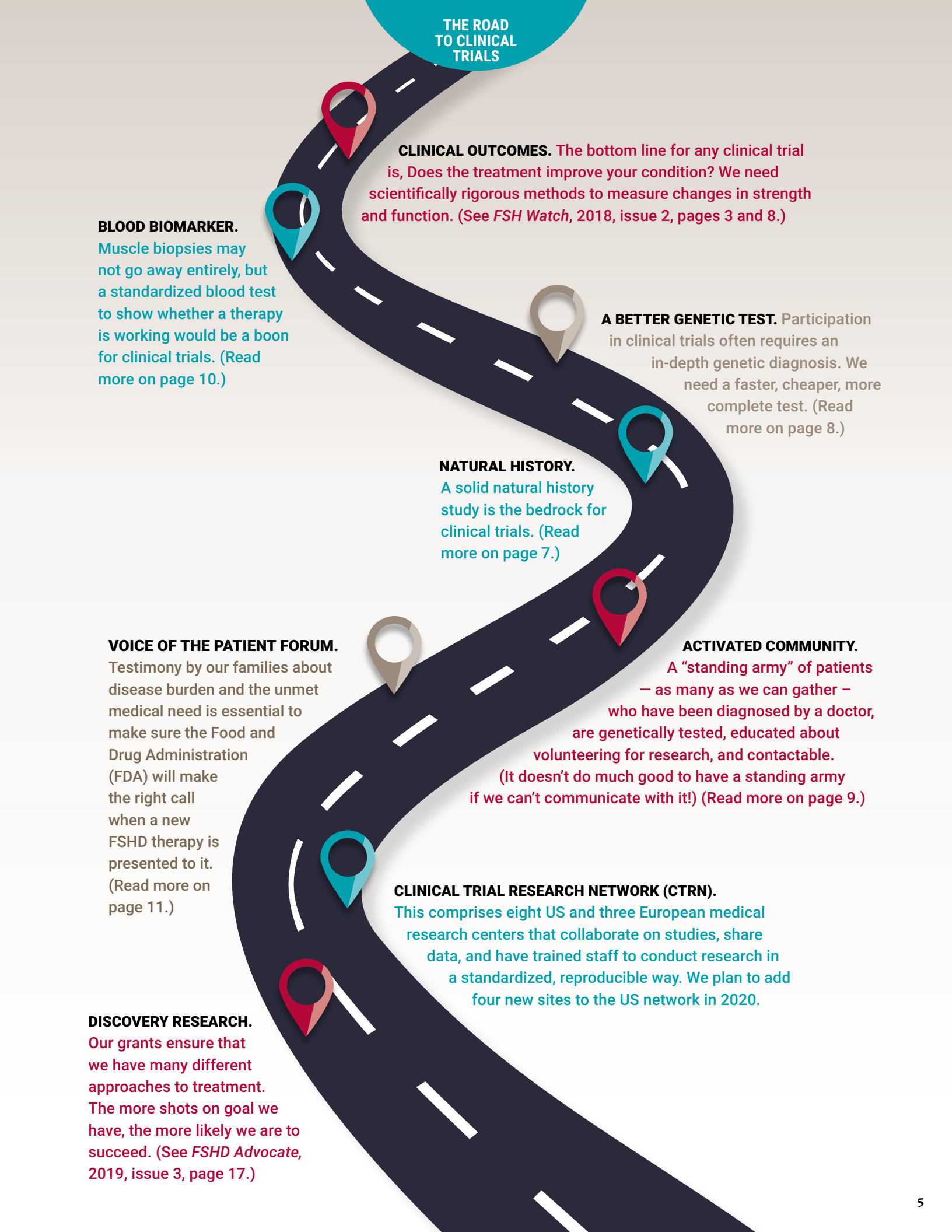
First, while we all hope for a treatment that will completely restore everything that has been lost, such regenerative therapies are still a long way from reality. What is a real possibility, today, are treatments that can slow or stop the symptoms. Such treatments might even allow surviving muscles to regain some function. We think everyone affected by FSHD would agree that a drug that stops muscle loss would be of enormous benefit.

Second, if you've ever walked into a roomful of people who have FSHD, you'll know that this condition is highly variable. Some people need a wheelchair before age 20. Others make it to retirement with only a slight limp. The weakness progresses in unpredictable fits and starts. Exercise helps many people regain some strength and function for a time. All of this makes it difficult to prove that a treatment is slowing or stopping the disease, especially within the six- to 12-month duration of a typical clinical trial.

The FSHD Society's Therapeutic Accelerator and Community Activation initiatives take aim at solving this challenge and making sure our entire community is well prepared to enroll in clinical trials.

Overcoming gaps in the road

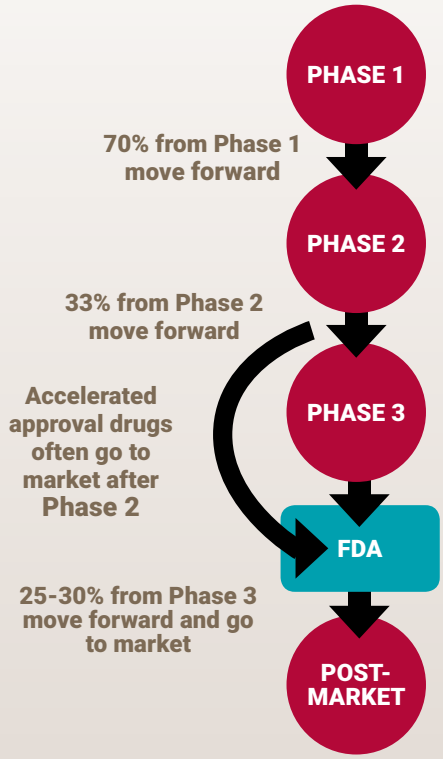
Over the past few years, we have made enormous progress toward trial readiness. All of our activities, from our national chapter program and global outreach, to our workshops, conferences, Clinical Trial Research Network (CTRN), and research initiatives, are aligned to achieve the goals outlined on the facing page and get us to a treatment by 2025.


