PEN

inside

Volunteering for a Gene Therapy Clinical Trial?

Paul Clement

This year marks three decades since the *New York Times* headline first promised a cure for hemophilia through gene therapy. Though the concept of gene therapy appeared simple—introduce good copies of a gene into the body to make factor—accomplishing this goal safely has proven extraordinarily complex. But now? We're finally on the cusp of commercially available gene therapies for hemophilia, with the first wave of therapies expected in the US market possibly as soon as 2020.

But to make gene therapy a reality, biotech companies involved in this research need our help: they need people with hemophilia to volunteer to participate in clinical trials.

You've probably heard of clinical trials—the testing of medical interventions, such as drugs or medical devices, on people. Perhaps you were asked by your doctor whether you'd like to participate. Clinical trials help researchers determine the safety and effectiveness of a drug, and your participation may benefit you directly, plus help others if the drug is later approved by the US Food and Drug Administration (FDA).

But the decision to participate in a gene therapy clinical trial shouldn't be taken lightly. All clinical trials have risks and benefits. What should you look for when deciding? What questions should you ask?

The Drug Approval Process

To understand where you—a potential patient volunteer—would fit into the development process of a drug or therapy, you need to know a little about the research and approval process for drugs. In the US, it takes about 12 years for an experimental drug to make its way from the laboratory through the approval process to your medicine cabinet. Most drugs don't make it: only about 1 in 5,000 drugs ever gets to market. In the US, drug candidates follow this development and approval process governed by the FDA:

Discovery and Development: *The first step in identifying promising candidates for drugs or therapies*. Potential drugs are identified, tested, and screened for their effect on a particular disease

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welcome

A cure by year 2000… Remember that cover article from 1990? Many of us older parents do, and we were lulled into thinking a cure was coming soon. Ten years went by, then 15, and some of us almost gave up hope. But in the meantime, we had great new therapies available, prophylaxis became the standard, and our community grew strong and connected.

But a cure is coming now. Clinical trials are showing great results, and many trials are underway. Recently, I learned that two colleagues in the hemophilia community are participating in those trials. What brave men they are! It made me wonder: What compels someone to become a volunteer for a clinical trial? What questions did they ask themselves, and their doctors? How did they arrive at their decision? What are their concerns?

We decided to explore those questions. We want to give you the information you need in case you're considering joining a clinical gene therapy trial for hemophilia. The companies researching a cure need volunteers. But if you consider joining, make sure you read Paul Clement's feature article first, and learn the right questions to ask.

Not everyone is enthusiastic about gene therapy. Read Jeff Johnson's piece to appreciate an alternative view to gene therapy—and why someone might not be thrilled to no longer have hemophilia.

And if you know anyone participating in gene therapy trials, thank them. Like our veterans in wartime, they are fighting on the front lines so that one day, we can all enjoy more freedom. Freedom from health issues. Freedom to live our lives pain-free and bleed-free. We are so grateful!

Brave men are all vertebrates; they have their softness on the surface and their toughness in the middle. — G. K. Chesterton

Laurie Kelley

inbox

BACK IN THE DAY (2003) WHEN my boy was born, LA Kelley Communications' books pretty much saved me. No Facebook, and the nearest chapter over 250 miles away. I love that the newer generation of moms has access to much stronger support systems and resources.

Cheryl Ashmore
MAINE

WITHOUT THESE BOOKS, I THINK I'd be lost. They help me when I'm feeling down or frustrated. It's also a great way to get a better understanding of what my boys are going through so I can help them through it as well.

Casey Leigh Miché
UTAH

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In the past, it was incorrectly believed that only men could have hemophilia, and women with the gene were labeled asymptomatic "carriers." It's now recognized that women are not just carriers of hemophilia, but can also have hemophilia and experience symptoms if less than 50% of their factor is active. Most diagnosed patients are male. For editorial simplicity in PEN articles, when we refer to a person with hemophilia, we may alternately use "he," "she," or "they."

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as i see it

Jeff Johnson

Gene Therapy? Not For Me

"Your scientists were so preoccupied with whether or not they could, they didn't stop to think if they should."

–Ian Malcolm, Jurassic Park

When it comes to hemophilia gene therapy, I'm a skeptic. My skepticism runs along a few avenues: personal philosophical objections relating to the very nature of being a hemophiliac; skepticism of the technology itself when dealing with altering the genetic code of living beings; and the effects and costs of a cure in relation to the needs of hemophiliacs worldwide who don't even have access to factor and may be left without access to such a cure, or even basic treatment.

I am a hemophiliac. I bristle when told—most often by someone who doesn't share my condition—that I am "a person with hemophilia." Thanks, but no. I am most certainly a hemophiliac. There is not me, and then my hemophilia floating next to me, present but not part of me. Hemophilia is me, and I am hemophilia. I was born this way, I live this way, and I'll die this way. While it has indeed been a painful, challenging, and rough road at times, it has also been a rewarding and defining part my life. I am the man that I am because of it. To separate me from my hemophilia would be to separate me from a major part of my identity, as much as if I were no longer a musician, or left-handed, or a husband and father, or an obsessive Star Wars fan. I don't wish to be anyone other than me. That means accepting, and even embracing, the condition I was born with, and which has charted much of my life's path, including the people I have known, jobs I have held, my community involvement, and even my passions for music and writing and travel. I can't imagine a life without the people I have known and loved, the experiences I have had, the sense of purpose and determination I have grown up with, and the strength and resilience I developed in order to survive. All of those things are the result of having been born a hemophiliac. So I am not inclined to pine for a life without hemophilia—not now, not in my past, not in my future. There isn't a "cure" for who someone is; so for me, there can be no "cure" for hemophilia that isn't also a "cure" for "me."

Looking at the science of gene therapy, I'm not convinced that it will ever even be truly possible. Gene therapy has been a promise lying just over our horizon since I was a child. If you have followed the development of this elusive cure, you know that results have never been as promising as we have been told. Pop culture tells us that a gene is an on/off switch, and, if you can figure out how to flip it, you can simply turn on or off a certain trait: the color of one's eyes, one's metabolism, or having hemophilia. But the reality is more complex than that, and science has yet to determine just how independently our genes work. We may end up flipping off the hemophilia "switch" someday, but what if flipping it also unexpectedly turns off something else important, such as our ability to make fibrinogen, or factor VII or platelets, or even the liver's ability to regenerate? Is possible liver failure a worthwhile risk of "curing" hemophilia? Speaking of the liver, its ability to regenerate is one of the human body's greatest attributes. Hemophilia gene therapy involves altering the liver so that it produces clotting factor, but what happens if the liver's ability to regenerate—essentially becoming a new liver every few years—results in a hemophiliac reverting to being a clotting factor deficient hemo again after 10 years of not dealing with the disorder? Gene therapy can't, as far as we know, be given again, so hemos would suddenly have to resort to factor to treat bleeds again. Is that really a "cure"?

Personally, I think not, especially considering alternatives. Factor replacement therapy for hemophilia has improved so drastically in my lifetime that it's nothing short of miraculous. In four decades, I've progressed from cryoprecipitate infusions that took hours and helped little; to clotting factor concentrates

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Cazandra Campos-MacDonald

Show and Tell: Disclosing a Diagnosis in the School Setting

School's in session! And with the start of a new school year comes a question for the principal: "When can I meet my child's teachers to discuss his hemophilia?"

I feel a sense of apprehension at the beginning of each school year, as I find my notes and instructions for emergency care, and determine the basic information I need to cover, including my youngest son's connection to the disorder. Every piece of information I give the school paints a broader picture of my son's struggles as he lives with hemophilia and an inhibitor. Disclosing information about hemophilia and inhibitors prepares my son's principal, teachers, and caregivers in the event of a bleeding episode.

Disclosing your child's bleeding disorder allows the educational team at the preschool, elementary, middle school, and high school levels the opportunity to provide the necessary support to empower your child's learning and well-being.

