



inside

- 3 As I See It: The Power of Comedy
- 4 Inhibitor Insights: What's in a Number?
- 5 Richard's Review: Hemophilia Onstage
- 6 YOU: What Does Gene Therapy Mean?

GENE THERAPY: What's the Prognosis?

Paul Clement

“Cure for Hemophilia Is Seen by Year 2000” read the *New York Times* headline on March 24, 1994. The article reported a prediction by the World Health Organization. Hemophilia magazines and chapter newsletters had promoted similar forecasts for several years, based on statements made by National Hemophilia Foundation (NHF) and the World Federation of Hemophilia (WFH). Hopes were high that a cure for hemophilia was close. To speed things up, in 1998 NHF launched “It’s Time for a Cure,” a campaign to raise funds for gene therapy research. After raising more than \$9 million, NHF’s campaign ended in 2008.

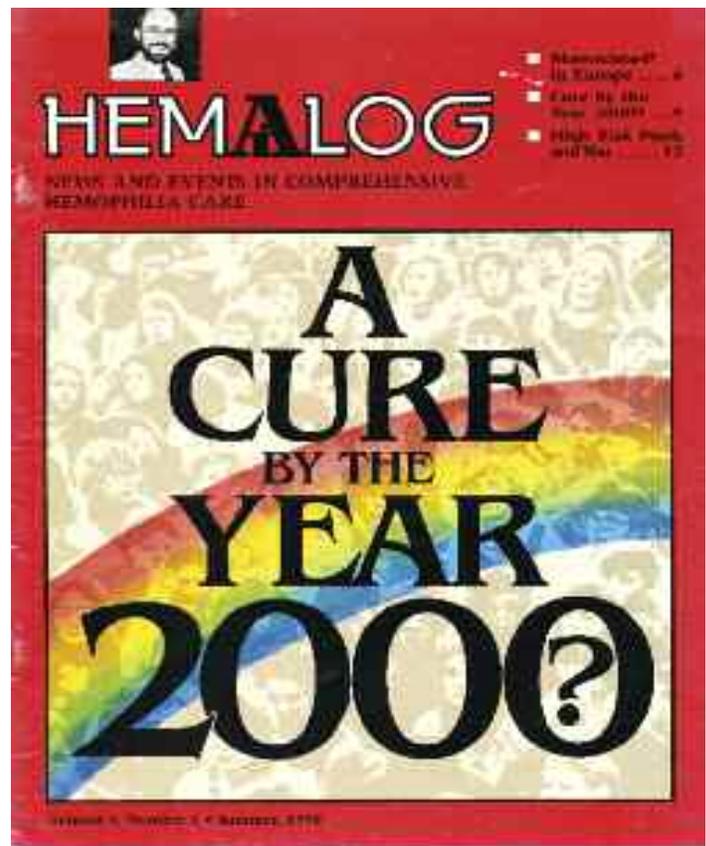
Fast forward—2017, and *still* no gene therapy treatment for hemophilia on the market. What’s taking so long? And what’s the prognosis for hemophilia gene therapy?

Background: Origins of Hope

Why were our hopes so high for a cure for hemophilia in the early 1990s?

First, gene therapy had some initial success. In 1990, in the first human gene therapy clinical trials, two young girls were cured of adenosine deaminase deficiency, a genetic disorder that damages the immune system and causes severe combined immunodeficiency (SCID, or “bubble boy disease”).

Second, hemophilia was high on the list of disorders targeted for gene therapy research (see chart, page 11). Why? Both hemophilia A and B are caused by a defect in a single (but different) gene. This made hemophilia gene therapy more straightforward, compared to working with disorders caused by defects in multiple genes. The genes for factor IX and factor VIII were also among the first to be cloned, meaning they could easily be copied for use in gene therapy research. And researchers already had hemophilic mice and dogs to test effectiveness and safety of therapies. There was also a low bar for success: an increase in factor level of only a few percent would change a person with severe hemophilia into a person with moderate or mild hemophilia, and only a small percentage of cells needed to be converted through gene therapy to make therapeutic levels of clotting factor. And, unlike other disorders in which too much or



too little of a deficient protein can kill you, factor levels expressed as a result of gene therapy could vary from a few percent to 150%—with no ill effects. Finally, and perhaps most important for researchers, relatively simple tests to measure factor levels provided an easy way to test the effectiveness of gene therapy.

The first human gene therapy clinical trial for hemophilia began in 1998. But gene therapy research soon faced a crisis.

In 1999, 18-year-old Jesse Gelsinger, who had a rare metabolic disorder, died while participating in a gene therapy trial. The virus carrying the therapeutic gene triggered in him a massive immune response.

» page 7

welcome



Dr. Glenn Pierce's review of new therapies in our May 2016 issue garnered much praise, but also a question from one reader: "What about gene therapy? I don't read anything about that anymore." He was under the impression that all gene therapy for hemophilia had stopped. Truth is, there's a lot happening with gene therapy, and results are

being published in scientific journals and presented at symposia. In this issue of PEN, Paul Clement brings you a user-friendly update on current gene therapy trials for hemophilia.

But what does gene therapy mean to you, as a parent or patient? We asked our Facebook groups, and got some interesting answers. Read about them in YOU.

Cazandra MacDonald, mother of two boys with hemophilia and inhibitors, looks at hemophilia inhibitors by the numbers in *Inhibitor Insights*, and adds a human touch to what numbers can mean to you.

Finally, with the play *Hamilton* drawing rave reviews, Richard Atwood reviews hemophilia at the theater, highlighting some prominent plays featuring bleeding disorders. While we wait for gene therapy to become a reality, stay informed about hemophilia treatment and products, and maybe take in a play about hemophilia! ☺

Laurie Kelley

inbox

PEN'S BIENNIAL RESOURCE GUIDE

GREAT SELECTION OF RESOURCES! I see a few things I have already read and loved, and plenty more that I need to look into. Thanks in particular for the historical context. Safe, convenient treatment hasn't always been readily available (and for some of us still isn't). It will forever be my hope that this changes for the better. Raising awareness of where we came from is part of that process.

Angel Parrett
KENTUCKY

MY FIRST FACTOR GIFT BOX

I RECEIVED YOUR GENEROUS GIFTS, and I am ecstatic! Alanni absolutely loved everything and even asked me to read the books to her at bedtime. So I did, and she started understanding now why Troy gets "poked" when he goes to the doctor. I was in tears, so happy, that these books, literally in an instant, cleared things up for her. Right away she understood. Even though I've tried to explain myself, it was the books that got through to her. This is a beautiful gift. Just with the books I've read so far, she understands and can point out the factor on the images, the needle, the syringe, and she tells me that the bandage comes after the medicine. This is so wonderful! I have such high hopes for her being more comfortable around her brother and not always on edge and afraid. Thank you, so so so much. You've touched my heart.



Alanni understands hemophilia better with the help of her My First Factor books.

Tori Sandoval
TEXAS

»» page 19

PARENT EMPOWERMENT NEWSLETTER | MAY 2017

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Patrick James Lynch

The Power of Comedy

Growing up, my little brother Adam and I shared having hemophilia. And we shared a bedroom, with bunk beds. Some nights, when we'd argue about who'd cheated in what video game that afternoon or gripe about some similarly inconsequential event, sharing a bedroom felt like punishment. But that's just part of being brothers. Mostly, it was a lot of fun—especially because we had a TV in there! We spent more than a few late nights clicking around in search of one last thrill for the day, which led us to discover many pieces of entertainment together.

Channel hopping at night was how I first discovered one of my childhood idols, George Carlin. Carlin mesmerized me with his ability to seamlessly navigate an energetic act that made the topic of capital punishment as funny as fart jokes, and suicide as silly as dog behavior. In fact, it was Carlin who first planted the idea in my head that anything could be funny:

"I believe you can joke about anything. It all depends on how you construct the joke. What the exaggeration is. Because every joke needs one exaggeration. Every joke needs one thing to be way out of proportion."*

Late-night channel hopping introduced me to another highly influential comedian, Eddie Izzard. Adam was asleep the night I found Eddie's Emmy-winning *Dress to Kill* special (1998). As Eddie weaved his way through surrealist pieces on European history and culture, tears streamed down my face and muscles in my gut screamed from being clenched so tight. I didn't want to wake Adam, but this guy was just too funny!

The next day, I had to share the special with Adam immediately. Fortunately, he found Eddie as funny as I did. Or perhaps this wasn't so fortunate, as Adam's confirmation prompted me to share the special with a friend. Then another friend. Then another. And so began a compulsive quest of sharing comedy I enjoyed with friends.

In college, any roommate I had was inundated with albums from Dave Chappelle, Robin Williams, and Steven Wright. At parties we'd host, at some point in the night I'd turn the music off in favor of sharing a Sarah Silverman or Chris Rock album. I was "that guy!"

After college, I worked as a theater actor, and I was on the road quite a bit. On our nights off, I'd coax cast members over



Patrick shared hemophilia—and a love of comedy—with his little brother Adam.

with drinks and food so that I'd have friends to share Mitch Hedberg, Lewis Black, or Dylan Moran's work.

