The Science Fair from BelieveLIMITED

OFFICIAL PROGRAM

2020 VIRTUAL SCIENCE FAIR

The Science Fair is created & produced by

BelieveLIMITED

The Science Fair wishes to thank our Founding Sponsor

Spark THERAPEUTICS

Three years ago my team and I began developing an educational experience that aimed to teach and clarify some of the most important bleeding disorders science for our community. We focused on two primary audiences: parents of newly diagnosed children, and young community members who have not yet absorbed the science behind their bleeding disorders and treatment.

We asked ourselves, ***"If WE were to start relearning the science of bleeding disorders, HOW would we want to learn it?"*** The answer was easy: we would want to be moving around, using our hands, and engaging our intellect. We took a team field trip to the California Science Center in Los Angeles and entered new worlds, pulled levers, and pushed buttons. We gave ourselves over to the experience of manipulating objects to witness cause-and-effect firsthand (literally!). We left inspired.

Over the six months following that trip, we brainstormed our own larger-than-life modules that community members could touch, feel, and alter in order to achieve specific foundational knowledge - creating a clot by hand by combining factors 8, 9, and 10, or sending vectors into a liver undergoing gene therapy treatment, while working factor proteins emerge from the other side...

The inaugural event was held at the 2019 Bleeding Disorders Conference in Anaheim, California. Our hosts and clinicians guided just under 900 visitors through the Fair in a single day. While we can't wait to bring this incredible live experience back to BDC in 2021, we hope you enjoy the interactive online experience we've created this year.

Guided by our virtual host, Dr. Morales, this year's online Science Fair is a family-friendly, fun way to learn the fundamental science of today, the breakthrough science that brought us here, and the cutting-edge science guiding where we go next. Our modules are comprised of videos and posters teaching the science around hemophilia, vWD, rare factor deficiencies, women with bleeding disorders, and so much more-including the exciting science behind gene transfer!

We would like to thank the **National Hemophilia Foundation (NHF)** for supporting this event in the real world and virtually. We would also like to thank our Founding Sponsor, **Spark Therapeutics** for hearing our vision for The Science Fair three years ago and taking the leap with us. Without the support of both of these teams, The Science Fair would not exist. Thank you!

Health & Happiness,

Patrick James Lynch
Founder & CEO
Believe Limited

BUILT WITH GUIDANCE FROM LEADING CLINICIANS & EXPERTS

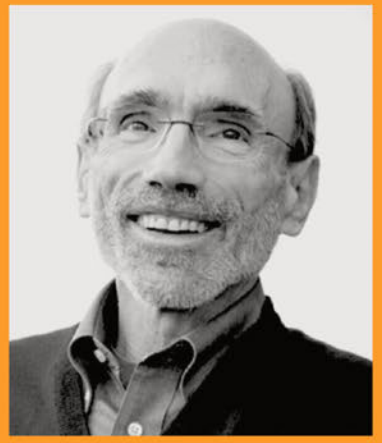
Believe Limited & The Science Fair wish to thank the generous clinicians from around the country who have donated their time to helping us grasp and translate some of the most important scientific concepts in our community into tactile learning opportunities for young people and families.