THE ROAD TO CLINICAL TRIALS
CLINICAL OUTCOMES. The bottom line for any clinical trial is, Does the treatment improve your condition? We need scientifically rigorous methods to measure changes in strength and function. (See FSH Watch, 2018, issue 2, pages 3 and 8.)
BLOOD BIOMARKER. Muscle biopsies may not go away entirely, but a standardized blood test to show whether a therapy is working would be a boon for clinical trials. (Read more on page 10.)
A BETTER GENETIC TEST. Participation in clinical trials often requires an in-depth genetic diagnosis. We need a faster, cheaper, more complete test. (Read more on page 8.)
NATURAL HISTORY. A solid natural history study is the bedrock for clinical trials. (Read more on page 7.)
VOICE OF THE PATIENT FORUM. Testimony by our families about disease burden and the unmet medical need is essential to make sure the Food and Drug Administration (FDA) will make the right call when a new FSHD therapy is presented to it. (Read more on page 11.)
ACTIVATED COMMUNITY. A "standing army" of patients — as many as we can gather – who have been diagnosed by a doctor, are genetically tested, educated about volunteering for research, and contactable. (It doesn't do much good to have a standing army if we can't communicate with it!) (Read more on page 9.)
CLINICAL TRIAL RESEARCH NETWORK (CTRN). This comprises eight US and three European medical research centers that collaborate on studies, share data, and have trained staff to conduct research in a standardized, reproducible way. We plan to add four new sites to the US network in 2020.
DISCOVERY RESEARCH. Our grants ensure that we have many different approaches to treatment. The more shots on goal we have, the more likely we are to succeed. (See FSHD Advocate, 2019, issue 3, page 17.)

Clinical Trials 101

BY JUNE KINOSHITA, FSHD SOCIETY

CLINICAL TRIALS ARE CONDUCTED IN PHASES



- **10–20 people**
- **Researchers try to find safe doses, observe how the drug interacts with the body, and look for side effects**

TIME INVOLVED: Several months

- **Dozens to hundreds of people**
- **Researchers observe how the drug affects the body, gather safety data, and observe side effects**

TIME INVOLVED: Several months to 2 years

- **Hundreds to thousands of people**
- **Researchers gather more safety data, see if the drug is effective, and compare it with placebo or existing treatments**

TIME INVOLVED: 1 to 4 years

Regulators review data from trials, consider patient perspectives on benefit vs. risk, etc., to determine if a drug should be approved

- **Thousands of people**
- **Researchers gather more data on safety and efficacy**

TIME INVOLVED: Up to 5 years

Late in 2019, we passed a momentous milestone in the quest to develop treatments for FSH muscular dystrophy: A drug called losmapimod went into what's called a Phase 2 clinical trial. While there have been other clinical trials in the past, this is the first to target the genetic mechanism of FSHD. As such, if it is effective, it should stop the unrelenting, lifelong weakening of muscles that imposes such hardship and pain on affected individuals.

Excited and anxious patients flooded our social media channels, email inboxes, and phone lines with questions. How can I get in? Isn't this a cure? Why was I told I don't qualify? Why do we have to wait?

Why, indeed? The government requires that all new drugs undergo clinical trials to ensure that they are safe and effective. A clinical trial is a scientific experiment. *It is not a medical treatment*. In a clinical trial, a drug that has been thoroughly investigated in the laboratory (e.g., in a test tube or mouse) is tested in human volunteers for safety and efficacy.

Drug developers must provide data from the clinical trial to the Food and Drug Administration (FDA) or its counterpart in other countries. The agency requires convincing evidence that the drug is safe enough for its intended purpose and delivers a therapeutic benefit before it will approve the drug for public use.

FAQs about clinical trials

Visit our website (*fshdsociety.org/clinical-trials*) for answers to your questions, including:

- What can I expect if I volunteer?
- What questions do I ask?
- How do I enroll in a clinical trial?
- What are the different types of clinical trials?
- What determines the length of a clinical trial?
- Will I receive medical treatment as part of the trial?
- What is an IRB?
- What is "Accelerated Approval"?
- How can I tell if a trial or treatment is legitimate?

Natural history – the bedrock of clinical trials

Every drug developer needs this

BY JUNE KINOSHITA, FSHD SOCIETY

When we talk about a natural history of FSHD, we mean data about the normal progression of the symptoms in people who have the condition. This is the very first question a drug company asks when exploring the possibility of developing a drug: Is there a natural history study? That's how important it is. Without a natural history, it's difficult to show that a drug works.

FSHD is a rare disease, and only a fraction of patients volunteer for natural history studies such as the US national registry* at the University of Rochester. Today there are about 900 patients enrolled in this registry. This may not be enough. However, if we look around the world, there are thousands more enrolled in a dozen national registries. The FSHD Society has helped to establish a worldwide standard for the core data every registry should collect. If researchers could access and analyze the data in all of these registries, they might gain valuable insights.

Analyzing this data trove is a challenge. One solution we are exploring is to use artificial intelligence. In this way, we might identify subsets of patients who have predictable rates of symptom progression. Such patients would be ideal to recruit for clinical trials. Again, the more people who volunteer, and the more diverse they are, the more likely we are to identify such subgroups.

