PEN's Insurance Pulse
Inspiring Advocacy

Inside

My Payer Won't Approve My Factor!

10 Questions to Answer Before You Approach Your Payer

Paul Clement

With several new factor products now available and more on the way, including several with a prolonged half-life, you may be wondering: Will my payer understand my factor brand choices? How do I defend my choice to the payer if my product is rejected?

Selecting a factor brand may be as simple as asking your hematologist for a new script. In other cases, especially if a new factor brand is more expensive, your hematologist may have to justify to the payer—your private health insurance company or state/federally funded program—why the product is necessary and whether the benefits outweigh the

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Welcome

PEN'S INSURANCE PULSE

Editor-In-Chief
Laureen A. Kelley

Contributing Writers
Paul Clement
Kelly Gonzalez
Wendy Owens
Michelle Rice

Senior Editor
Sara P. Evangelos

Science Editor
Paul Clement

Layout Designer
Tracy Brody

Publications Manager
Jessica O'Donnell

Manager, Projects & Production
Zoraida Rosado

Published by
LA Kelley Communications, Inc.

37-39 West Main Street, #8
Georgetown, MA 01833 USA

978-352-7657 • fax: 978-352-6254
info@kelleycom.com

www.kelleycom.com

In our last issue of Pulse, we focused on why payers might want to restrict choice of factor brands. Spiraling costs of specialty drugs (like factor) and restricted healthcare budgets have scared private insurers as well as federal and state insurers. Since that issue, we've seen new factor products arrive at breathtaking speed. Three products within three months so far in 2016…and more are coming. Payers aren't the only ones who need to come up to speed on the new products. We as consumers do, too.

We need to know differences in how products are manufactured and who manufactures them. And we may need to know price differences—don't forget, out-of-pocket costs can be affected. But above all, we need to know how a product responds in our own bodies: What is your product's half-life? Does your body respond effectively to that half-life? Should you choose a product based on its half-life?

In this issue, our science editor Paul Clement will help you make the pitch to your payer (or hematologist) about which product you prefer. Paul offers 10 questions that you'll probably need to answer when choosing a product to best meet your needs.

In the 26 years I've been working in the bleeding disorder community, I've never seen change happen so rapidly. The market is flooded with products now. Be an active participant in your choice of product, and know that choice restrictions may become more common among payers. We all need to read and ask questions like never before—and this issue of Pulse is a great place to start!

Laurie

Note: Pulse usually refers to a person with hemophilia as "he," though of course both males and females can have hemophilia.

Funding provided for PEN's Insurance Pulse with an unrestricted grant from Baxalta, now part of Shire.

Passing the Treatment Baton

Wendy Owens

A child born today with hemophilia is expected to live until he's about 79* years old. That's the same as the US national average life expectancy for an adult without hemophilia. Great news! And with the expectation that your child with hemophilia will live as long as his peers, making sure he understands the value of using the best factor product to meet his needs is equivalent to giving him the best education possible. The reason: other than regular visits to a hematologist, treatment is your child's best way to maintain the quality of life he wants and the one you want for him.

Unfortunately, selecting a treatment is becoming tricky. With the introduction of many new factor products to the market, and the promise of many more in the near future, navigating treatment selection requires broader education. Educating your child about selecting a treatment that is optimal for him, and for his lifestyle, is a key element in his becoming his own self-advocate. You can't start this education process too soon, though the best time for most kids may be their preadolescent years.

Janis Kosak-Ceaser of Grand Prairie, Texas, has worked for years to educate her son to be his own self-advocate. Now 18, her son has a dual diagnosis of mild hemophilia A and von Willebrand disease. "From the age of two on, I have included my son in age-appropriate discussions about his bleeding disorders and encouraged his participation in his care," says Janis. When he was 12, "I turned treatment decisions over to him, but I kept the right to override his decision. If I overrode his decision, we sat down and I explained why."

Janis handed her son the reins for his care and for selecting his factor when he became an adult. "Now that he is 18, his factor choice is his. I explained to him how I'd made factor choice decisions when he was young, and said that if he ever decides to explore other treatment options, I will direct him to reliable sources of information."

Dr. Guy Young, director of the Hemostasis and Thrombosis Center at Children's Hospital Los Angeles, reminds us that timing is everything when you begin educating a child or teenager about selecting a factor product. "Teenagers are all different," says Young. "Some are more involved in their care and take control of their care early. Others not at all, and leave all care and treatment decisions up to their parents. Ultimately, though, the teenager will have to be the decision maker and drive their own ship."

How to frame the discussion about transitioning teens to manage their own treatment decisions? Young advises, "Have them think about the next five years. Listen to their plans, be it go to college or travel the world or work. Then emphasize to them that to achieve these goals, they need to evaluate if they stay with their current treatment or change it. Impress upon them that they will need to use a treatment that will allow them to accomplish what they want."

Some parents, like Sarah Hueston of Bloomington, Indiana, have faced the choice of switching to one of the new factor products on the market. "My son just turned 15, and I have always encouraged him to be involved in the processes of his care and selecting his treatment," says Sarah. A few years ago, Sarah decided not to put her son on a prolonged half-life factor product that his hematologist said would require fewer infusions. "I explained to my son why I didn't want him to make that switch. Then last year at his clinic visit, when his new hematologist brought up switching, my son knew all the right questions to ask about the product the hematologist recommended. Super proud mommy moment that day."

According to Kim Schaefer, pediatric nurse coordinator at UC Davis Hemophilia Treatment Center, teaching your teen how to check with your insurer about which factor products are covered is a key part of transitioning him to manage his care and treatment. "When they are 15 or 16, explain to them who pays for factor and how," advises Schaefer. "A couple of years later, start having your teen order his own factor from your home care company. Then, in preparation for college,

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* The national average lifespan for a child born today is 78.74 years. http://www.cdc.gov/nchs/fastats/life-expectancy.htm.

