THE COALITION FOR HEMOPHILIA B

HEMOPHILIA B NEWS

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GETTING TO KNOW DR. CLARK

ACHIEVING A BETTER LIFE WITH AN ABLE ACCOUNT

ASHLEY'S STORY

30 YEAR ANNIVERSARY THE COALITION FOR HEMOPHILIA B

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30 YEAR ANNIVERSARY
THE COALITION FOR HEMOPHILIA B

MISSION

TO MAKE QUALITY OF LIFE THE FOCAL POINT OF TREATMENT FOR PEOPLE WITH HEMOPHILIA B AND THEIR FAMILIES THROUGH EDUCATION, EMPOWERMENT, ADVOCACY, AND OUTREACH.

Current Products For Hemophilia B Treatment

BY DR. DAVID CLARK

Many new families may not be aware of the large number of products available for treatment of hemophilia B. This is a brief survey of the products currently available in the U.S.

One of the most important principles in medicine is that every patient is different. Although we all share many similarities, we also have unique genetic and medical backgrounds. An advantage of the large number of products available is that a patient who does poorly on one product might have better results with another.

Currently, all hemophilia B patients, except those with inhibitors, are treated with factor replacement products. These products contain the factor IX protein to replace the defective factor IX molecules produced by their own bodies. They all require periodic intravenous infusions to maintain the amount of factor IX in the patient's blood at the level at the required for good hemostasis (adequate clotting).

There are a number of improved factor IX products currently under development, many with easier subcutaneous injection, as well as a number of non-factor products – see the *Industry News* section of the newsletter. The current products fall into three general categories: standard half-life (SHL) products, extended half-life (EHL) products, and inhibitor treatment products.

These four products all consist of normal human factor IX. They are all descendants of the original plasma-derived concentrates that were developed in the 1960s. The original products were called Factor IX Complex or Prothrombin Complex. They were mixtures of several clotting factors including factors II, VII, IX, and X plus the anticoagulants protein C and protein S. These proteins all have similar chemical structures, which makes them difficult to separate from each other.

The complexes were a huge leap forward in treatment of bleeds, but it was soon apparent that they could not be used in large amounts or for prolonged periods of time because they would cause thrombosis, dangerous unwanted clotting. This prevented their use for prophylaxis or surgery. Factor IX complex products are still on the market but should not be used for hemophilia B treatment because of their safety risks. They are currently used mainly for treatment of liver disease.

AlphaNine was one of the first products to contain highly purified factor IX without the other factors. It has proved to be safe from thrombotic complications and is still used by a number of patients. The other big change in factor IX products was the introduction of methods for viral inactivation and removal, which happened in the mid-1980s. Prior to the introduction of those methods, plasma-derived products often were contaminated with infectious agents like hepatitis B and C and HIV, the AIDS virus. Plasma-derived products are now considered completely safe. There have been no incidences of viral transmission from clotting factor products since the late 1980s, or from any other plasma-derived products since the early 1990s.

One of the main reasons for introduction of recombinant products was viral safety – to eliminate the dependence on human plasma for these products. Another was the ability to produce unlimited amounts of a product without dependence on the limited supply of plasma. Recombinant products are made in animal cells that have been genetically engineered to produce the desired protein. All three SHL factor IX products are made in Chinese hamster ovary (CHO) cells that are grown in large tanks in a process called cell culture.

A little-appreciated fact is that all recombinant products are also treated for viral inactivation and removal. Although the cells used for cell culture are thoroughly screened to make sure they are safe, it was discovered early on that some of these cells may contain hidden virus genes in their DNA. These viral genes could under some production conditions be "turned on" and introduce infectious viruses into the products. Now, in addition to having manufacturing steps to inactivate and remove any viruses, every batch of

HEMOPHILIA B (Factor 9) PRODUCTS

Standard Half-Life Products (SHL): Table 1 shows the SHL products currently available in the U.S.

Table 1: Standard Half-Life (SHL)* Products			
Brand Name	**Generic Name**	**Manufacturer**	**Type**
AlphaNine SD	Coagulation Factor IX (Human)	Grifols Biologicals	Plasma-derived
BeneFix*	Coagulation Factor IX (Recombinant)	Pfizer/Wyeth	Recombinant – CHO cells
Ixinity	Coagulation Factor IX (Recombinant)	Medexus/Aptevo	Recombinant – CHO cells
RIXUBIS	Coagulation Factor IX (Recombinant)	Takeda/Baxalta	Recombinant – CHO cells

**Some manufacturers have an FDA-approved dosing scheme that lets people use higher doses once a week for adequate prophlaxis.*

Extended Half-Life Products (EHL): Table 2 shows the EHL products currently available in the U.S.

Table 2 – Extended Half-Life (EHL) Products			
Brand Name	**Generic Name**	**Manufacturer**	**Type**
Alprolix	Coagulation Factor IX (Recombinant), Fc Fusion Protein	Sanofi	Recombinant – HEK cells
Idelvion	Coagulation Factor IX (Recombinant), Albumin Fusion Protein	CSL Behring	Recombinant – CHO cells
Rebinyn	Coagulation Factor IX (Recombinant), GlycoPEGylated	Novo Nordisk	Recombinant – CHO cells

Inhibitor Treatment Products: Table 3 shows the inhibitor treatment products currently available in the U.S.

Table 3 – Inhibitor Treatment Products			
Brand Name	**Generic Name**	**Manufacturer**	**Type**
FEIBA	Anti-inhibitor Coagulant Complex	Takeda/Baxalta	Plasma-derived
NovoSeven RT	Coagulation Factor VIIa (Recombinant)	Novo Nordisk	Recombinant – BHK cells
Sevenfact	Coagulation Factor VIIa (Recombinant)-jncw	HEMA Biologics	Recombinant – transgenic rabbits

product, whether plasma-derived or recombinant, is also tested to make sure there are no infectious agents present in the final product.

Most hemophilia B patients use recombinant products, but there are some patients who still use Alphanine because it works better for them. The reason for this is unknown, but there are two important possibilities. One is that the recombinant products only contain a single version of factor IX, the most common variant, which is considered "normal" factor IX. However, plasma, which is collected from thousands of donors, contains a whole range of factor IX variants. Many people have small mutations in their genes and produce a factor IX that isn't modified enough to produce hemophilia, but still has some changes that may make it work better or worse in some patients.

Another possibility is that the animal cells used in cell culture glycosylate the factor IX product differently than human cells do. Many of the clotting factors, including factor IX, are glycosylated after the protein is made. That means that they have carbohydrate chains attached to various parts of the molecule. The carbohydrate chains are strings of sugar molecules linked together (glyco- comes from the Greek word for sweet or sugar). There are many different types of sugars beyond what we think of as "table sugar." We don't completely understand the reasons for these sugar chains, but we know that human cells add on different combinations of sugars than CHO cells do, for instance. These differences may cause variations in how well the products work in some patients.

The body is constantly removing old copies of proteins from the bloodstream and replacing them with new copies. This is part of the process for keeping the body in good working order. The half-life is the amount of time it takes for half of the protein to be removed. The typical half-life of normal factor IX is 23 – 25 hours, although that can vary significantly from person to person.

The SHL products all have half-lives similar to that of normal factor IX derived from plasma. That means that a patient using an SHL product has to infuse new factor IX every three days or so. (Note that some of the SHL products, like BeneFix have developed alternate dosing schemes using higher doses to keep factor IX levels in the needed range for a week or more.) The EHL products use various methods to keep their factor IX in circulation for longer periods of time. These products can be dosed at intervals of one to two weeks, again depending on the patient's individual response.

Alprolix contains factor IX molecules attached to the Fc region of an antibody molecule. Because they are more difficult to make, the body has a special mechanism to keep antibodies in circulation longer than most other proteins. Antibody molecules are shaped like a Y. The two arms of the Y are the Fab regions of the molecule that bind to viruses, bacteria and foreign proteins to remove them from circulation. The base of the Y is the Fc region that attracts immune cells to destroy anything that the arms bind to. The Fc region is also the part of the molecule that interacts with the system that keeps antibodies in circulation longer. It turns out that linking factor IX to an Fc molecule also keeps the factor IX in circulation longer.

Idelvion uses a similar method. Its factor IX is linked to an albumin molecule. Albumin is the most prevalent protein in plasma. It thickens the plasma and also carries many other molecules around in the circulation. There is also a special mechanism in the body to keep albumin in circulation longer. Linking factor IX to albumin also improves its half-life.

Rebinyn uses a different method to keep its factor IX in circulation longer. Polyethylene glycol (PEG) is a long water-soluble polymer that has found many uses in medicine including improving the half-lives of many drugs. Rebinyn uses factor IX with PEG chains attached to the ends of the carbohydrate chains described above in the SHL section. These long PEG chains wave around and coil up randomly around the factor IX molecule. They

form a loose shell that tends to hide the factor IX molecules from the liver cells that normally remove factor IX from circulation.

Another aspect of Alprolix is that it is made in cell culture in human embryonic kidney (HEK) cells. Using human cells to produce the product potentially produces a factor IX that is glycosylated (has carbohydrate chains attached) more similarly to the factor IX molecules made naturally in the human body. Whether that actually improves the performance of Alprolix is unknown.

Although the SHL products are very similar to each other, the EHL products are each quite different and may perform differently from person to person. This has been seen in a number of clinical studies of patients switching from SHL to EHL products. Therefore, if one product doesn't work, don't assume the others will also not perform well.

Inhibitors are antibodies that the immune system produces because it thinks that an infused factor IX product is a foreign protein that could be dangerous. Some of these, known as non-neutralizing antibodies, bind to factor IX but don't interfere with its function. Inhibitors are neutralizing antibodies that bind to factor IX in locations on the molecule that prevent it from working. Inhibitors also occur against factor VIII in hemophilia A where they are a major problem. Inhibitors occur much less frequently in hemophilia B. Only about 3 – 5% (the numbers are hard to pin down) of hemophilia B patients develop inhibitors, but when they do, it can be a very serious problem.

Factor VIII inhibitors can often be eliminated by a process called immune tolerance induction (ITI). However, ITI works poorly in many hemophilia B patients with inhibitors. In addition, many hemophilia B inhibitor patients also develop allergic reactions to factor IX including anaphylaxis, a severe reaction that can be life-threatening. Hemophilia B inhibitor patients are also prone to a kidney disorder called nephrotic syndrome. Because of all this, many hemophilia B inhibitor patients end up just living with their inhibitor and using bypassing agents.

Inhibitor treatment products are called bypassing agents because they trigger other parts of the clotting system, bypassing the factor VIII/IX step. They work for both hemophilia A and B inhibitor patients, but they don't work as well as a regular factor product would work in a hemophilia patient without inhibitors. They have very short half-lives, requiring frequent infusions to treat bleeds, and are expensive. They can be used prophylactically, but most patients just use them for on-demand treatment of bleeds. They are all we've got at present, but fortunately, there are a number of new inhibitor treatments under development.

FEIBA is a plasma-derived version of factor IX complex in which the clotting factors have been activated using a proprietary method. It is used by some hemophilia B inhibitor patients, but because it contains factor IX, it carries a risk of allergic/anaphylactic reactions. The way FEIBA works is not fully understood, but it contains activated factor VII like the other two bypassing agents. The other activated factors in FEIBA probably also trigger other parts of the clotting system.

NovoSeven is a recombinant activated factor VII product. The overall clotting system consists of two pathways, one that depends on factors VIII and IX, and the other depends on factor VII. Adding activated factor VII enhances that alternative pathway to eventually form a clot. Note that NovoSeven is produced in cell culture using a different organism, baby hamster kidney (BHK) cells. The choice of cell type is usually determined by which type works best to produce a particular product.

Sevenfact is a new recombinant activated factor VII product. It is similar to NovoSeven but made by a completely different process. For Sevenfact, rabbits have been genetically engineered to produce factor VII in their milk. The rabbits are milked and the milk purified to capture the factor VII, which is then activated to produce the final product. This is called transgenic production, and it has been used for other previous pharmaceutical products approved by FDA. Its advantage is that very large amounts of protein can be produced at relatively low cost. It was originally seen as a way to produce high-quality but lower-cost products for developing countries, but that aspect has yet to be realized.

The large number of products available for treatment of hemophilia B increases the chances that every patient can find a product that works well for them. Selecting the best product may be a process of trial and error, but working with an experienced hemophilia treater can shortcut the process. If you think you could be getting better results, don't hesitate to ask your physician.

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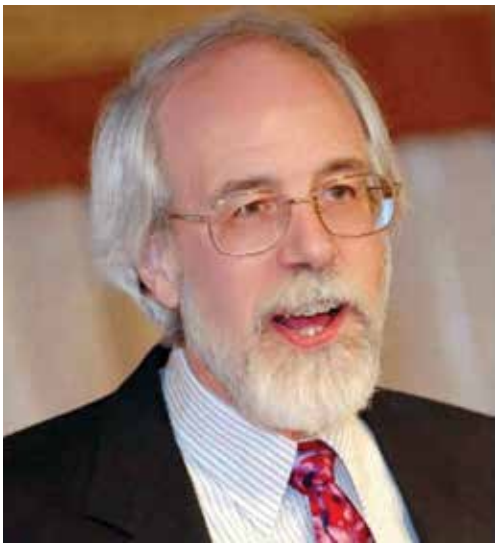
“THE OPPORTUNITY OF MY LIFE”

GETTING TO KNOW DR. DAVID CLARK

BY RENAE BAKER



Readers of The Coalition for Hemophilia B’s quarterly publication, Hemophilia B Newsletter (formerly Factor IX Newsletter) have seen many a byline reading “By Dr. David Clark” for Treatment News, Research Update, Women with Hemophilia, Hemophilia Health News, Emerging Therapies, and other features. An active Chairman of the Coalition, Dr. Clark regularly participates as an educator at US-based events and attends national and international meetings to keep current on the hemophilia front.

Dr. Clark’s articles offer cutting-edge hemophilia B information and help readers become better advocates for themselves and their families. Dr. Clark is a veteran and expert in hemophilia research, product development, and reporting. His wealth of knowledge might seem imposing, but those who know “Dr. Dave” describe him as humble. Indeed, that is how he struck me during our interview. “I tend to be very shy,” he shared, “but I enjoy attending Coalition events and interacting with everyone. Being with the community tends to bring me out of myself a bit.”

It has been the good fortune of the Coalition to have Dr. Clark onboard since its inception. As we mark the thirtieth anniversary of the Coalition, we wanted to shine a light on the person who has been helping us become more knowledgeable. We sat down for a Zoom interview to discuss his interesting background, expansive and varied professional path, concerns, and all those pearls of wisdom, drawn from his personal experiences and from his interactions with parents and their children.

“I grew up fairly poor in Ohio. It was education that brought me out of that and to where I am today!” I received a very good education through the Akron public school system. He remembers enjoying his high school chemistry class. “I was already into science. The whole country was big into science those days. Our country’s interest in science was spiked with Russia launching Sputnik, the world’s first satellite. Being competitive, the US was highly motivated at the idea of no longer being the number one superpower. Russia was in space, and we weren’t - we were going to the moon!”

Dr. Dave and Linda married for 27 years and going strong! They love traveling, hiking and spending time in nature.

Although Sputnik was a great motivator, Dr. Dave believes getting children involved in science at an early age is important and easy to do, “Kids get really interested in science, especially natural science: wandering in the woods, looking at everything, learning about plants… and then there’s dinosaurs and outer space…” Clark shifts his focus to parents, “There are all sorts of ways parents can get their children interested in science and that can be a great thing for their long-term success.”

Dr. Clark points to a singular moment in his youth that set a trajectory toward a meaningful path forward, “My high school held an event where representatives from big colleges came to recruit students. One woman talked about Cornell University… I didn’t expect to get in, but I applied on a whim. Not only did I get in, but they gave me a full scholarship! It was the opportunity of my life! I could never have afforded to go to a school like Cornell on my own. It pulled me out of life as a poor kid and took me to a future of all sorts of amazing things.

“My advice?” he asks. “Find what you’re interested in and learn more about it.” Dr. Clark realizes certain subjects may be more challenging to some, but he says, “Don’t be afraid of education. Don’t say, ‘I don’t understand math.’ The whole purpose of education is to help you understand.” He recommends trying them on a small level to see if you have an interest and an inclination toward those subjects.

Fully enjoying his undergrad experience at Cornell, Dr. Clark went on to earn a master’s and PhD there as well. “After earning my PhD, I looked for a job.” It was a difficult time. He sent more than a hundred letters to prospective companies but was able to land only 10 interviews. Of those, he was offered one job. It was a postdoctoral fellowship at Textile Research Institute in Princeton, NJ. There, he worked on the wetting and absorbency of fabrics, “We did some interesting things. We worked on baby diapers, tea bags, and all sorts of fabrics and fibers that soak up liquids.”

Dr. Clark retraces the steps of his unlikely path. “Next, I got a job at the National Bureau of Standards outside of Washington D.C. This was during the energy crisis in the 1970s and Congress had awarded funds to work on re-refined motor oil, basically to clean and reuse it. Given the hefty funding, we had all the latest equipment and could do amazing things! It was a pretty cool thing! Although I hadn’t done anything in analytical chemistry before, the people I worked with were analytical chemists and I learned an amazing amount from them.”

“After that, I worked for the dean of research at George Washington University (GWU). He had a little research group on the side where we worked on artificial hip joints.” The experience led to another job where Dr. Clark worked on artificial kidneys. “I kept getting into these new fields

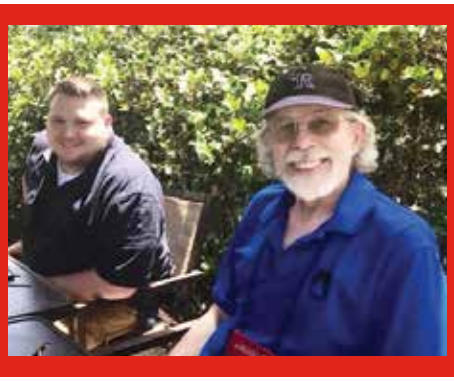
Dr. Dave with Bill Drohan’s daughters, Kathleen, Colleen and Maureen, giving out the William N. Drohan Scholarships at the Eternal Spirit Award Dinner.

and that really helped me have exposure.... It really helps as a researcher because with each experience you’ve learned a lot and that experience may point you toward solving the problems you’re currently working on.”

The pinnacle of Dr. Clark’s career began in the early 1980s with a twenty-year stint working for the Red Cross, where his work with hemophilia centered around developing new products. He looks back at that time with fondness. “My boss at the Red Cross was Dr. Doris Menache. As a young physician in Paris, France, she had been part of a group that developed the first factor IX concentrate, Coagulation Factor IX. This was a big deal at the time, but the problem was it couldn’t be used in very large quantities. For instance, prophylaxis was not an option. It was also proved to be very dangerous in surgery because it could cause thromboembolic complications,” a clot inside a blood vessel could break loose and stop the flow of blood.