I won't even pretend that I still don't behave this way! Just this past October, after a long travel day, while stuck in standstill traffic with Josh and Rob, my colleagues from Believe Ltd., a mere mention of New Orleans prompted me to play "A Love Letter to New Orleans," followed by several more tracks from *Hannibal Buress Live From Chicago* (2014). I think they enjoyed it ...

Some things never change.

As readers may know, Adam, who like me was born with severe hemophilia A, passed away from an intracranial bleed in 2007 at age 18. His death was, and continues to be, the single greatest source of pain in my life. It is also my single greatest motivation to continue creating content like *Stop the Bleeding!* I want to harness the power of comedic storytelling to engage and empower young people and families affected by bleeding disorders. But that is not my only goal.

Watching George Carlin and Eddie Izzard from our bunk beds, I found that Adam and I were interested in—and learning about—topics foreign to us, topics that a classroom might struggle to connect us to. We were engaged, we were curious, and we were thinking. Comedy has that power, and it's for this reason that I intend to continue using comedy and storytelling to benefit the bleeding disorder community, by creating content not only for us, but also about us, for others. What exactly that content is, how it happens and when, I don't yet know, though I already have a couple of irons in the fire. And as you now know, I've got a decent track record of persistency when it comes to sharing with others the content I believe in. Stay tuned! ☺

*George Carlin, *Parental Advisory: Explicit Lyrics*, 1990.

Patrick James Lynch, 31, has severe hemophilia A. He is co-founder and CEO of Believe Ltd., through which he created and produces the award-winning hemophilia comedy series Stop the Bleeding! (stbhem.com) and the inspirational speaker series Powering Through (poweringthrough.org). He's the 2013 recipient of HEA's Terry Lamb Award and the 2014 recipient of NHF's Loras Goedken Award. He lives in Los Angeles. Patrick dedicates his work to the memory of his brother Adam. Read more at patrickjamslynch.com and BelieveLTD.com.



Cazandra
Campos-MacDonald

What's in a Number?

Numbers, numbers, numbers. Our society is flooded with numbers. From Social Security numbers to birthdays, PINs, passcodes and checking our weight, we can hardly get through a day without numbers. When you are living with a bleeding disorder, you monitor the assays of your factor, track the number of bleeds per month, check how many doses of product are on hand, and measure the circumference of a swollen knee. But when you live with an inhibitor, there's another number that can become the focus of treatment: the Bethesda unit (BU).

The Bethesda inhibitor assay is a test that measures the titer (strength) of the inhibitor, described in Bethesda units. Inhibitor titers may range from less than 1 BU to thousands of BU. Knowing this number will help determine how bleeds are treated. If the inhibitor registers as low titer (less than or equal to 5 BU), bleeds may be treated with high doses of standard factor concentrate. If the inhibitor registers as high titer (greater than 5 BU), standard factor concentrates are ineffective and special factor concentrates called bypassing agents are used instead. Attempting to treat bleeds in the presence of inhibitors is less effective than treating bleeds without inhibitors—so the goal is to eradicate the inhibitor. If the inhibitor registers as less than 10 BU, this is when many providers will have patients begin immune tolerance therapy (ITT), also called immune tolerance induction (ITI), a treatment protocol designed to eliminate the inhibitor.¹ Knowing your BU is crucial in order to take the next step in working toward that goal.

It's easy to put your faith completely in the numbers. Knowing your current BU is important, but know first that every individual is unique and there are several different ITT protocols. Each person does not react to ITT in the same way. One body may accept ITT easily, and his BU will come down in a short time. Others on the protocol may take years to get the same results. Numbers do not dictate that the treatment

for one person will be the same as for another. For example, two brothers, both with severe hemophilia and inhibitors and with the same parents, can live very different lives with an inhibitor. My older son, Julian, was one year old when he was diagnosed with a low-titer inhibitor; it never rose above 5 BU. He immediately had a port inserted, and he started ITT for two and a half years. He *tolerized*, meaning his inhibitor dropped to zero, and he has never had an inhibitor resurface.

My younger son, Caeleb, was 11 months old when diagnosed with a high-titer inhibitor that registered over 2,200 BU. His titer dropped to 0 BU at one point after ITT, but now he is living with a low-titer inhibitor, and he receives factor daily to maintain his tolerance. My sons both reached 0 BU after ITT, but they had different outcomes.

The numbers can be promising and sometimes disappointing. But ultimately, the numbers are a key component to treatment.

Everyone who tracks his BU has an ultimate goal in mind: to lower the titer to zero. If your titer is 323 BU, your goal may first be 299 BU, then 250 BU.² Another person may be hoping to get to double digits, and another to single digits. Of course, when you're tracking your BU, you want to get to zero and stay there. When you reach 0 BU, you may think that the inhibitor is now a thing of the past—but not necessarily. Once 0 BU is attained, the next step is to monitor the half-life of the factor. To be successfully considered tolerized (this is also called *complete tolerance*), the following must be maintained:

- The inhibitor titer can no longer be measured.
- Factor recovery is greater than 66% of normal.
- The half-life of factor VIII is greater than six hours.³

But someone may live with 0 BU for many years without these three characteristics. This is called *partial tolerance*. For example,

»» page 17

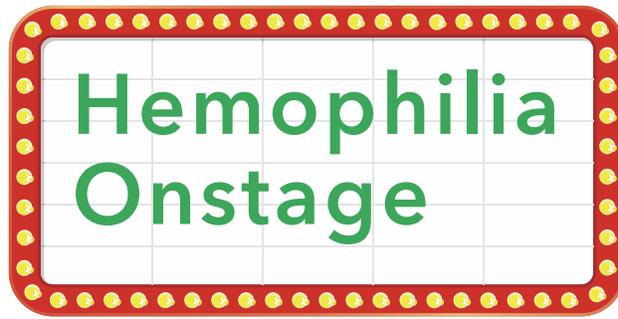
1. ITT is a proven treatment toward eradicating inhibitors. Larger-than-normal doses of factor are given in the hope of overriding the inhibitor. ITT protocols can differ in frequency of infusing, depending on the physician's and individual's needs. 2. Once you achieve 10 BU, it doesn't matter if the BU gets lower, because all infused factor is inactivated in minutes. Even so, families living with an inhibitor will find emotional relief when the numbers get closer to zero. 3. D. M. DiMichele, W. K. Hoots, S. W. Pipe, G. E. Rivard, and E. Santagostino, "International Workshop on Immune Tolerance Induction: Consensus Recommendations," *Haemophilia* 13 (2007): 1-22.

richard's review

Linda Weaver's Studio



Richard J. Atwood



Booking tickets to the hit Broadway show *Hamilton* presents a challenge. Every performance of this popular musical production is sold out. Consider instead going to a play that includes hemophilia.

I enjoy plays because playwrights emphasize dialogue over action. Plus, the actors connect with the audience during a live performance. Check out the following plays that either include a character with hemophilia or mention hemophilia.

Comedic Plays



The award-winning playwright William Mastrosimone wrote two plays involving hemophilia. Both are found in the book *William Mastrosimone: Collected Plays* (1993). In the satiric play *The Woolgatherer*

(1981), Rose, a shy sales clerk, tries to extricate herself from the unwanted sexual advances of a suitor. She falsely claims that she could bleed to death from her rare blood disease, hemophilia. In the coming-of-age play *Shivaree*



