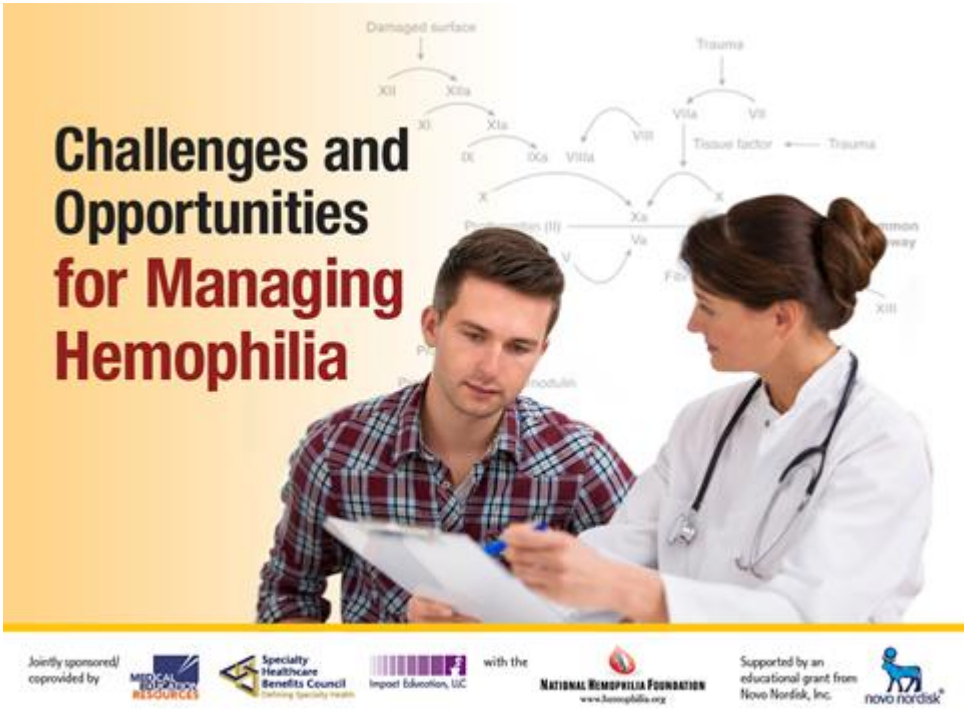
Challenges and Opportunities for Managing Hemophilia 2014