DR. MICHAEL WANG, MD

DR. DORIS QUON, MD

BRENDAN HAYES

DR. STEVEN PIPE, MD



DR. GLENN PIERCE, MD

DR. CHRISTOPHER WALSH, MD, PhD

DR. CINDY BAILEY, PT, PhD

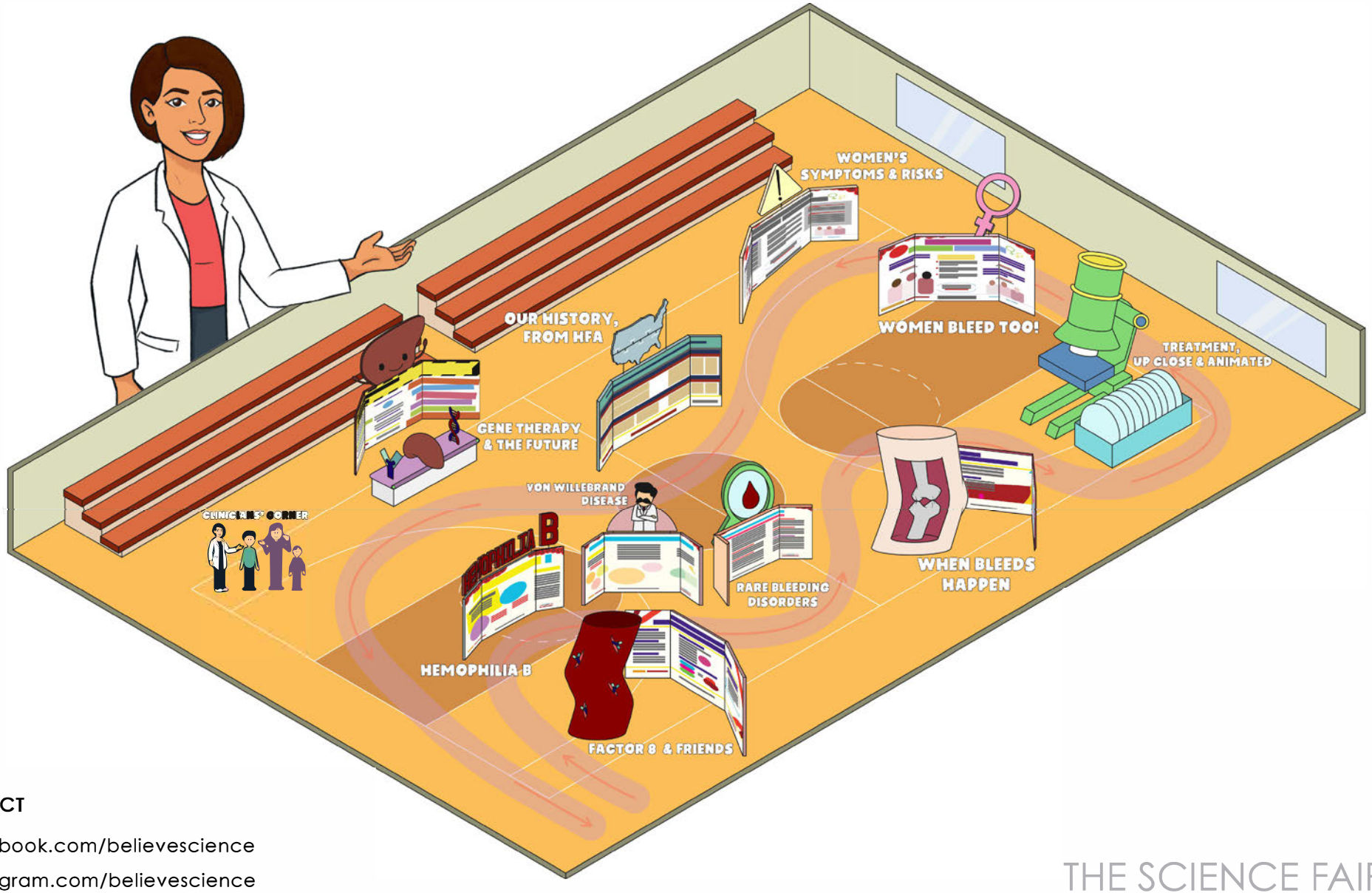
DR. MICHAEL TARANTINO, MD

Science fairs are a cornerstone of science education. Believe Limited has translated both the **fundamental and breakthrough science of hemophilia and bleeding disorder**s into a larger-than-life Science Fair comprised of modules with both **visual and hands-on experiences**.

This year, we've turned the Fair into a powerful **VIRTUAL** exprience.

Enjoy!

YOUR 2020 VIRTUAL SCIENCE FAIR



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FACTOR 8 & FRIENDS

THE SCIENCE FAIR

BELIEVE LTD | VIRTUAL | 2020

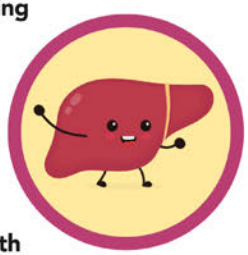
The Story of FACTOR 8 & Friends

Did You Know?

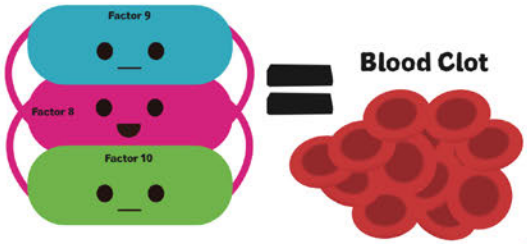
- **FACTOR 8** is only activated when there is damage to repair, which is how the body naturally protects itself against thrombosis.
- **FACTOR 8** deficiency results in hemophilia, deficiencies of **FACTORS 1, 2, 5, 7, 10, 11, 12**, and in bleeding disorders.
- One of the liver's main jobs is to produce proteins that it sends into the bloodstream? In total, the liver is responsible for producing 59% of human proteins.
- There are over 60,000 miles of blood vessels inside the average child. When one of those vessels tears, blood escapes, and that is what we commonly refer to as "a bleed."

What is FACTOR 8?

In a properly functioning clotting cascade, the protein known as FACTOR 8 is made in the liver. Once in the bloodstream, when bleeding occurs, FACTOR 8's job is to connect FACTOR 9 with FACTOR 10, so that together, they can help create a blood clot.



How FACTOR 8 helps form a blood clot



FACTOR 8 as Matchmaker

> *You're missing* **FACTOR 8**. *What does* **FACTOR 8** *do?* **FACTOR 8** *is sort of like the facilitator, like a matchmaker. It gets* **FACTOR 9** *and* **FACTOR 10** *close to each other like a matchmaker would bring two people together."*
>
> **– Dr. Michael Tarantino**