Dr. Menache and the research group were seeing a lot of success treating bleeds with this product. Unfortunately, as the first to use it in surgery, Dr. Menache’s patient died. The heartache she experienced over this loss ignited a life-long mission to develop a safer factor IX concentrate.

This work led her to the United States and to the Red Cross where she set about to working to accomplish her goal. Knowing of her work, Dr. Clark was energized to be a part of her team. He reveals, “The first project I worked on was trying to create a better factor IX concentrate.”



At the time, Baxter was contracted to process all the Red Cross's plasma. As part of that, the team was able to use their research facilities to work on the factor IX concentrate. The Red Cross had never developed a product like this before. A pharmaceutical company might typically have a team of fifty people working on such a product, but the Red Cross team consisted of Dr. Clark and just a few others.

"We weren't really sure what we were doing, and we didn't have enough people to do the work, but we pushed ahead anyway. Despite the challenges, we did very well," Dr. Clark shares, "We developed the product, figured out how to produce it on a large scale, and began clinical studies. We were able to show this product did not cause thrombosis. It was successful."

At the time though, there was no time to celebrate their victory, as the AIDS crisis took the world by storm. Medical minds were directed toward finding a cure or at least finding relief for this mysterious virus. Dr. Clark recalls, "We had to scramble to come up with viral inactivation methods. Baxter had been developing a dry heat method for inactivating HIV and other viruses in their products and we were able to apply that method to our product and it worked."

Another important element of their process was maintaining the transparency the Red Cross espouses. "We were very open about what we were doing. I held many discussions in multiple settings about our progress in the development and purification of our product," Dr. Clark explains.

"Though we were unable to get our product licensed, I believe our influence had a lot to do with the development of safer factor IX products." Naturally, commercial pharmaceutical companies picked up on the excellent work Dr. Menache's team was doing. Alpha Therapeutics soon came out with AlphaNine, which was inspired by what the Red Cross team developed. It was approved for use in 1996 (Alpha Therapeutics was acquired by Grifols in 2003).

"This was fine with us," Dr. Clark commented, "We just wanted patients with hemophilia B to have a safe product." The Red Cross then collaborated with Alpha using the plasma they collected to make their product. Another company, Armour Pharmaceutical (now CSL Behring), was next in line to develop Mononine, another highly purified factor IX product that was safe from thrombosis. Dr. Clark remembers the satisfaction he felt, with the knowledge that there were now at least two safe products for patients with hemophilia B.

The Red Cross team followed up by working on a variety of products purified from plasma, including Antithrombin III, Protein C, Protein S, and Factor X. "We were doing a lot of research, study, and development of several products. We did clinical trials and were fairly successful," Dr. Clark says. "The Red Cross philosophy holds they are stewards of the blood supply. They manage this valuable supply of blood from the American public and want to get as much use out of it as possible, and we were trying to do the same."

"It was an amazing experience," Clark recalls with gratitude. "They were all research scientists and biochemists. They hired me as a chemical engineer to try to make this product on a large scale. I had no idea that this is what I was going to be doing, but it turned out to be

such a wonderful thing, and I learned so much from all the people and the projects we worked on."

The gratifying experience with the Red Cross would be part of a recurring theme in Dr. Clark's professional life. It is a theme he embraces and encourages others to be open to in their lives. "What I really wanted to be was a physical chemist, but I became a chemical engineer to make a living. It turned out to be a great path for me because I found it hands-on and useful. A chemical engineer gets a basic background in science and engineering and with that experience can really do well in a lot of different fields."

Following The Red Cross, Dr. Clark went to work with Clearant along with several people who used to work for the Red Cross. Using radiation to kill viruses, Dr. Clark found this work fascinating, "We did a lot of work on plasma products, but mostly worked with donated human tissue products." After Clearant, Dr. Clark became an independent consultant for a few of the tissue banks. "This was a whole different field, but it was related to plasma in that it's material that comes from human bodies.

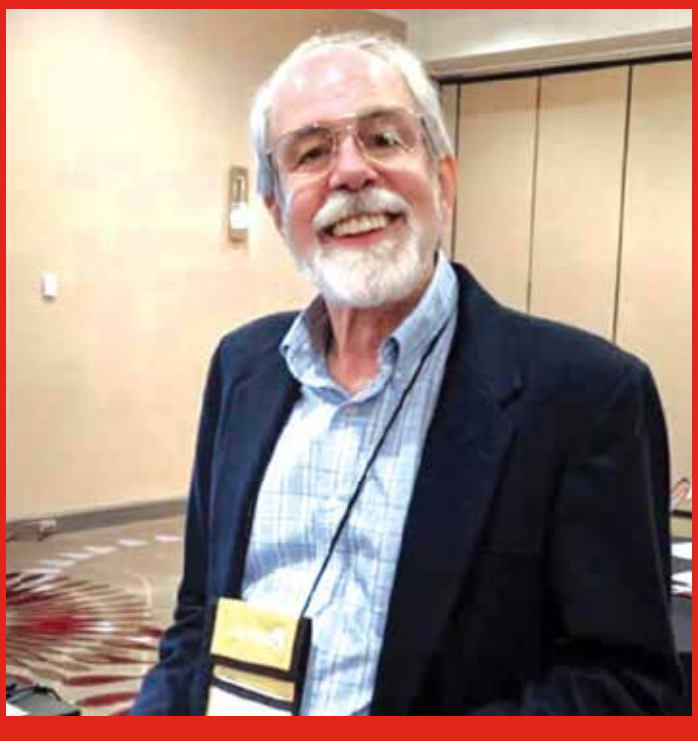
The primary company with whom Clark worked as an independent consultant was Tissue Banks International in the San Francisco Bay area. As part of this work, he and a friend developed methods for sterilizing tissue using radiation. They improved upon the methods he'd learned during his time at Clearant.

A spark was clearly ignited as Dr. Clark relates this introspection about his journey, "This is my life story, and this is what I want to emphasize. In my career, I've jumped from one field to another. Again, it's about education. If you have a good education, you realize you can learn more and become comfortable and well-versed in a new field."

Dr. Dave had a blast working with Patrick Lynch at the Science Fair. He loves working with various organizations and is always eager to help!

With a nod of energized satisfaction, he says, "You also find a lot of the experiences you've had in the past are valuable to what you're doing now. People might call it 'thinking outside of the box,' but it's really thinking in terms of the boxes you've been in before. You're in a new box, but you have ideas to add from the older boxes."

I muse about the wonderful aspect of Dr. Clark's life taking him on paths he could not have foreseen while he was a student in school. "Yes!" He exclaimed, "The big



thing back in grad school was all this bio stuff, but I never wanted to do what everyone else was doing, so I decided I wasn't going into biochemical engineering. Well, here I am now," he laughs with a self-effacing shake of the head, "I've spent most of my career as a biochemical engineer. It just goes to show you never know where you might be heading. My philosophy has always been, 'Don't try to decide where you're going. See where life takes you.' Life has taken me toward all sorts of interesting things and places."

"Sometimes I get criticized because people think you need to set a specific goal and work towards it. I've never done it that way, instead, going where life has led me. This approach has taken me to places much better than any goals I would have set for myself." It's unusual advice and Dr. Clark concedes that many parents may not want to hear it. "I'm different, but I don't know my way is necessarily a bad way."

I asked Dr. Dave how he came to work with The Coalition for Hemophilia B. "One of my later lab heads at the Red Cross was Dr. Bill Drohan. He was the head of the plasma derivatives lab and was a great guy to work for. He was always guiding us toward new ideas such as recombinant and transgenic products, which are not made from human blood."

Dr. Drohan met John Taylor, founder of the Coalition, and began writing articles for the Factor IX Newsletter (now called Hemophilia B Newsletter). He soon enlisted Dr. Clark's help, eventually turning the task over to Dr. Clark entirely. "I've been writing for the newsletter ever since," Dr. Dave says with a big smile. "I never thought I could write but learned I have a knack for it. Someone once told me that to do a good job, I need to know my audience. So, I try to write as though I'm speaking to a parent of a young child with hemophilia, who may have limited medical knowledge along with limited time and wherewithal to figure out the technical verbiage."

Concentrating our conversation on hemophilia B, I ask Dr. Clark if he has any frustrations or concerns. He states emphatically that he is concerned with the plight of women with hemophilia and wants to see them receive more recognition and not struggle to be diagnosed. "There are excellent treatments for hemophilia and better ones coming down the pipeline. No one should be bleeding and yet, many women are being ignored and having trouble finding appropriate care. These women are suffering, and they don't need to be!"

I asked Dr. Clark where he thinks the root of this mindset stems from. "It's part ignorance and part arrogance. We think we know more than we do. Once we had some limited, primitive knowledge of the genetics of hemophilia, we decided since women have two factor IX genes (because they have two X chromosomes), they shouldn't have a problem with bleeding. We figured if one was bad, the other one would compensate in most cases. One of the things I've learned in my science career is there are rarely simple answers. If you think you have a simple answer to an issue, you are probably wrong. For years we believed women genetically could not have hemophilia. We just didn't know enough to realize there were other reasons that they would."

Dr. Clark scratches his head, sympathetically, "Throughout history, society has not typically taken women seriously enough. I don't understand this. We have some wonderful physicians treating hemophilia around the country and many of them are starting to take women's bleeding issues more seriously which is a good thing.

Another concern for which Dr. Clark sends up a cautionary flare is regarding the speed at which new products are being developed to tweak the coagulation system. "Currently, there is so much going on in new product development for hemophilia. I think it's good, but at the same time, I wonder if we are getting ahead of ourselves. We're trying to do things we think we understand but don't completely, and that can lead to problems. I wonder sometimes if new products are pushed too fast before we fully understand the implications. It's science. We're always going to run into problems that need to be solved.

Dr. Clark says he sees himself more as a curator of information than advice. He points out there will always be people who want the latest and greatest treatment, and they will take a product as soon as it's available. "In a way, their bravery is valuable for the rest of us. Through them, we find the potential problems. Then there are other

people who are too afraid to try anything new, even though it can potentially help them a lot. I don't have hemophilia, so I don't want to push someone to try something that may not be right for them.

The fact that hemophilia B is getting so much attention lately gives Dr. Clark hope. "There are a lot of exciting things going on and I believe the future holds some amazing treatments for hemophilia." He is especially excited about developments in gene therapy. "We have a way to go yet, but there may lie a potential cure for hemophilia B in gene therapy." His eyes light up at the thought of how this fascinating work could change lives for the better.

"When people ask for advice," he says, "I always tell them to speak with their doctor. I'm not a clinician. Doctors are valuable not only because of their knowledge, but also because they develop ways of working directly with patients, and this is just as important as the science."

Dr. Clark threads that needle beautifully in his hemophilia B articles by informing readers about research, products, potential problems and benefits, and letting patients and families make their own informed decisions. He believes we can exercise care by talking with many people and getting information about what these products are all about.

In closing, Dr. Clark says, "Through the years, I've become more and more involved with the Coalition and the hemophilia B families which it proudly serves. I love this community. They're amazing people!"

Thank you, Dr. Dave, for illustrating how taking education seriously can lead us to purposeful, exciting journeys, and even to the opportunities of our lives. Thank you for being part of this important education. You are a treasured part of *The Coalition For Hemophilia B. Happy 30th Anniversary!*

"I've known Dave for over 20 years his passion for this community is second to none! Dave speaks at all programs nationwide. I especially love when he comes to the retreats and brings everyone up to date on research and current scientific updates in a way we can understand and then he hangs out with all the guys and they just love talking and hanging around with him. He's a very special person and we are very lucky to know him and have him as part of our community!" – Wayne Cook

"Dave is amazing! I remember when I first started there was so much to learn and he made it so easy for me to understand. I must have asked him a million questions, I still do! He always has a smile on his face and such wonderful patience. He truly loves the work that he does and cares so deeply for our community. His passion shines brightly. Dave is a true Gem, we should all cherish greatly! I feel so blessed everyday to know him!
– Kim Phelan

"Dr. Clark understands the science of bleeding disorders (especially hemophilia B!) and current and emerging therapies better than anyone I've ever met. His ability to explain science and difficult medical concepts is unrivaled, and he is the first person I turn to when I need to understand something complex having to do with my bleeding disorder. In addition to his incredible expertise and willingness to share it, he is one of the kindest people I have ever known." – Lori Long

TAKE CONTROL TO A HIGH LEVEL WITH REBINYN® IN HEMOPHILIA B

Clayton, 34 years old, is a pilot and enjoys hiking and camping in his spare time. Clayton lives with hemophilia B.

Rebinyn® elevates factor levels above your normal levels[a]

+94% Factor IX (FIX) levels achieved after an infusion[b]

83-hr (3.5 day) average half-life in adults[a]

With a single dose of Rebinyn® 40 IU/kg in adults with ≤2% FIX levels[a]

Achieve higher factor levels for longer

Compared with Alprolix®[c], Rebinyn® provides

4x greater factor coverage

6x higher factor levels at 7 days

Image of hemophilia patient shown is for illustrative purposes only.

[a]In a phase 3 study of adults, single dose pharmacokinetics were tested during the first Rebinyn® 40 IU/kg dose in 6 adults.

[b]Based upon a 2.34% increase in factor levels per IU/kg infused in adults.

[c]Based upon a phase 1 study comparing a single 50 IU/kg dose of Rebinyn® to a single 50 IU/kg dose of extended half-life rFIXFc in 15 adults. To allow for direct comparison between products, all patients received the Alprolix standard 50 IU/kg dose.

INDICATIONS AND USAGE

What is Rebinyn® Coagulation Factor IX (Recombinant), GlycoPEGylated?

Rebinyn® is an injectable medicine used to replace clotting Factor IX that is missing in patients with hemophilia B. Rebinyn® is used to treat and control bleeding in people with hemophilia B. Your healthcare provider may give you Rebinyn® when you have surgery. Rebinyn® is not used for routine prophylaxis or for immune tolerance therapy.

IMPORTANT SAFETY INFORMATION

What is the most important information I need to know about Rebinyn®?

- **Do not attempt to do an infusion yourself unless you have been taught how by your healthcare provider or hemophilia treatment center.** Carefully follow your healthcare provider's instructions regarding the dose and schedule for infusing Rebinyn®.

Who should not use Rebinyn®?

Do not use Rebinyn® if you:

- are allergic to Factor IX or any of the other ingredients of Rebinyn®.
- are allergic to hamster proteins.

What should I tell my health care provider before using Rebinyn®?

Tell your health care provider if you:

- have or have had any medical conditions.
- take any medicines, including non-prescription medicines and dietary supplements.
- are nursing, pregnant, or plan to become pregnant.
- have been told you have inhibitors to Factor IX.

How should I use Rebinyn®?

- Rebinyn® is given as an infusion into the vein.
- **Call your healthcare provider right away if your bleeding does not stop after taking Rebinyn®.**
- Do not stop using Rebinyn® without consulting your healthcare provider.

What are the possible side effects of Rebinyn®?

- **Common side effects include** swelling, pain, rash or redness at the location of the infusion, and itching.
- **Call your healthcare provider right away or get emergency treatment right away if you get any of the following signs of an allergic reaction:** hives, chest tightness, wheezing, difficulty breathing, and/or swelling of the face.
- **Tell your healthcare provider about any side effect that bothers you or that does not go away.**
- Animals given repeat doses of Rebinyn® showed Polyethylene Glycol (PEG) inside cells lining blood vessels in the choroid plexus, which makes the fluid that cushions the brain. The potential human implications of these animal tests are unknown.

Please see Brief Summary of Prescribing Information on the following page.

Rebinyn® is a prescription medication.

You are encouraged to report negative side effects of prescription drugs to the FDA.
Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Learn more at rebinyn.com and connect with your local HCL

Novo Nordisk Inc., 800 Scudders Mill Road, Plainsboro, New Jersey 08536 U.S.A.

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rebinyn®
Coagulation Factor IX (Recombinant), GlycoPEGylated

rebinyn®

Coagulation Factor IX (Recombinant), GlycoPEGylated

Brief Summary Information about:
REBINYN® Coagulation Factor IX (Recombinant), GlycoPEGylated

Rx Only

This information is not comprehensive.

- Talk to your healthcare provider or pharmacist
- Visit www.novo-pi.com/REBINYN.pdf to obtain FDA-approved product labeling
- Call 1-844-REB-INYN

Read the Patient Product Information and the Instructions For Use that come with REBINYN® before you start taking this medicine and each time you get a refill. There may be new information.

This Patient Product Information does not take the place of talking with your healthcare provider about your medical condition or treatment. If you have questions about REBINYN® after reading this information, ask your healthcare provider.

What is the most important information I need to know about REBINYN®?

Do not attempt to do an infusion yourself unless you have been taught how by your healthcare provider or hemophilia treatment center.

You must carefully follow your healthcare provider's instructions regarding the dose and schedule for infusing REBINYN® so that your treatment will work best for you.

What is REBINYN®?

REBINYN® is an injectable medicine used to replace clotting Factor IX that is missing in patients with hemophilia B. Hemophilia B is an inherited bleeding disorder in all age groups that prevents blood from clotting normally.

REBINYN® is used to treat and control bleeding in people with hemophilia B.

Your healthcare provider may give you REBINYN® when you have surgery.

REBINYN® is not used for routine prophylaxis or for immune tolerance therapy.

Who should not use REBINYN®?

You should not use REBINYN® if you

- are allergic to Factor IX or any of the other ingredients of REBINYN®
- if you are allergic to hamster proteins

If you are not sure, talk to your healthcare provider before using this medicine.

Tell your healthcare provider if you are pregnant or nursing because REBINYN® might not be right for you.

What should I tell my healthcare provider before I use REBINYN®?

You should tell your healthcare provider if you

- Have or have had any medical conditions.
- Take any medicines, including non-prescription medicines and dietary supplements.
- Are nursing.
- Are pregnant or planning to become pregnant.
- Have been told that you have inhibitors to Factor IX.

How should I use REBINYN®?

Treatment with REBINYN® should be started by a healthcare provider who is experienced in the care of patients with hemophilia B.

REBINYN® is given as an infusion into the vein.

You may infuse REBINYN® at a hemophilia treatment center, at your healthcare provider's office or in your home. You should be trained on how to do infusions by your hemophilia treatment center or healthcare provider. Many people with hemophilia B learn to infuse the medicine by themselves or with the help of a family member.

Your healthcare provider will tell you how much REBINYN® to use based on your weight, the severity of your hemophilia B, and where you are bleeding. Your dose will be calculated in international units, IU.

Call your healthcare provider right away if your bleeding does not stop after taking REBINYN®.