# Track 1: Clinical Update

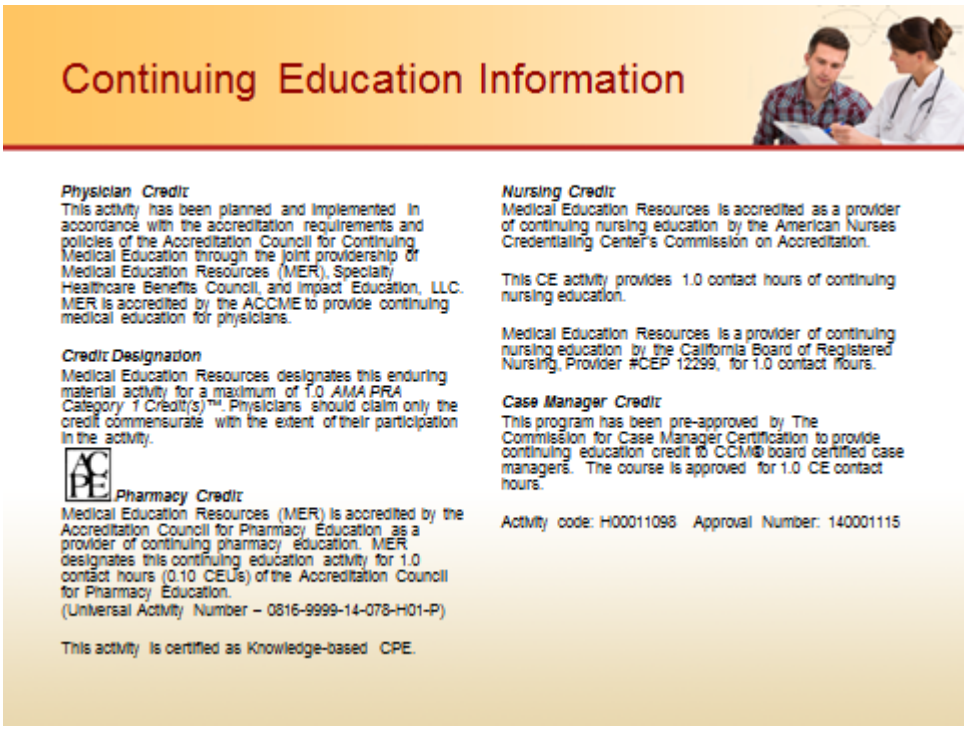



**Slide 1: Challenges and Opportunities for Managing Hemophilia**

Welcome to Challenges and Opportunities for Managing Hemophilia 2014 Continuing Education Series.

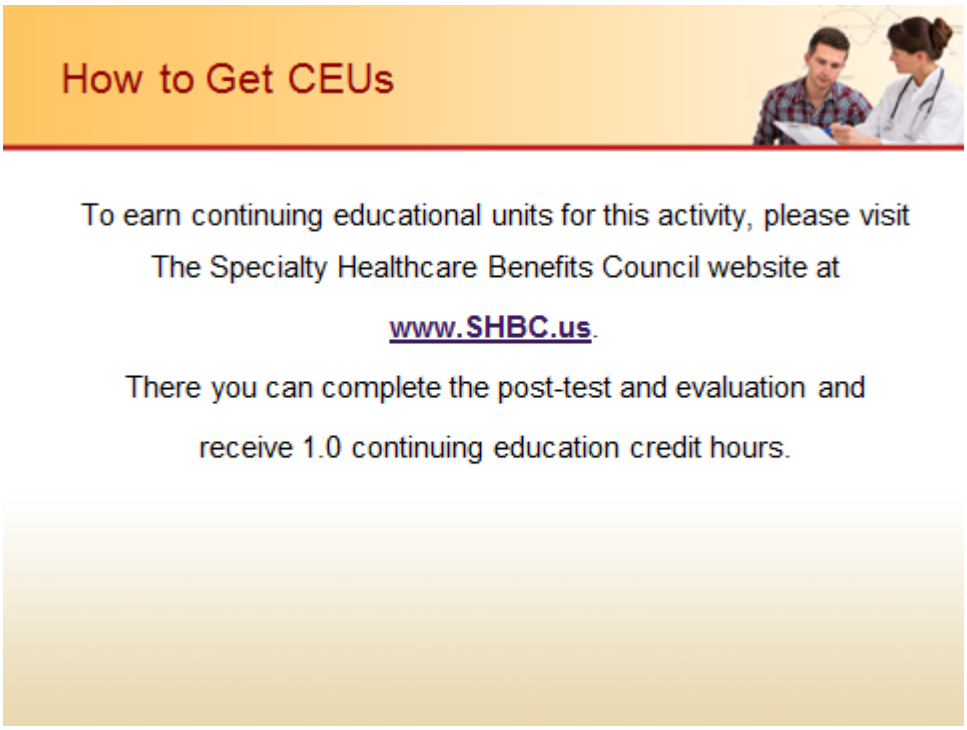
This series of three tracks is jointly sponsored by Medical Education Resources, the Specialty Healthcare Benefits Council, and Impact Education, LLC, in collaboration with the National Hemophilia Foundation.

This activity is supported by an educational grant from Novo Nordisk, Inc. and we would like to thank them for their support.




**Slide 2: Continuing Education Information**

Continuing education for this activity is provided by Medical Education Resources, or MER. They have designated this activity for one (1) credit hour for each track, or a potential total of three (3) hours if all three tracks are completed. This credit is for physicians, pharmacists, nurses, and case managers.