Closely related to natural history studies are clinical outcome studies, such as ReSOLVE, which is recruiting 220 patients in the US and Europe with the aim of developing tools to measure changes in muscle structure, chemistry, strength, and function – tools that are essential to prove whether new treatments are effective.

As Jinsy Andrews, MD, a clinical trial expert at the Columbia University Medical Center in New York City, noted, while many patients aspire to be in a drug trial, volunteering for research registries and ReSOLVE is even more important in terms of the impact on accelerating the development of treatments.

** https://www.urmc.rochester.edu/neurology/national-registry*

The national registry needs more volunteers, and more diversity

"We need many more patients to join the national registry and greater diversity in severity of symptoms and ethnicity/race to better understand the natural progression and identify factors that affect severity of FSHD in different populations."

— RABI TAWIL, MD, UNIVERSITY OF ROCHESTER

A better genetic test

A no-brainer for both patients and researchers

BY JUNE KINOSHITA, FSHD SOCIETY

We are entering a time of great hope for individuals with FSH muscular dystrophy, as new treatment approaches target the root genetic cause of the disease. An expert neurologist can usually diagnose FSHD based on an exam and review of family history, even without a genetic test. This type of diagnosis is perfectly valid.

But a genetic test is important in certain circumstances. A genetic diagnosis can be helpful for making medical and healthcare decisions (see "FAQs about genetic testing" on page 15). If you want to enroll in a clinical study or trial specific to FSHD, you are often required to have a genetic diagnosis. Researchers typically want as much genetic data as possible, including the number of D4Z4 repeats (for FSHD1), methylation of this region, the specific *SMCHD1* mutation (for FSHD2), and even the entire genome sequence of each individual.

Here's the challenge. If you ask your doctor for a genetic test, your DNA will be sent to a clinical testing lab, which currently uses a decades-old technology called a Southern blot. The technique is time- and labor-intensive, and so the cost is high, about $2,000 to $3,000 per test. If your insurance does not cover the cost, that's a big hit to the wallet – even more so if you have other family members who wish to get tested. Even if finances are not an obstacle, many patients have difficulty finding a doctor who is willing and able to order the testing.

In addition, the current genetic test is only set up to provide a yes-no answer to the question, Does this individual have FSHD? It does not collect the comprehensive data that scientists want, nor are the genetic data linked to individuals' clinical data (such as health data, strength and function tests, etc.), which could yield tremendous insight into the role genetic risk factors play in FSHD.

Right now, this type of analysis is only done in research labs and requires a separate study, patient recruitment, and redoing the original genetic testing from scratch. If a more complete analysis could be done during routine genetic testing, and we put in place a system for patients to consent to link their anonymized health data and allow researchers to use the data, this would be transformative. It would save time and resources, capture data that could help better predict the course of the disease in individuals, and reveal new strategies for treatment.

This is why the FSHD Society is partnering with companies and academic researchers to validate new technologies for diagnosing FSHD – faster, cheaper, and more completely – and build a system to empower research. As one of the key projects of our FSHD Therapeutic Accelerator, our genetic diagnosis initiative is a no-brainer. It will benefit patients and families directly while providing important new scientific insights.

An activated community – why now?

BY JUNE KINOSHITA, FSHD SOCIETY

Our community has been promised for decades that "one day" there will be treatments for FSHD, and so it's amazing to realize that day is almost upon us. In 2019, we saw two Phase 2 trials – for Acceleron's ACE-083 (now halted) and Fulcrum's losmapimod. More than a dozen companies and academic groups are working hard on the next wave of therapies, and we anticipate more clinical trials during the next few years. It's very important that we use what we have learned so far to speed up the process and get treatments to our families as soon as possible.

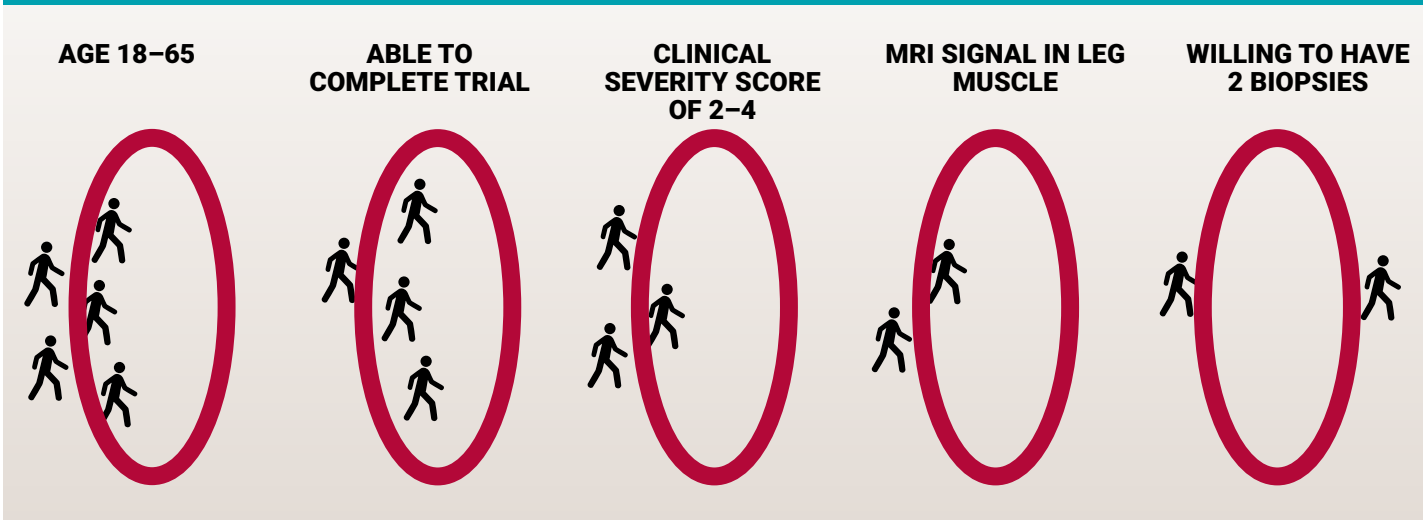
Here's the sobering truth: We need to *double* the number of patients who are actively engaged, especially younger and moderately affected individuals. While companies are investing millions of dollars into research and trials, they can't succeed without us. Our community must engage fully with the process. Across all research, 85 percent of trials face delays and 30 percent never even get off the ground because of the shortage of volunteers. This dramatically slows research, which means our families must wait longer for treatments.