If your bleeding is not adequately controlled, it could be due to the development of Factor IX inhibitors. This should be checked by your healthcare provider. You might need a higher dose of REBINYN® or even a different product to control bleeding. Do not increase the total dose of REBINYN® to control your bleeding without consulting your healthcare provider.

Use in children

REBINYN® can be used in children. Your healthcare provider will decide the dose of REBINYN® you will receive.

If you forget to use REBINYN®

If you forget a dose, infuse the missed dose when you discover the mistake. Do not infuse a double dose to make up for a forgotten dose. Proceed with the next infusions as scheduled and continue as advised by your healthcare provider.

If you stop using REBINYN®

Do not stop using REBINYN® without consulting your healthcare provider.

If you have any further questions on the use of this product, ask your healthcare provider.

What if I take too much REBINYN®?

Always take REBINYN® exactly as your healthcare provider has told you. You should check with your healthcare provider if you are not sure. If you infuse more REBINYN® than recommended, tell your healthcare provider as soon as possible.

What are the possible side effects of REBINYN®?

Common Side Effects Include:

- swelling, pain, rash or redness at the location of infusion
- itching

Other Possible Side Effects:

You could have an allergic reaction to coagulation Factor IX products. **Call your healthcare provider right away or get emergency treatment right away if you get any of the following signs of an allergic reaction:** hives, chest tightness, wheezing, difficulty breathing, and/or swelling of the face.

Your body can also make antibodies called "inhibitors" against REBINYN®, which may stop REBINYN® from working properly. Your healthcare provider may need to test your blood for inhibitors from time to time.

You may be at an increased risk of forming blood clots in your body, especially if you have risk factors for developing blood clots. Call your healthcare provider if you have chest pain, difficulty breathing, leg tenderness or swelling.

Animals given repeat doses of REBINYN® showed Polyethylene Glycol (PEG) inside cells lining blood vessels in the choroid plexus, which makes the fluid that cushions the brain. The potential human implications of these animal tests are unknown.

These are not all of the possible side effects from REBINYN®. Ask your healthcare provider for more information. You are encouraged to report side effects to FDA at 1-800-FDA-1088.

Tell your healthcare provider about any side effect that bothers you or that does not go away.

What are the REBINYN® dosage strengths?

REBINYN® comes in three different dosage strengths. The actual number of international units (IU) of Factor IX in the vial will be imprinted on the label and on the box. The three different strengths are as follows:

Cap Color Indicator	Nominal Strength
Red	500 IU per vial
Green	1000 IU per vial
Yellow	2000 IU per vial

Always check the actual dosage strength printed on the label to make sure you are using the strength prescribed by your healthcare provider.

How should I store REBINYN®?

Prior to Reconstitution (mixing the dry powder in the vial with the diluent):

Store in original package in order to protect from light. Do not freeze REBINYN®.

REBINYN® vials can be stored in the refrigerator (36-46°F [2°C-8°C]) for up to 24 months until the expiration date, or at room temperature (up to 86°F [30°C]) for a single period not more than 6 months.

If you choose to store REBINYN® at room temperature:

- Note the date that the product is removed from refrigeration on the box.
- The total time of storage at room temperature should not be more than 6 months. Do not return the product to the refrigerator.
- Do not use after 6 months from this date or the expiration date listed on the vial, whichever is earlier.

Do not use this medicine after the expiration date which is on the outer carton and the vial. The expiration date refers to the last day of that month.

After Reconstitution:

The reconstituted (the final product once the powder is mixed with the diluent) REBINYN® should appear clear without visible particles.

The reconstituted REBINYN® should be used immediately.

If you cannot use the reconstituted REBINYN® immediately, it should be used within 4 hours when stored at or below 86°F (30°C). Store the reconstituted product in the vial.

Keep this medicine out of the sight and out of reach of children.

What else should I know about REBINYN® and hemophilia B?

Medicines are sometimes prescribed for purposes other than those listed here. Do not use REBINYN® for a condition for which it is not prescribed. Do not share REBINYN® with other people, even if they have the same symptoms that you have.

More detailed information is available upon request.

Available by prescription only.

For more information about REBINYN®, please call Novo Nordisk at 1-844-REB-INYN.

Revised: 11/2017

REBINYN® is a trademark of Novo Nordisk A/S.

For Patent Information, refer to: http://novonordisk-us.com/patients/products/product-patents.html

Manufactured by:
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For information about REBINYN® contact:
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Plainsboro, NJ 08536, USA

USA17BIO03951 12/2017

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Springing Into Wellness with the Coalition

BY GLENN MONES

Spring seems to breathe new life into us. It cleanses our spirit and our hearts. We feel a renewal of our own energies emerging.

What better way to start spring and mental health awareness month then to spend time every Saturday working on our mind and body. To kick off the season and help our members in this vital pursuit, The Coalition for Hemophilia B presented a Wellness Series every Saturday in May (except Mother's Day weekend.)

Participants were encouraged to bring their morning cup of joe outside so we could all spend time together and get moving! For many who have been cooped up all winter, this was a welcome chance to get out of the house and into the outdoors.

Every session opened with meditation and Tai Chi (simple rhythmic movements designed to improve balance, strength, flexibility, and maintain or strengthen bone mass). This ancient physical and mental practice was led by Rick and Cassandra Starks, a father-daughter team who are well known in the community. Interestingly national health organizations, including the Arthritis Foundation recommend Tai Chi for pain relief. It's perfect for adults of all ages and will support you in your health journey. It was a great way to start the day and get everyone up and moving!

Each week featured a special guest speaker who left us inspired, motivated and added a tool to our self-care tool kit and journey. These included Health/Life Coach and Nutritionist, Catherine Canadeo; Certified Mental Health First Aid Instructor and hemophilia mom, Debbie De La Riva LPC from Mental Health Matters Too; professional golfer with hemophilia Perry Parker; and Diane Dimon, Dr.RS, a Mind/Body Coach from Matters of the Mind. We were all empowered!

The feedback we received from participants has been extremely positive:

"I very much enjoyed the CHB Spring into Wellness events because they help me remember that I want to focus on my mental health as well as my physical health. I liked that we not only learned from the speakers, but also participated by getting to meditate and do Tai Chi. I really wish the program would continue on a regular basis."

"The Wellness Series was AMAZING! It was so great to connect on Saturday mornings and just spend an hour gaining skills, knowledge and techniques to help take care of my own mind and body. I can never express how

grateful I am to The Coalition for Hemophilia B and CSL Behring for putting on these invaluable events.

“Self-care and wellness are so important. As a mother, wife, sister, aunt, and even just a friend, it is hard to sometimes take a step back and take care of myself. This is something I have to remind myself to do as it does not come naturally for me. I want to personally say thank you to all of you for helping us along the way. I truly never understood how important it is to have help emotionally, mentally and even physically along the way to a healthy life.

“The Wellness Series was such an amazing experience. The Coalition really goes out of their way to set our minds at ease and help us relax from our everyday busy – sometimes overwhelming lives. The guided meditation, Tai Chi, and multiple programs really showed us how to engage and focus on our mental health and wellness. I am absolutely grateful for these events because now I know how I can work on my mental health, my family’s and even my friends! I really enjoyed the experience and gained knowledge from it. Thanks to The Coalition for Hemophilia B I am taking away such beautiful gifts of peace of mind!

“I’ve learned a lot of new things about myself and ways to shape my mind, body and soul in times of crises such as when bad bleeding episodes occur. I was encouraged to find a meditative way to overcome pain.”

“I really appreciated the Tai Chi movement and wellness speakers. Having young kids, I often focus on getting them going in the mornings and forget to take time for myself. This was a great way to schedule some self-care time and has given me new tools to incorporate into my mornings.”

These represent just a sample of the many great comments we received.

We want to express our sincerest thanks to CSL Behring, our sponsor for this series. Without the shared vision of partners like CSL, these programs would not be possible.

CSL Behring

The Coalition for Hemophilia B is committed to providing our community with a variety of opportunities to connect with other members and learn together about physical and mental wellness and self-care. Please check our website, emails and social media pages regularly for future programs and events.

From Awareness to Action!

In the wake of COVID-19, millions of people have uncovered new mental health conditions and millions more have had their existing challenges exacerbated. While more people than ever before are comfortable discussing mental health, many fall through the cracks in the space between awareness and action – particularly those who have been marginalized or underserved by existing institutions. That is why a coalition of more than 1400 nonprofits, brands, government agencies, and influential leaders came together to drive our culture from awareness to action on May 20th for the inaugural Mental Health Action Day. Global participation included 8K posts on IG and trending on Twitter with 6K+ tweets, including President Biden, Arianna Huffington, Kerry Washington, and more. There were also 620M views on GIPHY, 60M views on TikTok, 500K+ engagements, and 1700+ press hits with an audience of 20M viewers/readers.

We look forward to working with our partners again next year!

Hemophilia Health News

BY DR. DAVID CLARK

A number of the items shown below were presented at the European Association for Haemophilia and Allied Disorders (EAHAD) Annual Congress, 2/3-5/21. The abstracts (summaries) of the studies are available at no charge on the EAHAD web site at https://eahadcongress.com/abstracts/abstract-submission/.

CLINICAL AND ECONOMIC BURDEN OF HEMOPHILIA B IN THE U.S.

3/2/21 and 3/20/21 Two recent, related articles analyzed results from the CHESS US and CHESS US+ studies on the burdens of severe hemophilia B in the U.S. CHESS US was based on medical record analyses and physician reported information. The complementary CHESS US+ study was based on patient reported information collected by questionnaire.

In 44 severe hemophilia B patients, all on prophylaxis, the median annualized bleed rate (ABR) was 2.0 (range 0–5). The fact patients on prophylaxis still had bleeds demonstrates there are still unmet needs in hemophilia treatment. 18% of patients reported at least one target joint and 11% reported at least one problem joint. 56.1% reported chronic pain at a level of 1–5 (out of 10) and 28.1% reported chronic pain at a level of 6–10.

In the economic analysis, the average annual medical cost was $614,886, most of which was for factor ($611,971). Breaking it down by type of factor products, the average annual factor costs were $397,491 for those on standard half-life (SHL) products and $788,491 for extended half-life (EHL) products. The actual average factor usage was 287,141 IU for SHL and 232,278 IU for EHL.

Most of the same authors also participated in another study (Li et al.) to model the estimated adult lifetime costs from the CHESS data. They estimated the total adult lifetime costs for patients with severe and moderately severe hemophilia B are $21,086,607 for those on SHL prophylaxis, $22,987,483 for those on EHL prophylaxis and $20,971,826 for those on on-demand treatment. For those on prophylaxis, the factor costs represent >90% of the total costs. Those using on demand treatment have lower factor costs but much higher medical costs. [Burke T et al., Orphanet J Rare Dis, 16(1), 143, 2021 and Li N et al., J Med Econ, 24(1), 363 372, 2021]

CLINICAL BURDEN OF INHIBITOR TREATMENT IN EUROPE

2/4/21 At EAHAD, a study was presented that looked at data from CHESS II, a similar European study of the burdens of hemophilia B in patients with inhibitors. In 24 patients with inhibitors, they found an average ABR of 6.6, compared to an average ABR of 3.5 in 53 patients who had never developed an inhibitor. Of the subjects with inhibitors, 38% had problem joints compared with 26% in the non-inhibitor group. 29% of those in the inhibitor group had joint surgery, compared with 23% of the non-inhibitor group. The authors point out the number of inhibitor patients was relatively small and further research is needed. [EAHAD abstract ABS068]

LIFE EXPECTANCY FOR PEOPLE WITH HEMOPHILIA IN NORDIC COUNTRIES, INCLUDING CARRIERS

2/4/21 At EAHAD, researchers presented results from a study of 3246 people with hemophilia and hemophilia carriers (A and B), looking at life expectancy and co-morbidities (other diseases/disorders) from 2007–2017. In spite of recent improvements in treatment, both, people with hemophilia and carriers had a significantly lower life expectancy than controls from the non-hemophilia population. This lower life expectancy is not just due to HIV infection. They found higher prevalence of arthritis and HIV and hepatitis infections, as expected. However, they also found higher prevalences of hypertension (high blood pressure), diabetes, kidney disease and epilepsy. Carriers had similarly higher rates of these co-morbidities. [EAHAD abstract ABS155]

MILD TO MODERATE HEMOPHILIA

People with mild to moderate hemophilia, including many women with hemophilia, have been neglected in research studies. Most clinical research studies are focused on

men with severe hemophilia A, with a smaller number covering men with severe hemophilia B. Much of our other knowledge of hemophilia has been extrapolated from the results of those studies. However, it is becoming apparent both men and women with mild or moderate hemophilia have unmet needs that are different from those with severe hemophilia. In addition, many of the new treatments being developed, such as gene therapy, may end up changing severe hemophilia to mild, adding to the mild/moderate population.

We began to recognize some of the differences in the B HERO S study performed a few years ago in which the Coalition participated. Now the journal, *Haemophilia*, the official journal of the World Federation of Hemophilia (WFH), has devoted a special supplementary issue to the problems of mild to moderate hemophilia. The issue is available for free access on the internet at https://onlinelibrary.wiley.com/toc/13652516/2021/27/S1. The following are a few highlights from that issue.

The problems start with diagnosis. Since they often don't bleed spontaneously, many milds and moderates are diagnosed later in life, often after trauma or surgery. Many people may think they just have "bad knees" or "bad ankles" while not understanding it is the result of many small joint bleeds since childhood. Many will not know how to recognize a bleed nor that it can be treated. As many of you are all too aware, most people without hemophilia, even doctors, don't know much about hemophilia.

Even after diagnosis, many milds and moderates have difficulty obtaining care. This is especially true of women with hemophilia and carriers who have never been diagnosed as having mild or moderate hemophilia, but even men have been neglected. Even if their hemophilia is recognized, many have trouble getting factor and few know how to self-infuse. This results in treatment delays, if they can get treated at all. Only a small percentage of moderates who may have routine small bleeds, are on prophylaxis. Too many milds and moderates are essentially forced by unknowing doctors and insurance companies to just let their joints degrade over time.

Studies have shown milds and moderates have normal life spans, however, their quality of life often doesn't last. They and their caregivers may also suffer from similar social and psychological problems as severes, but without the benefit of help from HTCs. They are also often not connected with the hemophilia community, and we know the connection can be a huge benefit.

Women may experience heavy periods and increased risk of bleeding during pregnancy and after childbirth, yet not understand these problems can be treated. It is known milds and moderates with hemophilia A can still develop inhibitors, but essentially nothing is known for hemophilia B. All of this points out the real need for more research on mild and moderate hemophilia and more awareness that those patients don't just have it easy compared to severes.

So much of the history of hemophilia treatment has focused on severes and we are making great strides in their treatment. Now we need to recognize there are others in our community who have unmet needs. We have finally started to recognize that many women are not "just carriers," but actually have mild or moderate hemophilia. We also need to recognize that many men also fall into that category.

What can you do? Advocate for more recognition from your chapters and the national organizations that there are still community members who are not being served. If you come from a hemophilia family, make sure your relatives know they could have mild or moderate hemophilia and not know it. If you are having trouble getting care, print the articles from the special issue of *Haemophilia* and show them to your doctor or HTC. Often the first step in solving a problem is just making people aware a problem exists.

FACTOR IX ASSAY DISCREPANCIES IN MILDS AND MODERATES

2/5/21 There are two main types of factor IX assays, the tests to determine the level of factor IX in the blood. They are a clotting assay, also called a one stage assay (OSA) and a chromogenic assay (CA). In an OSA, a patient's plasma sample is mixed with reagents (chemicals) that activate clotting and provide the other ingredients needed to form a clot. The time from mixing to the formation of the clot is measured and compared with the time it takes for a sample with a normal level of factor IX (a "standard") to clot.

In a CA, the sample is mixed with different reagents plus a "chromogenic substrate" that changes color when it is exposed to the activated clotting factors. The time and intensity of the color change is measured and also compared to a normal factor IX standard. Different labs use different versions of each test. By using the same standard, they can compare results from lab to lab.

For people with severe hemophilia, the OSA and CA assays usually give the same result. A Dutch study presented at EAHAD shows this might not always be true for patients with mild/moderate hemophilia. In a study of 58 patients with non-severe hemophilia B, the researchers found that for 17% (10/58) of the patients the OSA (clotting) result was significantly higher than the CA (chromogenic) result, sometimes twice as high or higher. Nine of the patients would be classified into a more severe category depending on which assay was used. This is another case of milds and moderates needing different attention than severes. [EAHAD abstract ABS008]

BLEEDING PATTERNS IN MILDS/ MODERATES

2/5/21 Another Dutch study looked at bleeding patterns in people with mild or moderate hemophilia A and B. This

kind of study can be done more easily in many European countries because their government healthcare systems have records of almost everyone's treatment over their whole lifetime. In 133 patients (102 As and 31 Bs) with mild or moderate hemophilia, 81% had experienced at least one bleed over their lifetime that required treatment with factor, and 44% had hexperienced at least one joint bleed. The median annualized bleeding rate (ABR) was 0.8 for the moderates and 0.2 for the milds. [EAHAD abstract ABS199]

CARRIERS AND WOMEN WITH HEMOPHILIA

Women, first please read the above section on mild and moderate hemophilia and recognize that could be you or your relatives or friends. While there are some women with severe hemophilia and some who are truly only carriers and have factor levels in the normal range, many women with defective factor IX genes fall into the mild or moderate categories. Theoretically, the "average carrier" has a factor level of 50%, the lower limit of the "normal" range. However, studies have shown that women can bleed at levels up to 60%, so even the "average carrier" may have mild hemophilia. Even if you think you are "just a carrier" talk to your doctor or HTC to have your levels checked. Your son, daughter or relative who has been diagnosed with hemophilia would like their mother, aunt, cousin or whoever to get the care they need.

PREGNANCY, DELIVERY AND POSTPARTUM CARE IN WOMEN WITH HEMOPHILIA

12/24/20 through 3/20/21 Four recent review studies have focused on management of carriers and women with hemophilia during pregnancy, delivery and postpartum care. The studies point out there is a lack of screening and diagnosis for women at risk and a lack of treatment guidelines for their care and the care of their baby. One review [Chaudhury et al.] also covered care during menstruation and other bleeding episodes. There is a definite lack of research in this area. The lack of treatment guidelines means treatment plans must be created from scratch and may be based as much on experience and intuition as on data.

A special risk is inherent in women who are not perceived to be at risk because of unknown carrier status and/or factor levels. Even women with known risk factors may not realize the need to seek additional care or may be denied sufficient care. The general consensus is to maintain factor levels above 50% in late pregnancy through the postpartum period. Even then, women may face significant risks of postpartum hemorrhage as well as miscarriage and stillbirth.