**Slide 3: How to Get CEUs**

To earn continuing educational units for this activity, please visit The Specialty Healthcare Benefits Council website at www.SHBC.us. There you can complete the post-test and evaluation and receive 1.0 continuing education credit hours.

## Financial Disclosures

The faculty and planners reported the following financial relationships with commercial interests whose products or services may be mentioned in this CE activity:

| Name of Faculty | Reported Financial Relationship |
|---|---|
| Craig Kessler, MD | No financial relationships to disclose. |
| Amy Shapiro, MD | Grants/Research Support: Adventrix, Bayer, Baxter, Biogen Idec, Bio Products Laboratory, CSL Behring, Inspiration, Kedrion Biopharma, Novartis, and Octopharma<br>Consultant/Advisory Board: Baxter, Novo Nordisk, Bayer, Biogen Idec, Inspiration, LFB Biotechnologies |
| Celynda Tadlock, PharmD, MBA | No financial relationships to disclose. |

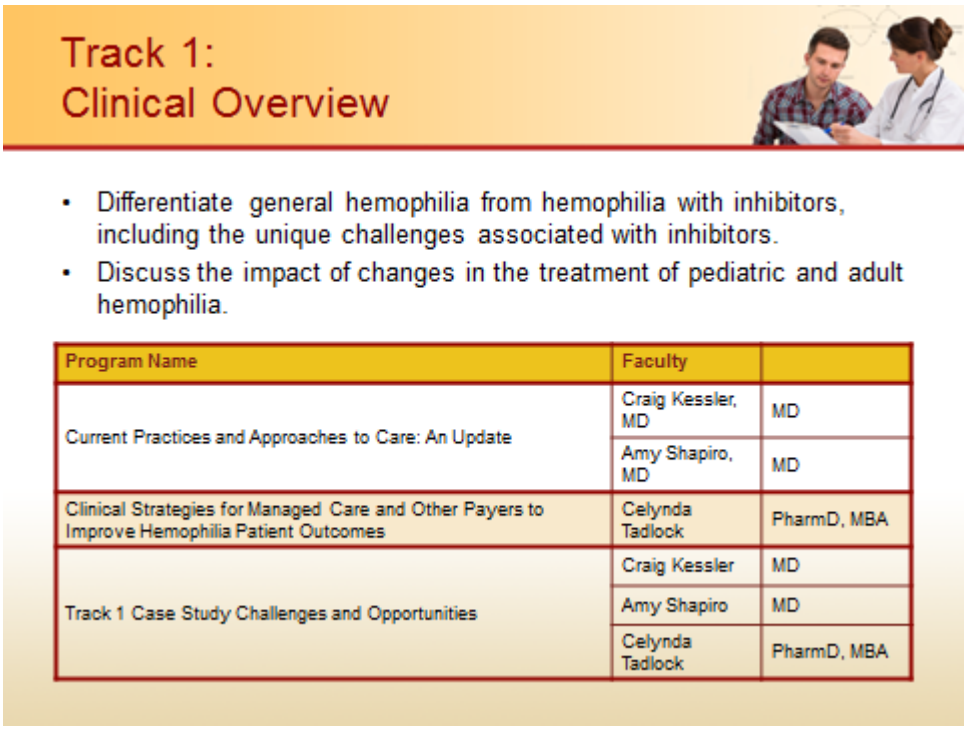
## Financial Disclosures

The faculty and planners reported the following financial relationships with commercial interests whose products or services may be mentioned in this CE activity:

| Name of Content Manager/Planner | Reported Financial Relationship |
|---|---|
| Joe Eichenholz (SpecialtyHealthcare Benefits Council) | No financial relationships to disclose. |
| Nathan Scott (Medical Education Resources) | No financial relationships to disclose. |
| Marla Feinstein (National Hemophilia Foundation) | No financial relationships to disclose. |
| Michelle Rice (National Hemophilia Foundation) | No financial relationships to disclose. |
| Steven Casebeer (Impact Education, LLC) | No financial relationships to disclose. |
| Keith Engelke (Impact Education, LLC) | No financial relationships to disclose. |

**Slides 4 and Slide 5: Financial Disclosures**

The faculty and planners reported the following financial relationships with commercial interests whose products or services may be mentioned in this continuing education activity.