When your child is a preschooler, you are responsible, as parent or guardian, for informing the school of his or her bleeding disorder. Meeting with the teacher and staff may be nerve-wracking, so reach out to your hemophilia treatment center (HTC) for guidance. The balance between educating and frightening a teacher can be tricky, but if you stay positive and approachable, and encourage questions, you can establish a healthy and open relationship.

Both of my sons attended daycare before entering elementary school. My husband and I provided in-service to the principal and teachers directly involved in our sons' care. I emphasized how important it was for teachers and staff to call us after an injury occurred. I told them that I preferred they call me right away to report an incident, instead of waiting until the day was over. If they wanted either of us to come to school to check on our son, we would drop what we were doing and arrive as soon as possible. If an accident did happen, it usually wasn't necessary to give my son an extra infusion or take him to the HTC. After a few weeks of reassuring visits to the school, or talking through the incident over the phone, the calls from the school clinic became fewer. We made the school staff comfortable, insisting that we would not place blame on anyone, but we were prepared to teach and treat as necessary.

As children get older, it's important to allow them to become involved in their own care. In the early elementary years, you will continue to disclose and educate school staff about your child's bleeding disorder. But when your child can verbalize his condition, it's time to let him speak with adults and classmates about his bleeding disorder. This gives him the chance to take control. When my youngest son, Caeleb, was in first grade, I came to his classroom to read the story *Joshua, Knight of the Red Snake*, by Laureen A. Kelley. The story is about a preschooler with hemophilia. Many of the children had never heard of hemophilia, so reading about this young boy living with a bleeding disorder, and close to their age, made Caeleb's condition more understandable. *Joshua* offers an excellent way to engage children and allow them to ask questions. Caeleb answered his classmates' questions, and disclosing his hemophilia became a positive experience. During the year, when Caeleb missed school due to bleeds and often returned in a wheelchair, his friends were very empathetic and understood that he needed some extra help. Seeing these young children rally around their friend was an experience that any parent would be grateful for.

Once your child reaches middle school, your role may begin to change. I have made it a point to contact the nurse and principal at the beginning of each school year during middle school. Because my youngest son has a 504 Plan[1] in place, I meet annually to review changes that need to be made in Caeleb's 504 Plan, and to discuss medical limitations related to hemophilia. I have also included Caeleb in these meetings starting in sixth grade. He doesn't say much, but sometimes teachers will ask him questions, and this allows him to be actively involved in his care. I emphasize that disclosing his condition is up to Caeleb. It's not the place of the teacher to tell any students about his hemophilia. Fortunately, Caeleb keeps the people

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1. Section 504 of the Rehabilitation Act of 1973 (PL 93-112) is a civil rights law prohibiting discrimination against people with disabilities in any program or activity receiving or benefiting from federal financial assistance.

richard's review

Linda Weaver's Studio

Richard J. Atwood

Early Factor Concentrates

Most historical reviews of hemophilia treatments, especially those found in timelines, do not include medical developments between the increased use of plasma, starting in the 1930s, and the discovery of cryoprecipitate, in 1964. This omission disturbs me because of the significant medical advances made during that time. Those improvements laid the groundwork for the eventual introduction of factor concentrates, and, sadly, foreshadowed future problems.

Fraction I and Its Derivatives

During the 1930s, Edwin J. Cohn, a chemist at Harvard Medical School, created an ethanol-water system to separate proteins in plasma. This process is called *plasma fractionation*, meaning that plasma is separated into its component parts. For bleeding disorders, the goal is a purer form of the isolated factor proteins. Cohn even built a pilot production plant in 1941, mainly to isolate human albumin. The American military, especially the Navy, was interested in albumin production while preparing for war. Luckily, albumin was available when Pearl Harbor was bombed. Albumin saved the lives of many burned servicemen.

Cohn's plasma fractionation, or what he called *cold ethanol precipitation* of pooled human plasma, resulted in several fractions. The notable one for bleeding disorders was Fraction I, containing 85% fibrinogen and factor VIII activity. This product, having about 35% of factor VIII activity of normal plasma, proved more effective than plasma for treating hemophilia. During World War II, six pharmaceutical companies,[1] plus Cohn's plant, fractionated human plasma mainly for its albumin, while Armour fractionated bovine and human plasma.

After the war, two companies, E.R. Squib & Sons and Cutter Laboratories, produced Fraction I. The Squib product was handled by the American Red Cross, which distributed it, after approval by a national commission, to medical researchers and hematologists. The Cutter product was commercially available. Treatment for hemophilia came in 200 mg vials of powdered Fraction I that were mixed with 10 cc saline solution for intravenous injection. This regimen, with its ease of administration, continues today with factor concentrates. Yet it began with Fraction I.

Despite being therapeutically effective, problems with Fraction I included limited supply, unpredictable potency, expense, and potential inhibitor formation. By 1966, the company Merck Sharp & Dohme commercially produced factor VIII–rich Fraction I that cost $35 for each 2 g in a vacuum bottle, which was expensive. For 15 years, Michigan State Laboratories, in the Michigan Department of Health in Lansing, produced a Fraction I product just for Michigan residents. The threat of blood-borne disease transmitted by Fraction I became real when multiple cases of hepatitis infection were reported.[2]

Fraction I wasn't just an American product. Like Cohn in America, Ralph Kekwick in England developed an ether Fraction I (probably for patent reasons). In England and Wales, the Blood Products Laboratory at Lister Institute in Elstree produced an ether Fraction I that was not for sale; the SouthEast Scotland Regional Transfusion Centre in Edinburgh did the same. The UK product increased its potency three to five times, or about twice the American product.

In Stockholm, Sweden, Margareta Blomback and Birger Blomback at the Karolinska Institute modified Cohn's alcohol fractionation for an even better product, Fraction I-O. The factor VIII concentration and purification increased 25 to 50 times. Fraction I-O was produced in Canada by Connaught Laboratories, in France by the Centre National de Transfusion Sanguine, and in Australia by the Commonwealth Serum Laboratories. Even Argentina, Holland, and Switzerland produced some form of Factor I. This was truly a worldwide phenomenon.

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1. The six pharmaceutical companies were Lederle Laboratories, Upjohn Co., Eli Lily Laboratories, E.R. Squib, Cutter Laboratories, and Sharp and Dohme. 2. The first known hemophilia treatment to be recalled because of hepatitis transmission was a fibrin foam and thrombin first developed in 1943 for the US Army by Cohn as a hemostatic to be used in battlefield surgery. The commercial fibrin foam and thrombin produced by Upjohn Laboratories was effective in treating lacerations and tooth extraction in patients with hemophilia before being withdrawn by 1950 due to hepatitis contamination.

Could a Cure for Hemophilia Be Personalized?

Laurie Kelley

Has your hematologist ever asked that your child have pharmacokinetic (PK) testing? Chances are, the doctor wants to know how factor behaves in your child's body, so factor dosing can be tailored to get the maximum factor coverage on your child's most active days. *Personalized medicine* is the tailoring of medical treatment to your individual biological characteristics, and to your lifestyle, for the best therapeutic results. Personalized medicine in hemophilia often refers not only to when you dose with factor concentrate, but also to PK testing to discover your child's half-life—how long factor lasts in his body—so you can choose the right dose, dosing schedule, and product.

In this issue of PEN, we focus on gene therapy, which may be available commercially in the next few years. Is it possible that gene therapy—or any form of a cure—could be personalized to meet the needs of individual patients? To find out, we asked the experts at three biotech companies involved in gene therapy research: uniQure, Spark Therapeutics, and Sigilon Therapeutics.*

What About Gene Therapy Could Be Personalized?

Dr. Rogerio Vivaldi

Personalization for a cure in hemophilia starts with the hemophilia diagnosis. Dr. Rogerio Vivaldi, CEO of Sigilon, says, "Gene therapy is, by its nature, personalized to a patient's genetic profile. It seeks to deliver healthy copies of the specific gene that is dysfunctional in a given patient. The healthy genes are paired with a promoter that prompts them to express the specific enzyme, protein, or factor that the patient is missing. Restoring the balance in expression of that enzyme, protein, or factor should reduce or even eliminate symptoms and improve the patient's health." He adds, "However, it's important to note that these therapies aren't customized to individual patients. They are designed to cover all patients with a specific genetic mutation—for example, all patients with low factor VIII levels."