Neglecting care for the mother can also put the fetus/baby at risk. Low maternal factor levels are associated with retardation of fetal growth in some cases. In general, because of the lack of significant knowledge in this area, expectant mothers who are at risk for bleeding disorders should seek care from experienced doctors and treatment centers. [Chaudhury A et al., Haemophilia online ahead of print 12/24/20; Murakhovskaya I and Demasio KA, NeoReviews, 22(2), e95 e103, 2021; Togioka BM et al., J Anesth, 35, 288 302, 2021; Punt MC et al., Blood Rev, online ahead of print 3/20/21]

NEW EUROPEAN PRINCIPLES OF CARE FOR WOMEN AND GIRLS WITH INHERITED BLEEDING DISORDERS

2/4/21 At EAHAD, the *EAHAD Women and Girls with Bleeding Disorders Working Group* presented ten Principles of Care (PoC) for women and girls with inherited bleeding disorders (WBD). This is an important step. Quoting from the abstract:

Ten complementary PoC for WBD were developed, emphasizing the importance and benefits of a centralized, multidisciplinary, comprehensive family centred approach to support and manage WBD during all stages of life:

10 European Principles of Care for Women and Girls with inherited Bleeding Disorders

1. Equitable access and quality of care for all individuals with bleeding disorders, irrespective of gender
2. Timely and accurate diagnosis of bleeding disorders in women and girls
3. Awareness of the additional challenges faced by WBD throughout life
4. Comprehensive care of bleeding disorders requires a family centred approach which includes WBD
5. Inclusion of a dedicated obstetrician and gynaecologist in the multidisciplinary team
6. Education of WBD and their families regarding the challenges associated with the menstrual cycle and their management
7. Early recognition and optimal management of heavy menstrual bleeding
8. Provision of pre-conception counseling and access to prenatal diagnostics
9. Provision of a patient centred comprehensive management plan throughout pregnancy and the post-partum period
10. Involvement of WBD in registries, clinical research and innovation

These PoC will improve awareness on the unique challenges for WBD and serve as a benchmark for diagnosis and comprehensive multidisciplinary management of WBD. They offer a framework to guide HTCs in providing equitable care for all WBD, both in their own services and other healthcare settings. Implementation and adherence to these principles is aimed to positively impact on the health, wellbeing and quality of life for WBD. [EAHAD abstract ABS291]

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EMERGING THERAPIES

BY DR. DAVID CLARK

A number of the items shown below were presented at the European Association for Haemophilia and Allied Disorders (EAHAD) Annual Congress, 2/3-5/21. The abstracts (summaries) of the studies are available at no charge on the EAHAD web site at https://eahadcongress.com/abstracts/abstract-submission/.

Catalyst Publishes Updates on DalcA

2/4/21 Catalyst Biosciences is developing dalcinonacog alfa (DalcA), a subcutaneous variant factor IX with an increased activity and longer half-life for prophylaxis in hemophilia B. In their Phase I/II study of 11 males aged 12–65 with severe hemophilia B, comparing subcutaneous (subQ) DalcA with intravenous (iv) BeneFIX, they found that DalcA had 24 times greater activity than BeneFIX and a half-life of 54– 07 hours. The median factor IX level reached after 6 doses was 15.7%. Two patients (cousins with presumably similar genetics) developed inhibitors to DalcA. [You CW et al., J Thromb Haemost, online ahead of print 2/4/21]

5/6/21 Catalyst also published a report on their Phase IIb study of DalcA, which is aimed at producing circulating factor IX levels of 12% or greater. There were no reports of serious adverse reactions or thrombosis. However, several patients experienced injection site reactions (ISRs) including one subject who discontinued participation because of ISRs. In the remaining five patients, three experienced factor IX levels of at least 12% by day 7 with all five having levels of 12% by day 29. Splitting the doses into additional subcutaneous injection sites reduced the numbers of ISRs. [Mahlangu J et al., Haemophilia, online ahead of print 5/6/21]

Catalyst Presents on MarzAA and Begins Phase III Studies

2/3/21 Catalyst Biosciences is also developing marzeptacog alfa activated (MarzAA), a subQ variant activated factor VII with an increased activity and longer half-life for treatment of hemophilia A or B patients with inhibitors. At EAHAD they reported on animal studies of MarzAA in hemophilic rats and dogs. MarzAA was effective in treating spontaneous bleeds in both types of animals. [EAHAD abstracts AB5027 and AB 5028]

5/5/21 Catalyst announced that they have dosed the first patient in their Phase III study of MarzAA. The study seeks to recruit 60 inhibitor patients age 12 or older for the study at multiple sites in several countries. They expect to complete the study by mid-2022. [Catalyst press release 5/5/21 and Hemophilia News Today article 5/12/21]

CSL Publishes on Modified Factor X for Hemophilia Treatment

4/23/21 CSL Behring is exploring the development of a modified factor X product for treatment of hemophilia A or B with or without inhibitors. Factor X is a key clotting factor that converts prothrombin (factor II) to thrombin (IIa), which converts fibrinogen to fibrin to form a clot. Factor X is activated by the activated factor VIII/IX complex. Patients with either defective factor VIII (hemophilia A) or defective factor IX (hemophilia B) have trouble activating enough factor X to produce good clots. CSL researchers have modified factor X so it can be activated by factor XIa, eliminating the need for factors VIII or IX. This would also serve as a bypassing agent for A or B inhibitor patients. The modified factor X showed good results in laboratory coagulation tests and in mice. More research is needed to investigate the molecule's potential as a hemophilia treatment. [Ebert M, et al., Blood Cells Mol Dis, online ahead of print 4/23/21]

A Factor IX Salad for Inhibitor Eradication?

5/5/21 A group of academic researchers is exploring the development of a plant-based factor IX product for use in immune tolerance induction (ITI) in hemophilia B patients with inhibitors. Current ITI protocols give usually-daily doses of clotting factor to try to teach the body to tolerate infused factor VIII or IX. ITI is often successful in hemophilia A patients but more often unsuccessful in hemophilia B. The researchers showed in 2017 that recombinant factor IX produced in genetically-engineered lettuce plants could be used to tolerize mice and dogs with hemophilia B and inhibitors when given orally. The recombinant factor IX is also linked to the cholera non-toxin B subunit, which helps the factor IX pass through the walls of the intestines.

Now, in preparation for a human clinical study, the group has performed toxicity studies in rats and dogs to show that the product is safe. They found no evidence of toxicity. Note that the lettuce is freeze-dried, ground up, and mixed with the animal's food. (For the dogs they added a little bacon flavoring!) For humans, the product would probably be ground up and placed in capsules. [Srinivasan A, et al., Plant Biotechnology Journal, online ahead of print 5/5/21]

FDA Mixup on Pediatric Prophylaxis Indications

2/17/21 FDA has temporarily rescinded the indication for prophylaxis in children for Aptevo/Medexus' Ixinity and Pfizer's BeneFix. This is an administrative and labeling issue and does not reflect on either product's safety or efficacy for that use. Both products are still indicated for prophylaxis in adults. Baxalta's (now Takeda's) Rixubis was approved for prophylaxis in children in 2014, and since it had Orphan Drug Status, has an exclusive right to that indication for seven years, until 9/12/2021. FDA mistakenly overlooked Rixubis' exclusivity when it approved pediatric prophylaxis indications for BeneFIX and Ixinity. Both companies will be able to re-apply for a pediatric prophylaxis indication at the end of Rixubis' exclusivity period. Since physicians can prescribe any licensed product off-label, this will not affect any patient's current use of either product. [FDA letters 2/17/21]

REBALANCING AGENTS: REBALANCING THE COAGULATION CASCADE

A number of organizations are developing products to treat hemophilia without clotting factor infusions by inhibiting various of the anticoagulants that control the clotting system. Until recently, this area has not had a uniform name, but lately the consensus seems to be "rebalancing the coagulation cascade."

That's actually a good description of what these products are intended to accomplish. In a person without a bleeding disorder, the clotting system (the coagulation cascade) is in balance between the clotting factors that cause clotting and the anticoagulants that keep the clotting under control. Anticoagulants are sometimes called the "brakes" on the clotting system. This balance allows the blood to clot when needed but not allow thrombosis, which is unwanted clotting that can be dangerous or even deadly.

The defective clotting factors that cause hemophilia upset the balance to tilt the scales more toward the side of not clotting. By inhibiting some of the anticoagulant activity in the system, the products being developed hope to even out the balance and restore the ability of the blood to clot when necessary. However, it's a tricky balance to achieve without pushing things too far and causing thrombosis. Some of the anticoagulants that are being targeted include antithrombin, tissue factor pathway inhibitor (TFPI), protein C and protein S.

One of the biggest challenges is treating breakthrough bleeds, bleeds that occur in patients while on the products. Clotting factor doses for non-inhibitor patients or bypassing agent doses for inhibitor patients have to be closely controlled in order to not push the balance too far toward thrombosis. Many of the developers have had problems with this in their clinical studies.

Many of the rebalancing products under development have attractive features. They are administered subcutaneously and require less frequent injections than the current clotting factors. They can be used to treat both hemophilia A and B, and even patients with inhibitors. But, achieving that "tricky balance" has been a challenge with many of the products. Hopefully, that's a problem that will be solved.

Apcintex Presents on SerpinPC

2/4/21 Apcintex is developing SerpinPC to inhibit activated protein C (APC) with the aim of rebalancing the coagulation cascade. APC is an anticoagulant that normally circulates in an inactive form that is activated at the site of clotting. Many of the clotting factors, II, VII, IX and X, and anticoagulants, proteins C and S, have similar chemical structures and are called serine proteases because they have the amino acid serine in the active site of the molecule. Inhibitors of serine proteases are called serpins, short for serine protease inhibitors.

Apcintex thinks that SerpinPC will be an attractive rebalancing candidate because it only works on the protein C that is activated at the site of injury/clotting and therefore may be less likely to cause thrombosis throughout the rest of the circulatory system. It is being studied for both intravenous (iv) and subcutaneous (subQ) injection, but they are hoping for monthly subQ dosing.

At EAHAD, they reported on the initial results of their Phase I/IIa clinical study. In 12 subjects, they found that SerpinPC was well-tolerated with no adverse reactions and no increase in D-dimer levels. An increase in D-dimer levels is an indication of possible thrombosis. They found a 55% decrease in bleeding rate and a 72% decrease in spontaneous and muscle bleeds at the initial non-optimized dose levels. All of the bleeds that did occur were successfully treated with clotting factor infusions, again with no evidence of thrombosis as measured by D-dimer. The studies are continuing with 23 subjects treated with monthly subQ injections for six months in three different dosage groups. [EAHAD abstract ABS296]

2/16/21 In other news, Apcintex has joined nine other small biotechs are part of Centessa Pharmaceuticals. This is expected to give them access to better funding and additional scientific experience and expertise. [Centessa press release 2/16/21]

Novo Presents Updates on Concizumab

2/3/21 Novo Nordisk is developing concizumab to inhibit the anticoagulant TFPI with the aim of rebalancing the coagulation cascade. At EAHAD, they gave updates on their Phase II and III clinical studies in hemophilia A and B patients, with and without inhibitors. Their studies had been paused after three inhibitor patients had experienced a total of five thrombotic events after receiving treatments

for breakthrough bleeds. Based on the data from those events, Novo has revised their dosing protocols and has resumed the studies. They also reported on patients who had received concizumab for up to 76 weeks in an extension of the original clinical study. They found an annualized bleed rate (ABR) of 4.8 at the highest dose level (16% of patients had no bleeds). There were no thrombotic events, but some patients exhibited a tendency toward thrombosis based on assay data. [EAHAD abstracts AB5188 and AB5194]

4/5/21 Novo researchers also published laboratory studies of the effects of concizumab along with additional factor VIII, factor IX, or inhibitor bypassing agents (VIIa or FEIBA) on clotting performance in hemophilia plasma. They found that the effects were mostly additive. There were no large synergistic interactions in which concizumab plus another product would result in a more than an extra 25% increase in clotting activity when combined. This should aid in estimating doses of additional products used in treating breakthrough bleeds in patients on concizumab. [Kjalke M, et al., J Thromb Haemost, online ahead of print 4/5/21]

Sanofi Presents Amended Dosing for Fitusiran

2/5/21 Sanofi is developing fitusiran to inhibit production of the anticoagulant antithrombin to rebalance the coagulation cascade in people with hemophilia A or B, with or without inhibitors. In their Phase III clinical studies, fitusiran patients experienced five serious thrombotic events, one of which was fatal. After a hold on the studies, investigation has suggested that these events were due to levels of antithrombin that were too low to adequately control clotting. Sanofi had been targeting antithrombin levels of less than 10% of normal with monthly subQ dosing of 80 mg of fitusiran. They will now increase their target to 15–5% of normal antithrombin levels with subQ doses of 50 mg every other month. Studies have resumed under the new dosing guidelines. [Joint statement from the European Hemophilia Consortium (EHC), World Federation of Hemophilia (WFH) and the National Hemophilia Foundation (NHF) 2/22/21 after announcement at EAHAD 2/5/21]

GENE THERAPY

Some of the following updates are from the American Society of Gene & Cell Therapy (ASGCT) Annual Meeting, May 11–14, 2021. The abstracts (summaries) of the studies are available at no charge on the ASGCT web site at https://annualmeeting.asgct.org/.

Who Is Eligible for Gene Therapy?

3/14/21 An HTC in Brussels, Belgium did a survey of their current hemophilia patients to see how many would be eligible for gene therapy. Out of 260 registered patients with hemophilia, 87 have severe hemophilia A or B, which would potentially make them eligible. Out of these 87 patients, 11 would be excluded because their age is greater than 65, five because of uncontrolled co-morbidities, six because of inhibitors, two because they are female, one because of active hepatitis C, one because of insufficient factor exposure, two because of alcohol abuse, and two because they were participating in other studies.

That left 57 possible patients. Seven of those were excluded because of geographic distance from the center, language barriers, socioeconomic factors and/or major disability. Of the remaining 50, 29 refused for various reasons and another seven were deemed unsuitable. Of the 29 who refused, three cited fear or lack of confidence in the treatment, 16 were satisfied with their current treatment, and 12 reported a lack of motivation to participate in a study.

That left 14, seven of which were excluded because of pre-existing anti-AAV antibodies (6) or poor liver condition (1). That left only seven (8% of the starting 87) who were actually willing and able to be treated. Based on their knowledge of the patients, the center estimated that 36 of the 87 patients would accept gene therapy, if it were a licensed procedure with fewer exclusion criteria and not a clinical study. [Krumb E, et al., Res Pract Thromb Haemost, 5:390-394, 2021]

Low Risk of Cancer from AAV Gene Therapy

5/12/21 One of the fears around gene therapy is that it could trigger cancer, possibly years after treatment. In a study presented at ASGCT, a group of researchers treated tumor-prone mice with a high dose of AAV2 gene therapy. They looked at both intravenous administration, which is the method being studied in the current clinical studies, as well as intramuscular administration, a potential future method. They found no evidence of increased tumor generation (cancer) in the mice. Although these results were in mice, not humans, and for only one strain of AAV, they help support the overall safety of AAV gene therapy. [ASGCT abstract 346]

BAX 335: Lesson from a Failed Gene Therapy Study

2/11/21 Baxalta, now part of Takeda, discontinued their BAX 335 gene therapy clinical studies several years ago because of poor results. The clinical investigators on that study recently published an extended analysis of the results that could shine some light on problems that they and other gene therapies under development have experienced. Often in reading about gene therapies you will see the genes described as “codon-optimized.” That means that the coding elements in the gene have been modified slightly to make production of its protein more efficient. This optimization is done all the time in making recombinant proteins in a pharmaceutical plant where the increased efficiency is important. However, it may

not make much difference, or could be detrimental, when making proteins inside the human body. After all, the genes in our cells are present in a non-optimized format, and that may be for a reason.

The research suggests that the factor IX gene in BAX 335 treatment might have been optimized in a way that inadvertently created a series of "CpG sequences" in the gene. These CpG sequences do not affect production of the protein from the gene, but recent research has suggested that they might be telling the immune system: "Hey, here's something you should pay attention to!" That is, the CpG sequences might be alerting the immune system that the new factor IX coming out of the transformed cells could be a foreign protein that it ought to get rid of – it's not the same old factor IX that this human has always produced (even though that factor IX was mutated and didn't work well). That might be one of the reasons that some gene therapies don't last. The immune system might be destroying the cells that have been transformed with the new gene.

It turns out that many infective agents have CpG sequences in their genes, and the immune system might be programmed to recognize those and start an immune response. Gene therapy developers probably thought that codon optimization couldn't hurt. However, what works for efficiently making proteins in a pharmaceutical plant (which doesn't have an immune system) might instead cause problems in the human body. This study should provide useful information for all gene therapy developers. [Konkle BA et al., Blood, 137(6), 763-774, 2021]

Catalyst Publishes on Potent FIX Variant for Gene Therapy

3/18/21 Catalyst Biosciences is developing a gene therapy for hemophilia B based on their high-potency factor IX variant CB 2679d-GT, which is also being developed as DalcA for factor IX replacement therapy, see above. Several hemophilia B gene therapy developers are using the higher-potency Padua factor IX variant to reach improved factor IX levels with lower AAV vector doses. High AAV vector doses have demonstrated risks of liver toxicity and inflammation in some cases. In a mouse model of hemophilia B, Catalyst has shown that CB 2679d-GT has about three-fold higher clotting activity compared to FIX-Padua. This could allow even lower AAV doses to produce adequate factor levels and clotting performance. [Nair N et al., Blood, online ahead of print 3/18/21]

Freeline Updates Results from Phase I/II Gene Therapy Study

12/14/20 and 2/4/21 Freeline Therapeutics is developing verbrinacogene setparvovec (FLT180a), a gene therapy for hemophilia B. In late 2020 and at EAHAD, they provided updates on their Phase I/II results, which showed durable factor IX expression levels of 36 to 176% (transiently up to 250% in one patient) out to almost three years for some patients. The study included ten patients at four different vector dose levels. Several patients experienced liver inflammation, which required treatment by immune suppression and resulted in loss of factor IX production. There were no other serious adverse events. Freeline believes that these results suggest that they can achieve factor IX levels in the normal range (50–150%) using lower vector doses than are used by other gene therapy developers. [Freeline press release 12/14/20 and EAHAD abstract ABS114]

Genascence Developing Gene Therapy for Osteoarthritis

5/12/21 Genascence, a California-based biotech company, is developing a localized gene therapy for treatment of osteoarthritis. Osteoarthritis is the common form of arthritis, often experienced in aging. Although not directly targeting hemophilia joint damage (hemophilic arthropathy), the treatment may apply to that indication as well. GNSC-001 is an AAV-based gene therapy that carries a gene for interleukin-1 receptor antagonist, an inhibitor of interleukin-1 (IL-1). IL-1 activity is considered one of the key causes of joint inflammation and cartilage destruction in osteoarthritis, and may be associated with hemophilic arthropathy as well. GNSC-001 is a one-time injection directly into the affected joint, which causes the surrounding tissue to produce IL-1 receptor antagonist. At ASGCT, Genascence presented results from a Phase I clinical study in ten patients. This was a safety study that showed that the treatment is safe and well-tolerated. Genascence is planning a Phase II study of efficacy, which has already received FDA approval. [ASGCT abstract 595]

GeneLeap Developing a Gene Therapy for Hemophilia B

5/12/21 GeneLeap Biotech is developing a gene therapy for treatment of hemophilia B using proprietary AAV8 vectors. GeneLeap is a U.S. subsidiary of Luye Life Sciences Group from China. Their product, GLB-2001, is currently in pre-clinical studies. At ASGCT, they presented information on their high-potency high-expression factor IX genes and vectors in laboratory experiments and in hemophilia B mice. They also reported on their production process, which gives high yields and excellent separation between gene-containing and empty AAV vector capsids. Eliminating empty capsids helps to reduce the overall vector dose and potentially reduce immune reactions to the product. [ASGCT abstracts 340 and 834]

Pfizer Publishes on Assay Discrepancies with FIX-Padua Gene Therapy

2/26/21 Pfizer is developing fidanacogene elaparvovec, a gene therapy for hemophilia B based on the higher-potency Padua variant of factor IX. In a recently published study they found that assays to determine

factor IX activity levels in patients after gene therapy with the Padua variant are problematic. They can give different values depending on the specific assay used, the reagents (chemicals) used in the assays and the laboratories performing the assays. They looked at samples from gene therapy patients as well as at donated hemophilic plasma spiked with FIX-Padua or BeneFix. The results suggest that the assay discrepancies are inherent in the FIX-Padua molecule and not specific to its use in gene therapy.