My Payer Won't Approve My Factor! *from cover*

higher cost. To increase the chance that your brand request will be approved, you need to do your homework before talking to your hematologist.

Let's look at 10 questions that may influence your decision to choose a factor brand. You should know the answers before approaching your hematologist or payer.

1. Why do you want to change products?

Do you want to choose another product because it's the newest? Because it's more convenient? Requires fewer infusions? Has assay sizes that better meet your needs? Are you selecting it to obtain higher trough levels?[1] To increase adherence?[2]

Be sure you can justify your product choice medically or for better quality of life. For example, manufacturers of prolonged half-life factors stress their products' convenience based on fewer infusions. But your hematologist may see switching to a prolonged half-life product as an opportunity to raise your trough level rather than reduce your number of infusions. Some hemophilia treatment centers (HTCs) with patients who have switched to prolonged half-life products are starting these patients off on the same prophylaxis (prophy) schedule they were previously using, and then slowly increasing the interval between infusions, while checking trough levels and monitoring for bleeds. Talk to your hematologist about the benefits of increasing your trough level versus the convenience of reducing the number of infusions in your prophy schedule.

2. Is the factor product you're considering covered by your health plan?

Factor concentrates are classified as specialty drugs. Specialty drugs require special handling; most are infused and most are biologic drugs. Specialty drugs may be covered by your health plan under the medical benefit, pharmacy benefit, or both. If your factor is covered under the medical benefit, then your hematologist typically has greater flexibility in ordering your product of choice. If your factor is covered under the pharmacy benefit, then your hematologist may be restricted to ordering from a list of drugs covered by your health plan: a formulary.

If the factor you want is not on the formulary, all is not lost. Your hematologist can request drug approval by using prior authorization, and will have to provide clinical reasons to justify why the non-formulary drug is the most effective therapy for you. Obtaining a prior authorization may not always be easy, and using "for convenience" as a reason to switch to a more expensive factor brand will not cut it with your payer.

Health plans use prior authorization as a means to control their pharmacy benefit costs, especially with expensive biologic drugs such as factor. There's a "hassle factor"—it's often time-consuming to request a prior authorization. Health plans may also use prior authorization as a trigger to implement another cost-containment strategy called *step therapy*. Step therapy requires patients to try and fail one (or more) formulary-covered medication before providing coverage for a non-formulary or non-preferred medication. For a factor product to fail, you would have to experience bleeds, and this is a dangerous policy.

Currently, about half of factor scripts are filled under the medical benefit and about half under the pharmacy benefit. Because of the way scripts are coded for billing under the medical benefit, it's hard—if not impossible—for insurers to identify and track drugs. On the other hand, drugs ordered under the pharmacy benefit are billed using a different code that gives insurers detailed information about the drugs being ordered. Health plans prefer the detailed information on drug use and costs provided by the pharmacy billing code. You can bet that the number of plans switching factor coverage from the medical to the pharmacy benefit will increase in future, as pressure rises for plans to rein in escalating healthcare costs, and as the number of very expensive biologic drugs coming to market each year continues to rise.

3. What is the half-life of the factor product you are considering?

If you're considering a factor product because of its prolonged half-life, then you need to know the half-life of all the products for that type of factor. Why? Knowing the half-lives will help you

1. The "trough" is the lowest factor level between prophylactic infusions. 2. In this context, "adherence" is a measure of how well you follow or adhere to your prophy schedule.

make an apples-to-apples comparison and a more informed decision. Consumers can be easily misled by advertising, and there is no consensus about what constitutes a prolonged half-life product. (Some standard half-life products have the same half-life as prolonged half-life products.) Instead of relying on ads, look at the half-life printed on the product insert (PI) for the appropriate age group to obtain a more realistic comparison.

Are you assured of getting the same half-life printed on the PI? Not likely! Several things affect half-life: one of the most important is age. In young children, factor may have a significantly shorter half-life, maybe only half of that for adults. On the other hand, in older adults, factor may have a significantly longer half-life than what's printed on the PI. No two people are alike; that's why it's important to have a pharmacokinetic study (PK, or half-life study) done before and after switching to determine the half-life of your previous factor product and the new factor product in your body. The half-life of a factor product in your body is unique: you may respond differently to different products. For example, some people have reported no increase in half-life when using one product and a significant increase in half-life when using another.[3]

Finally, we might have to temper our excitement about prolonged half-life products with a dose of reality. If you have hemophilia B and use factor IX, prolonged half-life products might be a game changer, allowing you to infuse prophylactically once a week or even once every two weeks instead of twice a week. For people with hemophilia A, the extension in half-life for prolonged half-life factor VIII products is much less dramatic, and some won't see any change in their prophy schedule.

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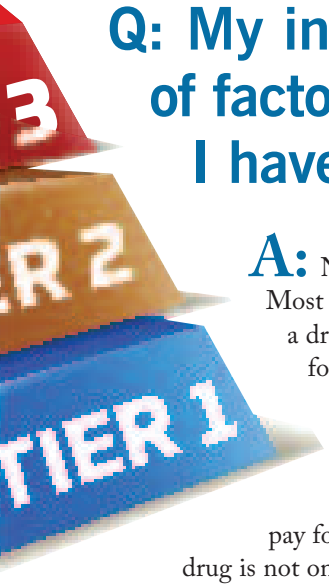
3. It's believed that some people who report no increase in half-life have developed non-neutralizing antibodies that do not decrease the effectiveness of the factor but do cause the patient to clear the factor at a faster rate.

Ask the Expert

Michelle Rice
Senior Vice President, Public Policy & Stakeholder Relations, National Hemophilia Foundation

Q: My insurance company says my brand of factor is non-preferred. Does this mean I have to choose another product?



A: Not necessarily. Most health plans have a drug formulary. A formulary is a list of medications your insurance company approves, and will help you pay for. If your prescribed drug is not on this list, your plan may not cover it, so you may need to pay out-of-pocket for the drug.