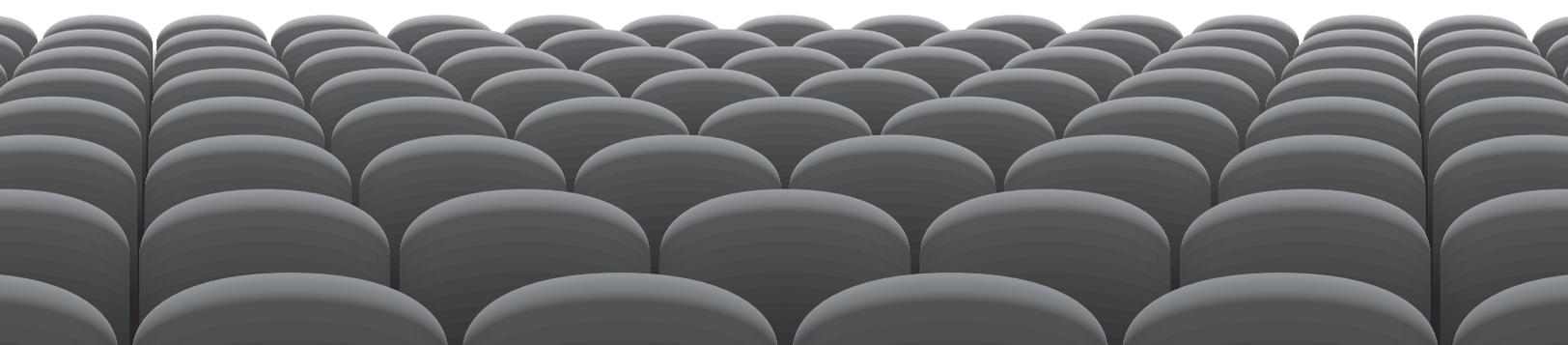
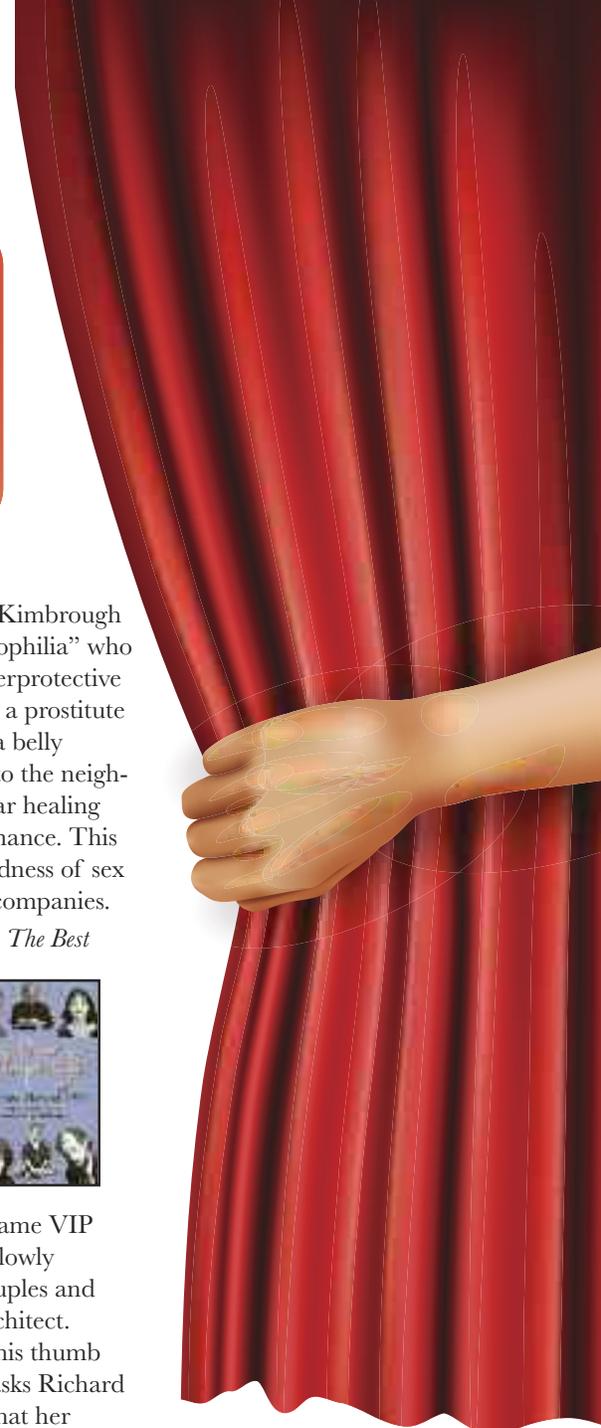
(1984), main character Chandler Kimbrough is a 19-year-old with “classic hemophilia” who treats with plasma. To defy his overprotective mother, Chandler tries to procure a prostitute with his ice cream money. When a belly dancer named Shivaree moves into the neighboring apartment and does the Zar healing dance, Chandler learns about romance. This humorous play about the awkwardness of sex is periodically revived by theater companies.

The collection *New Playwrights: The Best Plays of 1999* (2001), edited by Marisa Smith, includes a play by award-winning playwright Jeffrey Hatcher.



The satire *What Corbin Knew* (1999) comments on middle-aged lifestyles with comic farce. The play’s five characters keep returning to the same VIP entertainment skybox over time, slowly revealing the backstory of two couples and Richard Corbin, a 40-year-old architect. When one of the characters cuts his thumb trying to open a drawer, his wife asks Richard for a bandage and falsely claims that her husband’s family has a history of hemophilia and he needs a transfusion.

»» page 18





What Does Gene Therapy Mean to YOU?

Laurie Kelley

Ladonna Pettus remembers the cover of *Hemalog*, a hemophilia magazine from 1990, promising “A Cure by the Year 2000?” It seemed at once like a vision and a done deal. Ladonna’s son with hemophilia was around two at the time. She recalls, “I had such hope. He is almost 30 now.”

Many parents who remember that magazine cover had those hopes. Their children are adults now, and although gene therapy trials are underway, it seems that the passion and dreams for a cure have been tempered. Alvin Luk, head of clinical research and operations at Spark Therapeutics, is working on hemophilia gene therapy. He offers, “We all underestimated the complexity of gene transfer.”

Maybe this is why, when I repeatedly asked 2,600-plus hemophilia “friends” on Facebook about their thoughts on gene therapy, only a handful of people replied. I’m sharing their comments here. Normally, the hemophilia community is vocal and active. Does this lack of response indicate that we are mostly unaware when it comes to gene therapy? Are we not sure what it is?

Defining gene therapy: A cure?

Parents and patients sometimes use the terms “gene therapy” and “cure” interchangeably. But the definitions aren’t the same. When we think of a cure, we think of eradicating the disorder or disease. In other words, a person with hemophilia no longer has it. In fact, a permanent cure for hemophilia already *does* exist. Steven Riedle notes that his brother with hemophilia had a liver transplant in October 2016, and is indeed cured of hemophilia.



Ray Stanhope believes levels of circulating factor would have to be closer to 50% (normal) for gene therapy to be considered a cure.

But a liver transplant is not a feasible option.¹ Many patients and caregivers are waiting—hoping—for a safe, widely available therapy that will cure hemophilia permanently. Yet we may need to adjust our definition of cure. Community members who responded to my questions seem to realize that most current gene therapy trials promise to make hemophilia less severe by increasing circulating levels of factor in the blood.

Very few patients or parents understand gene therapy as thoroughly as Ray Stanhope, former National Hemophilia Foundation president, and person with hemophilia. He defines gene therapy as “the use of a viral vector to modify cells in the body to produce an additional specific protein which is either missing or produced at a lower than normal level in a person with hemophilia.”² What Ray describes is not necessarily a cure, but an improved therapy.

What level of success?

If current gene therapy trials promise to increase circulating factor in the bloodstream, what level would be considered



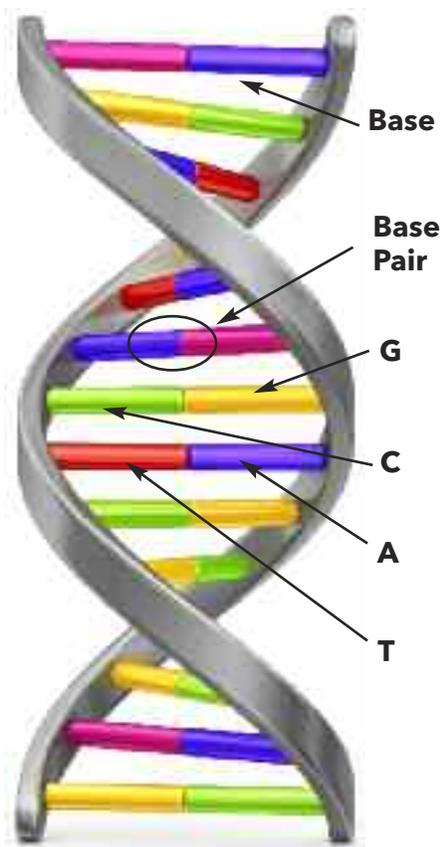
»» page 16

1. Factors VIII and IX are produced primarily in the liver, although the cells lining the blood vessels also produce and hold reserves of factor VIII for release into the bloodstream when needed. Replacing the liver indeed cures hemophilia, but this is not deemed a viable option for treatment because it is too risky. Only patients with hemophilia who face liver failure are considered for this operation. 2. A vector is a modified virus used by molecular biologists to deliver genetic material into cells.

Jesse's death sent shockwaves through the gene therapy research community and brought intense scrutiny from all angles. Congressional hearings followed. The US Food and Drug Administration (FDA) increased oversight of gene therapy trials, as did the Recombinant DNA Advisory Committee of the National Institutes of Health. Trials across the nation were halted. University institutional review boards increased their oversight. Research grants shriveled as investors shied away from new gene therapy ventures and shelved projects already begun.

But gene therapy was not sunk. Research continued, but with greater oversight and at a slower pace. It would be almost a decade, in 2010, before the first success in hemophilia gene research would happen: in a clinical trial at University College London, four of six men with hemophilia B produced enough factor (about 5%) to be able to stop their prophylaxis regimen. And now gene therapy research has surged, with more than 2,400 gene therapy trials conducted since 1990. Of the 12 current or planned hemophilia gene therapy trials, 6 started in the last two years and 5 are starting this year (see table, page 12).