This could be a problem for all of the companies developing gene therapy treatments using FIX-Padua. Assays are critically important for any new product being developed. It is often said in the pharmaceutical industry that if you don't have an assay, you don't have a product. The manufacturers will need to address this issue. [Robinson MM et al., J Thromb Haemost, online ahead of print 2/26/21]

Pfizer Presents on Clearance of Gene Therapy Vector

2/4/21 At EAHAD, Pfizer presented the results of a study of the clearance of their gene therapy vector from the body. In 15 hemophilia B patients who have received their fidanacogene elaparvovec gene therapy, the researchers found that the genetic material was cleared from (undetectable in) urine by week 7 after treatment, saliva by week 8 and semen by week 12 in all patients. Serum (plasma) and peripheral blood mononuclear cells (PBMCs) took the longest to clear at 22 weeks and 52 weeks, respectively. PBMCs include various types of white blood cells, which are part of the immune system. The significance of the gene therapy DNA persisting for periods of time after treatment is unknown. [EAHAD abstract ABS064]

uniQure/CSL Gene Therapy Deal Finalized

5/6/21 uniQure is developing etranacogene dezaparvovec (AMT-061), a gene therapy for treatment of hemophilia B. In June 2020, uniQure announced an exclusive worldwide licensing deal with CSL Behring for the treatment. Now that antitrust and regulatory reviews have been completed, the arrangement has been finalized. uniQure will still be responsible for completing the clinical studies and for initial manufacturing of the product. CSL will be responsible for regulatory submissions and commercialization. [uniQure press release 5/6/21]

uniQure Gene Therapy Study Clinical Hold Released by FDA

12/21/20 and 4/26/21 uniQure's Phase III study was placed on a clinical hold by FDA after a patient treated in October 2019 was recently diagnosed with hepatocellular carcinoma (HCC), a form of liver cancer. An independent investigation shows that AMT-061 is highly unlikely to be the cause of the patient's HCC. uniQure submitted the findings to FDA and the hold was released on 4/26/21. They do not expect any significant effect on the timing of their development program since all patients have already been treated and are now being followed up.

The affected patient has multiple risk factors for HCC including a 25-year history of hepatitis C, hepatitis B and non-alcoholic fatty liver disease, plus advanced age. Chronic hepatitis B and C infections are associated with approximately 80% of HCC cases.

With some gene therapy vectors, the new genes can integrate into the genome (that is, insert themselves into the genes on a cell's chromosomes) in uncontrolled places. If the new gene inserts itself in the middle of another gene, it will disrupt that gene. If that happens in a gene that causes cancer, it can activate the cancer gene. That happened in an early non-hemophilia gene therapy clinical study and caused two boys in France to develop leukemia. One of the major reasons that AAV is now used as a vector is that it has an extremely low integration rate and is considered much safer.

This was, of course, a concern with the patient who developed HCC. However, an external lab analyzed more than 220,000 liver cells from the patient's biopsied tumor and found only 60 integrations (0.027%). None of those integrations were in areas of the genome that are known to activate HCC or other cancer-causing genes. In addition, whole genome sequencing of the tumor showed that the patient had large abnormalities on chromosomes 1 and 8 that are commonly associated with HCC, plus other mutations in cancer-associated genes. The results all suggest that the patient had an already-developing HCC that was not a result of the gene therapy treatment.

All of the other patients in uniQure's hemophilia B gene therapy program, including in all previous clinical studies as old as ten years ago, have now been examined and no additional HCC cases have been identified. All patients will continue to be followed, as is the case for all gene therapy clinical studies. [uniQure press releases 12/21/20, 3/1/21, 3/29/21 and 4/26/21]

uniQure Presents Additional Clinical Study Updates

2/4/21 uniQure gave three presentations at EAHAD on their Phase I/II, IIb and III clinical studies of gene therapy for hemophilia B. For their Phase III study of AMT-061, they reported on results from 54 patients who have completed 26 weeks of follow-up. No subjects were excluded because of pre-existing antibodies to the AAV5 vector. For the 23 patients who had pre-existing antibodies up to a titer of 1:678, there was no effect of antibody titer on subsequent factor IX levels. Only one patient who had a very high titer of 1:3212 showed no response to the treatment. Fifty-two patients were able to discontinue prophylaxis and 39 of

those reported no bleeds. The patient's mean factor IX level was 37.2%. Nine patients required treatment for liver inflammation. There were no serious adverse events and no indications of inhibitor development. [EAHAD abstract ABS089]

In the Phase IIb study, which covered the switch from a normal factor IX gene (AMT-060) to the higher-potency Padua factor IX gene (AMT-061), the three patients had sustained factor IX levels of 31%, 41% and 50% a year after treatment. There have been no post-treatment bleeds and no requirements for factor IX infusions, except for one patient who underwent successful hip replacement surgery for a pre-existing condition. Although some of the patients had pre-existing antibodies to the AAV5 vector, there appeared to be no effect on their response to treatment. There were no signs of liver inflammation, no need for steroid treatment and no inhibitor development. [EAHAD abstract ABS100]

uniQure also reported results from their original Phase I/II study of AMT-060 after four years of follow-up. For the five patients in the lower-dose group, the mean factor IX level was 5.1% and for the five patients in the higher-dose cohort the level was 7.4%. The mean annualized bleeding rates (ABRs) in the last year were 3.3 for the low-dose group and zero for the high-dose group. There were no additional safety concerns and no evidence of inhibitor development. [EAHAD abstract ABS043]

5/12/21 At ASGCT, uniQure presented additional data showing no effect of pre-existing anti-AAV5 antibodies on safety, performance and factor levels for their gene therapy treatment. These findings support broader eligibility for their AAV5-based gene therapies and the potential for re-dosing patients who have had previous AAV gene therapy treatments. [ASGCT abstracts 88 and 741]

University of Florida Gene Therapy for Children and for Re-Dosing Adults

5/12/21 A group at the University of Florida is working on an AAV-based gene therapy for children with hemophilia. Because children's livers are still growing up to about age 10 – 12, any early gene therapy treatment will tend to be diluted out as new liver cells develop that haven't had the treatment. Since the children will need to be re-dosed as they grow, the Florida researchers have developed a synthetic AAV vector that does not produce an immune response. (Note that other organizations are developing other methods for treating children with gene therapy.) This work could also lead to methods for re-dosing adults whose previous gene therapy treatments have failed. The group is also looking at the possibility of enclosing AAV vectors in exosomes for further protection from the immune system. Exosomes are tiny lipid-encapsulated vessels that cells use to communicate with other cells. [ASGCT abstract 360]

RIXUBIS® [Coagulation Factor IX (Recombinant)] Important Information

What is RIXUBIS?

RIXUBIS is an injectable medicine used to replace clotting factor IX that is missing in adults and children with hemophilia B (also called congenital factor IX deficiency or Christmas disease).

RIXUBIS is used to control and prevent bleeding in people with hemophilia B. Your healthcare provider may give you RIXUBIS when you have surgery. RIXUBIS can reduce the number of bleeding episodes when used regularly (prophylaxis).

Detailed Important Risk Information for RIXUBIS® [Coagulation Factor IX (Recombinant)]

Who should not use RIXUBIS?

You should not use RIXUBIS if you

- are allergic to hamsters
- are allergic to any ingredients in RIXUBIS.

Tell your healthcare provider if you are pregnant or breastfeeding because RIXUBIS may not be right for you

What should I tell my healthcare provider before using RIXUBIS?

You should tell your healthcare provider if you

- have or have had any medical problems
- take any medicines, including prescription and non-prescription medicines, such as over-the-counter medicines, supplements or herbal remedies
- have any allergies, including allergies to hamsters

What should I tell my healthcare provider before using RIXUBIS? (cont'd)

- are breastfeeding. It is not known if RIXUBIS passes into your milk and if it can harm your baby
- are pregnant or planning to become pregnant. It is not known if RIXUBIS may harm your unborn baby
- have been told that you have inhibitors to factor IX (because RIXUBIS may not work for you).

What are the possible side effects of RIXUBIS?

Allergic reactions may occur with RIXUBIS. Call your healthcare provider or get emergency treatment right away if you get a rash or hives, itching, tightness of the throat, chest pain or tightness, difficulty breathing, lightheadedness, dizziness, nausea, or fainting.
Some common side effects of RIXUBIS were unusual taste in the mouth and limb pain.

Tell your healthcare provider about any side effects that bother you or do not go away.

Your body may form inhibitors to factor IX. An inhibitor is part of the body's defense system. If you form inhibitors, it may stop RIXUBIS from working properly. Consult with your healthcare provider to make sure you are carefully monitored with blood tests for development of inhibitors to factor IX.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see RIXUBIS Important Facts on the following page and discuss with your healthcare provider.

Takeda

RIXUBIS
[COAGULATION FACTOR IX (RECOMBINANT)]
MOVING FORWARD

Important facts about RIXUBIS®:

RIXUBIS
[COAGULATION FACTOR IX (RECOMBINANT)]

This leaflet summarizes important information about RIXUBIS. Please read it carefully before using this medicine. This information does not take the place of talking with your healthcare provider.

What is RIXUBIS used for?

RIXUBIS is a medicine used to replace clotting factor (Factor IX) that is missing in people with hemophilia B. Hemophilia B is also called congenital factor IX deficiency or Christmas disease. Hemophilia B is an inherited bleeding disorder that prevents blood from clotting normally. RIXUBIS is used to prevent and control bleeding in people with hemophilia B. Your healthcare provider may give you RIXUBIS when you have surgery. RIXUBIS can reduce the number of bleeding episodes when used regularly (prophylaxis).

Who should not use RIXUBIS?

You should not use RIXUBIS if you

- are allergic to hamsters
- are allergic to any ingredients in RIXUBIS

Tell your healthcare provider if you are pregnant or breastfeeding because RIXUBIS may not be right for you.

What should I tell my healthcare provider before using RIXUBIS?

You should tell your healthcare provider if you

- have or have had any medical problems
- take any medicines, including prescription and non-prescription medicines, such as over-the-counter medicines, supplements or herbal remedies
- have any allergies, including allergies to hamsters
- are breastfeeding. It is not known if RIXUBIS passes into your milk and if it can harm your baby
- are pregnant or planning to become pregnant. It is not known if RIXUBIS may harm your unborn baby
- have been told that you have inhibitors to factor IX (because RIXUBIS may not work for you).

What is the most important information I should know about RIXUBIS?

Allergic reactions have been reported with RIXUBIS. Stop using the product and call your healthcare provider or get emergency treatment right away if you get a rash or hives; rapid swelling of the skin or mucous membranes; itching; tightness of the throat; chest pain or tightness; wheezing; difficulty breathing; low blood pressure; lightheadedness; dizziness; nausea; vomiting; tingling, prickling, burning, or numbness of the skin; restlessness; or fainting.

Your body may form inhibitors to factor IX. An inhibitor is part of the body's defense system. If you form inhibitors, it may stop RIXUBIS from working properly. Consult with your healthcare provider to make sure you are carefully monitored with blood tests for the development of inhibitors to factor IX.

The use of factor IX containing products has been associated with the development of blood clots. Talk to your doctor about your risk for potential complications and whether RIXUBIS is right for you.

What are the possible side effects of RIXUBIS?

Some common side effects of RIXUBIS were unusual taste in the mouth, limb pain, and atypical blood test results. Tell your healthcare provider about any side effects that bother you or do not go away. These are not all the side effects possible with RIXUBIS. You can ask your healthcare provider for information that is written for healthcare professionals.

What else should I know about RIXUBIS?

Consult with your healthcare provider to make sure your factor IX activity blood levels are monitored so they are right for you.

You should be trained on how to do infusions by your healthcare provider or hemophilia treatment center. Many people with hemophilia B learn to infuse their RIXUBIS by themselves or with the help of a family member.

Call your healthcare provider right away if your bleeding does not stop after taking RIXUBIS.

Medicines are sometimes prescribed for purposes other than those listed here. Do not use RIXUBIS for a condition for which it is not prescribed. Do not share RIXUBIS with other people, even if they have the same symptoms that you have.

The risk information provided here is not comprehensive. To learn more, talk about RIXUBIS with your healthcare provider or pharmacist. The FDA-approved product labeling can be found at https://www.shirecontent.com/PI/PDFs/RIXUBIS_USA_ENG.pdf or by calling 1-877-825-3327.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Issued 05/2018
S46187 02/19

Takeda

"On the Road" (Virtually) with the Coalition for Hemophilia B

The Coalition for Hemophilia B Family *Meetings on the Road* is our way of "bringing the Coalition to you." In the past, the program consisted of one-day educational meetings held in cities across the country. This year, as we continued to deal with the limitations imposed by the pandemic, we decided to take the entire program virtual!

A series of nine meetings were held Saturdays in January, February and March. We grouped participants according to regions of the country so they could interact with other community members from the same area in smaller group settings. The programs were extremely successful with many attendees choosing to attend more than one meeting.

While not every program was identical, all participants had the opportunity to hear from a variety of experts who shared information community members can apply to their own lives. Popular sessions included "What's So Funny? and the" Rhythm is Going to Get You!" with Robert Friedman; "Your Stories, Your Advocacy" with Natalie Sayer; and "The Courage to Dream – Raising a Child with a Bleeding Disorder" with Shonda Joshua.

Many participants enjoyed a session called "Discovering Creative Ways to Connect with One Another" with Lee Kim. Community member Rick Starks led several sessions throughout the series including one called "The Path to Resilience – Finding Confidence in Yourself and Managing Your Condition," and another on the benefits of the "Gentle Art of Tai Chi." Attendees also received updates on the latest scientific and medical information including an interactive assessment of hemophilia B control and a summary of the latest knowledge on hemophilia and

COVID-19 presented by Coalition Chair Dr. David Clark.

The feedback we received from participants was overwhelmingly positive. Here are just a few examples of things attendees had to say:

“They gave such wonderful information about how to manage stress and how we can overcome that with gratitude.”

“YOU GUYS! I didn’t know what to expect going into this thing, but it was so fun! It was so awesome how you truly connected with the whole family and how we got a chance to connect with others in the community.”

“For me, the greatest value I obtained during the online conference was just being in a zoom conference with individuals that I believe were able to identify with the dynamics of my life. Many things are unspoken, many things cannot be verbalized, perhaps it becomes a deep part of our psyche that we intuitively realize that only those that have had similar experiences can understand.”

“The conference experience was uplifting. I had many laughs and had an enjoyable evening just hanging out with others without my being the focus of attention. I look forward to any events you may conduct in the future.”

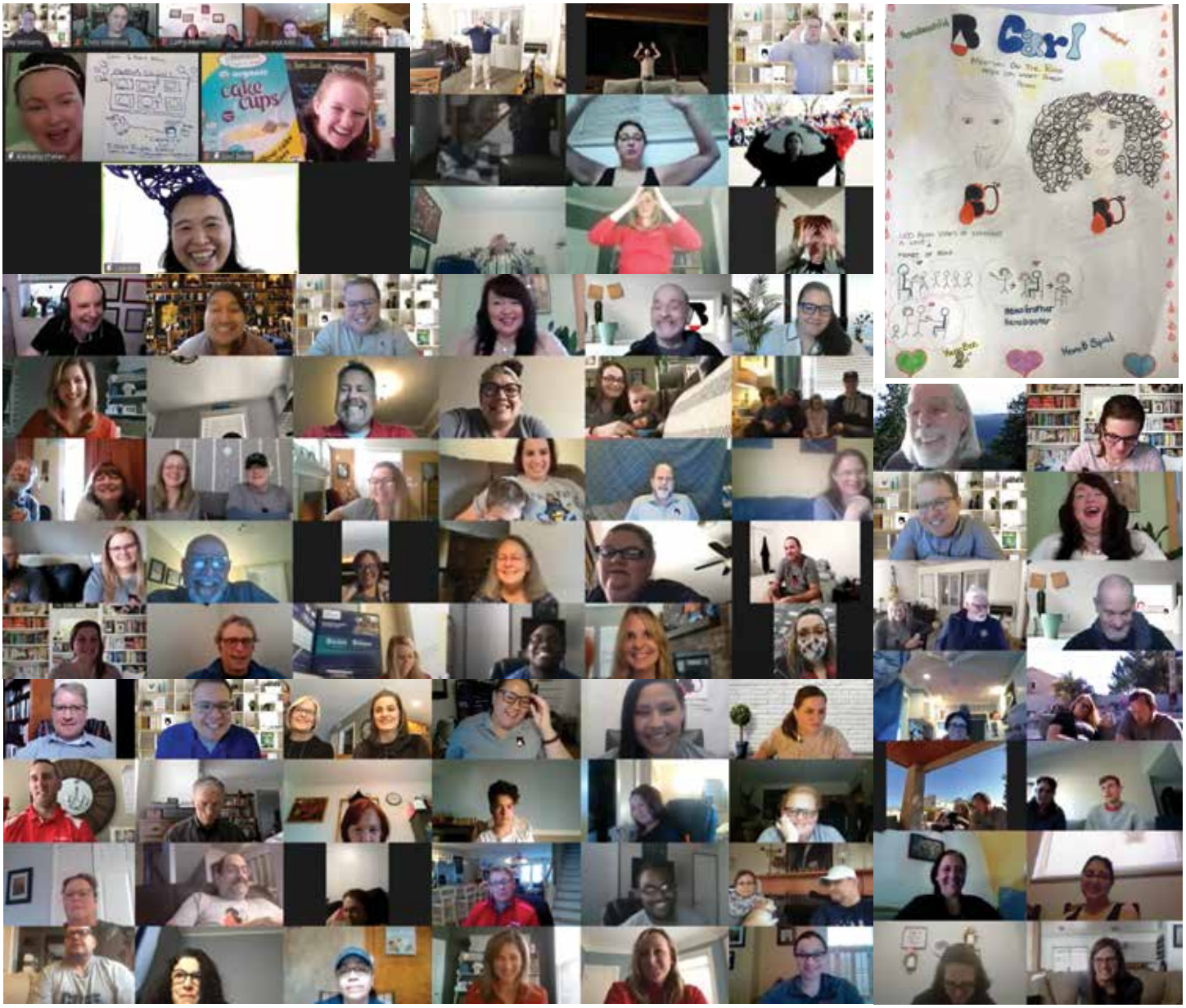
We want to thank our generous sponsors who made this program possible!