Formulary lists are regularly reviewed and typically updated at least once a year. Within the formulary, medications are usually divided into three or more groups, or *tiers*. A tiered formulary (also called a preferred drug list or PDL) provides financial incentives for patients to select lower-cost drugs. For example, under a three-tier formulary, tier 1 typically includes generic drugs and has the lowest cost share for you, the insured—maybe only $10 per prescription. Tier 2 includes preferred brand-name drugs and has a higher cost share—maybe $30 per prescription. Tier 3 includes non-preferred brand-name drugs and has an even higher cost share—maybe $75 per prescription. Other plans have a fourth or fifth tier; these are normally reserved for high-cost specialty medications or drugs requiring proof of medical necessity. Rather than a flat fee, like the first three tiers, fourth or fifth tiers require the individual to pay a percentage of the actual drug cost—maybe 20% or more. This is called *co-insurance*.

The good news is that if your medication appears on any of these tiers, it is covered. Remember that the main difference between preferred and non-preferred drugs is the cost to you. Some health plans require additional steps before allowing you to purchase a non-preferred medication, such as requiring a letter of medical necessity from your physician, or requiring you to "fail" on a preferred medication.

The key takeaway: Don't be discouraged if the medication you want is listed as non-preferred. Remember, if it's included in the formulary, it's covered—it just may come with a higher copay or require additional steps to access it.

Q: How can I make the prescription process easier?

A: Having the right information can save you time and money. Make sure you understand your health plan coverage options. Before choosing a plan, review the plan documents to determine how your medication is covered. Factor concentrate has historically been covered under the major medical benefit, but in the past few years, we have seen a growing trend to move factor to the pharmacy benefit. This is an important distinction, as it may affect where you can obtain your medication and what your cost share will be.

Take these steps to minimize problems associated with filling your prescription:

1. Review your plan's drug formulary to see if your medication is included. If it is, at what tier? And how much is your copay? If you don't see your medication or other factor products on the formulary list, contact the health plan directly and ask if factor concentrate for self-infusion is covered under the medical benefit.
2. Ask if the health plan has a list of in-network providers. Is there a preferred provider? Do you have out-of-network benefits if you choose to use a non-preferred provider? Typically, if the medication is covered under the pharmacy benefit, you must use an in-network pharmacy or the plan will not pay.
3. Take notes documenting any calls you make. Include the time and date, and the name and phone number of the representative you spoke to. Ask if the representative can direct you to the page in your plan document that explains how and where factor is covered. Ask if the rep can provide you with written verification.

Healthcare coverage has changed a lot in the past couple of years and will probably continue to change. The Affordable Care Act is one of the largest initiatives ever passed in legislation, and we will probably see tweaks and changes for the foreseeable future. It's important to educate yourself, because the goal of these changes is to ensure that your health needs are met.

The Road to Advocacy

Kelly Gonzalez

Our path to advocacy began when I realized that I was the only person persistent enough to advocate for my child. I vowed nothing would stand in the way of protecting my loved ones.

It started when our oldest daughter Jacey was only three, and was diagnosed with cancer. She'd had bouts of fever, fatigue, bruising, and pain, so I took her to the doctor and to many hospitals, but I was told I was a nervous mother.

I knew something wasn't right, so I documented Jacey's fever and pain. When her next fever exceeded 105 degrees, I grabbed my daughter and a backpack and flew to Children's Hospital Los Angeles. The ER nurses gave Jacey a fever reducer, so when the doctor arrived after we'd waited hours, the fever had broken. When I begged the doctor to listen to our story, citing my notes from the past three months, he filed admission paperwork before even examining Jacey. That's when I knew that it wasn't all in my mind, that something was genuinely wrong.

It took only three hours to confirm: Jacey had leukemia. The doctor said we were lucky to have found it, and our vigilant tracking of her symptoms was the reason.

When her chemotherapy was nearing an end, Jacey still suffered from bruising, bloody noses, and fatigue. Again, I felt something wasn't right, so I talked to the hematologist/oncologist, who inquired about my own bleeding, bruising, and failure to heal. I revealed my history: menses lasting two to three weeks; 21 days of bleeding post-tonsillectomy; six-week recovery from wisdom teeth removal; bleeding during my pregnancy and six months postpartum. I shared similar stories from my mother's history. Jacey and I were tested right away, and learned a few weeks later that we all have von Willebrand disease. My mother was tested too, and she also has VWD!

I was placed on consistent hormone therapy. Jacey began her menses with

Jacey and her little sister Maddie

prolonged bleeding (menorrhagia) and started hormone therapy combined with other trial therapies. Having failed two other treatment methods, she was placed on factor replacement therapy combined with two other medicines. Eventually her breakthrough bleeds and menorrhagia were well controlled.

At the end of 2013, we learned about a change in our insurance. I received documentation and verbal confirmation that the plan I was choosing included our HTC doctor and continued factor usage.

Our 2014 began with a bang: we were expecting twins! Unfortunately, I had extensive sub-chorionic hemorrhaging, with threats of miscarriage. I was hospitalized multiple times, and was bed-rested.

During this stressful period, Jacey had unexpected breakthrough bleeding. When it was time to renew her factor order, it was denied. Despite the documentation we had confirmed in 2013, the insurance company was no longer covering our HTC!

We were forced to see a different hematologist to get treatment for

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Community Forum

What is the future of current factor products in the US?

Community forum contributors represent unique perspectives and areas of expertise in the bleeding disorder community.

In the past few years—especially in recent months—we've seen an explosion of new products and technologies for clotting factors. Today, we have more than 25 products for hemophilia alone. Where will the rapid pace of product development lead? Pulse asked key community leaders what to expect from the factor product market in the near future.