**Slide 6: Track 1: Clinical Overview**

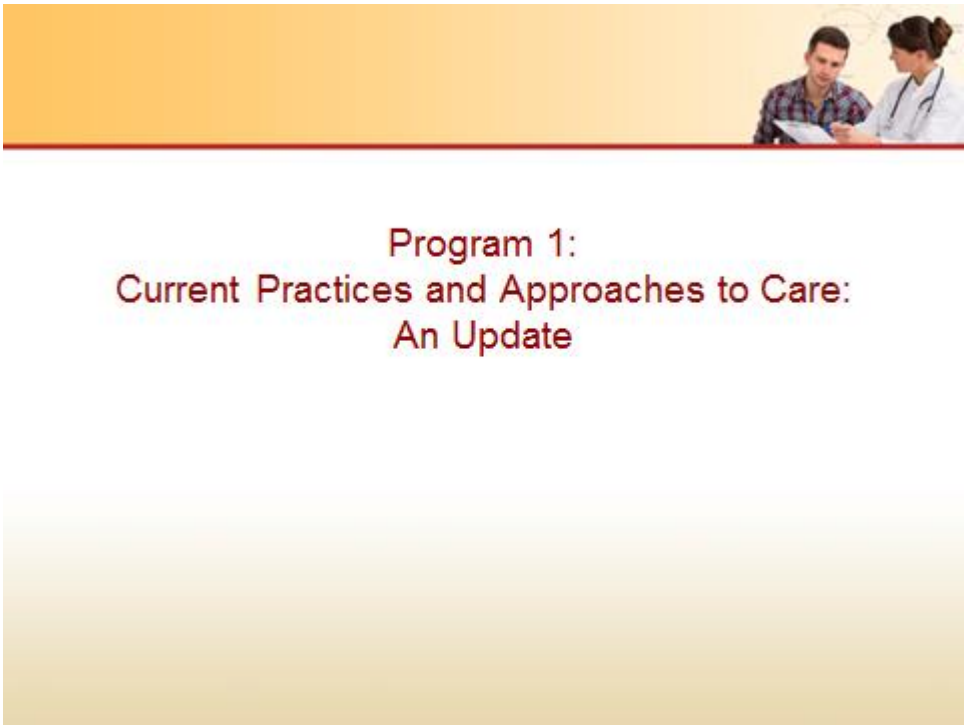
Welcome to Track 1 of a three part series. This track, entitled Clinical Update will focus on the clinical challenges and opportunities for managing hemophilia within a managed care setting.

Upon completion of this learning track, the learner will be able to:

1. Differentiate general hemophilia from hemophilia with inhibitors, including the unique challenges associated with inhibitors.
2. Discuss the impact of changes in the treatment of pediatric and adult hemophilia.