CSL Behring (eight meetings)

Novo Nordisk (one meeting)

We are currently planning new programs for the remainder of 2021 including more “hybrid programs (combining in-person and virtual elements). Stay tuned and visit our website at www.hemob.org.

"On the Road" (Virtually) with The Coalition for Hemophilia B



2021 SYMPOSIUM

UPDATE

- UPDATE NO MASKS INDOOR OR OUTDOOR for fully vaccinated attendees.
- Parents with infants 2 and under can attend as long as they stay with a parent in the hotel. Parents should ask their pediatrician if they can travel and follow CDC guidelines.

30 YEAR ANNIVERSARY THE COALITION FOR HEMOPHILIA B

Biotherapies for Life® CSL Behring

KNOWING HER SON IS PROTECTED FROM BLEEDS GIVES MILINDA PEACE OF MIND

When Milinda's son Andrew was younger, his frequent bleeds made him miss out on a lot. Their family life was hectic with his many doctor appointments and hospital visits. Now Milinda and Andrew have more free time to spend with family and friends.

Find out more about powerful bleed protection at **IDELVION.com**

> ***"I'm a mom, I'm going to worry no matter what. But with IDELVION, we both feel more confident in his bleed protection."***
>
> *—**Milinda**, whose son Andrew switched to IDELVION in 2016*

*Hemophilia FIX Market Assessment. Third-Party Market Research.

Important Safety Information

IDELVION®, Coagulation Factor IX (Recombinant), Albumin Fusion Protein (rFIX-FP), is used to control and prevent bleeding episodes in people with hemophilia B. Your doctor might also give you IDELVION before surgical procedures. Used regularly as prophylaxis, IDELVION can reduce the number of bleeding episodes.

IDELVION is administered by intravenous injection into the bloodstream, and can be self-administered or administered by a caregiver. Do not inject IDELVION without training and approval from your healthcare provider or hemophilia treatment center.

Tell your healthcare provider of any medical condition you might have, including allergies and pregnancy, as well as all medications you are taking. Do not use IDELVION if you know you are allergic to any of its ingredients, including hamster proteins. Tell your doctor if you previously had an allergic reaction to any FIX product.

Stop treatment and immediately contact your healthcare provider if you see signs of an allergic reaction, including a rash or hives, itching, tightness of chest or throat, difficulty breathing, lightheadedness, dizziness, nausea, or a decrease in blood pressure.

Your body can make antibodies, called inhibitors, against Factor IX, which could stop IDELVION from working properly. You might need to be tested for inhibitors from time to time. IDELVION might also increase the risk of abnormal blood clots in your body, especially if you have risk factors. Call your healthcare provider if you have chest pain, difficulty breathing, or leg tenderness or swelling.

In clinical trials for IDELVION, headache was the only side effect occurring in more than 1% of patients (1.8%), but is not the only side effect possible. Tell your healthcare provider about any side effect that bothers you or does not go away, or if bleeding is not controlled with IDELVION.

Please see brief summary of prescribing information on adjacent page and full prescribing information including patient product information at IDELVION.com.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.fda.gov/medwatch**, or call **1-800-FDA-1088**.

You can also report side effects to CSL Behring's Pharmacovigilance Department at 1-866-915-6958.

IDELVION®
Coagulation Factor IX (Recombinant), Albumin Fusion Protein

IDELVION®, Coagulation Factor IX (Recombinant), Albumin Fusion Protein
Initial U.S. Approval: 2016

BRIEF SUMMARY OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use IDELVION safely and effectively. Please see full prescribing information for IDELVION, which has a section with information directed specifically to patients.

What is IDELVION?
IDELVION is an injectable medicine used to replace clotting Factor IX that is absent or insufficient in people with hemophilia B. Hemophilia B, also called congenital Factor IX deficiency or Christmas disease, is an inherited bleeding disorder that prevents blood from clotting normally.

IDELVION is used to control and prevent bleeding episodes. Your healthcare provider may give you IDELVION when you have surgery. IDELVION can reduce the number of bleeding episodes when used regularly (prophylaxis).

Who should not use IDELVION?
You should not use IDELVION if you have had life-threatening hypersensitivity reactions to IDELVION, or are allergic to:
- hamster proteins
- any ingredient of IDELVION

Tell your healthcare provider if you have had an allergic reaction to any Factor IX product prior to using IDELVION.

What should I tell my healthcare provider before using IDELVION?
Discuss the following with your healthcare provider:
- Your general health, including any medical condition you have or have had, including pregnancy, and any medical problems you may be having
- Any medicines you are taking, both prescription and non-prescription, and including any vitamins, supplements, or herbal remedies
- Allergies you might have, including allergies to hamster proteins
- Known inhibitors to Factor IX that you've experienced or been told you have (because IDELVION might not work for you)

What must I know about administering IDELVION?
- IDELVION is administered intravenously, directly into the bloodstream.
- IDELVION can be self-administered or administered by a caregiver with training and approval from your healthcare provider or hemophilia treatment center. **(For directions on reconstituting and administering IDELVION, see the Instructions for Use in the FDA-Approved Patient Labeling section of the full prescribing information.)**
- Your healthcare provider will tell you how much IDELVION to use based on your weight, the severity of your hemophilia B, your age, and other factors. Call your healthcare provider right away if your bleeding does not stop after taking IDELVION.
- Blood tests may be needed after you start IDELVION to ensure that your blood level of Factor IX is high enough to properly clot your blood.

What are the possible side effects of IDELVION?
Allergic reactions can occur with IDELVION. Call your healthcare provider right away and stop treatment if you get a rash or hives, itching, tightness of the chest or throat, difficulty breathing, light-headedness, dizziness, nausea, or decrease in blood pressure.

Your body can make antibodies, called inhibitors, against Factor IX, which could stop IDELVION from working properly. Your healthcare provider may need to test your blood for inhibitors from time to time.

IDELVION might increase the risk of abnormal blood clots forming in your body, especially if you have risk factors for such clots. Call your healthcare provider if you experience chest pain, difficulty breathing, or leg tenderness or swelling while being treated with IDELVION.

A common side effect of IDELVION is headache. This is not the only side effect possible. Tell your healthcare provider about any side effect that bothers you or does not go away.

Based on July 2020 revision

Please see full prescribing information, including FDA-approved patient labeling.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

GEN IX 2021: REBUILDING TOGETHER

BY ROCKY WILLIAMS

The Coalition for Hemophilia B is leading the way for leaders in the hemophilia B community. Over three successive weeks in March, adult community members from across the country came together online each Monday and Thursday for the Generation IX Project Virtual Leadership Program. Participants learned and practiced skills and techniques through a variety of interactive experiences to become better leaders. The program centered around the theme of "rebuilding together," in which we explored what was, what is, and what could be.

This program is one integral part of Generation IX which also has components for advocacy and mentorship. Generation IX has been ongoing since 2014 and has since benefited over 200 individuals with hemophilia B. The program was presented in cooperation with GutMonkey, a company that specializes in experiential learning, and the program was made possible through the generous support of Medexus Pharma.

We kicked off on the first day of March with introductions and with Gen IX's very first Great Pancake Bakeoff! Using the tools and ingredients from the box we received, everyone was asked to create three unique pieces of pancake art: one that represented a fear of the future, one that represented a fantastic dream for the future, and one that represented a hope for the future. The results were colorful and amazing. The imaginative pancakes included hearts, hands holding hands, and campfires. Each team was also asked to create a SHOW STOPPER pancake, and one group did a tree to show rebuilding and our flourishing community.

Another highlight was an incredibly fun "what would you do" relay race. Each team was assigned a GutMonkey staff member literally running around in Portland's Peninsula Park. Each park location had a WALL-O-STUFF where team members picked a number and reached into a square to receive a challenge. These challenges included movie and music trivia, map skills, and even board games. Meanwhile, the rest of the team worked on a photo

scavenger hunt at home, posting photos and videos in Padlet. Challenges included posing with a live wild animal, eating kale, singing, infusing, and even cutting your own hair. The challenges were worth time off your race and the team with the fastest time won.

We built on the theme of rebuilding with composting, planting leaves which we called leaf babies, and by learning new ways to reuse items that may go discarded. We learned about what materials can be composted and created our own little compost jars to nurture for the rest of the program and beyond. Then, we learned a new skill. Taking plastic bags that may be thrown away after being used, we learned how to weave them into new things such as flowerpots or coasters.

We spent time talking about rest and rejuvenation. We discussed the different ways people recharge. We split into different rooms organized by how we like to recharge and spent some time with those like us. One group created a song called "Plain Chicken Nuggets, while the social room played a game. Everyone participated in exploring the

world of rest and rejuvenation, reimagined pool parties, and daydreamed about our future!

Throughout the program, we all worked on a special project: "choose your own adventure book report"! Each participant received a Choose Your Own Adventure book and was asked to use the book to create something in the theme of rebuilding. We asked everyone to focus on three questions:

- What in your world would you like to rebuild?
- Why would you like to rebuild it?
- What is your vision for rebuilding this?

We also asked participants to reflect on the activities we'd done during the program to help guide their adventure. For example, if they thought back to the composting activity, they could structure their book report around rebuilding something in their "soil" (personal space, habits, rituals, routines) while taking into account "neighboring plant life" (local community, HTC, local chapter, neighborhood) and the "macro environment" (government, healthcare, national organizations).

Kirstin presented her book report and shared, "The book shows you that you make decisions in life and sometimes the outcome is good and sometimes not so good, but we learn from it and take those lessons with us. Leadership provided a session on composting, and I've tried with my garden for several years, sometimes successful and sometimes not so much—but I'm hoping to take this composting lesson forward with the regrowth of my garden."

After the program, we asked participants to reflect on their Gen IX experience. Here's what they had to say. "Gen IX was fun, interactive, and a great way to connect with other people with hemophilia B!" said Cassandra. "The program was great," said Manny. "Gutmonkey always delivers great programming whether in person or virtual. They play an essential role into the culture that is GEN IX, which to me means family, community, and support." Aamina adds, "I have attended several Gen IX events in person and virtually. I can say proudly that Generation IX activities and lessons helped form me into a better person and leader."

The Coalition for Hemophilia B is grateful to GutMonkey, our program partner, and to Medexus Pharma, the sole sponsor of the Generation IX Project for making this wonderful program available to the hemophilia B community! The lessons learned and time spent together help us grow individually and together.

MEDEXUS PHARMA






GEN IX HANGOUT HAPPENINGS

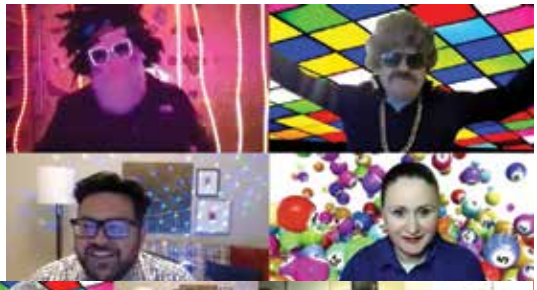
During the last season, we had the pleasure of hosting several fun, engaging virtual Gen IX programs.

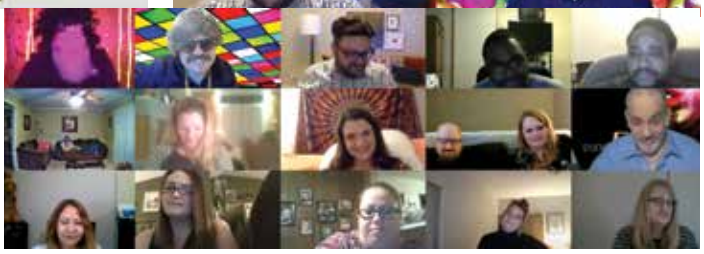
VIRTUAL HANGOUT

We started this event with a series of short breakouts,called Friendzies, that asked community members to choose and discuss colors representing both 2020 and 2021. The rest of the hangout was a Super Gen IX game party, complete with a Jumbotron that kept us competing in team challenges. We capped the night with attendees writing and sharing toasts to themselves.

DISCO BINGO

This was a super fun way to spend a Friday night while stuck at home during the height of the pandemic. Staff dressed up in 1970s disco attire and hosted bingo and trivia while dancing to the hits of the era. Unique rules kept things lively whenever particular letters or numbers were called. The night was full of laughter, dancing, prizes, and a special group lip-sync to the classic “We are Family.”





GEN IX REUNION

Community members who previously participated in Gen IX Membership, Leadership, and Advocacy workshops were invited to reunite with other program “graduates” for a fun virtual gathering. Attendees shared memories and goals achieved, reminisced about activities from relay races to hair-braiding, viewed a slideshow of past program highlights and much more! Mostly, participants were given the opportunity to share what Gen IX meant to them. This included words like family, love, support, fun, growth, community, connection, inspiration, and many more!

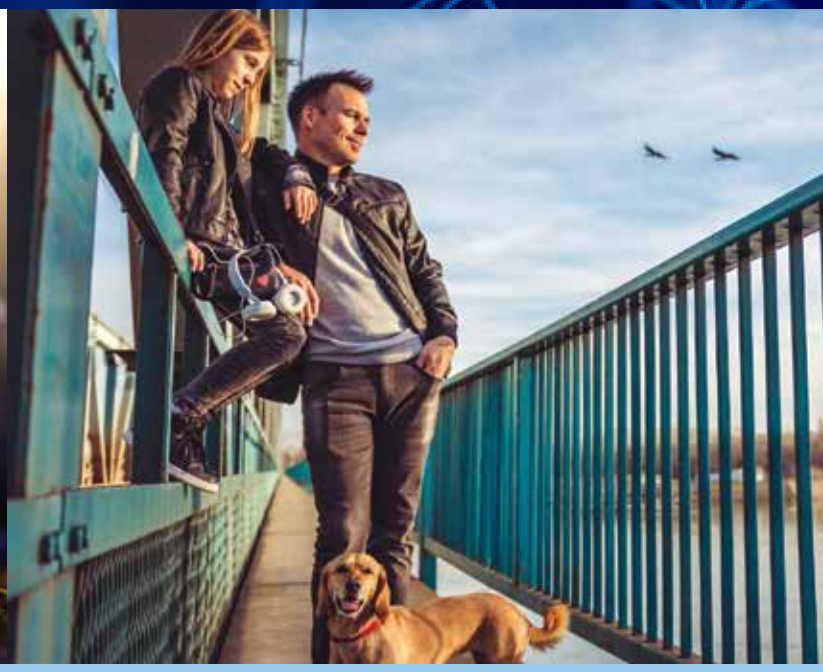
We want to say thank you to our creative partners at GutMonkey and to our generous sponsor, Medexus, who helped make these events possible. Thanks also to the many participants who came together to make lasting memories.

MEDEXUS PHARMA

We are a national organization committed to providing exceptional service with a family atmosphere.

[BIOMATRIX]

BioMatrix helps individuals and families improve health and successfully manage life with a bleeding disorder.



Dedicated to making a difference in the lives of people with bleeding disorders.

For more information,
call or visit our website:
(877) 337-3002 / biomatrixsprx.com

DEDICATED
TO MAKING
A DIFFERENCE

ZOOMING ALONG *Together*

BY ROCKY WILLIAMS

It's hard to believe we're halfway through 2021! We have had so much fun learning by "Zooming Along Together" and connecting at virtual events. We look forward to seeing people in person soon, and there will be a lot more opportunities to meet virtually as well. Let's look back at some of the highlights of the year so far!

POCKETBOOK BINGO

Ladies of the hemophilia B community gathered with Kim and Chris for an epic night of bingo—with pocketbooks as prizes! The ladies who participated were also treated to a wonderful surprise performance by Jayden on the ocarina. his Ocarina during Pocketbook Bingo night!

KAHOOT TRIVIA NIGHTS

We gathered families throughout April and May to compete in Kahoot! trivia nights. There was something for everyone, with topics ranging from toys, video games, and animals to health and hemophilia. It was fun and educational for everyone who participated.

FEED MIND AND BODY

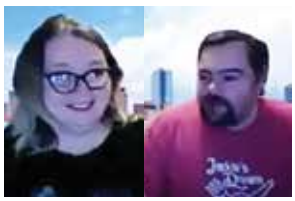
Professional chef Mike Hargett is the world's first person with hemophilia to have received a double heart/ kidney transplant! During this special event, presented by Biomatrix and sponsored by Medexus, Chef Mike told his story while also sharing some of his delicious recipes and amazing techniques. Community members followed along as Chef Mike made his "Bada Bing Chicken à la King" with an elegant side salad, complete with homemade vinaigrette dressing. The evening also included Kelly Gonzalez sharing her story and teaching us *It's Ok to Not be Ok* – but it's not ok to stay silent! You are not alone!

MEDEXUS PHARMA

BIOMATRIX

DYNAMIC DUO

Our Dynamic Duo night for couples was amazing! The workshop began with Bob Kalison leading improvisation exercises that heightened our awareness and skills at listening and supporting each other. The exercises included creating simple three-line scenes with two participants, and a short video about becoming more aware of our circumstances. Couples then split into breakout rooms to find out how much they truly knew their partner. It was very revealing – and very funny! To conclude the evening, Carl and Gwyn Weixler hosted an intimate group rap session. Special thanks to Medexus for sponsoring this programming.



MEDEXUS PHARMA

LADYBUG CUPCAKE DECORATING

On Valentine's Day weekend, we Zoomed from our kitchens and joined Daniela Delgado of Daniela's Little Wish to decorate ladybug-themed valentine cupcakes. These kid-approved treats were fun to make and eat. Check out the photos of our creations on Facebook! Special thanks to Medexus for sponsoring this programming.