Eric Hill
Chief Operating Officer
Diplomat Specialty Infusion Group

New product choices are fundamentally good for patients. Choice may also prove to be fundamentally good for insurance carriers and government entities who pay for these extraordinarily expensive drugs. In the coming years, we will see a few more market entrants, including new inhibitor drugs and "me-too" factor products. I think we'll also see the manufacturers tweaking their new prolonged half-life products as they get more real-world knowledge about how these products are working over time across larger patient populations.

As we think about whether the market can sustain all of these products, we need to think beyond the US. Manufacturers want to sell their products across the globe. I think that the global market can probably support a fairly large portfolio of products, but each manufacturer will be in a knock-down knife fight for US and European market share.

Here's the real question: Will payers limit patient product choice? I can make a case either way, which leads me to believe that some payers may take a shot at reducing cost by cutting deals with a manufacturer for a preferred product, while others will not. So the case for limiting choice is obvious. A large insurer negotiates a rebate or other financial incentive directly with a manufacturer, and then puts a drug coverage policy in place that requires patients to try and fail that one (or more) preferred product before they can get approved for any of the other products on the market. Because we have more products on the market now, manufacturers may get more aggressive on pricing, and insurers win out with lower net drug costs.

The case against limiting choice is less obvious, but very real. Even in the largest health plans, the number of hemophilia patients using clotting factor is a small absolute number when compared to, say, diabetes, hepatitis C, or congestive heart failure. Even if a health plan can negotiate a rebate or incentive of, say, $0.15 per unit, that's a net savings of $45,000 per year for a patient using 300,000 units per year. That seems like a lot of money, but when you consider that the plan may have only 20 or 30 of those patients in its entire membership pool, and not all of them will be candidates for drug switches, the grand total in savings is really fairly small—compared to saving even 5% or 10% on a hepatitis or diabetes drug that can affect a much larger population. This amount of money, even on 100 patients, just doesn't move the financial needle.

Another issue weighs against limiting choice: risk of inhibitor development. If there is a chance that multiple drug changes increase the likelihood of inhibitor development, would you want to be the chief medical officer who approves that policy, only to find out that just one newly developed inhibitor completely eliminated the entire cost savings the insurer had hoped to achieve, and resulted in a lawsuit? If you are a mother of a child who has been well controlled on product A, and your health plan forces you to switch to product B, do you think you will sit idly while that happens? Or will you call your senator and write a letter to the CEO of the health plan?

The hemophilia community is well organized and highly vocal. Health plans understand that, and they do weigh "membership friction" when making decisions like this. If I were a health plan executive weighing the option of eliminating product choice, I'd want to do a lot of homework on just what my risks would be, as compared to how much real cost benefit I would get in the end. Those risks aren't only financial, but involve public image, membership and employer group friction, financial upside versus real downside risk, and even liability.

The next several years will be interesting to watch. I'm convinced that the technology introductions we've seen with the prolonged half-life products will get better, and our understanding of how to use them will get better. I'm also convinced that although the product

landscape is crowded, more choice and more competition are ultimately good for consumers, even if a little overwhelming right now.

Kimberly Haugstad
Executive Director
Hemophilia Federation of America (HFA)

It is such an exciting time in the bleeding disorder community and yet an overwhelming time, too. With so many newly approved therapies, current and upcoming clinical trials, and corporate changes, it can be difficult to keep up! To understand what the plethora of new and forthcoming options mean, I believe it is imperative that families are in regular communication and form true partnerships with their medical providers about what treatment optimally meets their needs. This is not the time for a popularity contest of what company you like best; it is time to consider what you want to get out of treatment and seek a strategy to get you there.

I believe it is highly likely that consolidation of pharmaceutical companies producing currently available treatments will occur over time, and we should look both within the US and globally for that evolution. There is demand for plasma-derived clotting factor, recombinant and prolonged half-life factor, emerging therapies, and gene therapy across the globe. I do not see any of these phasing out completely. However, do we need a dozen options in each category? Probably not. We should be prepared for growing competition among the various pharmaceuticals for patients to use their treatments. This is big business, and every single patient counts to a company's bottom line. I expect value-based pricing for treatments and a shift in demand to products that improve quality of life to drive future mergers and business partnerships in the coming years, with the likelihood of first- and second-generation factor products becoming obsolete. Treatments that prove most efficacious to the most patients will win.

I'm personally fascinated by the novel therapies and emerging nonbiologic chemical drugs that don't require the same infusion considerations as factor, and also by the various strategies for gene therapy. It's a fascinating time, but I also have concerns. Call me pragmatic versus cynical.

In addition to working at HFA, I have a very personal stake in this game. My teenaged son has severe hemophilia, and he is an ideal candidate for the trials of these new options and therapies, once approved. Between work and home, the reality of our changing world is never far from my thoughts these days.

Based on current information and data, in virtually all current and emerging options, the need for factor will still exist. Factor may not be needed often, but even with a sustained 5%, 10%, or even 30% factor level, people will have bleeds and we must not forget that. Consider those you know in the community who are mild and moderate, including women. They have bleeds, and many have permanent joint damage. We need to be practical and thoughtful in how we proceed, and recognize that there are notable advances but not yet a true cure. We also need to remember there are numerous other bleeding disorders with still very few treatment options, and we must continue our advocacy efforts to support them. How exciting, though, to glimpse a time not long from now when most in the US living with severe hemophilia can move to being mild or moderate!

I think a great deal about how our community can continue to educate in the future, so we still know what our diagnosis is, how to identify a bleed, and how to advocate for our needs, and we can still be a tight-knit, supportive community. We continue to plan for this at HFA and welcome the challenge. It is an amazing time!

Ellis J. Neufeld, MD, PhD
Medical Director, Boston Hemophilia Center
Associate Chief, Dana-Farber/Boston Children's Cancer and Blood Disorders Center

With so many crucial unknowns, it's hard to know today what the future will look like.

Will the market sustain all of the current and newly available factors? Because factor VIII and IX products together will number more than 30 by 2017, it's unlikely, at least in the US market. I think there will be winners and losers in the new market.