Clearly, the diagnosis matters, notes Dr. Leonard Valentino, Medical Strategy Lead at Spark Therapeutics. "We don't have a universal approach to apply to the diagnosis of hemophilia in general. There are differences in trials for hemophilia A and B." So your diagnosis will determine how your gene therapy might work.

Dr. Leonard Valentino

Another influence is factor levels. Danielle Day, PhD, director, Medical Science Liaisons, GlobalMedical Affairs at uniQure, "With gene therapy, we've identified the missing or altered gene, and can deliver a functional copy of it…but across *all* gene therapy studies, there appears to be variability in *how much* factor is produced."

Danielle Day, PhD

Challenges to Personalization

A major challenge to personalizing gene therapy is the "neutralizing antibody profile." That is, does the patient have an *antibody* (inhibitor) to the *vector* (the virus being used to deliver the gene therapy into the liver)? According to Vivaldi, more than 40% of patients who might benefit from gene therapy have preexisting antibodies to the vector. This makes them ineligible for treatment. Also, patients who have liver disease, as well as pediatric patients (who have rapidly growing livers), are ineligible for gene therapy.

"Right now investigational gene therapies are 'one and done,'" notes Valentino. "Currently you can't redose gene therapy after the initial dose, due to the neutralizing inhibitor. Maybe down the road, if you used an AAV8 vector and it didn't work, you could go back and try an AAV5 vector, but this is not really a reality right now in clinical trials. Currently, you can't personalize based on different vectors. You can only personalize based on your personal antibody profile. So we still need to resolve the redosing issue."

Another puzzle to solve is why some patients in clinical trials show higher factor level expression than others. Could this become an area of personalization someday? Could patients pick their gene therapy based on how much factor expression they want? "When using wild type factor IX," Day reports, "levels were increased but not to the near-normal seen with the hyperactive Padua factor IX gene. We were just trying at that time to

*Biomarin could not be reached for comment.

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Volunteering... from cover

and to determine if the drug has enough safety and drug-like properties to be entered into human testing. Drug candidates may be better versions of existing drugs, such as extended half-life factor products; or entirely new drugs, such as Hemlibra®. The screening process may involve testing hundreds to tens of thousands of potential drugs.

Preclinical Testing: *Extensive testing of promising drugs identified in Discovery and Development to determine if they're effective and safe enough to be studied in humans.* The goal of these tests is to help scientists understand how the drug works and what the potential side effects might be. The FDA requires extremely thorough preclinical testing before the candidate drug is allowed to move on to the next stage and be studied in humans.

Investigational New Drug (IND) Application: *A request for authorization from the FDA to administer an investigational drug or biological product to humans in clinical trials, and to ship the drug across state lines to clinical investigators and trial participants.* The FDA reviews IND applications to assure the safety and rights of trial participants and help assure the quality of the scientific evaluation. In some cases, an IND may not be needed. In others, the FDA may require additional information from the applicant (usually a drug manufacturer or potential marketer); the study is placed on "clinical hold" until the FDA receives the information.

Four Phases of Drug Trials

If the IND is approved, next come four phases of clinical trials (testing on humans):

Phase I studies assess the safety of a drug or device in humans. This initial testing phase can begin 30 days after an applicant has filed its IND, and may take several months to complete. The study usually includes a small number of healthy volunteers (20–100) who are generally paid for participating. For rare disorders such as hemophilia, there are fewer volunteers (usually less than 50), and for hemophilia gene therapy studies, fewer still (3–15). The phase I study is designed to determine the effects of the drug or device: how it's absorbed, metabolized (broken down by the body), and excreted. Phase I studies also investigate any side effects and adverse reactions (unwanted and unexpected negative reactions) that may occur as dosage levels are increased. About 70% of drugs pass phase I testing.

Phase II studies test the efficacy (effectiveness in a controlled setting) of a drug or device. This phase can last from several months to two years, and may involve several hundred patients, or just three for a hemophilia gene therapy clinical trial. For drugs targeting the general population, phase II studies are often randomized trials where one group of patients receives the experimental drug, while a second "control" group receives a standard treatment or placebo. Often, these studies are "blinded" or "masked": either (1) the participants don't know if they're receiving the experimental drug or a placebo (called a single-blinded or single-masked study), or (2) neither the participants nor the researchers know who has received the experimental drug (called a double-blinded or double-masked study). Masking the study is done to eliminate bias for the investigator and participants. Using two groups—the experimental group and the control (which provides a benchmark for comparisons)—allows researchers to give the applicant and the FDA comparative information about the safety and effectiveness of the new drug.

For hemophilia therapy research, placebos are not used, and the control group, if there is one, consists of patients on standard therapy, such as factor replacement therapy. Most hemophilia studies, including all current gene therapy studies, are also "open" (or "open label"): they are not masked, and both the researcher and participant know who is receiving what drug. Because hemophilia is a rare disorder and it's sometimes hard to recruit participants, phase I and phase II studies are often combined, with about 30 participants total for both trials, as opposed to fewer than a dozen for a single, independent study.

About one-third of drugs successfully complete both phase I and phase II studies.

Phase III studies are much larger, and may involve several hundred to several thousand participants, or 40–150 for hemophilia studies. This large-scale testing, which can last several years, gives the applicant and FDA a better understanding of the effectiveness of the drug or device, the benefits, and the range of possible adverse reactions. Of the drugs that enter phase III testing, 70%–90% will successfully complete it. Once the phase III study is done, the applicant (usually a pharmaceutical company) can request FDA approval for marketing the drug.

New Drug Application (NDA) is submitted to the FDA after positive results in clinical trial phases I–III. The applicant is required to supply extensive documentation telling the whole story of the drug. Then FDA officials examine the drug's safety and efficacy data, test samples, and conduct factory inspections to verify the finished product will be manufactured properly and quality controls are appropriate. The FDA also checks the drug's labeling for accuracy and thoroughness. After the FDA's review, it notifies the applicant that its NDA is either approved, would be approved if changes are made, or can't be approved due to unresolved problems. In some cases, the FDA may require additional studies, or may grant approval but require prolonged monitoring of patients. Applicants for generic drugs can skip the submission of preclinical and clinical data by applying for an **Abbreviated New Drug Application (ANDA)**, which requires only that the company submit data that the drug performs in the same way as the brand-name drug.

Biologic drugs (biologics) such as factor concentrates, gene therapy products, vaccines, and medical products from a natural source (human, animal, or microorganism) must apply for a **Biological License Application (BLA)** rather than an NDA. Among other differences, a BLA requires closer scrutiny of the manufacturing process and facilities, to prevent contamination by viruses or bacteria.

Once the NDA or BLA is approved, the drug is ready for marketing.

Phase IV studies, often called Post Marketing Surveillance/Report Adverse Events, are conducted *after* a drug or device has been approved for consumer sale. At this stage, pharmaceutical companies must (1) monitor for side effects, adverse events, and adverse reactions in a large patient population (because uncommon side effects may not show up in the smaller samples of phases I–III);[1] (2) compare the effectiveness of a drug with other drugs already on the market; (3) monitor a drug's impact on a patient's quality of life; and (4) determine the cost-effectiveness of a drug relative to standard therapies or other new therapies.