NEW FACEBOOK GROUP!

Join Our NEW Facebook Group! You may already know about The Coalition For Hemophilia B Facebook PAGE, but we have now created a private Hemophilia B GROUP as an opportunity for families to connect, engage, and support each other. We encourage you to share photos from special events, celebrate milestones, and most importantly, build genuine relationships. Please join our GROUP today by searching for "Hemo B Community" on Facebook.

women bleeders

A NEW FEATURE SECTION

ARTICLES TO SUPPORT WOMEN WITH HEMOPHILIA B

Fortunate–Not Fortunate
Ashley's Story

BY RENAE BAKER

Ashley grew up watching her dad infuse so often that it seemed like an everyday occurrence to her. As a child, she accompanied him to his HTC appointments and felt she knew everything there was to know about hemophilia at the time.

Her father grew up in the 1960s with severe hemophilia B. It was a time when everyone was afraid of hepatitis and little was known about caring for a child with hemophilia. She has seen photos and heard stories about how he spent much of his time in the hospital. Her heart aches for the little boy who seemingly took up residence in a hospital - birthdays, holidays, and days filled with excruciating pain while away from his family.

"I've been fortunate and *not* fortunate to have been very familiar with hemophilia my whole life. You can look at my dad and see he has been physically affected by this. For me growing up, it was difficult because it impacted everything he did and took a toll on his mental health," Ashley says with notes of gravity and thoughtfulness.

Ashley knew from the get-go she was an obligate carrier. "I started to understand what that meant for me when I reached puberty. That's when my parents talked to me about what it could mean for me if I had children. And then I got my lovely period!" she says through a rueful, irresolute laugh. "I knew what I was going through could not be what every girl goes through. There was no way people bled the way I did. I knew something wasn't right." Ashley's father started to take her to HTC visits. Around this time she began having severe pain in her right knee. She had her first knee surgery at twelve years old. Currently at twenty-nine years old, she has logged eight knee surgeries and has more ahead of her.

Ashley decided to have children early in life. She had her first child at eighteen years old. She credits the HTC with the straight-talk guidance they gave her. It was encouraging with notes of caution: "They wanted to bring me comfort if I wanted to have kids. I knew the risks: if I had a boy, he could have hemophilia. If I had a girl, she could be a carrier. However, they said, "Your kid could be born with a number of things - your kid could have cancer or diabetes. You just happen to know there is this one

gene you carry, so if you want kids, don't let that stop you."

Perhaps the loudest point the HTC wanted Ashley to hear was, "Hemophilia today is not what you saw growing up with your dad." Ashley took that to heart and says, "Even if it was, I'm not sure it would have impacted my decision. It may have because it was very difficult watching what he had to go through, but I was so grateful for their support."

Going to Coalition, other national conferences and local chapter meetings has given Ashley a clear vision of what it's like in this generation for kids who have hemophilia. "These meetings brought me a lot of comfort," Ashley says. "It still isn't easy for people, obviously, but it isn't what I thought it could be."

With no disrespect to the boys and men, Ashley smiles and reveals, "I lucked out and had three girls!" Now Ashley finds herself at a point in her journey where she wants to give them answers. "As I said, I'm privileged. I know I'm a carrier, but they have no idea yet. I want them to have that knowledge, but I'm finding getting their carrier status tested practically takes an act of congress and a lot of money, so I'm battling through figuring out how to get them tested." Considering Ashley has a family history of hemophilia, one

wouldn't think it wouldn't be so difficult. Ashley explains, "What the HTC told me was that insurance looks at it as though it's a benefit for us when we want to have kids, but it's not covering our kids." Ashley is going to try to fight it by pointing out that if her daughters are carriers, it may affect them when they go through puberty, which is right around the corner for two of her daughters. "I want to know if they are more likely to bleed and need surgeries and those kinds of things." Ashley continues, "We're going to get their levels checked, but the issue I have with that is that although my levels are normal, I still bleed." This seems to be a common phenomenon among carriers.

Ashley has received some resources from the Coalition and is determined to do what is possible to get answers for her daughters. "It shouldn't be this hard, though." she laments. This is the change in the system Ashley would most like to see.

"As I go to women's retreats and other Coalition events, I keep hearing women say, 'I wish my family had talked about it.' For some, it was a tabu subject." Ashley sees that there is a lot of fear out there, because of a lack of information. She wants her daughters involved in the Coalition so they can grow up with the benefit of the education she had growing up.

"When they have kids, will it be scary? It might. Will having this education take a little bit of the fright out of it? I sure hope so!" Ashley asserts that having her eyes wide open to the realities and resources of hemophilia was a great benefit to her as she embarked on having children. See feels everybody ought to have the same opportunity. "If I would have had a son, I'd know how to get factor for him, I would know which HTCs to contact. I'd know what to tell the doctors who had maybe never dealt with hemophilia before. My daughters deserve that knowledge too."

"It makes me so sad to hear of people who say the first day they ever heard of hemophilia was when they gave birth, or their baby got a vaccination and just bled and bled. I think if we can get that information to people, why on earth wouldn't we?!"

Ashley complements the Coalition on a recent event where they focused on the importance of learning how to "Tell Your Story" as a vital component of self-advocacy. "I didn't realize how important it was until I started hearing other people's stories, Now I know that's exactly what I want to do. The more I can share about it on social media and get someone to google what hemophilia is, the better community it makes."

At eight and ten, two of Ashley's daughters have attended Coalition events. They are very interested in their connection to hemophilia. They sit through presentations with a maturity that has surprised Ashley and are beginning to riddle her with questions about it. "It's cool to see their brains start going and how these presentations provoke questions even weeks later. It makes their upcoming periods less scary."

Ashley recently pondered the question about whether after having three daughters and no sons, it was okay for her to keep coming to Coalition events. She wondered if she was taking a seat away from someone else who deserved to be there more than she did. The advice she received is that the up-to-date information was very valuable to her whole family, and the support of the community is something that would be very beneficial for her daughters.

Looking forward, Ashley thinks the Coalition has a unique opportunity to push the envelope further with the mental health aspect of hemophilia. "I would love to talk with other daughters who grew up with father with hemophilia who struggle with depression," she says. Ashley's father's tragic childhood took a toll on his mental well being. Watching her father suffer physically and mentally took a toll on Ashley's mental health. The bleeders and the children of bleeders who suffer from depression are only two of several mental health focus groups Ashley thinks would be beneficial to the community.

When asked what advice she would give others, Ashley says, "It's so important to start learning young. I have no regrets about learning about hemophilia at a young age, and I think it's important for people with hemophilia, carriers and spouses of carriers to learn as early as possible." Fortunately, the Coalition for Hemophilia B is here to offer education and support along our journey!

Mammograms & Vaccines

BY DR. DAVID CLARK

Please be aware that getting any of the COVID vaccines (or many other vaccines) can cause false-positive results on mammograms. The reason is that the vaccines can cause swelling in the lymph nodes under your arms.

The swelling is nothing to be concerned about and has nothing to do with breast cancer. It is just a normal reaction of your immune system. However, if you get a mammogram soon after you've received a vaccine, the swollen lymph nodes will show up on the mammogram and may be considered suspicious.

It's recommended that you try to have the mammogram scheduled before the vaccine or wait for about 4 – 6 weeks after your last shot, if possible. Physicians, however, recommend that you not delay your mammogram, so try to work around it.

This issue is becoming more widely recognized, so mammogram technicians will probably ask you whether you've had a vaccination recently. If they don't ask you, please feel free to tell them, if that is the case. This is not a dangerous situation. It's more of an inconvenience, but could be worrisome until you find out that it was only a side effect of receiving the vaccine.

ARE YOU READY TO TELL YOUR STORY?

Whether you have an incredible career, an extraordinary family, or a tale of triumph, we want to hear from YOU! We will have you will collaborate with an in-house writer to help communicate your story in a compelling and meaningful way. The best part is that no previous writing experience is necessary. So, what's holding you back? For more information on being featured in the CHB newsletter, please contact us at contact@hemob.org. We can't wait to read all about you!

OUR PLASMA HERO
Nemo Delgado

"Nemo has a very special and personal motivation for donating plasma – his 13 year old daughter, Daniela."

Nemo Delgado has donated plasma many times. He knows his donations help thousands of individuals with debilitating conditions who rely upon plasma-derived therapies for their health. However, Nemo has a very special and personal motivation for donating plasma – his 13 year old daughter, Daniela.

Daniela has severe von Willebrand Disease (VWD) Type 1C and Ehlers Danlos Syndrome, both debilitating conditions. VWD is a genetic condition like hemophilia that can cause uncontrolled bleeding, joint damage, and other complications. It is a lifelong ailment and there is no cure. Daniela's VWD is treated with regular intravenous infusions at home of a clotting factor made from donated human plasma. Without these donations, the medicine she uses would not exist.

Nemo and his wife Janine, who also has VWD and uses a plasma-derived product, have helped inspire Daniela to use her conditions as a force for good. When she was only four years old, she realized other kids with life-threatening illnesses or disabilities often need something to smile about. She decided to create special, beautiful customized cakes and present them at no charge to deserving children. Nemo and Janine are avid bakers, so it was no surprise Daniela chose baking cakes as the delicious means to her important mission. Today, through *Daniela's Little Wish* (www.danelaslittlewish.org), the organization she founded with her parents' support, Daniela continues to bake and present cakes while giving motivational talks and cupcake workshops throughout the community and across the country. Nemo, Janine and Daniela are also involved with the Coalition for Hemophilia B (www.hemob.org), some of whose participants have VWD.

Recently, Daniela led a virtual cupcake-making workshop for families in our community. The Coalition has strongly supported the Delgados' efforts in a variety of ways and is proud to have nominated Nemo Delgado as our *Plasma Hero*.

PLASMA SAVES LIVES

Did you know that people with hemophilia are not the only ones who rely on therapies made from donated human plasma? People with other life-threatening conditions, including Primary Immune Deficiency, use intravenous immunoglobulin (IVIG) and human serum albumin (HSA). Although most people with hemophilia now use recombinant products, some others with rare bleeding disorders, von Willebrand disease, or inhibitors would have no treatment without product derived from plasma donations.

The Coalition for Hemophilia B is working with a group of organizations representing patients who use plasma-derived therapies to create awareness around the importance of donating plasma. Many people with bleeding disorders may not be eligible to donate blood or plasma, but if there are people in your life who are not personally affected, please consider encouraging them to help. To learn more or to find a plasma donation center near you, please visit PlasmaHero.org.

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WELCOME TO OUR NEWEST TEAM MEMBER

JIBIN JOHNS

Jibin has joined our team as data analyst! He has hemophilia B and is from Trivandrum, India, but currently resides in Texas. He says, "I am excited to join the Coalition team and work where I'm needed most!"

WASHINGTON DAYS

New York State advocates for the bleeding disorders community met virtually with members of Congress on March 4 as part of NHF's Washington Days. We thank them all (some pictured here during a previous "in-person" event.)

We especially thank Chris Villarreal and Glenn Mones from our Coalition for Hemophilia B team for providing a "B Voice" for our community. On your behalf, they asked for continued federal funding for treatment centers and for legislation eliminating unfair insurance co-pay "accumulator adjusters." Stay tuned for updates!

ACHIEVING a BETTER LIFE EXPERIENCE with an ABLE ACCOUNT!

BY DONNIE AKERS, JD

A frequent and significant hardship experienced by persons with disabilities is that they are often reliant upon government assistance programs which have resource limits. Programs such as SSI (Supplemental Security Income) and Medicaid typically limit a person's financial resources in order to qualify. These limits result in many recipients living in virtual poverty with a marked reduction in their quality of life and that of their family.

The ABLE ACCOUNT is a savings account tool available to certain disabled persons. It is designed to ease financial burdens and provide a better financial standard of living, more opportunity and a more productive and independent life. Earnings on the account are not considered taxable income.

To be eligible for an Able Account, one must have a disability that meets the "Social Security Disability Standard" and which exists before they reach the age of 26. If one's disability did not exist before age 26, they are not eligible for the account. If one is on SSI, Social Security Disability (SSD) or Medicaid, they have met the Social Security Disability Standard and would qualify for an Able Account if other criteria is also met.

The owner of an Able Account is the disabled person who is also known as the "beneficiary." The account can be opened by the disabled person, parents, guardians or the courts. The account is opened with a designated state agency in states who have set up Able Account programs. Any person, including legal entities, may make contributions into the Able Account up to a combined limit of $15,000 per year based on current federal gift tax limits for 2021. All balances in the account up to $100,000 are exempt from being counted as a resource in applications and

qualification for public programs such as SSI and Medicaid and others.

New revisions to the law allow a working beneficiary to contribute an additional amount equal to the lesser of their annual gross salary or the individual Federal Poverty Level ($12,880 for 2021) if they or their employer do not contribute to a retirement plan. This allows a working disabled person to deposit up to $27,880 in an Able Account in 2021 and reach the exempt $100,000 limit faster.

Limitations on the use of the funds in the Able Account exist as they must be used for “qualified disability expenses” for the beneficiary. Expenses include those for education, housing, transportation, employment training and support, assistive technology and personal support services, health, prevention and wellness, Able Account service fees, legal fees, funeral/burial expenses, and other government approved expenses.

If a Medicaid recipient has an Able Account which exceeds the $100,000 maximum exemption from countable resources, the recipient retains eligibility for Medicaid without a time limit as long as they remain eligible otherwise. The amount in excess of the $100,000 maximum limit would be counted as a resource.

If a beneficiary receives SSI and their Able Account exceeds the $100,000 maximum exemption from countable resources, the SSI payments are suspended until these resources fall below the limits and the SSI is restored. There is no requirement for a new disability determination.

Some states have chosen not to have an Able Account program because of costs associated or because there is not enough need in their population. Some states also limit applicants to residents of their state while others allow for Able Account owners from other states to open an account which may more suitable or preferred for their needs. This allows all qualified individuals to have access to opening an Able Account.

Management of the Able Account program is typically provided in conjunction with a similar account used primarily for tax exempt educational savings known as a “529” account. The Able Account is also known as a “529A” account. The state chooses the type of financial institution or investment managed accounts eligible for deposits in their state. Some are broad and others have only one option.

A disabled person can have only one Able Account. Getting started in opening an Able Account if you meet the criteria is relatively simple. Start off with a search of your state’s program and available types of deposit programs. If you want more choice, you then can look at other state’s programs to see if you meet their criteria and prefer their investment options.

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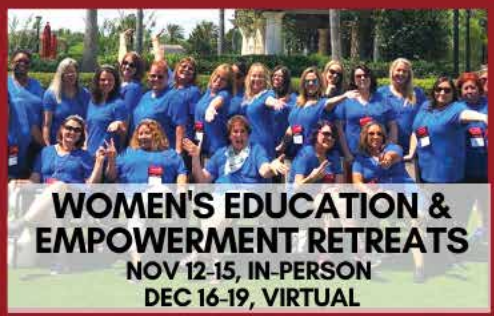
THE ETERNAL SPIRIT AWARD DINNER
AUGUST 12

LET'S PLAY IX GOLF TOURNAMENT
SEPTEMBER 23

SYMPOSIUM
SEPTEMBER 24-27

GEN IX ADVOCACY EXPERIENCE
OCTOBER 28-31

MEN'S EDUCATION & EMPOWERMENT RETREATS
OCT 28-31, IN-PERSON
DEC 9-12, IN-PERSON



WOMEN'S EDUCATION & EMPOWERMENT RETREATS
NOV 12-15, IN-PERSON
DEC 16-19, VIRTUAL

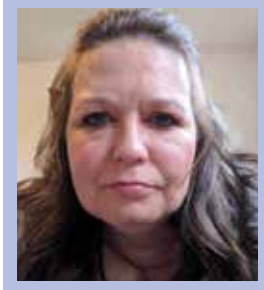
FOR MORE INFO & TO REGISTER: HEMOB.ORG/NEW-EVENTS

In Memoriam

Kaylean Marie Gentry

April 2, 1990 - March 29, 2021

With heavy hearts, we share that Kaylean Marie Gentry of Firth, Nebraska, passed away unexpectedly. She was the wife of Brandon and mother of 5 children Liam, Annabelle, Barrett, Nikolaus and Emmitt. Kaylean was well loved and active in our community. She was a "people-person" who never knew a stranger, always had a smile on her face, and was ready to support anyone who needed her!



Tanya Hunnewell

January 19, 1974 - March 13, 2021

We are sad to inform that Tanya Hunnewell of Dayton, Ohio, has passed away. She was an active, long-time community member. She was a loving and strong advocate for her family. She leaves behind her husband Bill, children, Krystal, Brad and Zach, and sister to Tina Sturgel Ascough.

Jack Thomas Silliman

October 4, 1975 - May 24, 2021

We sadly share the passing of blood brother Jack Thomas Silliman. Jack was a beloved father to his son Mason, a son, brother, teacher and friend. He grew up in the small Texas town of Fort Stockton and went on to receive a Bachelor's degree from New Mexico State University in Las Cruces. He spent 17 years teaching 5th grade at Enchanted Hills Elementary School in Rio Rancho, New Mexico. Jack will be greatly missed.

Jeremy Michael Sweeney

July 10, 1975 - February 28, 2021

We are broken-hearted to announce that Jeremy Sweeney of Simi Valley, California, passed away. Jeremy loved hanging out with his hemophilia blood brothers. He was a wonderful husband to Kim and father to Rachel. Jeremy will be greatly missed.

The thoughts and prayers of the Coalition are with each of these families.

If you would like to send a condolence message, please e-mail us at contact@hemob.org.

The Coalition for Hemophilia B

757 Third Avenue, 20th Floor; New York, New York 10017
Phone: 212-520-8272 Fax: 212-520-8501 contact@hemob.org

SCAN ME

VISIT OUR SOCIAL MEDIA SITES:

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Facebook: www.facebook.com/HemophiliaB/

Twitter: https://twitter.com/coalitionhemob

Instagram: www.instagram.com/coalitionforhemophiliab

Linkedin: https://www.linkedin.com/company/coalition-for-hemophilia-b/

For information, contact Kim Phelan
kimp@hemob.org or call 917-582-9077

B PREPARED! TRISTAN'S STORY

AN INTERVIEW BY RENAE BAKER

"It feels really good to be one step closer to being more independent,' says Tristan, who is fourteen and learning to self-infuse.

Becoming independent is pretty important to him because Tristan is one busy dude! Upon meeting this polite young man with his smooth southern accent and laid-back charm, it might be easy to miss the proactive mover and shaker that lies just beneath the surface! Not only is he a four-year black belt in Taekwondo, but he plays in the drum line of his school's marching band, and he is only four ranks away from becoming an Eagle Scout with the Boy Scouts of America.