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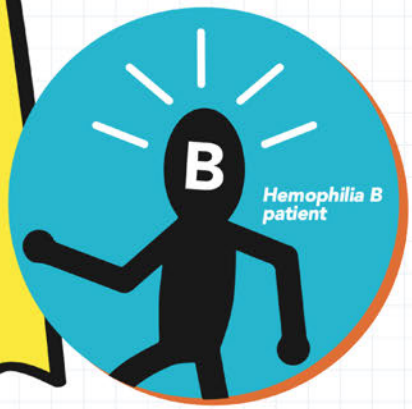
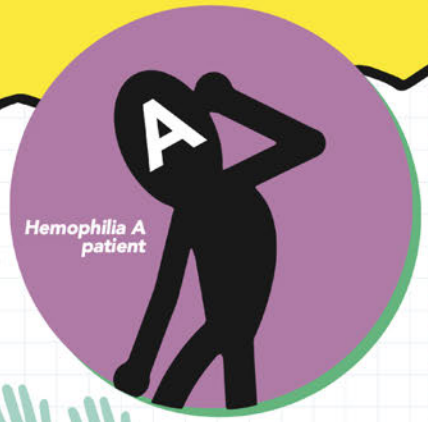
HEMOPHILIA B

People missing the FACTOR 9 protein have Hemophilia B.

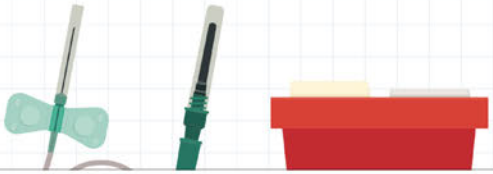
Hemophilia B is about 5x less common than **hemophilia A**, and while the presentation and symptoms can be very similar, different medication is required to treat each.





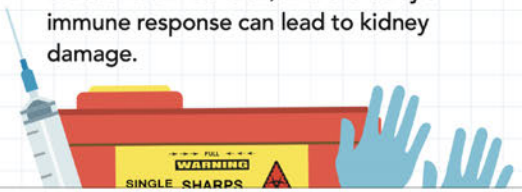
The risk of developing an inhibitor for hemophilia A patients is estimated at 30%.

The risk of developing an inhibitor for hemophilia B patients is a much lower 3-5%.



Did You Know?

- The **FACTOR 8** gene is extremely large and the **FACTOR 9** gene is considerably smaller and structurally simpler? This is partly why factor replacement products to treat **hemophilia B** generally boast longerhalf-lives than products from the same class that are used to treat **hemophilia A**.
- While around 30% of people with **hemophilia** A develop inhibitors, only about 3-5% of people with **hemophilia B** do? However, inhibitor development in a **hemophilia B** patient is much more serious. Immune tolerance induction (ITI) is largely ineffective, anaphylactic reactions can be fatal, and the body's immune response can lead to kidney damage.



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VON WILLEBRAND DISEASE

Did You Know?

Symptoms include mucocutaneous bleeds such as nose bleeds, bleeding from the mouth or gums, and heavy menstrual bleeding in women; however, symptoms can also include joint and muscle bleeds similar to those seen in hemophilia, which can complicate diagnosis and treatment decisions.

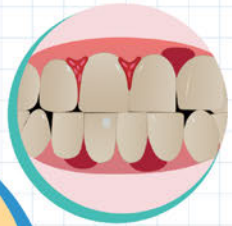
There are three types of vWD:

TYPE 1:
Low vWF levels; generally mild;
85%
OF PEOPLE WITH VWD

TYPE 2:
Normal vWF levels, but the protein behaves erratically; four subtypes (2A, 2B, 2M, and 2N);
10%
OF PEOPLE WITH VWD

TYPE 3:
Little or no vWF; generally severe;
3%
OF PEOPLE WITH VWD

Von Willebrand Factor (vWF) has two critical functions to play in helping to prevent or stop bleeding; it helps **develop platelet plugs** and it **protects inactive factor 8 proteins** floating through the bloodstream. When vWF is missing or deficient, a person is said to have **von Willebrand Disease (vWD).**



Nose bleeds and bleeding from the mouth or gums, are 2 common symptoms of vWD.

"There are individuals that have this disease but don't know it. Because we have such effective treatments, I want to try to identify those individuals who are sitting at home having difficulty with bleeding and don't realize, with an accurate diagnosis, there would be effective treatments available for them."

– Dr Paula James
Medical Director of the Women and Bleeding Disorders Clinic at the Kingston General Hospital.

It is believed that as few as 1 in 10 people who have von Willebrand disease have been properly diagnosed! ***Up to 90% of people with this bleeding disorder don't yet know it and suffer needlessly.***

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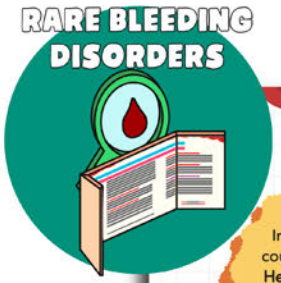
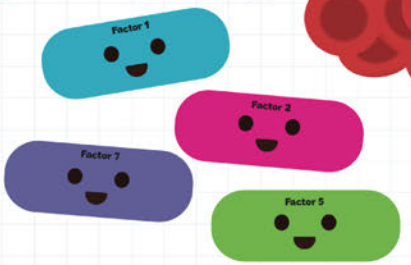


RARE FACTOR DEFICIENCIES

Information provided courtesy of the National Hemophilia Foundation (NHF) and Centers for Disease Control and Prevention (CDC)



FACTOR 1 (FIBRINOGEN) DEFICIENCY is a collective term for three rare inherited fibrinogen deficiencies. It was first described in 1920 by two German physicians. Fibrinogen helps platelets stick together to form the initial "plug" after an injury.