It's easiest to see this for the newer prolonged half-life factor IX products. These products are game changers, and will likely reduce market share of current factor IX standard half-life products. Regrettably, these new molecules come at a premium price.

In contrast to improvements in factor IX, so-called prolonged half-life factor VIII products are incremental advances over the current standard

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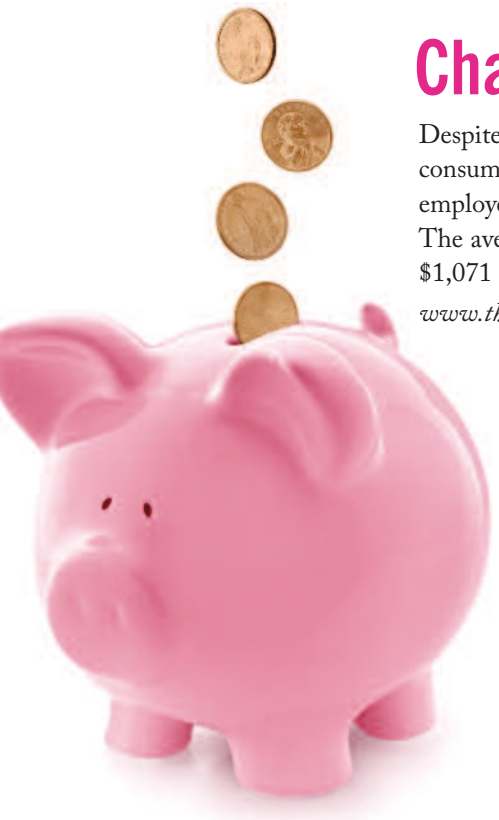
Tracks & Trends



Cha-Ching!

Despite the slower rate of growth in healthcare costs, consumers who get their healthcare through their employers will pay 5% more in premiums in 2016. The average premium cost for an individual will be $1,071 and for a family $4,955.

www.thefiscaltimes.com

Premium Premiums

The rise in premiums continues to cause hardships for people who need care. 31% of Americans say they have put off receiving medical care because they can't afford it.

www.gallup.com

Feel the Steal

Over the next five years, 1 in 13 patients will have personal information stolen via cyberattacks on medical records systems. Of those, 6 million people (25% of all patients) probably will become victims of medical identity theft, and 4 million people with stolen information will pay out-of-pocket costs of nearly $56 billion over the five-year period.

www.accenture.com

Telemedicine on the Rise!

Consumers can receive 24/7 healthcare in their homes via an Internet-connected device or phone. In the next five years, the market for telemedicine is expected to increase from $645 million to over $3.5 billion in 2020. The average cost of a telemedicine appointment is $25–$30.

www.thefiscaltimes.com

Roadblocks to Factor

Insurers are placing more restrictions on obtaining factor for hemophilia A and B. Two types of restrictions are prior authorizations and step therapy. 66% of prescriptions for hemophilia A factor and 75% for hemophilia B factor require no prior authorizations, but 34% of prescriptions for hemophilia A factor and 27% for hemophilia B factor require prior authorizations. This means that 3 of 10 hemophilia patients are impacted by prior authorization requirements. So far, there is no specific data associated with step therapy.

4. How do you justify the cost?

Cost is a major concern for healthcare providers and also pharmacy benefit managers (PBMs, third-party administrators often hired by health plans to track and help control drug costs). All prolonged half-life factor products are more expensive than standard half-life factor concentrates. If your physician must submit a prior authorization for the factor product you are requesting, the request may be denied simply because the new factor product is more expensive. But the reviewer of the request probably won't know that the higher-cost product may prove less expensive over time due to fewer infusions. Because of this, it's crucial for your physician to mention potential cost savings when submitting a justification for a prior authorization.

Also be aware that newer factor products may have higher copays. Health plans typically categorize their covered drugs into four to six tiers, with tier 1 drugs being the preferred lowest-cost generic drugs with the lowest copay, and high-cost specialty drugs like factor being assigned to tiers 4, 5, or 6 with the highest copays. If you're considering switching and you have a higher copay, check the manufacturer's website—most have copay assistance programs, some offering as much as $12,000 a year.

5. What's the inhibitor risk?

People with hemophilia have been reluctant to change factor brands. Thirty years ago, this was driven by the fear of blood-borne infections. Today, it's driven mainly by the fear of developing inhibitors. But this fear is not supported by scientific evidence. Several studies have found that, for previously treated patients (especially those with more than 50 exposure days), there is no measurable increased risk of inhibitors as a result of switching products. This doesn't mean that all products have the same risk of inhibitors, or that switching products will not cause an inhibitor; it only means that the risk of developing an inhibitor in previously treated patients as a result of switching products is too small to measure.

That being said, we don't know the risk of developing an inhibitor on a prolonged half-life product for previously untreated patients (PUPs), nor do we know of any difference in risk from one product to another, as neither of these has been studied. We do know that between 20% and 30% of hemophilia A patients will develop an inhibitor, and between 2% and 3% of hemophilia B patients will develop an inhibitor. It is hypothesized that prolonged half-life products may actually have lower inhibitor rates than standard concentrates because the technologies used to prolong the half-life may cover some of the *epitopes* (parts of the factor molecule that inhibitors recognize and attach to) on the factor. Or, in the case of one technology called PEGylation, the PEG (very long molecules attached to the factor) may physically keep inhibitors away from the factor molecule, preventing them from attaching to the factor—sort of like a horse's tail swatting flies away. So the "Zero Percent Inhibitors" currently being advertised by some manufacturers applies only to previously treated patients. If your child has not been exposed to factor, discuss the risk of inhibitors with your hematologist.