Last summer, Fulcrum Therapeutics launched its Phase 2 ReDUX4 trial of losmapimod, which has been shown to reduce the expression of a gene called *DUX4*, which causes FSHD. In the lead-up to this trial, Fulcrum conducted a "biomarker study" designed to evaluate the reliability of different measures of efficacy that will be used in the drug trial. We helped to recruit volunteers by sending emails to patients in the vicinity of the research centers involved in the study. We contacted nearly 700 patients and family members, and some 100 people responded. In the end, the study enrolled 17 volunteers, enough to complete the study, but it took a considerable effort.

Why is it so difficult for studies to recruit patients? Researchers need to start with a well-defined population in order to get a good signal from a study or trial. If patients are too diverse in their age, disease severity, etc., this can make the data difficult to interpret. For this reason, volunteers have to pass through many hoops to qualify. For the Fulcrum study, they had to be the right age. They had to be willing and able to complete multiple visits to the clinic over several months. They needed to be moderately affected – not too little, but also not too much. They had to have an actively affected leg muscle (identified by MRI). They needed to be willing to have two muscle biopsies of that same muscle (one at the beginning and one at the end of the trial), because analyzing muscle tissue is the only method currently available to accurately measure *DUX4* expression and the potential effect of losmapimod on the root cause of disease.

Given these complexities, it's easy to understand why only one in five would-be volunteers made the cut. Every study and drug trial will face similar challenges – and the more trials are ongoing, the greater the competition for volunteers. We must grow the pool of people who are "trial ready." And this is why we need many more of you – patients and family members – to be actively engaged.

VOLUNTEERS MUST PASS THROUGH MANY HOOPS TO QUALIFY



A blood biomarker for FSHD

BY JUNE KINOSHITA, FSHD SOCIETY

Over the years, researchers have relied on the generosity and courage of our patient community who volunteer for important clinical studies in FSHD. Many of you have given your valuable time, undergone complicated muscle strength tests, filled out endless questionnaires, and even volunteered to give muscle biopsies so that scientists can better understand FSHD disease progression. With regard to muscle biopsies, although many are now performed with minor discomfort, you may well wonder why they are required for some FSHD clinical trials.

The reason is that many of the new treatments being developed for FSHD take aim at the *DUX4* gene (widely thought to be the root cause of FSHD). An effective way of showing the drug is doing what it is supposed to be doing is to measure *DUX4* or *DUX4*-regulated gene levels. Right now, the only way to show this is by directly analyzing muscle cells from a patient, before and after the drug is given. And this is why muscle biopsies continue to be necessary.

What if there was another way to show that the drug has engaged its target – a method that doesn't require taking small pieces of your muscle? The FSHD Society's biomarker initiative is aimed at solving this problem. Because *DUX4* itself is difficult to measure, researchers typically monitor the chain reaction of toxic events caused by *DUX4*. This shower of genetic shrapnel unleashed by *DUX4* results in chemical changes – or biomarkers – that can be measured in patients' muscle. It is very likely that some of these chemicals get released into the bloodstream and could be detected with sensitive tests. This relationship has to be validated by analyzing muscle biopsies and blood samples from many patients, and showing that there is a strong correlation between *DUX4* expression in muscles with the chemical signature in the blood.

Once scientists have agreed that this signature is a reliable biomarker, we will work with companies to develop an assay, or test, to measure it. Having this biomarker assay will make clinical research and trials faster, cheaper, and more accurate. And this will be as easy as a routine blood test.

"I made my tissue donation for all the children growing up with the potential to carry the FSHD gene. It was important to me to give what I can to be part of the solution."

—HILARY HOOVER

Patient Hilary Hoover getting ready to give a muscle biopsy.

From left to right, global FSHD advocacy leaders Bine Haase, Eduardo Silveira, and Mitsuru Honda.

The patient's voice in drug development

Testimonies carry weight in the drug approval process

BY JUNE KINOSHITA, FSHD SOCIETY

At the end of the day, if there was a drug that stopped FSHD in its tracks, would you want it, even if it did not restore what you have already lost? What if a drug made you stronger temporarily, even if it did not stop the disease?

Only those who are directly affected by FSHD – the patients, family members, caregivers – can say what is a meaningful benefit and acceptable risk of a therapy. The "voice of the patient" in these matters carries great weight with the FDA when it considers an application by a drug company to put a new therapy on the market.

The FSHD Society's **Voice of the Patient Forum*,** scheduled for April 21, 2020, is our platform to present testimony by patients and family caregivers to the FDA. This is your chance to educate the FDA on how FSHD has impacted your life or the lives of your loved ones. It also provides an opportunity for you to describe what is most important to you, and how a successful therapy could improve your quality of life.

The resulting *Voice of the Patient* report will be published and submitted to the FDA's Division of Neurology Products, Office of New Drugs, for inclusion in the framework used to evaluate future FSHD therapies. The FDA will use that information as it evaluates the potential benefits and risks of a therapy to the FSHD patient community.