FACTOR 2 (PROTHROMBIN) DEFICIENCY was first identified in 1947 by Dr. Armand Quick. The incidence is estimated at 1 in 2,000,000. Factor 2 deficiency is inherited in an autosomal recessive fashion, meaning that both parents must carry the gene to pass it on to their children; it affects men and women equally.

FACTOR 5 (LABILE FACTOR, PROACCELERIN) DEFICIENCY (OWREN'S DISEASE, PARAHEMOPHILIA) was first described in a Norwegian patient in 1943 and reported by Dr. Paul Owren in 1947. Its incidence is about 1 in 1,000,000; fewer than 200 cases have been documented worldwide. It should not be confused with factor V Leiden, a clotting disorder. The factor 5 protein is a catalyst, accelerating the process by which prothrombin is converted to thrombin, the initial step in clot formation.

FACTOR 7 (LABILE FACTOR OR PROCONVERTIN) DEFICIENCY (ALEXANDER'S DISEASE) was first recognized in 1951. Its incidence is estimated at 1 per 400,000. It is inherited in an autosomal recessive fashion, meaning both parents must carry the gene to pass it on to their children; it affects men and women equally. Factor 7 is a protein that, when bound to tissue factor, initiates the clotting cascade, which leads to the formation of a blood clot.

In the US, a rare disease or disorder is defined as one that affects fewer than 200,000 people, making hemophilia A and B, and still less prevalent factor deficiencies such as 1, 2, 5, 7, 10, 11, 12 and 13, rare disorders. These very rare factor deficiencies, from factor 13 deficiency, the rarest, occurring in an estimated 1 out of 5,000,000 people, to factor 11 deficiency, occurring in about 1 out of 100,000, were all discovered and identified in the 20th century.

FACTOR 10 (STUART-PROWER FACTOR) DEFICIENCY was first identified in the 1950s in the US and England in two patients: Rufus Stuart and Audrey Prower. The incidence of Factor 10 deficiency is estimated at 1 in 500,000 to 1 in 1,000,000. Inheritance is autosomal recessive, meaning females and males can equally be affected. The factor X protein plays an important role in activating the enzymes that help to form a clot. It needs vitamin K for synthesis, which is produced by the liver.

FACTOR 11 (HEMOPHILIA C, PLASMA THROMBOPLASTIN ANTECEDENT (PTA) DEFICIENCY, ROSENTHAL SYNDROME) DEFICIENCY was first recognized in 1953 in patients who experienced severe bleeding after dental extractions. Its incidence is estimated at 1 in 100,000 in the general population. In Israel, FXI deficiency occurs in up to 8% of Ashkenazi Jews. Men and women are affected by FXI deficiency equally. FXI plays an important role in the clotting cascade. It helps generate more thrombin, a protein that converts fibrinogen to fibrin, which traps platelets and helps hold a clot in place.

FACTOR 12 (HAGEMAN FACTOR) DEFICIENCY was first identified in 1955 in John Hageman. Its incidence is estimated at 1 in 1,000,000. Factor 12 deficiency is inherited in an autosomal recessive fashion, meaning both parents must carry the gene to pass it on to their children; it affects men and women equally. It is more common in Asians than other ethnic groups. Factor 12 interacts with the activation of Factor 11 to Factor 11-activated to generate thrombin, a protein that converts fibrinogen to fibrin, which traps platelets and helps hold a clot in place.

FACTOR 13 (FIBRIN STABILIZING FACTOR) DEFICIENCY) was first reported in the literature in 1960. It is the rarest factor deficiency, occurring in 1 per 5 million births. It is inherited in an autosomal recessive fashion, meaning that both parents must carry the gene to pass it on to their children; it affects men and women equally.

We cannot paint all bleeding disorders with the same brush... Do not take a rare diagnosis for granted, especially if you have a mild form of the deficiencies, as issues may arise that require prompt treatment to help prevent mortality or life-long issues. You are strong and support is available through foundations, associations, HTCs, others in the community, and family and friends – at every level.

James Munn, RN-BC, BS, BSN, MS
Nurse coordinator at the Hemophilia and Coagulation Disorders Program at Michigan Medicine in Ann Arbor