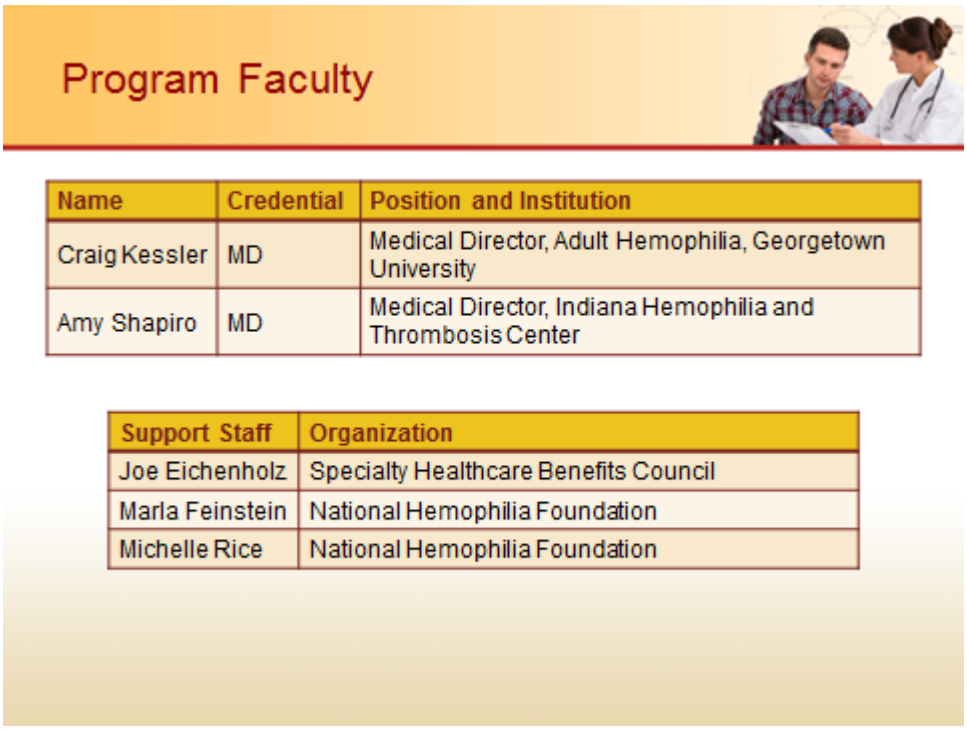
# Program 1:

# Current Practices and Approaches to Care: An Update



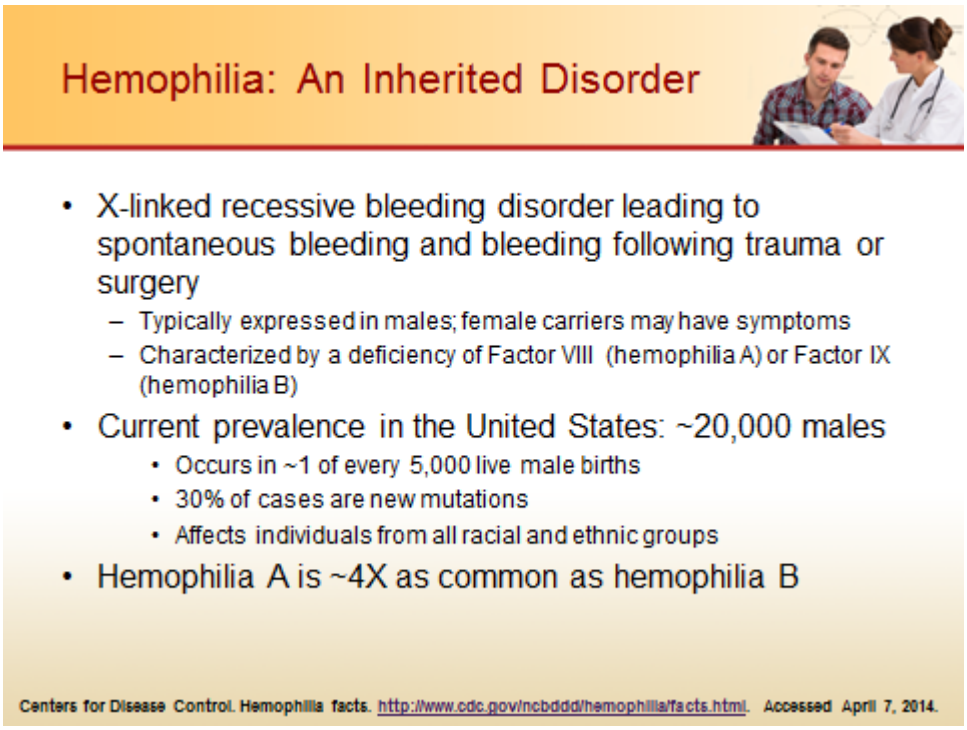

**Slide 7: Program 1: Current Practices and Approaches to Care: An Update**

The first presentation of Track 1 is entitled Current Practices and Approaches to Care: An Update, and represents the physician's perspective on hemophilia management.