Our meeting is a milestone event to gather and summarize input from patients and caregivers across the US and beyond, so we encourage everyone, at every stage of disease progression, to get involved, whether through in-person attendance at the meeting, online attendance and voting, or participation in surveys we will send out to gather data prior to the meeting.

The Voice of the Patient Forum is a key initiative of our 2020 FSHD Therapeutic Accelerator, and another way the FSHD Society is working to get treatments to you faster.

To register, visit *fshdsociety.org/vopf.*

** Also called the Externally-led Patient-Focused Drug Development meeting.*

Member of the team

Getting involved in research is about so much more than helping yourself

BY JIM ALBERT, ELDERSBURG, MARYLAND

Patients who are new to research may be trying to decide if clinical studies are something in which they want to participate. They might be wondering, Am I a good fit? Will this study benefit me? I hope this story might be helpful to someone trying to decide whether to get involved.

My involvement with FSHD clinical studies started in 2016. The first FSHD drug trial in close to a decade was about to begin. A few months before, at age 50, I developed weakness in my legs (tibialis anterior) for the first time. I was diagnosed 25 years earlier, and the impact of FSHD was mostly to my upper back muscles. I could still participate in many of the physical activities that I had enjoyed for much of my life.

For 25 years FSHD wasn't a daily roadblock. Now it was. I didn't do well mentally with weakened legs. When I saw that an FSHD drug trial was about to start, I thought, "Perhaps this drug will give me back what I want. Maybe I can hike long distances again. Maybe I can play tennis again. If I'm really lucky, just maybe I'll be able to put my arms over my head again." Obviously completely selfish reasons.

I didn't know much about drug trials, nor that very few drugs complete the clinical trial process all the way to an FDA approval. I was disappointed in the trial result. I received no physical benefit. However, during the trial at Kennedy Krieger Institute, I had the pleasure of meeting an extremely dedicated research team led by Kathryn Wagner, MD PhD. The entire team – from Dr. Wagner, to the coordinators who keep the many pieces of the studies flowing smoothly, to the nurse who joked with me while he drew my blood and the physical therapists who made the most tedious exercises fun – all truly made me feel like an integral part of the research team.

Members of the FSHD research team at the Kennedy Krieger Institute. The author, Jim Albert, is third from the left.

My frame of mind changed. This was no longer about "what's in it for me," but about being part of a team that really wants to solve very hard problems. Our relationship is truly symbiotic. I now look forward to research opportunities, whether they be natural history studies or drug trials.

My advice for anyone thinking about getting involved in a study is to think of it as an opportunity to be part of something that is so much bigger than oneself.

Getting myself trial-ready

Even with the best intentions, you may run into obstacles

BY IAN RYS, PORT ST. JOHN, FLORIDA

A year and a half ago, shortly after I attended my very first FSHD Connect conference in Las Vegas, I went to see Dr. Rabi Tawil at the University of Rochester. At that initial visit, he told me he believed I may be a good candidate for upcoming studies.

I was very excited. All I needed to do was get a genetic test and BAM! I'd be on my way to a clinical trial. Easier said than done, as it turned out.

I first asked my neurologist in Florida if he could help, but he wasn't interested and directed me to my primary care physician. She was willing but wasn't familiar with the process. No problem! I had already called Rochester and gotten the medical code for the test. (I thought I was so clever!)

With my doctor's order in hand, I went to the nearest diagnostic lab for a blood draw. A woman took the order, but after 15 minutes of conferring with her supervisor, she came back and I could tell by the look on her face that she had no clue what to do.

I asked June Kinoshita at the FSHD Society what to do, and she directed me to the University of Iowa, which performs the genetic test. When I downloaded their requisition form from the web, I immediately knew that my doctor wouldn't know how to fill it out. All of this had taken a lot of time and effort, and now I was way out of my league.

When I returned to the University of Rochester a year later, Dr. Tawil and James Hilbert helped me get my test kit out to Iowa, finally.

A hurdle for many is lack of insurance to cover the hefty cost of the testing. If that's a concern, you can join the national FSHD registry at the University of Rochester, and they will run the test for you with funding from the FSHD Society and Friends of FSH Research.

Joining the registry is just a good idea anyway. I was surprised to learn that there aren't more of us who have FSHD involved in many of these studies.

Back in Rochester, I had thought I would have to be on a waiting list because so many people would want to volunteer, but the obstacle for me was that I wouldn't have my genetic test results in time. Dr. Tawil explained that if the first round of studies showed positive results, there would be another round, and it would open up to more participants.

I left the appointment feeling good about everything.

I went many years not knowing about the FSHD Society and the incredible things they do. I had no idea how many of us there are. I lived 35 years thinking I was on my own. Today, I am very proud to be part of the FSHD community.

Research in the FSHD world is exploding. The hope for me and people like us is here, now. Let's get involved. Join the FSHD Society if you haven't already. There are multiple FSHD groups on Facebook that can keep you connected. Stay positive, be grateful, and love a lot!

"A hurdle for many is lack of insurance to cover the hefty cost of the testing. If that's a concern, you can join the national FSHD registry at the University of Rochester, and they will run the test for you with funding from the FSHD Society and Friends of FSH Research." — IAN RYS

FSHD affects the whole family

But never let it define you

BY FRANK GOLDSMITH, BOTSWANA

I saw that someone in our Facebook group had answered a set of questions about their relationship with a person with FSHD. I was so touched that I wanted to do the same thing. Here are my answers to the same questions about my relationship with my partner, Jill McCullough. We are both Peace Corps volunteers in Botswana.

How is it different dating someone with FSHD?