DNA Double-Helix Structure



Gene Therapy Terms to Know

DNA	Short for <i>deoxyribonucleic acid</i> , the chemical code that makes up genes. DNA is arranged in a twisted ladder structure called a <i>double helix</i> . DNA controls all functions of the cell.
Gene	A set of chemical instructions in DNA that cells use to make proteins.
Bases	A, C, G, and T, the chemical “letters” of DNA.
Base pairs	Combinations of A–T and C–G. Long strings of base pairs make up genes.
Genome	The body’s complete set of DNA.
Chromosomes	Structures in the cell’s nucleus made of DNA. Humans have 23 pairs of chromosomes in each cell.
Coding sequence	A subset of base pairs in a gene that carries instructions only for the structure of a protein.
Vector	A modified virus designed to transport a gene to a cell.
Transgene	A segment of DNA from one organism introduced into the genome of another organism.
Transduction	The process by which a vector inserts its DNA into a cell. In a transduced cell, the vector can’t make copies of itself. By contrast, a virus that infects a cell can make copies of itself.
Expression	A set of processes allowing a cell to read a gene, resulting in the production of a protein such as factor.

What Is Gene Therapy?

The concept of gene therapy is simple: a functioning copy of a gene is introduced into the body, to replace the function of a defective gene. In the case of hemophilia, this means inserting a “good” gene that makes the factor VIII (hemophilia A) or factor IX (hemophilia B) protein to take the place of the defective gene. Although the concept sounds simple, actually accomplishing this task is very complex.

Before discussing gene therapy in detail, let’s define a few terms.

A *gene* is a set of instructions, like a sentence or recipe, that a cell can read to make a protein. Proteins are the building blocks of the human body. Genes are made of chemicals called *deoxyribonucleic acid*, or DNA. And DNA itself is made of four *bases* (A, C, G, and T; see diagram at left). These bases can be arranged in different sequences to make different genes, just like letters of the alphabet can be arranged to make different words. Human genes vary in size from several hundred DNA bases to more than 2 million bases.¹ DNA is a two-stranded molecule that forms a *double helix* shape, like a twisted ladder. The bases from one strand of the DNA pair up with bases from the other strand, forming the rungs of the ladder: A always connects with T, and C always connects with G, to form units called *base pairs*. At 186,000 base pairs, the gene for factor VIII is one of the largest-known genes. The gene for factor IX is much smaller, at about 34,000 base pairs.

1. Not all the bases in a gene code for a protein. In other words, the size of the gene is not directly related to the size of the protein it codes for.

A *genome* is the body's complete set of DNA. The human genome contains about 3.2 billion base pairs, which are all contained in 23 pairs of *chromosomes*, housed in the nucleus of each of our cells. The entire human genome contains an estimated 19,000 genes.²

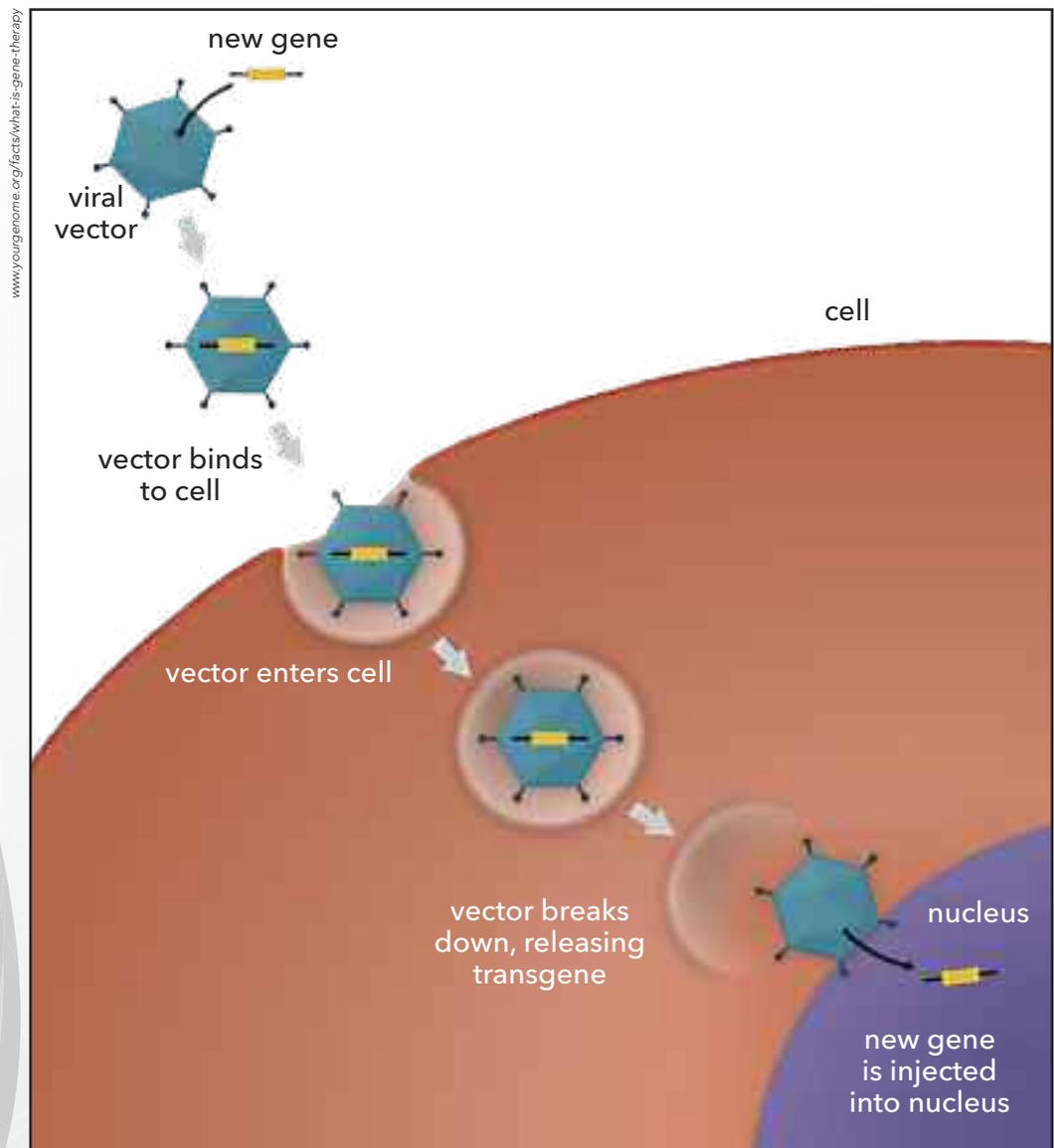
This all sounds technical, but having a basic understanding of these terms will help you understand the challenges and risks of gene therapy. And will explain why, for example, research into gene therapy for factor VIII has proven more difficult than for factor IX.

Gene Therapy Approaches

The goal of gene therapy is to get a functioning copy of a gene into the body so, in the case of hemophilia, the body can then produce functional factor VIII or IX on its own. To accomplish this, researchers are taking one of three approaches that sometimes overlap:

1. **Gene therapy.** Gene therapy involves adding a gene to cells, though in popular media, the term gene therapy often means any of these three approaches.

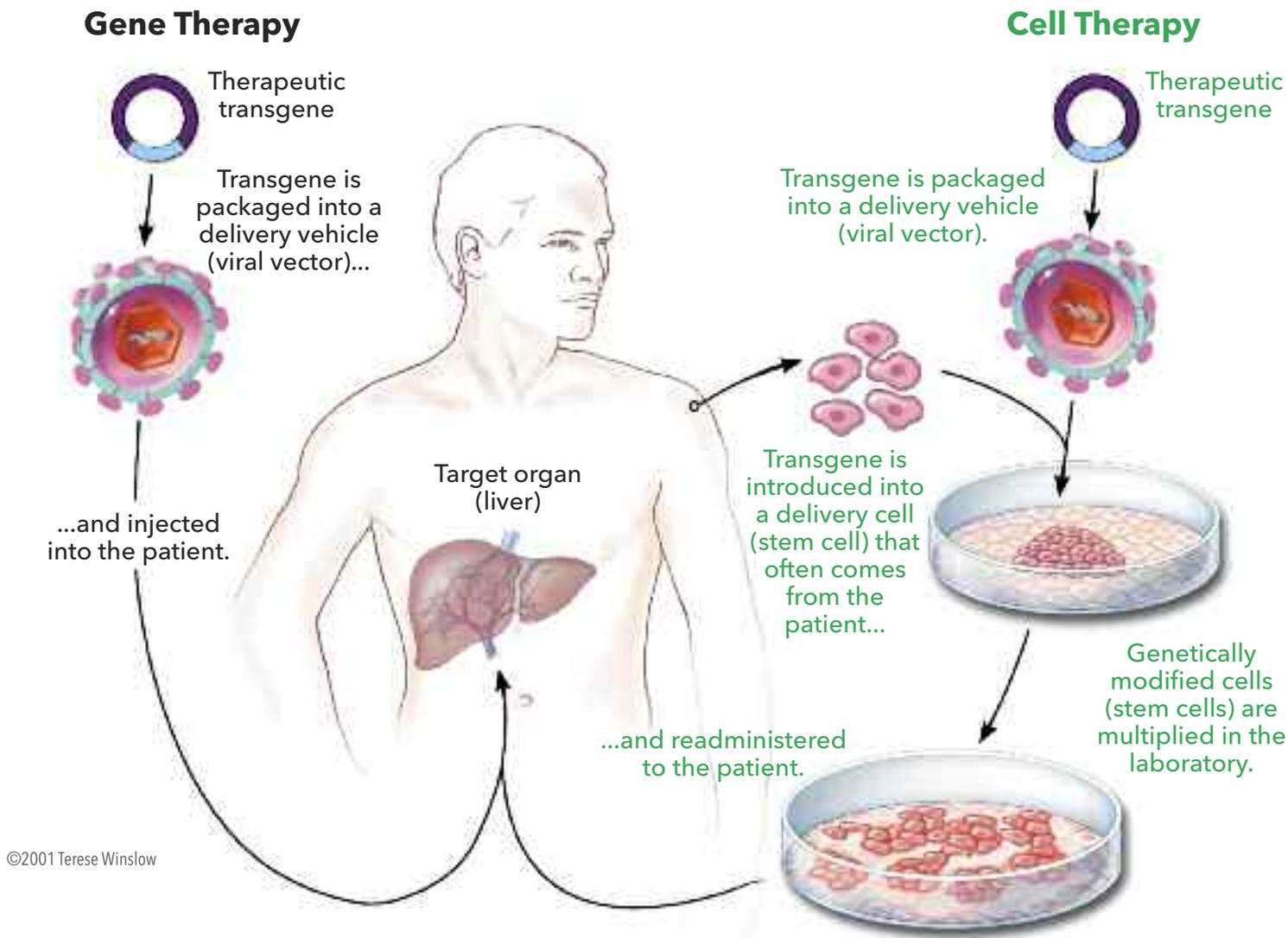
Transfer of a new gene into the nucleus of a cell using a viral vector