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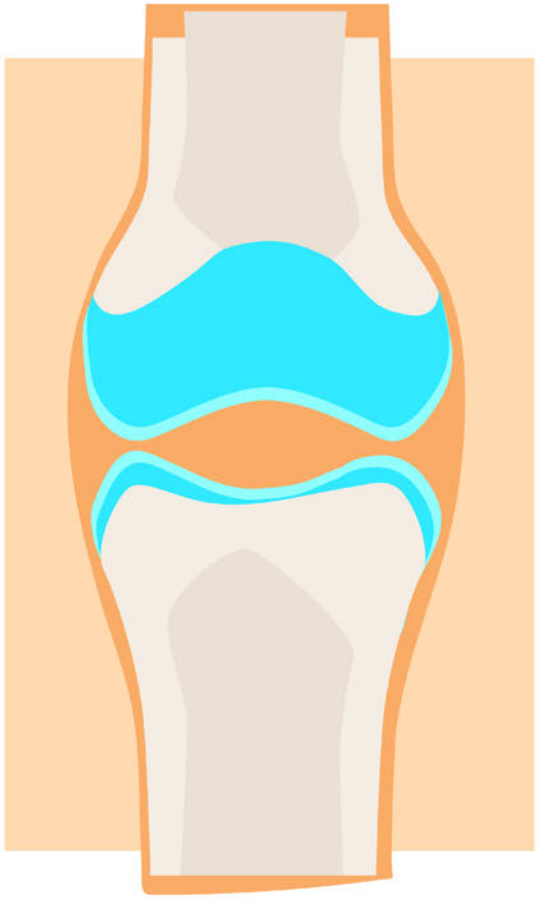
WHEN BLEEDS
HAPPEN


Bumps and bruises of daily life re
tears all the time, but if someone
their bloodstream, he or she w
per blood clot, resulting in un
manent damage.

MODULE 2: INSIDE A TARGET JOINT

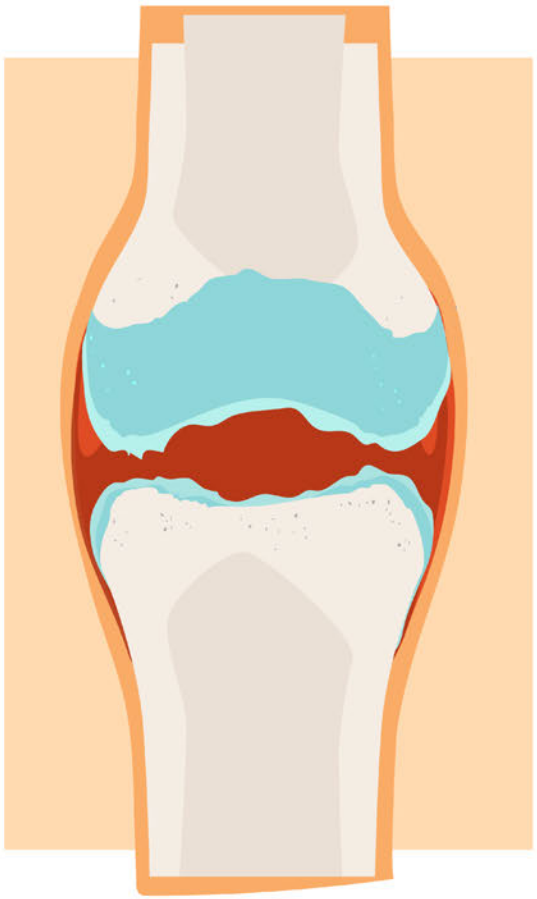
Blood vessels flow throughout our bodies, which is why bleeds can occur virtually anywhere; however, blood vessels within our weight-bearing joints tend to be the most vulnerable to bleeding. A joint that is repeatedly subject to bleeding is commonly referred to as a **target joint**.

HEALTHY KNEE



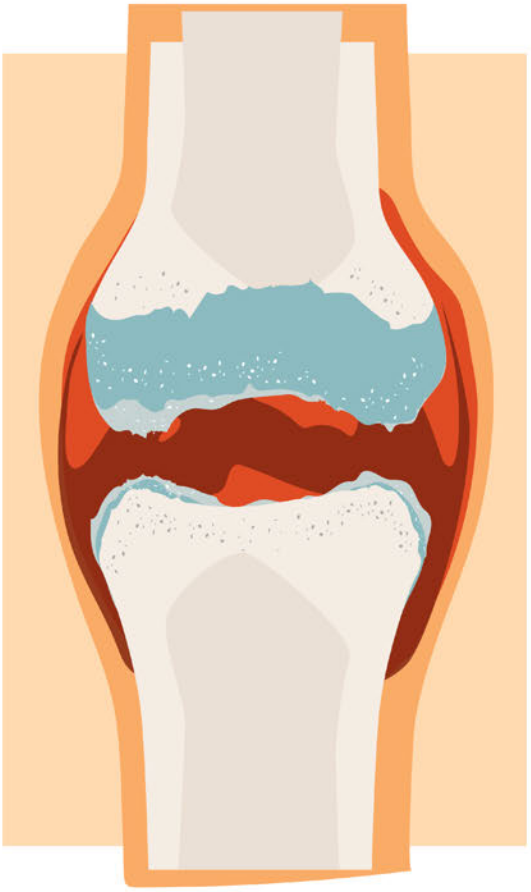
This is what a knee joint looks like if it has never had a bleed. See the smooth white surface? That is healthy cartilage. Healthy cartilage is smooth and glossy and is the first sign of a healthy joint. Notice the bone is smooth as well.

INCONSISTENT CARE



During a bleed, the blood fills the knee cavity. Just one bleed can cause deterioration of the cartilage! Proteins in blood eat away at the tissue and over time, if a joint has repeated bleeding, this can lead to serious, irreversible damage, and chronic pain.