6. How will switching to a different product affect my prophy schedule?

For most people with hemophilia A, we know that infusing three times a week with a standard half-life concentrate is the optimal prophy schedule to prevent spontaneous bleeds and long-term joint damage. National Hemophilia Foundation's Medical and Scientific Advisory Council (NHF's MASAC) recommends a three-infusions-weekly prophylaxis schedule for people with hemophilia A. But in the US, few HTCs and few patients follow these guidelines.[4,5]

There are many reasons people may not adhere to prophy. In young children, venous access is a major concern. Many patients cite time constraints. Teens may be rebelling against anything—like prophy—they feel forced into, or they may focus on short-term goals and think prophy isn't important. With fewer infusions, the prolonged half-life products, especially for those with hemophilia B, may be an answer to non-adherence.

4. "Survey Underscores HTC Prophylaxis Adherence," www.hemophilia.org/Newsroom/Medical-News/Survey-Underscores-HTC-Prophylaxis-Adherence (accessed Aug. 16, 2016). 5. E. P. Armstrong, D. C. Malone, S. Krishnan, and M. J. Wessler, "Adherence to Clotting Factors among Persons with Hemophilia A or B," *Hematology* 3 (Apr. 20, 2015): 148–53, www.ncbi.nlm.nih.gov/pubmed/25001343 (accessed Aug. 16, 2016).

7. Are you considering another port?

Difficult venous access in young children is a major deterrent to prophylaxis. Because of this, parents often opt to have a central venous access device, or port, implanted in their baby to facilitate infusions.

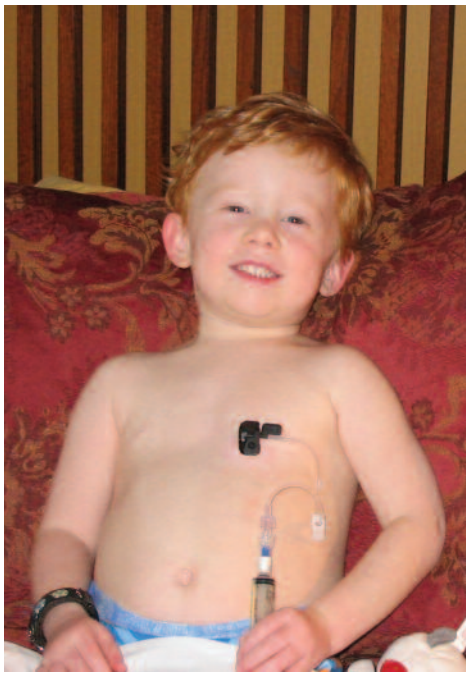
But ports are not without complications: 20% to 50% of people with ports will experience port infections, and, after having a port in place for a few years, more than 50% of people with ports will have developed a deep-vein thrombosis (blood clot).[6] Both complications often require the port to be removed.

Although prolonged half-life products will not help with venous access in babies, these products may cause you to think twice about having a second or third port implanted in your child. Older children are much easier to infuse than babies, and a prolonged half-life product may allow you to get by with fewer infusions and avoid another port and its associated complications.

8. What is your physical activity level?

High activity level (even though this is desirable for everyone), particularly in some sports, places you at higher risk of a bleed. Many people using standard half-life factor concentrates adjust their prophy schedule so infusions are given on days when games or other activities are planned, offering higher factor levels and greater protection against bleeds on those days. This brings us to a concern voiced in the medical community regarding prolonged half-life factor products:

After an infusion of factor, there is a rapid, sharp rise in the factor level in the blood, until it reaches a maximum called the "peak." After the peak, there is a



Barnes family photo

slower, but still fairly rapid drop-off in the amount of factor in the blood, until it reaches the lowest point before the next infusion, the "trough." Higher factor levels around the peak give more protection against bleeds than lower factor levels near the trough. This is true for both standard half-life factor products and prolonged half-life products. With standard half-life products, you have more infusions, giving you more peaks and greater ability to adjust your prophy schedule to accommodate infusions (and provide higher factor levels) on higher-risk days. With prolonged half-life products, you have fewer infusions, fewer peaks, less ability to adjust your prophy schedule, and, most important, you spend more time near the trough; this may put you at greater risk of bleeds on high-risk days.

Some hematologists have suggested that active people use two products: a prolonged half-life product for prophy and a lower-cost standard half-life product as a low-dose "booster shot" on high-activity days. (Of course, this requires more infusions, eliminating the convenience aspect motivating most consumers to switch to a prolonged half-life product.) Other hematologists see prolonged half-life products as an opportunity to raise the trough level. The 1% trough level used for years in US prophy protocols is an arbitrary number, originally chosen as a compromise based on factor availability and acceptable cost. We know that 1% is not an optimal trough level, and many people experience spontaneous breakthrough bleeds near 1%.

Discuss this with your hematologist: Do you want fewer infusions and more convenience, or less convenience and greater protection against bleeds? And is raising the trough level even an option financially?

9. What type of technology is used to manufacture the factor you are considering?

Most people aren't too concerned about the type of technology being used to manufacture their factor product. But unlike with previous factor products, we now have several different factor molecules and several different manufacturing processes. We now have single-chain factor VIII with a longer half-life (factor VIII normally circulates a two-chain molecule). We have factor VIII expressed by a human cell line, which may allow for more accurate "folding" of the factor protein and perhaps lower inhibitor rate. We have fusion and PEGylation technologies that prolong half-life of factor.

As a consumer, what, if anything, should you know about the technology used to produce your factor? What's the relative benefit of one technology over another? Do some research on the new products and draw up a list of questions to ask your hematologist before making a decision.

6. Janna M. Journeycake, Charles T. Quinn, Kim L. Miller, Joy L. Zajac, and George R. Buchanan, "Catheter-Related Deep Venous Thrombosis in Children with Hemophilia," *Blood* 98 (2001): 1727–31, www.bloodjournal.org/content/98/6/1727?sso-checked=true (accessed Aug. 16, 2016).