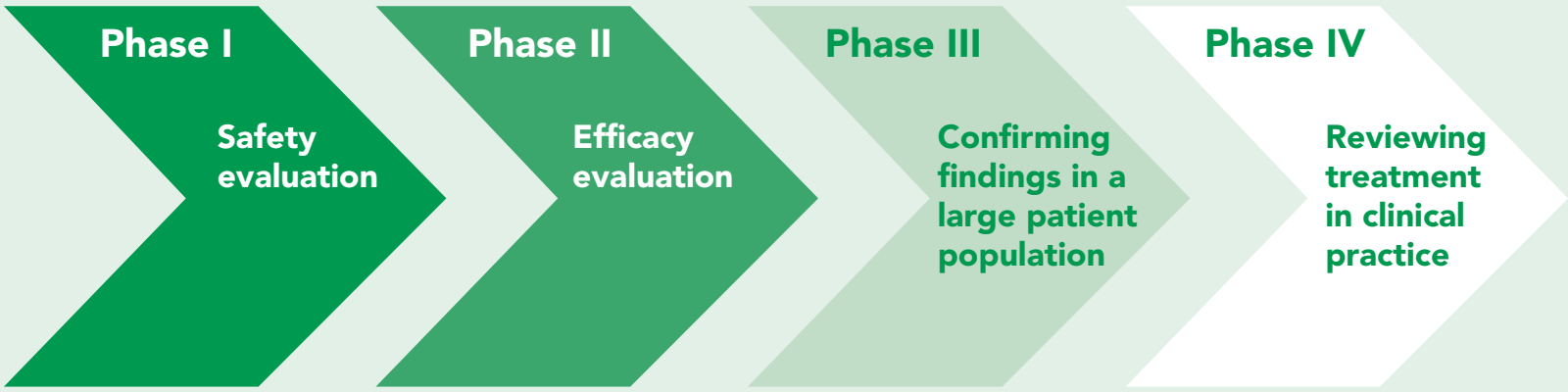
Phase IV studies can result in a drug or device being taken off the market or restrictions being placed on its use (such as the addition of a "black box warning"). By law, drug manufacturers must report all adverse reactions. But for health professionals and consumers, reporting adverse reactions is voluntary.[2]

Expedited Drug Approval

Although it takes about 12 years for an experimental drug to gain FDA approval, for drugs that qualify, the FDA has five programs to speed up the approval process. The FDA stresses that these programs don't alter the scientific or medical standard for approval or the quality of evidence required. Here's a list of the expedited FDA drug approval programs:

1. Although often used interchangeably, the terms side effect, adverse event, and adverse reaction mean different things. An adverse reaction is a response to a drug that is "noxious and unintended" at normal doses. An adverse event is a response to a drug–usually an unwanted, unexpected negative reaction–that may, or may not, be related to use of the drug. A side effect is an imprecise term used to describe known effects (usually negative) of a drug occurring at normal dosages. Side effect usually describes mild responses to a drug, while more severe responses would be called adverse reactions. For example, a vaccine may have side effects of soreness and swelling where the shot was given. A severe rash as a result of a vaccination would be an adverse reaction. 2. Adverse reactions can be reported to MedWatch, the FDA's Safety Information and Adverse Event Reporting Program: www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program.

Clinical Trial Phases



Adapted from "Understanding Clinical Trials," Roche, 2013, pdfs.semanticscholar.org.

Fast Track: Speeds the development and review of drugs that treat serious conditions and "fill an unmet medical need" (a condition that isn't treated adequately by available therapy). Benefits include more frequent meetings and written communications with FDA, and "Rolling Review": a drug company can submit completed sections of its BLA or NDA for review, rather than waiting until every section of the NDA is completed before review.

Breakthrough Therapy: Speeds the development and review of drugs found to be more effective for a certain condition than other drugs currently on the market. A drug that receives Breakthrough Therapy designation is eligible for all Fast Track designation benefits as well as intensive guidance from the FDA on designing an efficient drug development program (beginning as early as phase I).

Accelerated Approval: For drugs that fill an unmet medical need and have evidence of potential clinical benefit. Accelerated approval relies on "surrogate endpoints," indicators of a clinical benefit, but not necessarily proof. For example, a cancer drug under development is found to substantially shrink tumors (surrogate endpoint), but it's not known yet if the drug extends the patient's life (clinical benefit). Under Accelerated Approval, the drug would be approved for marketing based on its ability to shrink tumors; but in phase IV clinical trials, the drug would have to show a clinical benefit (extending life). If the phase IV trials don't show a clinical benefit, then the drug's approval would be withdrawn.

Priority Review: A commitment by the FDA to make a decision on a drug application within 6 months, compared to 10 months under standard review.

Regenerative Medicine Advanced Therapy (RMAT) Designation: the newest approval designation. Designed for gene or cell therapies that treat, modify, or cure a serious disease or condition, and that show preliminary clinical evidence that the product may address an unmet medical need. RMAT includes all the benefits of Fast Track and Breakthrough Therapy. But unlike Breakthrough, the RMAT designation doesn't require evidence indicating the drug may offer substantial improvement over available therapies.

Given that hemophilia is rare, with many "unmet medical needs," hemophilia therapies, including gene therapy, almost always qualify for one or more of these expedited approval programs. That means the approval process for hemophilia therapies is usually a lot shorter (possibly years shorter) than for the average drug, because trial applicants can take advantage of these special FDA programs. All novel hemophilia therapies, including gene therapy, have or will be using multiple FDA-expedited review programs to gain faster approval.

Why Do People Volunteer for Clinical Trials–Or Not?

This varies with the type of drug being tested, the phase of clinical trial, and the targeted patient population. For example, the motives of a healthy person looking to make some extra money by participating in a clinical trial will vary significantly from those of someone diagnosed with an incurable form of cancer.

In surveys of people who have participated, the top three reasons for volunteering for any clinical trials are "to help advance medicine," "to help improve the lives of others," and "to help improve my condition." Also mentioned are "to earn extra money," and "to receive free medical care." Fernando Rivera, a young man in California who is participating in a gene therapy trial, shared similar reasons: "to help improve the lives of others," and "to help improve my condition."

Why do people *not* participate in clinical trials? One of the main reasons may be simply not knowing about available trials. Another reason is fear of being injured by the treatment, or of receiving a placebo ("sugar pill") instead. Another is cost: Will my insurance pay for any additional tests associated with the clinical trial? Will I be reimbursed for travel and time? Another reason is inconvenience: How far is the nearest participating center from my home? Will I have to spend time in the hospital? How often will I have to travel? These are legitimate concerns. For example, Fernando was required to (1) spend a day in a hospital after receiving the therapy; (2) visit the center weekly for a year, and bimonthly the year after that; and (3) agree to be followed for five years or more.

How Do I Find a Clinical Trial?

Although most people, like Fernando, are asked by their physician to participate in a clinical trial, some may want to

search for a clinical trial on their own. The most comprehensive source of information on clinical trials is ClinicalTrials.gov, a large database maintained by the US National Library of Medicine, part of the National Institutes of Health. ClinicalTrials.gov has detailed information on 313,471 research studies in all 50 states and 209 countries. Currently, 10 US hemophilia gene therapy trials are recruiting, or will be recruiting, volunteers. Six of these are phase I/II trials enrolling 10–30 patients each, and four are phase III trials, enrolling 40–130 patients each. The website also has information on another five studies underway but not recruiting, and information on many more studies that have been either completed or terminated before completion. At least one more hemophilia gene therapy trial is expected to open by the time this issue of PEN is published.

The ClinicalTrials.gov website provides data on the purpose of each study, the kind of gene therapy being used, the location of participating centers, the number of participants enrolled, and whether the trial is "open" or "masked." If you want to participate in a clinical trial, read the section called "Eligibility Criteria," which has two lists: "Inclusion Criteria" and "Exclusion Criteria." These are lists of specific requirements for who can, or can't, participate in the trial. They're designed to help reduce "confounding variables" (factors that may make it harder to track the effects of a drug), and to help ensure the safety of participants.

For example, for hemophilia gene therapy trials, inclusion criteria often require participants to be male, adult, have severe hemophilia (A or B, depending on the trial), and have no inhibitors. Exclusion criteria often include having active hepatitis infection, liver disease, HIV with low CD4 counts, or having participated in another gene therapy trial within the previous year.

The eligibility criteria may differ for different trials, so don't assume you don't qualify for all trials just because you don't qualify for one trial. For example, most gene therapy trials exclude people who have preexisting immunity to the viral "vector" to be used in the gene therapy transfer process; but one company (uniQure) will accept participants with low antibodies to the vector used in its therapy.