For scouts and band, he often needs to travel. As much as Tristan appreciates his father's willingness to be there for him, being able to self-infuse will mean he won't have to be the only kid with a parent accompanying him on school trips just in case of an emergency.

"I grew up with the motto, 'When in doubt, infuse,'" Tristan relates. Perhaps it was learning about his dramatic brush with death at the time of his birth that keeps his discipline well-oiled and positioned for optimal wellness. "When my mom told me the story, I was like, 'wait - what?!" Tristan exclaims.

During the hours that lapsed between his difficult birth and the diagnosis of severe hemophilia B, Tristan's non-vital organs had shut down. Had it not been for an astute nurse who advocated that he not be released from the hospital after only one day and pushed for blood testing, Tristan's mother believes he would not have survived two days.

Tristan considers himself fortunate to have an approved prophy plan. His practice of sticking to his treatment plana nd infusing when in doubt likely contributes to the fact that, to date, he has never had a joint bleed. Learning to self-infuse has not been easy. "I am still having flashback issues," he admits, but Tristan is a determined student of the visiting nurse who comes to his home and shows him the ropes. He appreciates the nurse's patience and flexibility to work with the unconventional way in which Tristan is comfortable doing it.

With his growing independence, Tristan is becoming aware of the value in having friends from The Coalition for Hemophilia B who don't have to have hemophilia explained to them. He is also learning the value of comprehending that most people do not understand his unique needs.

"I've always had the challenge that not many people understand what I'm going through." Tristan illustrates with a story from the end of football season a year earlier. "We had band practice and I was on a trolley taking the ensemble equipment over to the field. Of course, I was being dumb and I had my legs just a tad bit outside of the trailer. The guy who was driving was a senior. He had pretty good experience as a driver. But he was like this close to hitting another trolley." he indicates about three inches, as his voice gets higher, and his eyes grow wider. "Of course, I hit it. There was a buckle on the tailgate of the other trailer and it went straight into my leg. It cut me up. It wasn't the worst thing in the world. I've had worse, but it was pretty bad."

Did he go straight to the hospital, I wondered? He plays it down, "It wasn't that bad. It was only like a centimeter deep cut into my leg."

"Still! That's pretty deep, isn't it?" I asked, not hiding my

incredulity at his nonchalant understatement.

"It is." he concedes with a sheepish grin. "It hurt. A lot. And of course, it had to be on a Tuesday; the day before I get my meds, so I'm pretty much at my lowest level, and I bruised up immediately. Once I got to the field, I realized there was blood running down my leg."

So, did he play? "Yes ma'am, I did. I did play. See, the blood just dried up, so all I did was wash off the dried blood." Tristan sees my surprise, and has a little chuckle to himself, because he knows what he's about to tell me. "The blood that did not go out," his laugh continues with a rueful shaking of his head, "was in my muscle; in the wrong place."

He describes the resulting two-inch hematoma as "pretty big. Not too good."

So, what did he learn from that event? "You know those Disney rides, where they say 'Keep your hands and legs inside the moving vehicle? Well ma'am, that's what I learned from this experience; to follow that!"

Something else Tristan learned, "One of the band moms was a nurse, so she was able to help me out, but all the others, like the band director and percussion tech, didn't know what to do. They were just like, 'Okay, we've just gotta slap a band aid on there and hope it works.'"

It was different in elementary and middle school. Tristan remembers it took a lot of advocacy on the part of his mom, but they were able to get an LPN aide to accompany him on school outings. Now that he is in high school, for the most part, he's handling his needs on his own, but he's quickly learning how important it is to be as self-sufficient as possible and to be able to articulate his needs during an emergency.

That's a natural idea for Tristan who as a boy scout is practically programmed to "Be Prepared." Recently, Tristan has been noticing common themes in the different areas of his life. "Similar to doing scales and memorizing music and choreography in band, I have to be disciplined about my practice in

Taekwondo. Going up from belt to belt, you have to fully learn, memorize and perfect certain moves."

It's true. You must memorize and practice these routines if you don't want to cause an accident (and look foolish doing it!). Tying the themes of practice, discipline, perseverance and being prepared into daily life with hemophilia, he offers this advice to help teens with hemophilia live their best lives: "If you haven't yet learned to self-infuse, I would encourage you to do so. Don't skip a prophylaxis dose. And if you get an injury, maybe it doesn't look bad, but infuse anyway. You don't know what's going to happen in the future. Be Prepared."

Sounds like good advice! And one more thing?" Tristan adds with a self-effacing smirk, "Don't do dumb stuff!"

Since the synovectomy, Bryen states he has had markedly fewer bleeds, “They’re basically down to zero, so I’d like to talk to my hematologist about that!” Bryen describes his relationship with his hematologist as an open one where he feels free to speak and ask questions. The biggest ask he has for his medical team (and everyone else) is, “Don’t bubble-wrap me! I know what I can and can’t do most of the time.”

He illustrates by pointing out that before he was self-infusing, it would sometimes take his father or grandfather multiple sticks to infuse him. “Sometimes it’d get so bad they’d have to do it on my ankle.” I shiver at the painful thought, but Bryen minimizes it by interjecting, “You’d think it would’ve hurt, but it actually tickles!”

What?! Well, it hasn’t tickled since he’s been doing it on his own, but once he started self-infusing at age eleven, he says, “I can easily do my infusions in one stick.”

Bryen and his family were to attend The Coalition for Hemophilia B Symposium that was supposed to have taken place in Orlando, Florida in 2020. Bummer. He does pretty well at hiding his disappointment, but who can begrudge him his slightly protruding lower lip on that loss? As he had already exhibited, Bryen is not one to wallow in self-pity as he turned the conversation to his appreciation of the online events. He particularly liked the educational and interactive events he and his parents could join as a family and also the Gen IX teen and mentorship program. He looks forward to participating in live events when they become available again.

Considering the role hemophilia has played in his life, Bryen sees it as both a shield and a sword. Since people know he has it, they try to protect him from getting injured, but sometimes that can lead to feeling left out. He gives the example of a “punches” hand game, where you hold your hands out and let your opponent punch them. “I know a good way to do that, where you don’t actually injure yourself because I read up on it, but most of the time it’s like, ‘No, we’re not gonna let Bryen play because we don’t want him to get injured and us get in trouble.’ Stuff like that.”

Sometimes that protective shield is helpful. “In gym class, the coaches keep a more watchful eye on me when we’d play dodgeball.”

Dodgeball?!

“Well, we use those foam balls, where no matter how hard people throw them at you, you can’t get hurt. The one time they had to call my parents was when I injured my shoulder by throwing the ball!” Oh, the irony.

Although hemophilia hasn’t had a dramatic effect on Bryen’s life, he isn’t feeling the blessing of it as he did when he was a small child. “When I was younger and went to Camp Ailihpomeh, (that’s ‘hemophilia’ spelled

backwards,) I was glad I had hemophilia because it was fun at camp. It was like I had a reason to have hemophilia. Now that I’ve aged out of camp as a regular camper, I’d say ‘There’s a cure? Sure, sign me up!’ ‘Gene therapy? I don’t care if it’s experimental; hook me up!’ Not having to infuse every week or however often would be less of a hassle.”

I can’t help but think live Coalition events can’t resume soon enough!

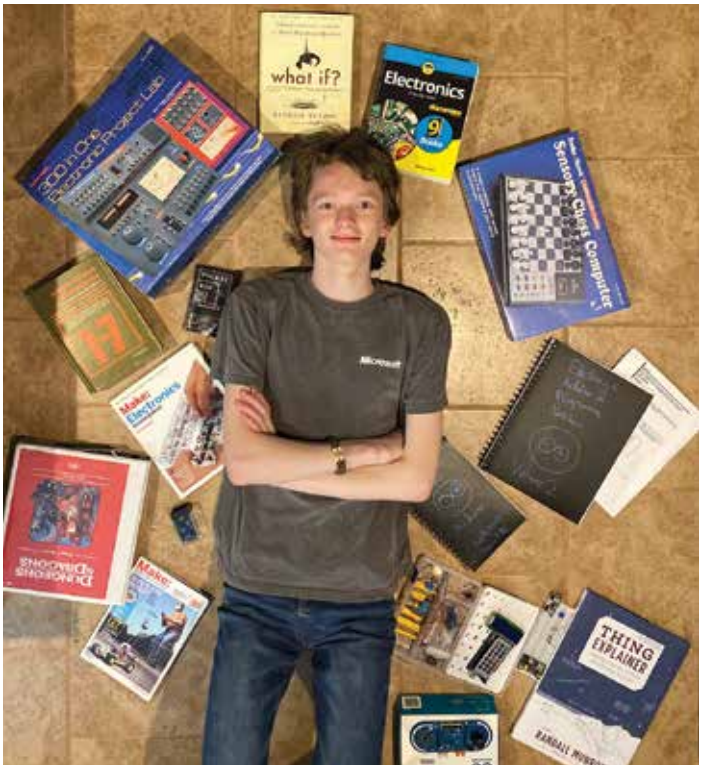
“The best advice I ever got was, ‘If you need something, say something.’ That works for a lot of things.” The best advice he can give to someone with hemophilia is “Rotate the use of your veins, for sure.” Bryen speaks from his own life experience. “I wanted to rotate my veins, but they didn’t want to be rotated. One vein became overused and took a deep dive. Now I have a bit of scar tissue and such. The new treatment gives my veins more time to heal, so that’s helping.” So, if you are having trouble rotating your veins, (i.e.: you need something,) say something to your hematologist. Perhaps a different treatment will help as it did for Bryen.

Through these seventeen years, Bryen seems to have found ways to navigate hassles and tricky social situations with a great attitude. The pandemic has taught him ways to concentrate and excel in areas of his life that are leading him to interesting avenues, which he expects to pursue as an adult - all of this while cultivating familial relationships and avoiding - yup – being bubble-wrapped.

Don't Bubble-Wrap Me

AN INTERVIEW BY RENAE BAKER

After weeks of trying to schedule our Zoom interview, I exclaimed to Bryen he seemed to be a very busy kid. "Some would debate that," he said, trying not to let the grin spread too widely across his face.



Just a few weeks shy of his 17th birthday, the first thing I noticed about Bryen was his strikingly deep voice. I'm not alone in being able to imagine his voice on TV commercials or narrating books or dramatic movies, Bryen uses it gently with no pretense at all as he describes his school situation. "Pre-COVID, I was going to Creekview High School, which is basically right down the street. I could walk to it."

Bryen's commute went from pretty-darn good to fan-flipping-tastic when the pandemic caused his school to start operating remotely. When Bryen started attending school via a computer screen from his home, his grades shot up. They were suddenly better than they'd been in years, and he found himself on his school's honor roll!

"What do you think makes the difference for you?" I ask.

"Honestly?" He shakes his head, "That's the million-dollar question. I can't really figure it out. All we know is when we started doing remote, my grades drastically improved."

He says some suspect it has to do with the fact that his parents are there, 24/7, which discourages him from wandering away from his work. In fact, Bryen's desk is strategically placed next to the desk at which his father has worked since before the pandemic.

"And what work is your father doing?" I ask.

"Good question!" Bryen jumps in, as though it's a familiar source of fun family conversation.

Outside his newfound academic success, Bryen's time home with his family during the pandemic has felt natural and "pretty much the same as it's always been." Bryen has been fortunate to have his grandparents be a regular part of his routine before and during COVID. Before the pandemic, they would often pick him up from school and spend time with him afterward. Although he has chosen to continue with the remote learning now that he has a choice, he and his grandfather are still finding ways to have meaningful time together.

Taking advantage of the Arduino platform, Bryen has been creating parking-assist devices for his grandfather, which help him pull his car straight into his garage and stop short of his workbench. Through these projects and courses available to him at school, Bryen has grown more and more interested in electronics, engineering, computer programming, and computer science.

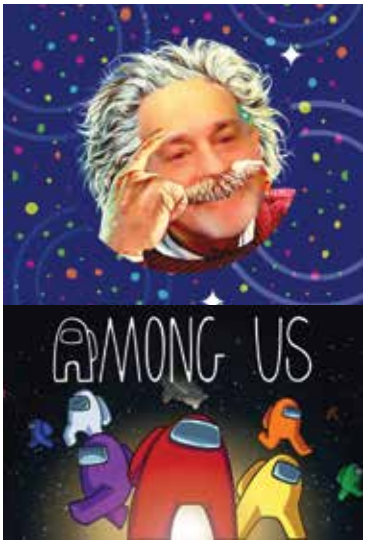
A young man of few words, Bryen, who was diagnosed as severe, sounds just about as nonplussed about his hemophilia B journey as he does about his world on COVID. "There's not much to tell," he relates. He shares with me he was on a twice-weekly factor regime and then tried an every-other-week treatment. "But I'd only make it like ten days, or I kept getting bleeds right on my factor date. So, we went to a once a weekly treatment, which was still an improvement over twice a week."

A self-proclaimed introvert, Bryen hasn't felt much of a sting from the reduced in-person social interaction. He does miss bowling, however. He had been enjoying being on a teen bowling team but had to take time off to rehabilitate after arthroscopic synovectomy surgery on his ankles and right elbow. Just as he had recovered his range of motion and was about to get the green light to rejoin the team, everything closed when COVID-19 turned the world upside-down.

WERE YOU “AMONG US?”

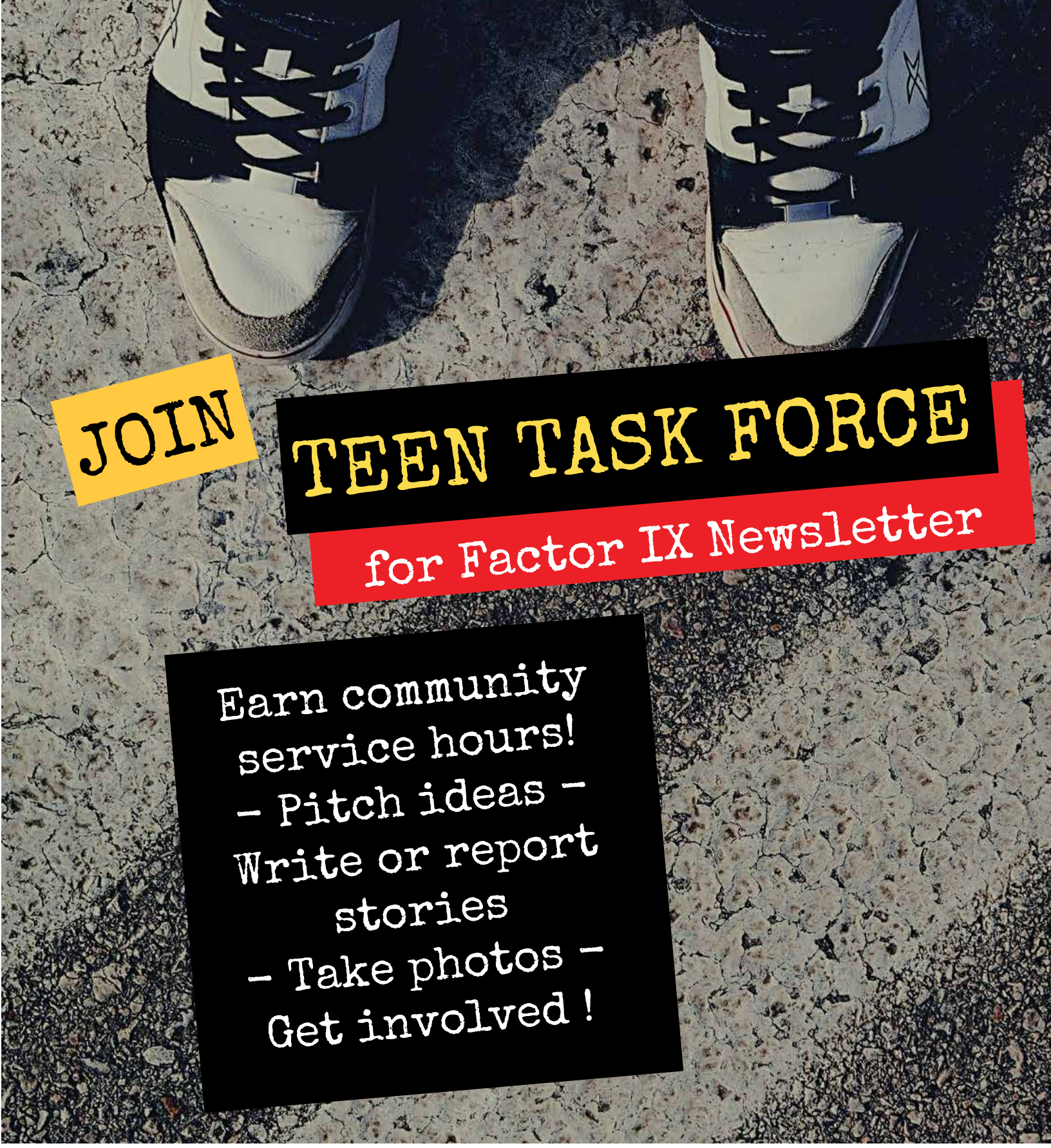
In April and May, our teens joined young adults as we gathered virtually to play an interactive game using smart phones and computers called “Among Us.” Players had to use teamwork as members of a crew fixing a broken spaceship. The twist is that one teammate is an imposter working to sabotage the ship and eliminate the crew.

What made it extra fun and special is that community member Bryen took on a leadership role, introducing the group to the “Hide and Seek” version of the game. The game was very popular and helped participants learn how to solve challenges by working together. Stay tuned for future games!



ARE YOU SMARTER THAN GLENN?

In January and February, we asked teens a very important question, “Are you smarter than Glenn?” To find out, Glenn hosted two game nights dressed and performing in character (accent and all) as Albert Einstein, the famed theoretical physicist who developed the theory of relativity. (In Glenn’s version, he also invented the paper towel and a whole lot of other useful things). Participants enjoyed Dr. Einstein’s trivia battles including Kahoot, Mad gabs, and Outburst. One thing we all learned from this fun, educational program: our teens are smart!



Join the Coalition for Hemophilia B Teen Task Force! Email Rocky Williams for more info: Rockyw@hemob.org

B inspired!

Stories and artwork from teens in the Hemophilia B Community

Spring 2021

IN THIS ISSUE:

B PREPARED!
TRISTAN'S STORY

DON'T BUBBLE-
WRAP ME: BRYEN

WANTED: TEEN CONTENT CREATORS!

Calling all content creators! If you have a heart for tweens/teens and a drive for content creation, then we would love for you to volunteer your time and talents with us. The Coalition for Hemophilia B is currently accepting volunteers to collaborate on a new section of the newsletter just for those special 11-18 year olds in our community.

No experience required as we have a team ready to polish your brilliant ideas for publication. If you have ideas for topics, events, and new sections, let's work on this together- reach out to RockyW@hemob.org for your next steps!