10. What does the PI say?

Increasingly, health plans are looking for ways to *not* cover factor; or to restrict access to factor, certain brands of factor, or new products. Some payers have an "exclude at launch" policy, in which new prescription products they believe may offer little or no additional healthcare value (read: are more expensive) are not covered at the time a new product is introduced to the market. This allows the payer time to evaluate the product medically before covering it. Some plans have begun interpreting PIs literally: one company denied a certain factor brand for children because it had not been tested on children under 12; another company denied factor for a man who had just turned 65 and had been on the particular factor brand for years, because the product had not been tested on people over 65. Several companies have denied certain factor brands requested for prophy, claiming this is an off-label use and not approved by the US Food and Drug Administration. (Of course this is hogwash, because any standard factor concentrate can be used for prophy, regardless of whether the product earned an indication for prophy from the FDA.) Last year, a Medicare services administration company, Novitas Solutions, Inc., required everyone using NovoSeven to infuse "under the direct supervision of a physician" (in the office!) as stated in the PI.

In most cases, we don't know whether these decisions about factor are being made out of ignorance (as in the Novitas decision) or are an attempt to frustrate patients and push them into switching health plans—or a combination of both. Carefully read the PI of the product you're considering before attempting to switch products, to avoid having your request denied as being off-label.

Today is the most exciting time in hemophilia! Tremendous advances have been made, and continue to be made, in hemophilia care. We now have an array of factor products, and new non-factor products on the horizon, complicating the decision about which product to choose. The biggest roadblock ahead may be whether new products are covered by your healthcare payer. This range of choices requires us to become more knowledgeable consumers, so we can make informed decisions in collaboration with our physicians—and get what we need covered by our payers.

Paul Clement is a retired high school science teacher, board member of Hemophilia Council of California, and longtime science editor and contributing editor of PEN as well as other LA Kelley Communications publications. He has a BS in biology and MA in science education from California State Polytechnic University. Paul lives in Southern California with his wife Linda and children Erika (31) and Brett (29), who has severe hemophilia A.

Transitions *from page 3*

explain to your teen how manufacturers' subsidies work." For teens whose parents don't have insurance that can cover them until they are 26, Schaefer adds, "It is important for children turning 18 whose parents are non-US citizens to know that they are eligible to purchase insurance via the insurance Marketplace once they are an adult."

Rachel Katzman of Westport, Connecticut, has a 13-year-old son with severe hemophilia A. He had an inhibitor for over 10 years, so the factor selection process came with a twist. With the onset of the inhibitor and the need for their son to have von Willebrand factor in the product he used, Rachel had to do her homework, a process Rachel hopes her son will undertake if he has to make the treatment decision for himself.

"If in the near future," explains Rachel, "our son had to switch his factor product, or if his inhibitor returns, and if there was time to make a decision, I would encourage him to (1) speak with his hematologist or a hematologist with inhibitor experience if his own wasn't experienced, (2) email and call the manufacturers of his product options, (3) talk to other community members who encountered his same situation, (4) search the Internet for important and useful information, and (5) attend local and national bleeding disorder meetings to speak face-to-face with other experts."

Parents and providers agree that early involvement in their care and treatment selection will prepare teens with hemophilia to take on the lifelong job of decision making and self-advocacy. Dr. Jerry Powell, a longtime pediatric hematologist and now medical director for North America Commercial Operations with CSL Behring, sums it up: "Self-advocacy means something more than saying no to change; it means doing what is best for yourself to achieve your life goals. When it comes to factor selection, parents need to educate their kid to take this responsibility over from them. Factor is patient choice, patient choice should be informed, and a patient of any age should listen to various sources of information."

My Life *from page 7*

16-year-old Jacey. The insurance-mandated provider refused to see Jacey, saying she had to go to a pediatric hematologist—but the only pediatric hematologist available was at the HTC the insurance company had just denied us! Over the next few months, I consistently called the insurance company and the mandated provider; neither could figure out a way to get Jacey seen. Meanwhile, Jacey suffered multiple bleeds and was hospitalized numerous times. Each time, the hospital consulted with the HTC doctor or nurse practitioner who had been treating us for years.

During this period I was hospitalized, still pregnant with the twins. At 23 weeks, I had premature labor and excessive hemorrhaging. I panicked about the plan to control my bleeding if a C-section was needed. Although the HTC had made a treatment plan, the orders were not accepted. The insurance company sent the mandated hematologist (the one who had yet to see my daughter) to the hospital to form another treatment plan; he chastised me for "not getting a plan put in place earlier," as if I knew I'd be hospitalized facing premature Cesarean births. He minimized my potential to bleed, because my von Willebrand factor level during week 19 had been a "stable 52%"—even though it's known that women's levels with factor VIII deficiency and/or VWD can as much as triple during pregnancy. Most likely my levels were falsely elevated, so I voiced my concern that I would have bleeding complications. Yet this doctor claimed I would need only DDAVP, even though I had clearly stated a previous allergic reaction.

During this time, Jacey was accepted to the insurance-mandated hematology group. The newly assigned hematologist said that although she'd had multiple trials of Stimate and DDAVP—which were ineffective and produced an allergic reaction—Jacey would be required to use and fail DDAVP again. For years, Jacey was on a successful factor regimen, but with this new provider she had to return to a treatment that had failed her, as well as injectable hormone therapy. The new hematologist never contacted us after multiple calls and hospitalizations for bleeding complications. We documented signs, symptoms, pictures, providers, and effectiveness of the factor. The ER at the local hospital also tried to contact the hematologist, but when no calls were returned, the ER consulted with our previous (and preferred) HTC. This process continued for 13 months and 11 hospitalizations.

Once when Jacey had a bleed resulting in unconsciousness, she was immediately transported to the hospital where I was still being bed-rested. When she was stabilized, they put her in my room and we cried in frustration, unable to understand why she wasn't allowed access to treatment and why she was constantly hospitalized.