2. In 2001, the Human Genome Project completed sequencing (determining the order of base pairs) of the entire human genome—all 3 billion letters. That's enough information to fill 500,000 double-sided, 8.5" x 11" single-spaced pages—a stack of paper 16 stories high!

Gene Therapy and Cell Therapy

Two Approaches to Curing Genetic Disorders



2. **Cell therapy.** Take cells from the patient (for example, stem cells that can specialize and continue reproducing), insert a good copy of the gene into these cells, grow the cells to large numbers (tens to hundreds of millions), and then inject the cells back into the patient.
3. **Genome editing.** Cut out a gene (such as the defective gene), supply the cell with a good gene, and then use the cell's DNA repair mechanisms to insert the good gene into the place where the defective gene was cut out. This is the most recent approach of the three.

Getting the Gene into Cells

Now comes the hard part: How exactly *do* you put a good copy of a gene into tens of millions or hundreds of millions of cells—enough

cells so the body can produce sufficiently high levels of factor?

To do this *in vivo* (Latin for “in the body”), researchers use viruses. Viruses are experts at infecting and replicating (reproducing). They infect a cell and inject their genetic material in order to take over the cell’s machinery. They then replicate themselves. They are also experts at evading the body’s immune system, which wants to destroy them.

There are 219 known viruses that infect humans.³ Only about a half-dozen of these are used in gene therapy research. In hemophilia research, only two viruses are currently being used: the *adeno-associated virus* (AAV) and the *lentivirus*. Of the 12 gene therapy trials in hemophilia, 11 either use or will use the AAV. To use a virus for gene therapy, most of the “guts” or genetic material of

3. There are probably thousands of viruses that infect humans: viruses we’re not aware of and that do not cause disease.

the virus is removed, and then a good gene for factor VIII or IX is inserted. The inserted 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. The virus is now called a *vector*, a stealth vehicle for delivering the transgene to specific cells. The vector is grown to very high quantities (sometimes as high as 4,080 trillion vectors for a 150-pound person) and injected into the patient. Here's a new term: rather than "infect," which means the virus can use the cell to make copies of *itself*, researchers prefer the word "transduce," meaning the vector can deliver a gene but cannot make copies of itself. By making vectors unable to infect cells and replicate, we prevent them from causing disease. This makes them safer to use.



When Viruses Are Good: AAV Benefits

It may seem strange to use a virus to deliver genes. But viruses like AAVs have infected mammals for hundreds of millions of years—they are the ultimate gene-transfer machines. AAVs have several key properties that make them good vectors for gene therapy.

As vectors, AAVs . . .

- Don't cause any known human disease.
- Have low toxicity, meaning they don't harm the cells they infect.
- Can be modified to *preferentially transduce* (choose to deliver the gene to) a particular type of cell, such as liver cells, where most factor VIII and IX is produced.
- Don't produce a strong immune response, which might endanger the patient's life or destroy the therapy.
- Can make transduced cells produce factor for prolonged periods.
- Transduce both dividing and non-dividing cells. This is important because in most hemophilia gene therapy, the target is the liver, which in adults is composed mainly of non-dividing cells.
- Mostly avoid the problem of *insertional mutagenesis*, which happens when a vector inserts its transgene into the wrong place in the genome. If the gene is put into the wrong place, it can either knock out another gene or cause cells to start reproducing out of control—resulting in cancer.

AAV Drawbacks

Over 150 variations of AAVs have been recognized, each identified with a number, such as AAV2 or AAV8. Each variation has a slightly different DNA sequence and proteins on the outer coat of the virus, giving it certain advantages and disadvantages.

Which AAVs are best for hemophilia gene therapy? First, researchers want an AAV variant that will preferentially transduce a specific cell type, and produce high levels of factor. But we must also consider patient immunity to the AAV. Why is this important? If you've previously been infected by a certain virus, then you are immune to that virus (and the vector made from it), and the gene therapy will not work. If *many* people are already immune to a vector, then the market for that particular gene therapy will be very limited. For example, up to 70% of humans have already been infected with AAV2, making it a poor choice for a vector. The most commonly used vector for hemophilia gene therapy is AAV8, to which only 33% to 50% of people are immune.⁴ Immunity to vectors may pose the greatest roadblock to widespread use of gene therapy.

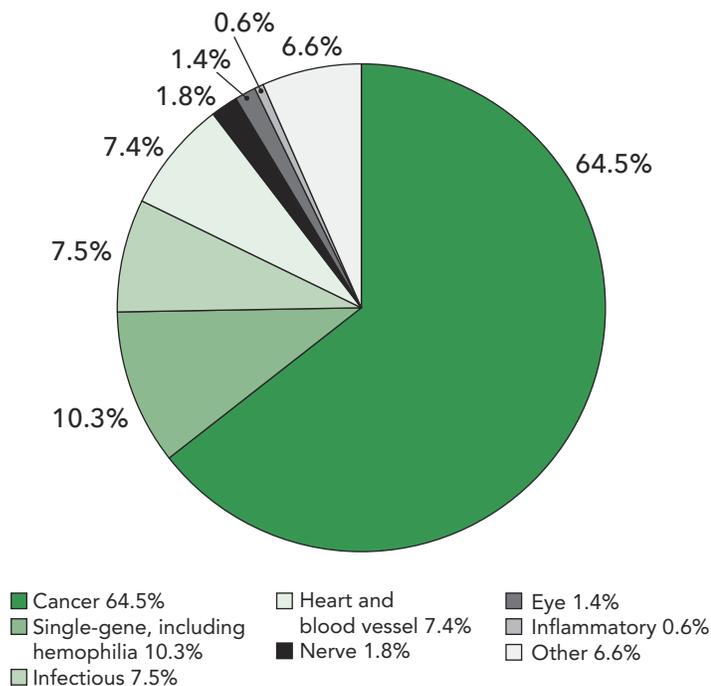
AAVs do have one major drawback: an AAV can only carry genes that are less than 5,000 bases long. Not a problem for factor IX, because the *coding sequence* of the gene—the essential part of the gene that tells the cell how to make a protein—is only 1,400 bases long. But it is a problem for factor VIII, which has a coding sequence of 7,000 bases—too long to fit in the AAV. Researchers are working with a smaller factor VIII variant that is 4,370 bases long, and working on ways to squeeze it into an AAV along with the other genes necessary to “turn on” the gene in the cell to make it produce factor.

Challenges Facing Gene Therapy

Research into gene therapy has come a long way since the first gene therapy trial in 1989. But there are still some challenges. The right gene therapy needs to accomplish these tasks:

4. There is a high level of crossover immunity. Infection by one AAV often trains the immune system to identify and attack other AAVs.

Diseases Addressed by Gene Therapy Clinical Trials



Adapted from Wiley & Sons: www.wiley.com/legacy/wileychi/genmed/clinical

Avoid the immune response. This can be done by (1) choosing vectors that are less likely to trigger a strong immune response (such as AAVs); and (2) choosing a less common vector, to which patients are less likely to be immune.

Target the right organ. For hemophilia gene therapy, the “right organ” means the liver or cells lining the blood vessels. Research is underway to customize vectors so they will preferentially transduce liver cells.