Joining a Gene Therapy Trial: Questions You Should Ask

Participating in a clinical trial shouldn't be a simple yes-or-no decision. Do some basic research about the study, so you can ask informed questions and understand the answers. Enlist the help of your hematologist in making the decision. If your hematologist is the one who asked you to join the trial and is part of the study team, get a second opinion from a doctor who's not part of the study. Experts say it's important to get the following general information when considering participation:[3]

- Why is this study being done?
- Who will be in charge of my care? Will the researchers work with my hematologist and hemophilia treatment center (HTC)?
- Who will I contact if I have problems, questions, concerns?
- How will the therapy be given?
- Will I have to be in the hospital for any parts of the study? If so, how often, for how long, and who will pay for it?
- If the study is only being conducted in certain areas, will I have to travel? How often? For how long?
- What side effects might I expect from the study treatment? Are there other risks?
- Will insurance cover the cost of the trial?
- If there are costs not covered by insurance, will the trial sponsor cover them?
- How long will the study last?
- Is long-term follow-up care part of the study? What would it involve?
- If I am harmed as a result of the research, what treatment will I be entitled to?
- Are there others currently participating in the trial that I can talk to?

3. List of questions to consider before participating in a gene therapy clinical trial adapted from American Cancer Society, www.cancer.org.

- Will I be able to find out about the results of the study?
- How long do I have to make this decision?

Answering your questions is part of the *informed consent* process, which requires researchers to give you, as a potential participant, enough information to allow you to make an *informed* decision about participating. (If you decide to participate, you'll be asked to sign an informed consent form as proof that this process took place. Signing the form isn't a contract—you can leave any clinical trial at any time.)

Informed consent is part of the protections for people participating in clinical trials codified in the 1981 Federal Policy for the Protection of Human Research Subjects, also known as the Common Rule (which was revised in 2019 for the first time since 1991). The Common Rule also governs Institutional Review Boards (IRBs, also known as independent ethics committees), which are charged with ethics oversight of human research. IRBs are committees within a university or other organization receiving federal funds to conduct research. IRBs review research proposals involving humans in order to protect the rights and safety of people who take part, before the research starts and as it proceeds. IRBs are responsible for ensuring that informed consent has taken place. Most, but not all, clinical trials in the US are approved and monitored by an IRB to ensure that the risks to participants are minimized and potential benefits outweigh the risks. You should ask the sponsor or research coordinator whether the study you're thinking about joining was reviewed by an IRB—if not, this is a red flag.

Gene Therapy Approaches

The goal of hemophilia gene therapy is to get many functioning copies of a gene into the body, so it can then produce functional factor VIII or IX on its own. Ideally, the person would then produce factor at high enough levels to eliminate the need for other therapies, such as factor replacement therapy. To accomplish this, researchers are taking one of three approaches, which sometimes overlap. Keep in mind that in popular media, the term "gene therapy" is often used to describe any of these three approaches:

1. *Gene therapy.* Adds functioning genes to a person's cells; in hemophilia therapy, the defective gene stays in place.
2. *Cell therapy.* Cells are taken from the patient or another source (such as embryonic stem cells), and a functioning copy of the gene is inserted into the cells. The cells are then grown to large numbers (tens to hundreds of millions), and then injected back into the patient.
3. *Genome editing.* Involves changing the DNA of a living cell. For hemophilia therapy, this might mean cutting out the defective gene coding for factor VIII or factor IX from the cell's genome, supplying the cell with a good gene, and then using the cell's DNA repair tools to insert the good gene into the place where the defective gene was cut out. This is the newest approach of the three.

Vectors: Getting Genes into Cells

Now comes the hard part: How exactly *do* you put a functioning copy of a gene into tens of millions or hundreds of millions of cells—enough cells so the body can produce high enough levels of factor?

Scientists make use of nature's experts at transferring genetic material into cells: viruses. Viruses are on the border of what we define as "living"—most viruses consist only of a protein shell (capsid) and a tiny segment of DNA.[4] Viruses can't do much on

GENE-RELATED TERMS TO KNOW

To better understand the benefits and risks of gene therapy, you need to know some basic terms, know what "gene therapy" involves, and be aware of things that may affect the benefits and risks.

A **gene** is like a sentence: It's a set of instructions, or recipe, that a cell can read to make a protein. Proteins are the building blocks of the human body. Clotting factors, like factor VIII and factor IX, are proteins.

Genes are located in the nucleus of the cell on structures called **chromosomes**. Humans have 23 pairs of chromosomes, or 46 chromosomes in all.

A **genome** is the body's complete set of DNA, about 19,000 genes. With the exception of red blood cells and gametes (sex cells), every cell in your body has two complete copies of your genome.

4. Instead of DNA, some viruses use RNA (ribonucleic acid), which acts as a messenger carrying instructions from DNA to other parts of the cell for the building of proteins.

their own: to reproduce (replicate), they must infect (insert their DNA into) a living cell. Once they infect a cell and inject their genetic material—a new set of instructions—into the cell, viruses can take over the cell's machinery to replicate and produce copies of themselves. Of course, our bodies don't want a hostile takeover of our cells by viruses: we're protected by our complex and highly developed immune system, designed to identify and destroy viruses and other invaders, including bacteria.

Viruses and humans have evolved together over millions of years, playing a cat-and-mouse game: viruses have become expert at evading the body's immune system so they can infect cells and replicate; and our immune system has become expert at detecting and destroying viruses before they do too much damage.

There are 219 viruses known to infect humans, but only two are being used in hemophilia gene therapy research: (1) most commonly, the *adeno-associated virus* (AAV); and (2) rarely, the *lentivirus*. Current hemophilia gene therapy trials are using AAV. To use a virus for gene therapy, most of the virus's genetic material (the "guts") is removed, and then a good gene for factor VIII or IX is inserted. The inserted human gene, which the virus will deliver to cells, is called a *transgene*. Without its own genetic material, the virus can no longer infect a cell and take over the cell's machinery to replicate itself or cause disease. The virus is now called a *vector*: a stealth vehicle able to evade the immune system long enough to deliver the hemophilia gene to specific cells. The vector is grown to very high quantities (sometimes more than 4,080 trillion vectors for a 150-pound person) and injected into the patient.

AAV vectors are preferred for gene therapy because they usually induce only a weak immune response and are mainly "nonintegrating." This means that vectors don't insert their transgene (such as the gene for factor VIII) into the cell's genome. Instead, nonintegrating vectors insert their transgene into the cell's nucleus, where it can still direct the production of the "protein of interest" (such as factor), but they don't become part of the person's genome. This means, though, that when the cell divides, the transgene is not copied, and the two daughter cells resulting from the cell division will not be able to produce factor. Lentiviral vectors, on the other hand, are naturally "integrating," but can be genetically modified to be nonintegrating. Integrating vectors insert their transgene into the cell's genome; the transgene is copied to daughter cells when the cell divides, and each cell continues to produce factor.

Integrating and nonintegrating vectors have advantages and disadvantages.

Integrating vectors: On the plus side, integrating vectors often provide long-term expression of the transgene—in other words, your cells will make factor for a long time. On the downside, integrating vectors are associated with "insertional mutagenesis"—if they stick themselves into the wrong place in the genome, they can disrupt the function of other genes or cause the cell to become cancerous. And even though we've become much better at targeting *where* a transgene will be inserted in the genome, we still can't insert a gene into the genome with 100% accuracy.

Nonintegrating vectors: On the plus side, they're much less likely than integrating vectors to cause cancer or disrupt other genes. Transgenes from nonintegrating vectors are also much less likely to show up in sperm and be passed on to future generations, which is prohibited in the US for fear of "designer babies." On the downside, nonintegrated genes are not copied as the cell divides, so they tend to become "diluted" over time as cells divide and reproduce. This means expression of the gene will probably decrease over time, and your factor level will fall. This would especially be a problem for gene therapy in a child: a child's liver (often the targeted organ in hemophilia gene therapy) grows in size by 80% as the child matures—meaning that by the time the child is an adult, the gene therapy might be only 20% as effective as it was originally.