POOR ADHERENCE



This is what a damaged joint looks like. The cartilage is deteriorated down to the bone. What was once smooth and glossy is now craggy, rough, deeply painful, and chronic.

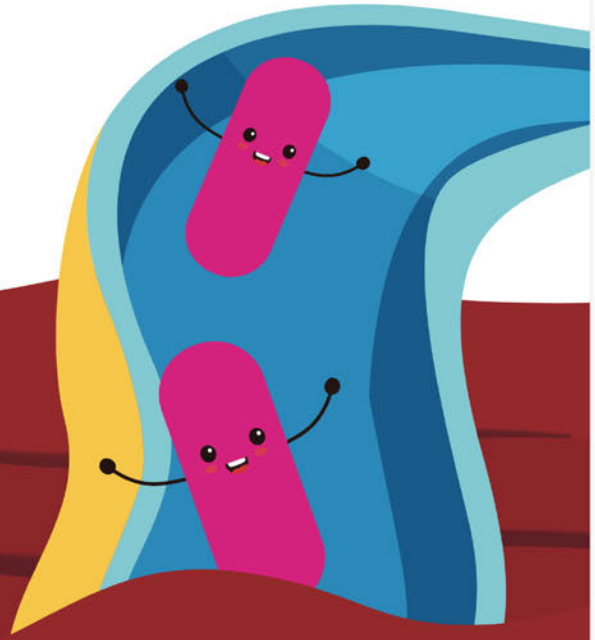
What Happens When Bleeds Happen?

> *Just one bleed can cause damage. The body can repair any damage to cartilage up to the ages of 10-12 years old. After that, any damage created will be permanent.*
> **– Cindy Bailey, PT, PhD**

Bumps and bruises of daily life result in blood vessel tears all the time, but if someone doesn't have FACTOR 8 in their bloodstream, he or she will not be able to form a proper blood clot, resulting in uncontrolled bleeding and permanent damage.

Did You Know?

- **Prophylaxis** or **"prophy"** is the **standard of care** in the United States, as it prevents not only damage caused by bumps and bruises, but also damage caused by traumatic events- such as a car accident or head injury- by resupplying **FACTOR 8** routinely into the bloodstream.
- Blood vessels flow throughout our bodies, which is why bleeds can occur virtually anywhere; however, blood vessels within our weight-bearing joints tend to be the most vulnerable to bleeding. A joint that is repeatedly subject to bleeding is commonly referred to as a **target joint**.



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TREATMENT,
UP CLOSE & ANIMATED


We Treat Hemophilia Treatment Options Throughout The Years
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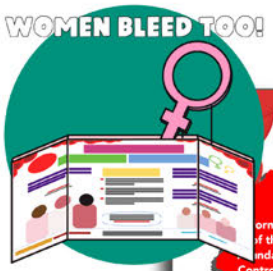

ormation provided courtesy
f the National Hemophilia
ndation, Centers for Disease
Control and Prevention, Victory
For Women, and the Foundation
for Women & Girls with Blood
Disorders.

WOMEN WITH BLEEDING DISORDERS

Our vision is that all women and girls with blood disorders would be appropriately diagnosed and optimally treated, at every life stage. For us that means educating hematologists, obstetricians, gynecologists, and other HCP so that they are able to improve the outcomes for women and girls with blood disorders.

– Dr. Andra James
Obstetrician/Gynecologist, Co-founder of the Foundation for Women & Girls With Bleeding Disorders

Did You Know?

- While it's estimated that as many as 1,600,000 million American women may have a bleeding disorder, according to ATHNdataset, fewer than 8,000 have been diagnosed (0.5%).
- 1 out of 5 women has heavy menstrual bleeding, and 1 out of 6 women who present to the Emergency Department with heavy menstrual bleeding may have von Willebrand Disease.
- Fewer than 20% of postpubertal girls and adolescents with heavy menstrual bleeding underwent von Willebrand Disease screenings, in spite of 15+ years of recommendations to do so from the American College of Obstetricians and Gynecologists.

There are numerous bleeding disorders treatment centers that offer clinics or services specifically devoted to the care of women and girls. To locate them, visit: fwgbd.org/clinics.

We will see adult women who have had bleeding and clotting disorders all of their lives and have been yet to be diagnosed, heavy menstrual bleeding, bleeding with childbirth, iron deficiency anemia, then as they get older and may develop cardiovascular disease, we need to know where things stand, so we can help them through those.

– Dr. Barbara Conke
Adult Hematologist, Co-founder of the Foundation for Women & Girls with Blood Disorders

It still takes multiple years for the average woman to get a diagnosis, so there's still a gap there. For us, we feel like the next step is to be doing a lot more research in this population, that's really the only thing that's going to move the field forward.

– Dr. Robert Sidonio
Pediatric Hematologist, Emory University/ Children's Healthcare of Atlanta

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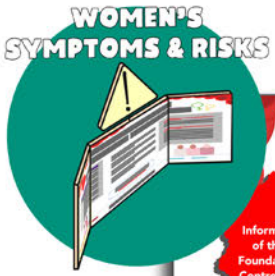

Information provided courtesy of the National Hemophilia Foundation, Centers for Disease Control and Prevention, Victory For Women, and the Foundation for Women & Girls with Blood Disorders.