Avoid insertional mutagenesis. Different vectors may insert their genetic material into different places: some, like AAVs, insert their genes into the cell nucleus, but not into the cell’s DNA (the cell’s genome). Other vectors may insert their DNA into the cell’s genome. If a vector carrying the functional hemophilia gene inserts it into the genome, it must be at the right place—to avoid causing cancer or knocking out another gene (which could cause another genetic disorder). Imagine trying to insert a sentence you want in a specific place in 1 million pages of single-spaced text! Theoretically, this can be done—it’s sort of like a Google search. The more words you add to your search string, the more specific your search becomes, until it returns only one selection that matches your search. Although AAVs don’t normally insert their genes into the genome, other kinds of vectors do; and because our current treatments are not yet specific enough to target only one place in the genome, this might cause problems if vectors insert their transgenes into unwanted locations.

Regulate the gene. Even if the right cell has been targeted and the gene is inserted in the right place, we then need to make sure the gene is “turned on” so it produces factor.

Ensure prolonged expression of factor. In many experiments, *expression* (or factor production) of the transgene decreases over time as cells die, divide, and inactivate or remove the transgene. In some cases this is a good thing, as in gene therapy for cancer, where the inserted gene needs to be active only until the treatment ends. But in hemophilia, we want gene therapy to last a lifetime. AAVs are able to establish long-term expression—at least a decade in animals—but *exactly* how long, we don’t yet know. And we want the initial expression rates high enough that, even if the factor level were to decrease over time, there would still be enough factor produced to adequately clot the blood.

Today’s Hemophilia Gene Therapy

Researchers are optimistic that several new gene therapies for genetic disorders will be licensed and marketed within the next decade. Worldwide, already half a dozen approved gene therapies are commercially available, including two in Europe and four in China. Although there are currently no FDA-approved gene therapies in the US, the first—for a type of inherited retinal disease that causes blindness—is expected to be approved this year.

In hemophilia factor IX gene therapy trials, Spark Therapeutics and Netherlands-based uniQure are in the lead. Spark’s factor IX gene therapy has produced impressive results, with an average factor level of 32%, which would make a person with severe hemophilia into one with mild hemophilia.

In factor VIII gene therapy research, BioMarin Pharmaceutical has had outstanding initial results, with six of seven patients in the high-dose group producing factor VIII in excess of 50% (normal range is 50% to 150%). In other words, the patients were cured of their hemophilia. Whether factor levels in these trials remain stable over time remains to be seen; the patients have been followed for only about a year. In the longest-running hemophilia clinical trial, started in 2010, six of seven patients at University College London and the Royal Free Hospital London treated in the high-dose group have had their severe hemophilia converted to mild hemophilia, with gene therapy using an AAV8 vector developed at St. Jude Children’s Research Hospital in Memphis.

Technically, gene therapy for hemophilia is almost ready for prime time. Many problems that have dogged gene therapy research are now solved, or are on the verge of being solved. Low factor expression levels—an ongoing problem—have been boosted into the normal range in some trials. We are better able to modify vectors so they preferentially transduce specific cells, such as liver cells. And we have improved our ability to target where a vector inserts its transgene into the genome, reducing the risk of cancer or other complications. Long-term expression of factor—a key objective in hemophilia gene therapy—through the use of AAVs has now been observed in humans for seven years (and longer in animals). We have learned to counteract immune responses that might inactivate a gene therapy treat-

Current and Future Hemophilia Gene Therapy Trials

Company	Therapeutic gene	Product (Vector)	# Subjects Date of first patients dosed	Peak factor activity (%) (Range)	Sustained activity (%) at follow-up period
Bioverativ	Factor IX Padua variant*	(lentivirus)	Preclinical		
Dimension Therapeutics	Factor IX	DTX-101 (AAVrh10)	1 subject, ongoing 2016		
Freeline Therapeutics	Factor IX	FLT-180 (rAAV)	Enrolling Expected 2017		
Pfizer/ Spark Therapeutics	Factor IX R338L Padua variant	SPK-9001 (AAV8)	7 subjects, ongoing 2015	44% (20%–44%)	Mean 32% at 12–52 weeks
Sangamo Therapeutics	Factor IX	SB-FIX-1501 (AAV2/6) ZFN-mediated in vivo genome editing	Enrolling 2016		
UCL/ RFH/ SJCRH	Factor IX	(AAV8)	10 subjects, re-opened, now 12 enrolled 2010 (new study starting 2017)	12% (2%–12%)	>5% for 6 of 7 high-dose patients at 7 years
uniQure	Factor IX	AMT-060 (cell therapy using AAV5)	10 subjects, ongoing 2015	13% (3%–13%) (5 high-dose patients)	Mean 7% for 5 high-dose patients at 6 months
BioMarin Pharmaceutical	Factor VIII	BMN 270 (AAV5)	9 subjects, ongoing 2015	271% (12%–271%)	>50% for 6 of 7 high-dose patients at 20 weeks
Dimension Therapeutics/ Bayer	Factor VIII	DTX-201	Expected 2017		
Sangamo Therapeutics	Factor VIII	SB-525 (AAV6)	Expected 2017		
Spark Therapeutics	Factor VIII	SPK-8011 (rAAV)	Enrolling 12/2016		
Shire	Factor VIII	BAX-888 (AAV8)	Enrolling Expected 2017		

*Padua variant: a super-active form of factor IX with seven times the activity of normal factor IX. Unless otherwise noted, all trials are in phase 1/2.

UCL: University College London
RFH: Royal Free Hospital (UK)
SJCRH: St. Jude Children's Research Hospital (US)

ment or endanger the life of the patient. And the short-term safety of current gene therapy approaches has been documented.

But some questions remain: Does a particular treatment carry an increased risk of cancer? Which gene therapy approach works best? Clinical trials currently underway or yet to be devised will provide the answers.

On the consumer side, we also have many questions: What sustained factor level will patients accept as a “cure”?⁵ Would you be willing to undergo a gene therapy treatment if it was not permanent? Will gene therapy work if you have liver disease? Will it work if you have an inhibitor? Can it be used for immune tolerance therapy to eliminate inhibitors? Will it work as well in babies or young children as in adults?⁶ Are children at higher risk of long-term complications as compared to adults? How do you balance the risks—unintentional mutations, cancer, severe immune response, even death—versus the benefits? And the million-dollar question: What will it cost?

These questions, and many more, must be answered before gene therapy becomes a reality. But one thing is certain: gene therapy for hemophilia is coming, and relatively soon! ☺

University College London Hospitals Biomedical Research Centre



Sebastian Misztal, 31, a patient in a UCL hemophilia gene therapy trial in 2011. After treatment, Sebastian no longer had spontaneous bleeding episodes.

5. In the minds of people with hemophilia, the word “cure” has different connotations. See the article in YOU (page 6) for a discussion of what cure means to members of the hemophilia community. 6. On one hand, gene therapy may initially be more successful in children because of their immature immune systems and lower immunity to vectors. On the other hand, the therapy may become less effective over time because as cells multiply, they tend to remove DNA not integrated into the genome; this would reduce factor levels. And as organs such as the liver grow larger as a child grows, the number of cells with the good gene become diluted (fewer in number relative to the size of the organ); this also would reduce factor levels.



Sponsor a child with hemophilia

It's rewarding and teaches unforgettable lessons

Facing another morning infusion, 10-year-old Andrew* looks at the picture of his beneficiary, 12-year-old Abil from the Dominican Republic, and sees Abil's swollen knees from repeated untreated bleeds. Each time this reminds Andrew just how fortunate he is to live in a country with factor.

Become part of our world family. A sponsorship is only \$22 a month!

A child is waiting for you at: www.saveonelifenet

Or email: contact@saveonelifenet

* name has been changed

headlines

nonprofit

Help Is Here!

Hemophilia Federation of America's Helping Hands Program aids hundreds of families affected by inhibitors with urgent basic living expenses (housing, transportation, utilities), reimbursement of durable medical items, medical or educational travel, and educational support (tutoring).

Supported by Novo Nordisk and Hemophilia Alliance. **Why this matters:** Medical costs can affect families with bleeding disorders who need extra help in paying everyday bills.

For info: www.hemophiliafed.org



Patrick Lynch interviews attendees at a recent event.

Power to the People

Powering Through is a free monthly podcast that features empowering panel conversations on what it takes to overcome life's challenges. Held live at bleeding disorder events around the country. Guests include iconic advocate Jeanne White-Ginder, TIME columnist Joel Stein, NHF CEO Val Bias, and many others. Sponsored by National Cornerstone Healthcare Service and produced by Believe Ltd. Hosted by Patrick James Lynch.

Why this matters: Podcasts are lively, current, audio ways to learn about hemophilia and community concerns from experts.