Weighing the Risks and Benefits

In a survey of 12,427 people, 83% rated "potential risks and benefits" as the most important factor influencing their decision to participate in a clinical trial.[5] But the risk/benefit assessment is very personal: only you know how much risk is acceptable to *you*. And it's likely that patients, research scientists, and physicians will all reach different conclusions about risk versus benefit.

So how do you do a risk/benefit assessment for yourself, when deciding whether to enroll in a gene therapy clinical trial? You'll probably need the help of your hematologist to do this, but we can make a few generalizations:

1. Phase I clinical trials are usually associated with the greatest risk, and phase III trials with the lowest risk. Even so, the risk of all phase I trials is not equal. For example, the risk posed by a phase I trial of a drug that is an improvement on a current therapy (for example, an extended half-life factor) is likely to be lower than the risk posed by a phase I trial of a completely new therapy.
2. The use of nonintegrating vectors for gene therapy reduces the risk of insertional mutagenesis or cancer. But over time, expression of the transgene may decrease, meaning your factor level will drop, possibly making the therapy less effective.

3. Gene therapy is often associated with an immune response to the injected vector ("innate immune response"). A severe immune response, and an accompanying inflammatory response, can endanger the patient's life and decrease the effectiveness of the therapy—or completely inactivate it. To lessen the immune response, the trial participant may be put on a short course of immunosuppressive drugs. One company is working on a cell therapy where the cells are encapsulated so they don't trigger an immune response, avoiding this problem altogether.[6]
4. After receiving gene therapy, your body will probably develop a robust immune response to the vector used in the therapy and will quickly inactivate the vector if you're exposed to it again. So if the gene therapy you receive isn't successful, you probably won't be able to receive another (possibly more successful) gene therapy using the same or a similar vector, because it will be inactivated by your immune system unless suppressed by immunosuppressive drugs.

The Decision Is Yours

Biopharmaceutical companies need our help in conducting clinical trials to make gene therapy for hemophilia a reality. Hemophilia is a rare disorder, and because of inclusion and exclusion criteria, the number of people who qualify to participate in a gene therapy clinical trial is very small indeed. This means that your participation in a trial could have a significant impact on whether a particular trial—and the therapy it's testing—moves forward or stalls due to lack of participants.

Consider participating in a clinical trial. Most people, like Fernando, find it a positive experience. In a 2017 survey of 3,153 clinical trial participants, 94% said they would be willing to participate in another clinical study.[7] But weigh your options carefully. Discuss the risks and benefits with your hematologist. Bring this PEN article with you. Ultimately, the decision is yours.

HEMOPHILIA GENE THERAPY TRIALS CURRENTLY ENROLLING

Company	Therapeutic Gene	Product Name	Vector	Trial Name, Phase Trial Identifier Number Estimated Number Enrolled
Pfizer/ Spark Therapeutics	Factor IX Padua variant[1]	PF-06838435 (SPARK100) fidanacogene elaparvovec	rAAV	phase III NCT03861273 55 participants
St. Jude Research Hospital	Factor VIII	AAV2/8-HLP-FVIII-V3	AAV2/8	GO-8, phase I NCT03001830 18 participants
University College, London	Factor IX Padua variant	FLT180a	AAV8	FIX-GT, phase I NCT03369444 18 participants
uniQure	Factor IX Padua variant	AMT-061	AAV5	HOPE-B, phase III NCT03569891 56 participants
BioMarin Pharmaceutical	Factor VIII	BMN 270 Valoctocogene Roxaparvovec	AAV5	phase III NCT03370913 130 participants
Bayer	Factor VIII	BAY2599023 (DTX-201)	AAVrh10	phase I/II NCT03588299 30 participants
Pfizer/ Sangamo Therapeutics	Factor VIII	SB-525	rAAV2/6	phase I/II NCT03061201 20 participants
Spark Therapeutics	Factor VIII	SPK-8016[2]	rAAV	phase I/II NCT03734588 30 participants
Spark Therapeutics	Factor VIII	SPK-8011	rAAV	phase I/II NCT03003533 30 participants
Takeda	Factor VIII	BAX-888	AAV8	phase I/II NCT03370172 10 participants

Chart current as of September 2019, from ClinicalTrials.gov. This list does not include observational clinical trials of patients who previously received a gene therapy. The trial identifier number is a unique number used to identify clinical trials on ClinicalTrials.gov.

1. Padua variant: a super-active form of factor IX with seven times the activity of normal factor IX. 2. SPK-8016: being developed specifically for treating patients with hemophilia A with inhibitors.

headlines

gene therapy

uniQure

In an ongoing phase IIb study of a single administration of its investigational hemophilia B gene therapy AMT-061, uniQure reported that two of three patients with severe hemophilia now have factor IX activity in the normal range. At six months post-treatment, average factor IX activity increased to an average of 47% of normal (51%, 33%, and 57%, factor IX levels). AMT-061 has received Breakthrough Designation by the US FDA and access to the Priority Medicine (PRIME) regulatory initiative by the European Medicines Agency. AMT-061 uses an AAV5 viral vector carrying a patent-protected Padua variant of factor IX (FIX-Padua), which produces seven times or more factor IX than the wild-type factor IX gene. This therapy is now being evaluated in the HOPE-B clinical trial, which is expected to enroll about 50 adult patients with severe or moderately severe hemophilia B. **Why this matters:** Positive results of this clinical trial bring us one step closer to a commercial gene therapy for hemophilia B.

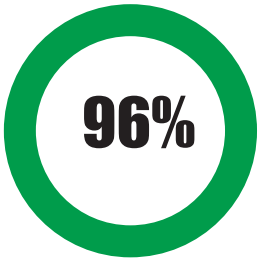
For info: uniqure.com

Sangamo Therapeutics

Sangamo Therapeutics and Pfizer reported that interim data from the phase 1/2 Alta study found that their investigational gene therapy for severe hemophilia A, SB-525, demonstrated a dose-dependent increase in factor VIII levels across four different dosages. Data was from 10 patients: three groups of two patients treated at three different dosages each, and four patients receiving the highest dose. The highest-dose group reached normal factor levels, and so far have not needed factor replacement therapy or experienced any bleeding events. Based on accumulating results from Alta, the US FDA has granted regenerative medicine advanced therapy (RMAT) designation for SB-525 to treat severe hemophilia A. RMAT is granted to regenerative medicine therapies intended to treat, modify, reverse, or cure a serious condition when preliminary clinical evidence indicates the medicine may address an unmet medical need. RMAT includes all benefits of fast-track and breakthrough therapy designation programs, including early interactions with FDA. **Why this matters:** Positive results of this clinical trial bring us one step closer to a commercial gene therapy for hemophilia A.

For info: investor.sangamo.com

BioMarin



In a three-year update to results of its investigational gene therapy treatment for adults with severe hemophilia A, BioMarin Pharmaceutical reported that bleed rate control with valocotogene roxaparvovec in the high-dose group showed a 96% reduction in annualized bleed rate (ABR) over three years, with continued absence of target joints and target joint bleeds during the three years of observation. Based on recent meetings with US and European health authorities, BioMarin plans to submit marketing applications for valoctocogene roxaparvovec (for adults with severe hemophilia A) to both the US FDA and the European Medicines Agency in fourth quarter 2019. **Why this matters:** Both submissions will be the first time a gene therapy product for any type of hemophilia will be reviewed for marketing authorization by health authorities.

For info: investors.biomarin.com

Sigilon Therapeutics

Sigilon Therapeutics' gene therapy candidate for hemophilia A, SIG-001, produced sustained levels of factor VIII for over six months and corrected bleeding in a mouse model. SIG-001 is a form of cell therapy in which human cells modified to express the factor VIII protein are encased in a shield made of a synthetic biomaterial, designed to prevent triggering the immune system, a common side effect of cell and gene therapy. Sigilon intends to start clinical trials of SIG-001 in hemophilia A patients in the second half of 2019. **Why this matters:** If successful, this cell therapy approach will eliminate the risk of an immune response and cancer, and will allow redosing of patients to increase factor production.