The level of partnership required to have a great relationship is immense. Every decision that requires effort, activity, and/or even movement at times requires both people to be on the same page. Preparing for events, celebrating each experience, and recovering from it require extra effort from both partners. Learning and accepting that it's not just one individual but the couple who is affected by FSHD is a great beginning for the partnership.

How do you see your partner struggle?

The most devastating impact of this disease on Jill is in her self-image. She talks about "when she was beautiful" and "before everyone thought she was lazy." The erosion of her self-image has been at least as severe as the erosion of her muscles.

How do you see your partner shine?

Jill has the most expressive and beautiful eyes I have ever seen. When we are working together on our next adventure, her eyes sparkle as her joy for life shines through. I have never met a more curious and adventurous person. I consider myself fortunate to be allowed to join her on her travels.

What advice can you give someone who is in a relationship with a person with FSHD?

Never ever let FSHD define your partner in your mind. It is a disease, not a person. And the moment you commit to your partner, recognize that your relationship now has the disease. It's no longer your partner's issue: It's now our issue.

What does FSHD mean to you?

At this point in my life, I have seen a lot of difficult and unfair things happen to good people. FSHD occurring to Jill doesn't seem difficult or unfair; it's downright cruel. Her childlike wonder, love of humanity and life, and her insatiable lust for adventure are uniquely attacked by this disease. In many ways, I think our partnership is a way of saying that while this disease can unfairly beat up one of us, together it will not win. Adventure, here we come!

Frank Goldsmith and Jill McCullough.

What do you personally do to support your partner?

I think Jill would say that my two biggest contributions to her are my massages and listening. When we need breaks, I massage the sore areas, and we talk and talk about life. Sometimes, when things are really rough, we can massage for three hours at a time, for four or five straight days. Then, when everything is as good as can be, it's back on the road for more adventures. I think my biggest contribution is my selfishness. I have never been more happy than when I'm with Jill. So every minute I'm massaging, or listening, or whatever, what I'm really doing is being selfish.

This article was excerpted from the Living with FSHD Facebook group and is reprinted here with the kind permission of the author.

FAQs about genetic testing for FSHD

BY JULIE COHEN, SCM, GENETIC COUNSELOR, THE CENTER FOR GENETIC MUSCLE DISORDERS, THE KENNEDY KRIEGER INSTITUTE IN BALTIMORE, MARYLAND

What is the genetic cause of FSHD?

Let me begin by saying that the genetics of FSHD is quite complex! There are two types of FSHD, called Type 1 and Type 2. The two types are distinguished based on their underlying genetic cause. The symptoms are the same in both types.

FSHD Type 1 (FSHD1) is by far the most common, accounting for about 95 percent of people with FSHD. FSHD1 is caused by a deletion of genetic material on chromosome 4. More specifically, the deletion affects a region called the D4Z4 region, which is located near the end of the long arm of chromosome 4 called 4q35. Individuals with FSHD1 have the deletion plus a genetic marker called the "4qA haplotype."

FSHD Type 2 is caused by a change in a gene called *SMCHD1,* which is located on chromosome 18. Individuals with FSHD2 have an *SMCHD1* gene change plus the 4qA haplotype.

Both types of FSHD result in expression of a gene called *DUX4* that is normally supposed to be turned off. It is thought that expression of *DUX4* is harmful to muscle cells. There is still a great deal of research going on to better understand the genetic causes of FSHD and the role of *DUX4*.

Why are some family members more severely affected than others?

Severity of symptoms and age of onset are influenced by various genetic and nongenetic factors, including the D4Z4 deletion size, methylation of the D4Z4 region, and *SMCHD1* mutations. These and other as-yet unknown factors are active areas of research. At this time, it is not possible to make predictions about severity, progression, or age of onset for an individual based on their genetic test result.

Someone who has a family risk of FSHD but has no symptoms currently might have difficulty getting insurance coverage for the test. What can they do?

Again, I really recommend that you work with a genetic counselor or neuromuscular specialist who is willing to go to bat for you with your health insurance company. If your insurance won't cover the test, you could consider paying out of pocket.

Does everyone with the FSHD "mutation" develop symptoms?

No, not everyone with an FSHD-associated genetic change (FSHD genotype) will show symptoms of FSHD. Based on current knowledge, it is estimated that about 80 percent of individuals with the FSHD genotype will show symptoms, whereas 20 percent will be asymptomatic. We don't know why some people show symptoms and others do not. There likely are other genetic and nongenetic factors playing a role. Importantly, if you have the FSHD genotype but are asymptomatic, you can still pass it on to a child who may show symptoms. Also, keep in mind that some people may have very subtle signs of FSHD that can only be noticed by a doctor, or their symptoms may not become apparent until later in life.

If someone without symptoms has a close family member with FSHD, what is their risk of also having FSHD?

FSHD1 is inherited in an autosomal dominant pattern, which means that children of an individual with FSHD1 have a 50 percent chance that they inherited the FSHD1 genotype. Parents of an individual with FSHD1 may have the deletion, or the deletion may have occurred new (de novo) in the affected individual. The risk to siblings of an individual with FSHD1 depends on whether the deletion was inherited from a parent (in which case the risk is 50 percent that the sibling has the FSHD1 genotype) or de novo (in which case there still is a risk to the sibling, due to the possibility of germline mosaicism, meaning that the deletion could be present only in a parent's egg or sperm cells). Because people can have the FSHD genotype but not manifest symptoms, the only sure way of knowing one's risk is by genetic testing.

NOTE

Read the full "FAQs about genetic testing" article online at *fshdsociety.org/faqs-about-genetic-testing/*.