For info: www.poweringthrough.org



A Legend Leaves Us: Corey Dubin

On January 4, 2017, the hemophilia community lost a legend. Corey Dubin, an extraordinary person, passed away at his home in California. Corey had hemophilia and contracted HIV from tainted blood products. He became one of the community's foremost advocates to win compensation for those infected by factor concentrates, and he helped draft the Ricky Ray Hemophilia Relief Fund Act. In 1992, Corey co-founded the Committee of Ten Thousand (COTT), a nonprofit that represents

the thousands with hemophilia who were infected with HIV. In 1995, Corey was elected president of COTT. From 1995 to 1999, Corey was appointed a voting member of the FDA Blood Products Advisory Committee, the first consumer to ever hold the position. He went on to participate in several state and national working groups on blood safety and AIDS education. Corey worked tirelessly to ensure safety of the nation's blood supply to prevent future HIV and hepatitis infections.

manufacturer

Reducing Bleeds without Factor

Alnylam Pharmaceuticals reported encouraging results with ALN-AT3, a once-monthly dosing of subcutaneously administered RNA interference (RNAi) therapy that targets antithrombin (AT). The results are from part D of a phase 1 trial of 16 hemophilia A and B patients with inhibitors. Based on these findings, the company plans to advance ALN-AT3 into pivotal clinical studies in early 2017. There were no reported thromboembolic events, and all adverse events were mild or moderate in severity. **Why this matters:** A subcutaneous, once-monthly infusion would greatly improve quality of life for patients with hemophilia, especially with inhibitors.

For info: www.alnylam.com

Peaks and Troughs

Researchers have found that a daily infusion of low-dose factor VIII improves trough levels in patients with severe hemophilia A—compared to infusions performed every other day—without increasing factor VIII consumption. Trough levels are the lowest amounts of factor in a patient's bloodstream. The study involved six Chinese patients with hemophilia A who were treated for two weeks. **Why this matters:** The ability to sustain higher trough levels with daily prophylaxis, and the presence of daily peaks, may be a more effective prophylaxis regimen in the long term and could result in less bleeding than the every-other-day regimen.

For info: *Haemophilia*, Jan. 22, 2017

- Shire results from a phase 3 clinical trial of **Vonvendi** demonstrated that the product effectively controlled intraoperative bleeding and blood loss in adults with VWD undergoing major, minor, and oral elective surgical procedures.
- More than 12 million people have been newly enrolled in **Medicaid** as a result of the ACA expansion, one of the positive achievements of the law.
- **46 NHF chapters** across the US help patients get involved in the bleeding disorder community.
- Listen to a podcast about the opportunities of prophylaxis as a treatment option in **developing countries**: elearning.wfh.org/resource/wfh-webinar-treatment-options-for-hemophilia-in-the-developing-world
- In what is believed to be a first, the parents of a 25-year-old hemophilia A patient in **Mumbai, India**, donated his heart and kidneys to save the lives of three terminally ill patients.
- Adynovate, Shire’s prolonged half-life recombinant factor VIII product, is approved for use in treating pediatric **hemophilia A patients** age 12 and younger, and also for use in surgical settings for both children and adults with hemophilia A.

insurance

Threat to Medicaid?

NHF is closely monitoring the Trump administration’s approach to Medicaid, in light of attempts to repeal the Affordable Care Act. More than one-quarter of the US bleeding disorder population relies on Medicaid to pay health expenses. Medicaid, a government health program for low-income Americans, is a federal-state partnership: the federal government provides guidelines, and states administer their individual programs. **Why this matters:** Medicaid comprises about one-quarter of total state budgets, making it a target for scrutiny. *For info:* hemaware.org/story/minding-your-medicaid

A First in the Philippines

In February, Philippines Senator Joel Villanueva filed Senate Bill 1335, Bleeding Disorder Standards of Care Act of 2017, to establish hemophilia treatment centers for the first time across the country. Currently the Philippine government funds no treatment for patients with hemophilia or von Willebrand disease. Andrea Trinidad-Echavez, president of Hemophilia Advocates–Philippines and a woman with VWD, helped draft and introduce the bill. **Why this matters:** This bill is the first serious effort of patient advocacy groups in the Philippines to lobby for government support.



Senator Joel Villanueva

For info: www.huffingtonpost.com

New from LA Kelley Communications



Raising a Child with Hemophilia

25th anniversary edition is here! This groundbreaking book is back, with information every parent needs on living with and managing hemophilia as a child develops. Free to families.

For info: www.kelleycom.com



science

Another Setback for ACE910?

In November 2016, Roche reported blood-clotting problems in four hemophilia A patients with inhibitors being treated with an aPCC (FEIBA) for breakthrough bleeding in the trial of ACE910 (emicizumab). Two of the patients developed thrombotic microangiopathy (TMA, or blood clots in tiny blood vessels: capillaries and arterioles). In February 2017, Roche reported the death of a patient in the ACE910 trial. The patient developed a serious rectal bleed, was given multiple doses of FEIBA, and started showing signs of TMA. The aPCC was discontinued and the TMA improved, but the patient refused a blood transfusion, and died as a result of the bleed. The study’s steering committee recommended not using an aPCC in patients receiving emicizumab; or, if needed, to use it starting with the lower range of the recommended labeled dose, under monitoring. **Why this matters:** This may be a setback for Roche, which has reported a promising safety and efficacy profile from long-term testing of ACE910 to treat hemophilia and people with inhibitors.

For info: www.ehc.eu/roche



YOU... from page 6

successful—a “cure”? Remember that severe hemophilia means less than 1% circulating factor, moderate means greater than 1% to 5%, and mild means 6% to 50%. Anything over 50% is considered in the normal range.³

For Ray, levels of circulating factor would have to be well over 40% and closer to 50% (normal) to be considered a cure.

But others think that even converting someone from severe to mild hemophilia could be considered a success. Nichole Foley writes, “I think taking a person from severe to mild hemophilia is enough of an advantage for some of these kids that have constant challenges, and hopefully it will alleviate inhibitor issues.”

Bryce Loehrke says, “If gene therapy could permanently bring me to the levels of even mild hemophilia, I would consider myself cured for the most part. Having severe hemophilia A, I’ve often said that those with mild hemophilia don’t even have hemophilia. I don’t mean to diminish the fact that they still have issues from it periodically, but often with much less severity or frequency, sometimes to the point of not knowing they have it until later in life.”

Tina Ruis takes this even further. “My 24-year-old son with severe hemophilia B—his left leg is unbearable. His calf is massive, and he can barely move without a walker. Levels of 11% to 15% would be worthwhile; over 25% would make me cry with joy.”

Stephen Brewer would be happy if gene therapy worked, even if it wasn’t permanent: “I would accept having mild hemophilia even if only for a few years.”

Chris Templin and his daughter both have hemophilia B. Chris notes that aiming for “mild” hemophilia is fraught with inconsistencies. “I think it’s interesting how people think all those with mild hemophilia bleed less than severe hemophilia patients. I know some milds who bleed more than some severe patients.”

The price of success

If gene therapy is successful and becomes available, how much would it cost? Some families think that because gene therapy trials are being held at university hospitals and hemophilia treatment centers, its cost may be lower than that of current commercial therapies. But this is not correct, because the trials are underwritten by pharmaceutical companies and the manufacturing process would ultimately need to be upscaled by a commercial pharmaceutical company.

The issue of cost for a new therapy is complex, and includes these questions:

- What is an acceptable therapeutic factor level: moderate, mild, normal?
- How long will the treatment last: three years? permanently?
- Will other factor products need to be used during the treatment period?

Ray estimates the cost of a one-time treatment of gene therapy at “close to \$1 million, given the low number of patients, the cost of research and development, and assuming



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Raphy
Hemophilia A
California

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that the therapy is successful for four years.” He adds, “For the manufacturers, as much as they can charge; for the insurers, the least amount they have to pay.”

Nichole Foley doesn’t care: “Cost-wise, I am sure it will be astronomical, but if [gene therapy] enables kids to live a normal life, I’d think it would be worth it!”

Bryce believes, “If there’s an effective lifetime cure, \$250,000 will be a lowball figure. We need to convince insurance providers of the long-term savings of a permanent or semipermanent cure.”

What if gene therapy is good for only a few years?

The term “cure” isn’t applicable at all if gene therapy—even if it brings your factor levels to normal—lasts for only a few years. This is a real concern.

Ray explains: “Given that the current vectors are viral and the immune system develops a response to that vector so that once used, it cannot be used again, this is problematic if the period of time that the treatment persists is short. There may not be time to develop an alternate type of vector. However, given the speed at which medical advances are occurring and

accelerating, having the treatment persist for more than ten years might be enough to get you to the next vector, whatever that might be.”³

Amber Brandt, mother of a child with hemophilia, worries, “Regular factor is so expensive, I don’t see gene therapy being cheap by any means. And I’m sure it would be a huge struggle to get insurance to cover it. But if it only lasts a few years, I don’t even think it would be worth [trying] it at all.”

Wait-and-see approach

Patients who don’t see any solutions to these concerns may adopt a wait-and-see approach. Some are inherently mistrustful of playing with genes, or of the whole commercial industry of factor manufacturing. Some feel that current therapies are good enough for now.

Brandi Worthington admits, “I don’t know anything about gene therapy.” Amber adds, “It’s fascinating, but I would never choose that option for my son. He can choose that if he wants when he is an adult.”

“I won’t be a first adopter for gene therapy by any means,” declares Bryce, “primarily due to distrust of the entire pharmaceutical

industry for various legitimate and historical reasons. We need to know the consequences as well as benefits [of gene therapy].”

Ray concludes, “Depending on the factor levels achieved and the duration of the treatment and the usable number of vectors...I might wait and see.”