For info: sigilon.com

patient resources

Being a Blood Brother

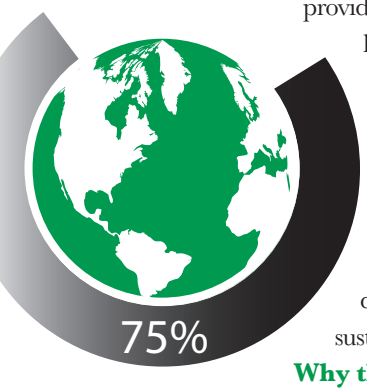
Blood Brothers: Strength Through Advocacy celebrates 10 years of the Blood Brothers program sponsored by Hemophilia Federation of America (HFA). The book shares personal stories of many men in the bleeding disorder community. **Why this matters:** Blood Brothers commemorates advocates who fought for blood and blood product safety and increased access to healthcare; their personal experiences can inspire others to advocacy.

For info: hemophiliafed.org

humanitarian

More Aid to Developing Countries

Bayer announced a five-year partnership with the World Federation of Hemophilia (WFH) Humanitarian Aid Program to supply factor VIII products to healthcare providers in more than 60 countries with limited access to advanced hemophilia care. The WFH will use this donation to improve provider training and education in accurately and safely administering treatments for acute bleeds, prophylaxis, and surgeries; the donation will also help ensure a sustainable impact in local communities.



Why this matters: 75% of the world's population with hemophilia has little to no access to factor.

For info: wfh.org

manufacturing

Hemlibra® Comes Out Strong

In the first quarter of 2019, about 8% of all US hemophilia A patients used Genentech/Roche's Hemlibra, according to the Marketing Research Bureau's new report, *Hemophilia Care & Price Monitoring*, Wave #26. Report findings were based on surveys of 20 hemophilia treatment centers collectively managing more than 6,700 patients with hemophilia A, hemophilia B, and von Willebrand disease. Takeda's Advate® held its leadership position with 41% of all hemophilia A patients followed by Sanofi's Eloctate® and Bayer's Kogenate FS®. **Why this matters:** Hemlibra, a nonfactor subcutaneous prophylactic treatment, is easier to administer than treatment with factor, and has been shown to prevent spontaneous bleeds better than prophylaxis with factor.

For info: marketingresearchbureau.com

Octapharma Presents New Data on Nuwiq®

The NuProtect study investigated the development of inhibitors in 108 previously untreated patients treated with Nuwiq. Final data was presented at the 27th International Society on Thrombosis and Haemostasis Congress in Melbourne, Australia. The incidence of high-titer inhibitors was 17.6%, and using Nuwiq for immune tolerance induction (ITI) resulted in inhibitor elimination in 8 of 10 (80%) patients treated so far. **Why this matters:** Inhibitor development remains a serious treatment complication of hemophilia A, with up to 35% of patients developing inhibitors to factor VIII.

For info: octapharma.com

nonprofit

NHF Annual Conference

Anaheim, California
October 3–5, 2019

National Hemophilia Foundation held its 71st national Bleeding Disorders Conference last month. Registration included three days of educational sessions, networking opportunities, and access to the Exhibit Hall, where dozens of companies and nonprofits display products or services. **Why this matters:** With thousands of participants, NHF annual Bleeding Disorders Conferences are one of the largest bleeding disorder community gatherings.

For info: www.hemophilia.org

Voluntary Recall of Kogenate FS

Bayer announced a voluntary recall of two lots of Kogenate FS 2,000 IU because they contain 3,000 IU of Jivi®, its PEGylated extended half-life recombinant factor. The recalled lots include

- Lot number 27118RK; exp date 6/12/2021
- Lot number 27119CG; exp date 6/12/2021

About 990 vials were affected by this recall. Most of the vials were recovered, but 990 were affected by the recall and were in the hands of consumers. **Why this matters:** If you use Kogenate FS, please check your vials for the affected lot numbers.

For info: Bayer, 888-842-2937

soundbites

- NHF CEO **Val Bias** will be ending his 11-year term in December 2019.
- HFA Executive Director **Kimberly Haugstad** resigned her position in August 2019 after almost 11 years.
- Roche's pending $4.3 billion acquisition of **Spark Therapeutics** has been pushed back again, as US regulators continue to analyze the deal for possible anti-competition outcomes.
- The aggregate market share of all **plasma-derived factor VIII** products used for on-demand treatment and prophylaxis accounted for less than 5% all US hemophilia A patients in the first quarter of 2019.
- A villain in the first half of season 6 of TV's *The Flash* will be "**Bloodwork**," alias Dr. Ramsey Rosso, a coroner with hemophilia who learns to gain control over blood's ability to clot, move, and make him grow to monstrous size.

- Researchers report that Casebia Therapeutics' **two-stage gene editing approach** using CRISPR technology successfully delivered the human gene coding for factor VIII in a mouse model of hemophilia A, leading to stable and increasing levels of the factor.
- **Dr. Shelby Dietrich Rector**, a pioneering and much-lauded physician in the hemophilia community, died of natural causes on August 12, 2019, in Pasadena, California. She was 95.
- **Novo Nordisk** announced that Concizumab (an anti-tissue factor pathway inhibitor antibody) was safe for preventing bleeding episodes in patients with hemophilia A (explorer™5 study) and hemophilia A/B with inhibitors (explorer™4 study).

As I See It... from page 3

that—once produced safely and cleanly—immediately resolve bleeds and can be taken before activities; to improved factor that lasts longer and takes much less time to inject; and now, to a novel therapy administered by subcutaneous injection. Looking at the timeline of hemophilia treatment over my life, I can only imagine what the next-next generation products will do for us.

If industry continues to refine and release hemophilia treatments to the point where managing our condition becomes as simple as managing allergies, what then is the benefit of altering our genetic code and taking on the associated risks? Gene therapy, once begun, can't be undone or stopped. You're in it for the long haul. If I start to have liver problems due to gene therapy, then I can only watch my liver falter, helplessly, and hope for the best. If a new factor product causes me to have an inhibitor response, or doesn't stop my bleeds, then I can stop taking it, and find another route to take. That flexibility is vital; it's something we hemophiliacs haven't always had, and have fought many battles to attain.

My last concern about gene therapy: What about the 75% of worldwide hemophiliacs who lack treatment altogether? Their joints are destroyed by puberty, and they're lucky to live past their teens. Currently, their only hope is factor donations, from charities or industry. If a gene cure comes along, it will be phenomenally expensive, and require post-treatment monitoring and care. What impact will this have on bleeding hemophiliacs in remote villages who currently rely on receiving a few units of factor occasionally from philanthropic efforts? If a gene cure wipes out pharmaceutical manufacturing to the point that products are no longer manufactured in mass quantities, then what becomes of the supply of donated medicine for these individuals? What if our thirst for a "cure" cuts off access to any and all treatment for them? Wouldn't it be a better situation for all involved—those of us who have access to treatment and those who do not—to see products continue to be refined and developed, to the point where efficacy and production costs are such that medication becomes cheap enough for all health authorities, worldwide, to provide them to all hemophiliacs in their care?

I don't begrudge anyone feeling the opposite; I truly hope that current gene trials pan out and give them what they want. I am personally fine with my hemophilia, and have worked hard over the course of my life to make my hemophilia not a weakness, but a strength. I'm happy with who I am, and while I suffer daily, my life is one that I love, and I don't feel any need to change it. But for those who yearn for a cure and a release from this condition, I wish you the best of luck. Proceed toward that goal with eyes wide open, however, and remain informed and aware skeptics. Attend every lecture and talk you can about the technology. Learn what gene therapy really means, and what its real risks are. Weigh those with potential benefits, and know what you are getting into.

We hemophiliacs suffered the greatest medical catastrophe in Western history, in part because we were clamoring for better treatments and leaped at the chance to take one when it came along. It would be a sad day indeed if, 5 to 10 years into treatment on gene therapy, hemophiliacs fall victim to some other unforeseen calamity arising from altering their genome. There is no more bitter pill than the one promised as a cure, which then becomes an ailment that needs yet another pill to treat.