WOMEN WITH BLEEDING DISORDERS

Do I Have a Bleeding Disorder?

A girl/woman may have a bleeding disorder if she experiences one or more of the following...

- Periods with large amounts of blood loss, that last more than 7 days.
- Soaking through an extra absorbency pad or tampon in one hour.
- Needing to wear two or more pads or tampons at a time to control bleeding.
- Passing blood clots the size of a quarter or larger.
- Having a menstrual flow so heavy it keeps you from usual activities.
- Low iron levels.

Bleeding and clotting disorders affect men and women, however women face unique reproductive health and quality of life challenges during menstruation, pregnancy, labor, and delivery. It is estimated that as many as 1% of women have bleeding disorders, though many are unaware. The most common bleeding disorder in women and girls is von Willebrand disease. Though rare, women and girls can also experience bleeding symptoms from mild, moderate, and severe hemophilia.

There are numerous bleeding disorders treatment centers that offer clinics or services specifically devoted to the care of women and girls. To locate them, visit:

fwgbd.org/clinics

ADD'L SYMPTOMS common to women with bleeding disorders:

- Frequent nosebleeds – lasting longer than 10 minutes and having more than 5 per year.
- Prolonged bleeding from minor cuts.
- Easy/unexplained bruising.
- Excessive bleeding after giving birth or after dental extractions/dental work, or other surgery.

UNTREATED, women with bleeding disorders are at risk for:

- Unnecessary medical procedures including hysterectomies and ablations.
- Postpartum hemorrhage.
- Recurring anemia.
- Having to limit or change activities because of heavy or prolonged menstrual bleeding.

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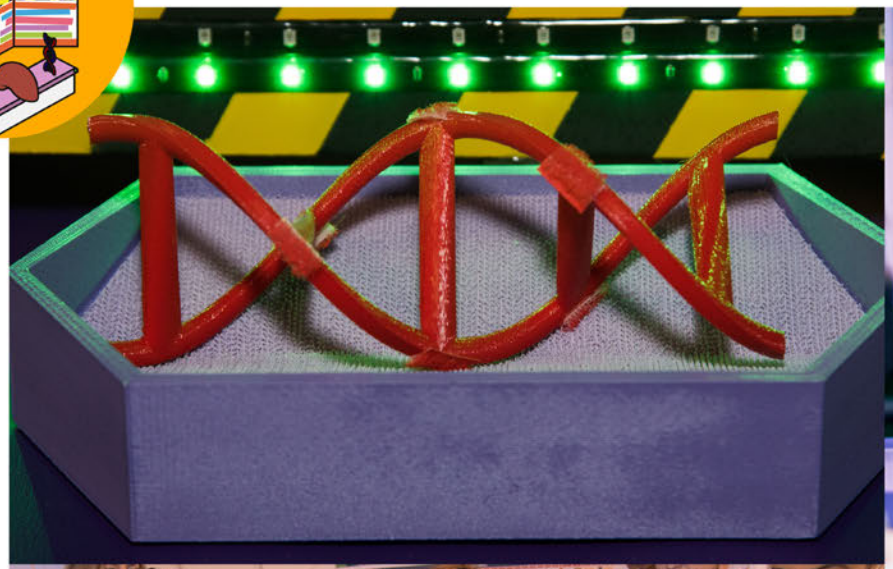
To view the entire timeline online, please visit:

www.hemophiliafed.org/updated-historical-timeline


GENE THERAPY
& THE FUTURE



TREATMENT OPTIONS OF TOMORROW

Gene therapy is an umbrella term for what's known scientifically as either gene transfer or gene editing. With respect to hemophilia, most of the science being explored falls under the category of gene addition, where a gene is added to the body in order to replace the function of a gene that isn't working.

Did You Know?

- Only about 1% of DNA is made up of protein-coding genes, such as **FACTOR proteins**; the other 99% of DNA is made up of genes that serve other functions.
- As the host cell replicates the working **FACTOR** gene, the liver will continue to produce the non-working **FACTOR** gene.
- While exploring gene therapy, science is continuing to seek ways to improve factor replacement therapy, as well as looking at other ways to counterbalance the bleeding and clotting systems of the body.

What is your bottom line about gene therapy in 2019?

Gene therapy, in one sense, is a type of long-acting factor treatment. It's based on using a person's own mechanisms for creating clotting factors. Many view gene therapy, as it exists in 2019, as the beginning of a gene correcting/editing/delivery era.

Dr. Michael Tarantino, Founder & Medical Director, Bleeding & Clotting Disorders Institute

Gene therapy is a reality, it is just a matter of "when," but I don't think a blanket approval will happen here. Safety and efficacy questions remain. Variability and durability are unknowns. We don't know about the health of the liver [over time]. That is my biggest concern.

Dr. Michael Wang, HTC Clinical Director, University of Colorado

The first gene therapy [treatment option] for Hemophilia A will be filed with Food and Drug Administration (FDA) in 2019. This is a major milestone.