Flying for science

FSHD fuels this college student's passion for research

BY BELINDA MILLER, MANASSAS, VIRGINIA

Picture this: fruit flies buzzing kamikaze style into a polycarbonate tube coated with a sticky substance akin to the stuff one finds on fly tape. No, that's not the beginning of some sci-fi novel or movie. These fruit flies are medical marvels. "Blech!" you say. "Fruit flies are nasty little pests!" Except in the laboratory of a remarkable, 20-year-old rising senior at Pennsylvania's Lehigh University, Russell Caratenuto.

Brilliant, talented, funny, and an aspiring doctor, this young man has everything going for him, and he happens to have FSHD. The disease began with weakness in his arms and a growing inability to continue in high school sports. He was diagnosed at age 15 by Dr. Day-Salvatore at St. Peter's Hospital. As Russell's arms progressively weakened, he strengthened his body through a tedious workout regimen and enabled himself to letter in volleyball his junior and senior years. While still in high school, he organized a fundraiser with the help of the volleyball team and the FSHD Society.

Having graduated from high school as president of the National Honor Society, he entered college, where his interests widened. He decided to use his disease not as a crutch but as an opportunity, a way to give back through his passion for science.

Russell has been experimenting with fruit flies at Lehigh in the laboratory of Daniel Babcock. Amazingly, the flies have 60 percent genetic similarity to humans, but they don't have the FSHD DUX4 protein. Using fruit flies that had the *DUX4* gene artificially put into them, Russell is measuring the effects of *DUX4* on the way other genes are expressed and lead to cell death. When the flies are ready to fly, they are released into those sticky little tubes, where he measures how far they can travel before they get stuck.

Russell Caratenuto in his lab at Lehigh University.

Russell's exuberance is contagious. Even though he is burdened with this disease weakening his arms and scapula, and atrophying his chest and upper back muscles, when I asked him, "What do you see and hope to be able to do?" he answered, "I see a problem that needs solving. I hope to be a part of the solution by attending medical school and becoming a physician who treats FSHD and other muscular dystrophies."

"Are you letting your diagnosis affect your dreams?" This gifted young scientist answered, "It does, but in a positive way. I use my diagnosis as motivation for myself to make a difference in the field. While the disease has brought its fair share of challenges and battles, it has also fueled me with passion."

Whether you are in our FSHD community or not, simply knowing this brilliant young man is out there working to affect all of our lives is enough to give us hope that a cure for FSHD will be found.

So the next time you see those buzzers flying around a piece of fruit, thank them for their sacrifice. Their family members, after all, are flying for a cure.

FSHD Connect – a game changer

BY JENNIFER EGERT, PHD, NEW YORK CITY

After being involved with the FSHD Society for more than 10 years, participating in fundraisers, social media, and events, I finally made it to the FSHD Connect meeting in 2018 in Las Vegas.

It's sort of ridiculous that I hadn't gone until then, especially when the Society is headquartered in Massachusetts, so close to my home in New York City. I'm not sure what kept me away. The effort of travel. The expense. The feeling that there was nothing to do about this disease, anyway, so why take a weekend talking about it?

Attending the Las Vegas meeting was a game changer.

It is quite something to be in a room with so many people who look like you! Though I come from a family of people with FSHD, meeting so many new faces with similar features and bodies immediately gives a sense of community. On the flip side, you also see great diversity in the ways people experience, adapt, and live with the disease. So many conversations gave me ideas about new ways of managing my own mobility issues and new perspectives on coping.

Being able to offer the community my own experience as a psychologist and mindfulness teacher in workshops and breakout sessions was a highlight and inspired me to do more to give back. And simply having drinks or a meal with new friends who understand what living with FSHD is all about, either as caregivers or patients – I'm so grateful to have had these moments.

Perhaps the most powerful aspect of attending the FSHD Connect meeting was the inspired energy generated by the FSHD Society staff, the researchers, and patients coming together in a positive, active, purpose-driven way. The enthusiasm researchers had for listening to patients' experiences, which helped them to understand what outcome measures they need to look at in future research. The sharing of the incredibly exciting time we are in when it comes to developing therapies to treat and cure FSHD. Listening to a panel of eight researchers: four working to arrest disease progression and four studying ways to rebuild muscle. Getting to know the people working to cure this illness and those behind the day-to-day running of the FSHD Society.

These are all such strong impressions that left me hopeful, energized, and excited for what is to come – and with a strong desire to be a part of making the cure happen.

So I hope you come to the 2020 FSHD Connect in Washington, DC. Especially if you are discouraged. Especially if you don't feel like it will be worth the effort. You won't regret it.

Register for FSHD Connect at *fshdmeetings.org/2020pc*.

"The enthusiasm researchers had for listening to patients' experiences helped them to understand what outcome measures they need to look at in future research."

— JENNIFER EGERT

The 2020 FSHD Connect will be held on June 27-28 at the Washington Hilton in Washington, DC.

$4.6 million raised in 2019

The FSHD Society's 2019 fundraising total blasted through previous records, thanks to the combined efforts of our major benefactors and our grassroots "army of activists." Our fundraising events alone raised more than $900,000. This outpouring of support means that we will be able to push forward on all of our strategic initiatives in 2020, including the Therapeutic Accelerator and the Voice of the Patient Forum on Drug Development. We will expand the Clinical Trial Research Network to four new US sites and add more local members to our national chapter program.

For all that you make possible, THANK YOU!

Our 2019 fundraising events activated hundreds of new participants and donors. Dan Levy's Omaze campaign alone raised almost $250,000.

FSHD Telethon *fshdsociety.org/2019/12/14/telethon/*

Listen to our GivingTuesday Telethon interviews. Streamed over Facebook Live, our telethon host Tim Hollenbeck interviewed dozens of leaders in our community – activists, celebrities, scientists, doctors, people doing awesome things – to raise worldwide awareness of FSHD. Their stories were utterly compelling, and the sense of optimism for a treatment in the near future was palpable.