Editor's Note: Almost a decade after the first gene therapy trials for hemophilia, there has been no evidence of liver problems.

Inhibitor Insights... from page 4

closest to him in the loop, and watching him take over his hemophilia brings me joy.

In the high school years, your child will become more independent and play a much bigger role in disclosing to teachers and staff. With more freedom comes more control over the bleeding disorder. With my oldest son, Julian, I didn't have annual meetings with the nurse at the high school level. Julian was never on a 504 Plan, so I had to make sure that his teachers received information about care. I made a phone call to the nurse and sent the updated medical information for his file. Julian went to the school clinic, and introduced himself to the nurse so they could put a name with a face. He even kept a dose of factor and ancillaries in the clinic in case of emergencies. Julian was also very good at keeping his close circle of friends in the know about his hemophilia.

At the preschool, elementary, and secondary levels of education, disclosing pertinent medical information to the team involved in your child's care is crucial for his education and security. Disclosing information about a bleeding disorder helps those in charge become advocates for our children's safety and welfare. Modeling how we disclose hemophilia to educators also gives our children the tools they need as they grow into young adulthood. I hope that as my boys grow older, the importance of sharing needed information will transfer into their adult lives. As parents or caregivers of children with a bleeding disorder, we do the best we can and hope that our examples positively influence their lives.

Richard's Review... from page 5

Researchers continued to modify Fraction I, hoping for improvements. Their efforts led to concentrated preparations, such as two-donor-fibrinogen (TDF) designed to reduce protein overload, circulating anticoagulants, and exposure to hepatitis. Other products included Fraction I-FL, Fraction I-T, Fraction I-O-Ta (a tannic acid purification of factor VIII, of 200 times the protein content), and Fraction AA (amino acid precipitation).

Animal Concentrates

The other major development for hemophilia treatment during the 1950s was animal concentrates. The factor VIII activity in ox (bovine), pig (porcine), and sheep (ovine) blood is between 5 and 15 times greater than in human blood. Another benefit is cost, as animal blood is available in large quantities from slaughterhouses. Using the same process for fractionation of human plasma, Ethel Bidwell, an English chemist, began producing animal concentrates in 1953. The animal product was freeze-dried and stored under dry nitrogen in sealed ampules, to be later re-dissolved in water. It was sterilized by ultraviolet light. The product became commercially available, first by S. Maw, Son & Sons, and later by Crookes.

Sheep blood was not used due to problems related to the wool, while ox and pig blood concentrates were commercially available for hemophilia treatment. One problem associated with animal concentrates was the lack of purity and sterility. Another was its antigenicity, because the formation of antibodies to animal proteins causes allergic reactions. Animal concentrates were regulated by the US Department of Agriculture.[3] An outbreak of hoof-and-mouth disease in England in the early 1960s led to a quarantine of animal concentrates in America and Australia. Animal products potentially contained blood-borne viruses not found in human blood; this led to federal restrictions on importation. A purer porcine product from polyelectrolyte fractionation, Hyate:C, by Porton Speywood in Wales, became commercially available in the 1980s for treating inhibitors.

Today, we may disregard products like Fraction I and animal concentrates because they have limitations. But before current factor concentrates, these products were an improvement over fresh-frozen plasma for treating hemophilia. And the commercial manufacturing techniques designed for Fraction I and animal concentrates were later applied to the low/intermediate purity factor concentrates of the 1960s and 1970s. To achieve medical advances, many small steps of laborious research are needed. We tend to ignore these steps and instead focus on the final outcomes. To me, those small steps are too important to be forgotten.

3. Yes, it's true: the US Department of Agriculture regulated a hemophilia treatment.

YOU... from page 6

get levels above 1%. And then some were getting over 10%. That variability is important. In the current factor IX trials, using the hyperactive Padua factor IX gene, you see a range of 14%–80% across trials. Now you wonder, does gene therapy even need to be personalized if patients are no longer bleeding, without having to be infused?"

Is Cell Therapy a Personalized Cure?

Vivaldi points out that Sigilon is developing a different approach to a genetic cure, called cell therapy: "It's another form of personalized medicine."

He explains, "First, we've engineered human cells to produce the specific enzyme, protein, or factor that the patient is missing, like a living protein factory. Separately, we've engineered a biomaterial that is meant to protect these cells. Normally when you implant any foreign tissue into a patient, the patient's immune system will identify it as a threat and attack it. Our biomaterial are tiny spheres capable of shielding our therapeutic cells from immune

attack. The spheres are also designed to ward off fibrosis, which is a scarring process that normally occurs as part of the body's reaction to a foreign implant."

In this therapeutic cure, thousands of the engineered cells are nestled into the special spheres. Nutrients and oxygen flow through the sphere's matrix-like walls and nourish the cells. The proteins, enzymes, or factors that the engineered cells produce are able to flow out of the spheres and circulate through the patient's bloodstream. The spheres are implanted into the patient's abdomen in a simple laparoscopic procedure.

"We believe this will vastly improve [patients'] symptoms, delivering a functional cure for hemophilia," says Vivaldi.

This functional cure can be personalized. "A key advantage to our approach is that you can redose the patient by adding more cells loaded into spheres, if he or she needs more therapy," Vivaldi notes. The spheres also have the potential to be removed, if needed. In contrast to gene therapy, there's no issue with preexisting antibodies. "And because our cells don't integrate into the patient's DNA," he adds, "there's no concern about off-target integration causing side effects."

Future of a Personalized Cure

"We don't know what we want from gene therapy yet," says Valentino. "Do we want a cure? Freedom from spontaneous bleeding? Freedom from infusions, or maybe normal factor levels? The community needs to put a stake in the ground for what they are looking for in potential gene therapies. We've heard that it will correct genetic defects, but what will that mean practically?"

Whether gene or cell therapy, Vivaldi notes, "Both should be far more durable than today's standard of care [infusions of factor concentrate]. A single treatment should last years. Another important advantage is that both therapies should result in a steady production of the protein, enzyme, or factor the patient is missing. There should not be spikes or plateaus, unless they are deliberately designed to be part of the therapy."

Day adds, "Some patients want a guarantee; they never want to infuse again. Everyone has different expectations. What do parents, spouses, and partners think about gene therapy? It's a big decision to make, a family decision—and that's a big part of personalization, choosing what's right for the patient and their family."

Vivaldi sums it up: "This is a very exciting time where we're seeing the future of medicine unfold before us. There's still a lot of work to be done, but there are a lot of terrific ideas and promising technologies."

Inbox... from page 2

THANKS FOR YOUR RECENT ARTICLE on helping adolescents to understand their bleeding disorder. From my 64 years of experience, the challenge of teens not being able to fully comprehend a bleeding disorder lies with adults. This is especially true of medical professionals who are uninformed about bleeding disorders. Just go to any emergency room, and this becomes apparent quickly. I was told by an ER doctor that factor is for severe head trauma only. An ER nurse told me she had never seen factor in 30 years. (This is why I learned to self-infuse at age 60.) I have asked my pharma reps to visit ERs to explain hemophilia. They usually leave without the opportunity to educate the docs. I also encounter numerous medical professionals who have inadequate training and education on bleeding disorders. I share the "domino" analogy with every medical professional I encounter. The response is "WOW, that makes it easy." Teens are in need of short, concise information. Attention spans are very short. Please promote it.

Steve Place
MASSACHUSETTS

THE INFORMATION AND SUPPORT THAT your organization provided me as I raised my son with hemophilia helped both of us tremendously! I am proud to say that he is now a healthy, happy Ivy League graduate starting a family of his own.

Caroline Graham
INDIANA

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Hey! Did you visit your HTC this year?

Takeda is here to support you throughout your journey and help you embrace life's possibilities. Our focus on factor treatments and educational programs, and our dedication to the bleeding disorders community, remain unchanged. And our commitment to patients, inspired by our vision for a bleed-free world, is stronger than ever.

Let's make today brilliant.

bleedingdisorders.com

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BAXALTA AND SHIRE ARE NOW PART OF TAKEDA