Dr. Glenn Pierce, World Federation of Hemophilia, Vice President, Medical

1. Our story begins with a **virus**! A virus is a small agent or particle that replicates only inside the living cells of an organism, is capable of binding to a cell, and can carry genetic material to a cell.
2. The virus is then stripped of its existing genetic material, leaving behind an empty shell, known as a **vector**.
3. The vector is implanted with a working **FACTOR** gene. The virus has now become what's known as a **viral vector**.
4. The viral vector is injected into the body with explicit instructions to go to the **liver**.
5. Once in the liver, the viral vector binds to a cell, which then becomes the **host cell** for the gene the viral vector was carrying.
6. The host cell will now start to produce **FACTOR proteins**.
7. The host cell will now **reproduce itself** with the working **FACTOR** gene, so that new cells will also produce **FACTOR** proteins.

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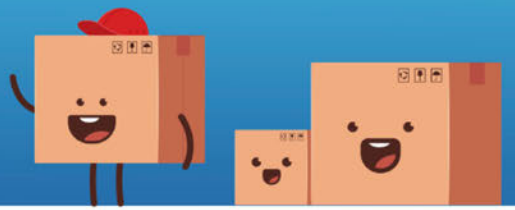
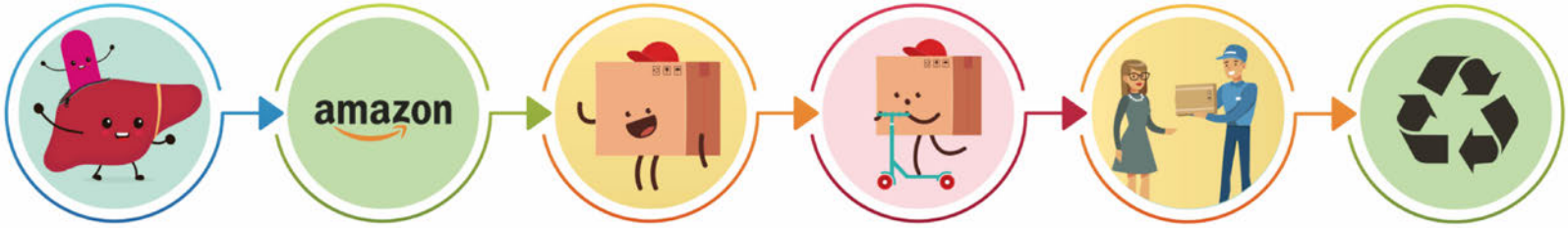
DR. PIPE'S AMAZON BOX ANALOGY



To help patients and families understand how gene addition works, Dr. Steven Pipe, the Chair of NHF's Medical and Scientific Advisory Council (MASAC), uses the accessible analogy of an Amazon delivery box to explain gene delivery and viral vectors.



1

What we've done in gene addition is we've eliminated the middleman. Now, we're taking a good, working copy of either the factor VIII or factor IX gene, and we're putting it directly inside your liver. Your liver is now the manufacturing facility and its machinery will make factor VIII or IX, for the first time, using that good copy of the gene. That's the first concept, the concept of gene addition.

2

The next concept is gene delivery. In gene delivery, we have to target the liver and make sure the good, working copy of the gene ends up specifically in the correct liver cells. To explain how this is achieved, I use the analogy of receiving an Amazon delivery box.

3

When an Amazon delivery box arrives at your house, there's almost nothing inside the box except what you want, a little bit of packing materials, and of course there's the delivery box that carries it all. In gene addition, this delivery box is what we call the viral vector.

4

If we think of our viral vector as a delivery box, this is basically how it works: first, a box at the factory is unpacked of any existing contents, leaving behind an empty box. Next, a little bit of packing material is placed inside the box, followed by the thing being delivered. Lastly, the box is stamped with its delivery address and sent off!

5

The viral vector, just like an Amazon box, has a "delivery address" that targets the liver. Once the viral vector is circulating in the body, the liver has mechanisms to recognize it, bring it in, and unpack it- much like when the Amazon box is delivered to your house, you take it inside and open it up.

6

Once everything is unpacked and you have what you want- in the case of gene addition: a working copy of the factor gene inside the body's liver cells- you recycle the Amazon box and discard of the packing materials. In our bodies, the immune system plays the role of "recycling police," and it's not blind to the fact that something is going on that isn't quite natural. In my opinion, this is the biggest challenge with gene addition at the moment.

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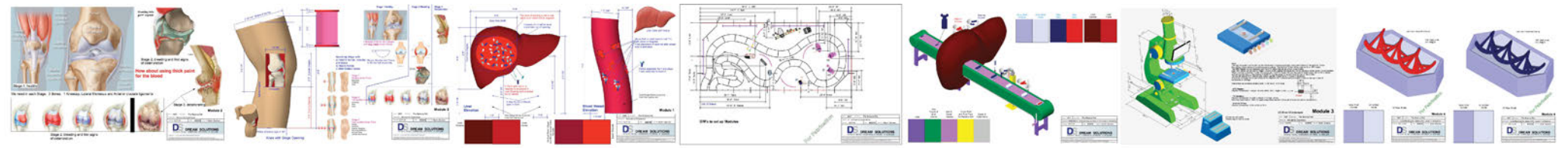

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