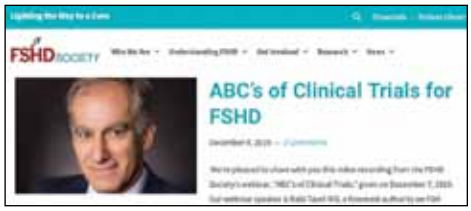
The future begins with you

On January 25, dozens of chapter directors and Walk & Roll leaders gathered in Chicago at our annual Volunteer Leadership Summit. Taylor Quigg from the Greater Philadelphia Chapter summed up the impact this way: "When I look at this photo, I see people living with FSHD, I see spouses, caregivers, family members, Society members. Most of all, I see a family of people who are a FORCE!! The 2020 Leadership Summit was fantastic, and I cannot wait to see all that happens this year because of the work that was put into this weekend!"

On the web *fshdsociety.org/blog*

Fulcrum's approach to treating FSH muscular dystrophy (video). Michelle Mellion, MD, medical director at Fulcrum Therapeutics, discusses the Cambridge biotech's approach to treating FSH muscular dystrophy.

ABC's of clinical trials for FSHD (video). Rabi Tawil, MD, a leading authority on FSH muscular dystrophy, explains the clinical trial process by which potential therapies are validated and approved by the FDA. You'll learn what Phase 1, Phase 2, and Phase 3 trials are. He lists questions for patients to ask themselves when considering whether to volunteer for a trial, and describes some of the special considerations the FDA gives for orphan indications like FSHD.



FSHD goes to school (video). With eight-year-old Katelyn Zwickau, researchers at Fulcrum Therapeutics, and Lexi Pappas (an amazing filmmaker who has FSHD herself) set out to create an educational presentation and video that FSHD-affected families could use in school and camps to bring a deeper understanding to the disease.

Upcoming

Visit *fshdsociety.org/fshd-events-calendar/*.

CONFERENCES

April 21, Hyattsville, MD, and by webcast
Voice of the Patient Forum

June 25-26, Washington, DC
27th International Research Congress

June 27-28, Washington, DC
FSHD Connect

WEBINARS

April 14, Preparing for the Voice of the Patient Forum
James Valentine & June Kinoshita

June 3, Stem cell research
Rita Perlingeiro, PhD, University of Minnesota

August 5, Scapular surgery
Anthony Romeo, MD

FUNDRAISERS

March 7, Annapolis, MD
Pickin' for a Cure

April 19, Naples, FL
Performing for a Cure

July 11, San Diego, CA
San Diego Walk & Roll to Cure FSHD

September 12, Castle Rock, CO
Colorado Walk & Roll to Cure FSHD

September 12, Barrington, IL
Chicagoland Walk & Roll to Cure FSHD

September 12, Dublin, OH
Columbus Walk & Roll to Cure FSHD

September 12, Chesterfield, MO
St. Louis Walk & Roll to Cure FSHD

October 3, Madison, CT
Connecticut Walk & Roll to Cure FSHD

WALK & ROLL TO CURE FSHD

VIRTUAL MEETINGS

Open to all!

FSHD Society Radio
First Wednesday of every month at 9 p.m. ET | 8 p.m. CT | 7 p.m. MT | 6 p.m. PT via Facebook Live. Podcasts are recorded and available in the video section of the FSHD Society Facebook page.

Connecticut Connections
Open to all New Englanders (and beyond), this chapter meets via web conference on the first Thursday of each month (except in summer), 7-8:30 p.m. EST.

Wisconsin Chapter Virtual Meetings
Serving not only Wisconsin but also Michigan and Minnesota, this chapter meets via web conference on the first Monday of each month at 8-9:30 p.m. CST.

Western Washington FSH Community
Meets via web conference on the fourth Saturday of each month (except in December), 10 a.m. PST.

Spring into action! $100,000 matching gift challenge

If we deliver on our promise to have therapies to our families by 2025, it will be because of your donation today. With your support, this year we will:

- speed up the development of a new, better genetic test and blood-based biomarkers for clinical trials;
- make sure patients' voices are heard by the Food and Drug Administration;
- continue to grow our national chapter program to bring hands and hearts to more families and unite our community around our goal of treatments by 2025.

A group of visionary leaders has pledged to match up to $100,000 in gifts made by May 31, 2020! We are so grateful to them, and to you!

TAKE ACTION:

- Donate at *fshdsociety.org*.
- Mail a check to FSHD Society, 450 Bedford Street, Lexington, MA 02420.
- Call (781) 301-7301.

FSHD Advocate

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VOICE OF THE PATIENT FORUM YOUR ROLE IN DRUG DEVELOPMENT

April 21, 2020

This is your opportunity to educate the FDA on how FSHD has impacted your life.

Your input will result in a *Voice of the Patient Report*, which will be submitted to the FDA for inclusion in the framework used to evaluate future FSHD therapies. Your views carry great weight with the agency. We encourage everyone – patients and family members, at every stage of disease progression – to participate. Ways to be involved are below.

SURVEYS (YOUR INPUT)

Read your emails and respond to surveys before the event. Your answers to pre-meeting surveys guide the discussion on April 21 and help to shape the final report.

LIVE WEBCAST (ANYONE CAN JOIN)

Register for the live webcast to listen to speakers and respond to questions in real time on April 21. After you register, watch your inbox and check your spam folder.

IN-PERSON (LIMITED SPACE)

You must register in advance for a spot at the live event in Hyattsville, Maryland. Please let us know if you must cancel so that people on the waitlist can be notified.

Registration and details at **FSHDSociety.org/VOPF**