Waking from my fog of frustration, I contacted the executive director of National Hemophilia Foundation, Nevada Chapter, describing Jacey's suffering and our documentation. The executive director put us in touch with Michelle Rice of NHF, who eventually got us a meeting with the insurance company in December 2014. From the initial denial of treatment to the meeting in December 2014, Jacey had been hospitalized 11 times. I had an emergency C-section over two months early and, contrary to the HTC's recommendations, the hematologist failed to order appropriate treatment. I had pain and bleeding into my abdominal cavity and outside my uterus. None of this was treated appropriately by the insurance-mandated provider. This later resulted in multiple corrective surgeries in 2015 and 2016 (while being treated for my VWD).

At our December meeting with insurance company executives, we presented photos, timelines, and 18 pages of records, detailing the medical problems and the effect of insufficient access to treatment caused by the mandate to see one provider. We had carefully documented every call and appeal to the company, every neglectful or dismissive action of the mandated provider. After our presentation, the company authorized us to see the HTC as our preferred provider, and to continue our prophylactic factor regimen. This was a victory for Jacey and me, but we wanted more from the insurance company. We wanted a promise to open dialogue, to help other patients in our bleeding disorder community with the same insurance plan. Our meeting blossomed into multiple meetings to ensure that policies changed and treatment options became available to others. Since then, the treatment door has opened for over a dozen patients with this insurance.

Jacey and I have become outspoken advocates in our community, attending state advocacy days and NHF's Washington Days. We feel compelled to continue teaching patients and parents the importance of documenting anything and everything related to health issues, and we explain how to navigate a difficult system. The more educated and outspoken we are, the stronger we are.

Kelly Lynn Gonzalez was an educator with the Clark County School District for 12 years. She holds a BS in business management, a BS in business administration, and an MBA and MA in education. She currently works for Factor Support Network as a care coordinator, and is the chair of her chapter's advocacy team. She has von Willebrand disease, as do both her daughters. Kelly lives in Las Vegas, Nevada, with her husband Joe, daughters Jacey (19), Maddie (8), and sons Joseph Jr. (4), Jaxon (2), and Jacoby (2).

half-life market leader. Hype from manufacturers notwithstanding, uptake of prolonged half-life VIII-Fc and PEG-VIII products is relatively slow. This doesn't guarantee that the market can sustain every current brand indefinitely, but the change is slow and evolutionary for factor VIII.

Will payers limit patient choice? Yes. This year, some payers are already limiting at least some choices. This will be a disturbing trend if the reasons for limitation aren't data-driven.

I strongly suggest to payers tempted to limit choice (for any reason, but often cost is key) that they do so with a transparent process that takes into account not only price per unit or predicted cost per year, but also (1) biological properties of factors including but not limited to likelihood of forming inhibitors, and half-life (because cost and convenience matter too); and (2) evolving research results that may or may not demonstrate advantages of a given product for a given population.

An example of this second point is found in the SIPPET study[1] published in May 2016. It was suddenly clear, when the results of this multinational, randomized trial became public, that plasma-derived factors might be better than recombinant factors for previously untreated patients (PUPs) in terms of inhibitor risk. NHF's Medical and Scientific Advisory Council has weighed in on these results, but what the community really needs is results from PUP studies done with each of the new factors. Early results are just now becoming available, and these new results will govern my own prescribing practice. We the prescribers need to be on the same page as the payers about the meaning of new research.

Could some existing factors be discontinued? There is simply no predicting. There isn't necessarily a need for a so-called first-generation recombinant product anymore, but they still exist.

Will some current factor products be acquired? This is possible. Just in the last 15 months, we have seen the spinoff of Baxalta and its acquisition by Shire, and the spinoff of Emergent hemophilia to Aptevo Therapeutics. The spinoff of Biogen's hemophilia unit is underway. Acquisition could potentially cement a market niche for any given factor in the marketplace, or alternatively lead to its demise, depending on the needs of the new owner and the overall shape of the market. Certainly there will be no shortage of choices in the short run.

Will factor be used for other indications? The SIPPET results strongly suggest yes. I have been a practicing hematologist since 1988, but the first time I prescribed a VWF-containing plasma-derived factor VIII product for a bleeding PUP patient was December 2015, after SIPPET results were made public.

Could existing factor find a new home in other markets? This is an attractive possibility. My HTC has been a World Federation of Hemophilia twin, with a center in Rajasthan in Northwestern India, where recombinant factor VIII is relatively unavailable, but the standard of care and available resources is rising. It's easy to envision that some of today's perfectly good recombinant factor VIII products may play a larger role in middle-resource countries sometime soon. This is important because at least 80% of the world's hemophilia patients aren't in high-resource countries, and they deserve an improved standard of care. This would be possible if today's standard half-life factor VIII and IX can be made and distributed in other parts of the world at a deep discount.

Could certain manufacturing processes be discontinued? Almost every brand name really defines a distinct manufacturing process (human vs. hamster cells, baby hamster kidney vs. CHO cells, B domain present or absent, and so on). Whether a brand or process might be discontinued (or moved outside the US) is probably a commercial decision more than anything else. Market share will likely play a role. This gets back to the inevitable question of what factors will be winners and losers in the new market. I strongly hope more than one or two remain in every space, to allow for competitive pricing, which helps all of us—consumers, payers, and society at large.

It's not possible to know for sure, but it's certain that some current factor brands will be in broad use for years to come. Uptake of new factors has traditionally been slow for the hemophilia community. Current factor brands are safe and, when used prophylactically, prevent bleeding extremely well. Many patients ask, "Why switch?" Finally, in the four-to-six-year time frame, there may be non-factor products, including the factor VIII mimetic bifunctional antibody emicizumab, known as ACE910 (Genentech/Roche/Chugai), and various strategies to reduce the body's own inhibitors of the clotting process, not to mention gene therapy, now clearly on the horizon. All of these new approaches may take a bite out of the factor market. How big a bite remains to be determined.

1. Flora Peyvandi, et al., "A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A," *New England Journal of Medicine* 374, no. 21 (May 26, 2016): 2054–64.

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INSIDE: My Payer Won't Approve My Factor!

September 2016
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