Stepping-stone to a cure

Ray understands well the nuances and importance of educating the hemophilia community about gene therapy. Parents and patients will one day need to make an informed decision about whether to participate in it. “We as a community first need to define the parameters of what we would consider a cure,” says Ray. “I have always had a strict interpretation of this word. A cure would be a single treatment that provides normal hemostasis over the lifetime of the person living with hemophilia. Anything less than this should be considered a stepping-stone toward a cure.”

Stephen still has hope and carries the definition of cure even further. “Looking forward, a cure would include increasing circulating factor levels, [and] eliminate hemophilia from future generations [of a family].⁴ This is the ideal I hope for.” ☺

3. Among the general population, normal factor levels are between 50% and 150%, with most people being close to 100%. 4. Changing the genetics of future generations is not gene therapy, but *human germline engineering*. This practice is currently banned. It’s highly unpredictable, dangerous, and considered unethical.

Inhibitor Insights... from page 4

if your child has 0 BU and a three-hour half-life of factor in his body, he will probably continue with the same ITT therapy, which may be daily infusions. ITT is not always successful: an ITT attempt in which inhibitor titers fail to decrease at least 20% over three to six months, or remain over 5 BU after three to five years, is considered a failure. This example shows that not only is BU important, but monitoring the number of hours for the half-life is critical to treatment. So how does a family live with the numbers?

“Lab work disappointment” is a phrase Kari Atkinson’s family used when the numbers were not what they had expected for their son. “We had so much hope that the inhibitor would go away.” But now, says Kari, “we are not as concerned about the number because we can tell when [the BU is] up and down by how our son bleeds.” How an individual’s body reacts to treatment is the ultimate measure of success. If you’re living a full life with few bleeds and an active inhibitor, the important thing is that you are healthy, happy, and thriving. Eric Frey’s son, age seven, has lived with an inhibitor for over five years. “After time, we learned two things: First, we already knew what the results [BU] were going to show by the way our son was bleeding, bruising, and behaving. Second, the Bethesda number is far less important than how our son was bleeding, bruising, and behaving.”

Despite living full, healthy lives with an inhibitor, many families still worry about the numbers. “Making peace” with the inhibitor is something that most people don’t want

to do. It can feel as if you’re giving in and accepting that the inhibitor will always be present. In order to live a life where hemophilia is not the center of everything, making peace is crucial. “We have had enough experience that we know if the inhibitor is under 7 BU, we are living pretty good,” says Kari. Her family is not focusing on 0 BU, but for now, they know that anything under 7 BU is acceptable. “It’s really hard to not focus on the numbers, especially when you have the active inhibitor and either you need to get below 10 BU to start ITT, or you are doing ITT and trying to get down to zero,” says Eric. “We understand how hard that is. Focus on health. Focus on wellness.”

Numbers are essential for people living with inhibitors. Keep track of bleeding episodes because this is a significant tool to see if your treatment is appropriate. Continue your regular blood draws according to your provider’s recommendations. Even if you’re not a slave to the BU, it’s vital to monitor the progress of your inhibitor. The key is to enjoy life. Savor every moment. When things aren’t going well, try to remember that life will get better. And when life is good, soak it in. ☺

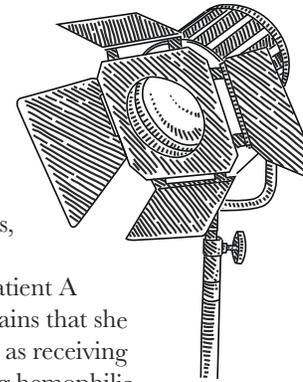
Cazandra Campos-MacDonald is a motivational speaker, educator, and patient advocate for families with bleeding disorders. She writes a blog chronicling the journey of her two sons with severe hemophilia and inhibitors, and has written articles and blog posts for other publications. Cazandra’s older brother, Ronaldo Julian Campos, died of complications from hemophilia as an infant. Cazandra lives with her family, Rev. Joe MacDonald, Julian (20), and Caeleb (11), in Rio Rancho, New Mexico.

AIDS Plays



The collection *Theatre for Young Audiences: 20 Great Plays for Children* (1998), edited by Coleman A. Jennings, contains the award-winning play *The Yellow Boat* (1993) by David Saar. This playwright wrote about his son's struggle with hemophilia and AIDS. The play is a biography of Benjamin Saar (1979–1987), who infuses factor VIII and expresses himself through visual arts during his short life. Using his imagination, Benjamin describes his feelings of physical and emotional pain with a blaze of colors and shapes in his drawings and paintings. After Benjamin tests positive for HIV, his friends pull away. No one comes to his seventh birthday party, he cannot attend school, and he is ineligible for AZT treatment.* This emotional play, written for children but appreciated by adults, continues to be produced onstage.

Two plays mention having hemophilia as one of the risk factors for acquiring AIDS before factor concentrates were made much safer. Award-winning playwright Christopher Durang published *Baby with the Bathwater* and *Laughing Wild* (1989). The surprising comic play *Laughing Wild* contains a series of monologues and dream sequences for two characters. In one rant, a character reveals his bisexuality and questions God's purpose for punishing homosexuals, drug addicts,



and hemophiliacs. Playwright Lee Blessing published *Patient A* (1993), based on a true story. This one-act play concerns Kim Bengalis, who was infected with HIV at age 22 by her Florida dentist. CDC investigators label her Patient A when they explore her unusual case. Kim explains that she doesn't have any of the usual risk factors, such as receiving blood transfusions, being a drug user, or having hemophilia. Hers was the first known case of HIV transmission from a healthcare worker to a patient, which occurred very rarely.

Early Plays

Plays dating back to the 1930s include hemophilia onstage. The collection *The Best Plays of 1935–1936 and the Yearbook of the Drama in America* (1936), edited by Burns Mantle, includes the play *Victoria Regina* (1935) by Laurence Housman, who had more plays censored than any other English dramatist. His play about Queen Victoria opened in New York City. Unfortunately, Housman included incorrect information about the introduction of the royal hemophilia gene by claiming that Victoria's cousins, Prince George and Prince Albert, had hemophilia, so Victoria should not marry either of them. Today we know that Queen Victoria most likely had a spontaneous mutation for the hemophilia B gene that was passed on to her descendants.

James Reach wrote *The Case of the Laughing Dwarf* (1938). This fast-paced, frolicking murder mystery play has roles for six men and six women, who perform in one interior scene, the lobby of a secluded hotel in Georgia named the Laughing Dwarf. Whenever someone dies, a shrill laugh is heard. After two guests die, the police inspector methodically reveals the murderer, who uses a fountain pen that fires a tiny bullet. The bullet explodes inside the victim's body, transforming the atomic structure of the blood to cause hemophilia, so the victim bleeds to death. This scenario is simply too improbable to be believable except in this entertaining play, but of course it was set in 1938.

So have a pleasant evening attending a play that includes hemophilia. I recommend both *Shivaree* and *The Yellow Boat*. But you may act like me, and criticize any medical inaccuracies. ☺

* Azidothymidine (AZT) is an antiretroviral medication used to prevent and treat HIV/AIDS.





Looking for a new, fresh perspective on living with hemophilia?



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PROJECT SHARE

I HAVE RECEIVED 24 VIALS of factor VIII you sent for my sons. I am so grateful, and we are very happy! May the good Lord continue blessing Project SHARE so that others may benefit as I have done.

Chimwemwe Chande
MALAWI

MY DEEP THANKS for the generous donation you sent to our nephew Andrew. The factor reached Egypt safely, and he started using it after his case got worse in the last few months.

Those vials were lifesaving. Only now has Andrew started to resume his normal activities. We appreciate that you could send so much, as it has been even more challenging to find these vials in Egypt these days.

No words can express our appreciation for the huge impact your dedicated efforts have had on Andrew's life. Thank you so much.

Mariam Shokralla
EGYPT



INITIALLY I REQUESTED FACTOR FOR Kovacs Levente for a dental procedure. In the meantime, he developed a huge abdominal hematoma and was taken by ambulance to the local hospital. There he received plasma.

Kovacs is allergic to plasma, but that's all they had to give him. The hematoma was getting bigger and bigger, reaching 30 cm, according to the doctor. The pain was excruciating.

This factor arrived just in time to save his life. I don't know how to thank you!

Adriana Henderson
President, STAR Children's Relief
ROMANIA

MY SINCERE GRATITUDE for your selfless service to our society and people with hemophilia in Kenya in 2016. Last year was one of our most successful regarding factor availability. I look forward to the opportunities and challenges ahead, especially on organizing and conducting our first boys' hemophilia camp. Thank you all.

Kehio Chege
Jose Memorial Haemophilia Society
KENYA

THANK YOU VERY much for the factor you sent for two patients. Garay is now out of the hospital and is continuously being treated as an out-patient. Yrog-Irog also is out of the hospital and has fully recovered. For the help and support you have extended to our community members, we are more than grateful.

Mary Ann Navasquez
PHILIPPINES

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Walter O. Mwanda, MD
Chief Hematologist, Kenyatta Hospital
Patron, Kenya Haemophilia Association
KENYA



Dr. Walter Mwanda (left) of Kenya and his team, with Laurie Kelley

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