**Slide 8: Program Faculty**

The faculty for this presentation includes Dr. Craig Kessler, Medical Director of Adult Hemophilia at Georgetown University and Dr. Amy Shapiro, Medical Director of the Indiana Hemophilia and Thrombosis Center. Support staff for this presentation includes Joe Eichenholz, Executive Director of the Specialty Healthcare Benefits Council, and Marla Feinstein and Michelle Rice, from the National Hemophilia Foundation's Public Policy Team.



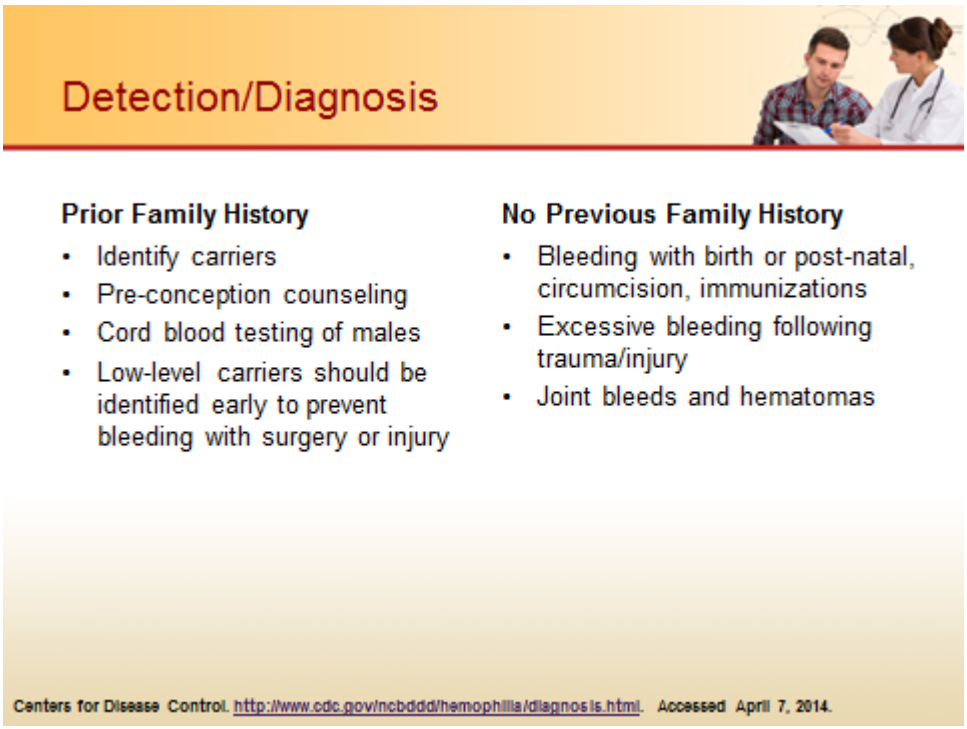

**Slide 9: Hemophilia: An Inherited Disorder**

Hemophilia is a genetic coagulation disorder that results in a bleeding tendency. Hemophilia is a term most commonly utilized to include hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency).

Both factors VIII and IX are coded for on the X chromosome and are sex-linked recessive disorders. This results in a predominately male affected population. Females are usually called carriers of the disorder. Female carriers may have varying levels of the deficient coagulation factor and may have levels that place them in the mildly deficient range. It is important that carriers' levels are established and care provided to those with levels placing them at hemostatic risk. Approximately 30% of diagnosed cases of hemophilia are new mutations; therefore a lack of family history does not preclude the diagnosis.

The incidence of hemophilia A and B is approximately 1 in 5,000 live male births. Hemophilia affects all races and ethnic groups equally. Overall, there are at least 30,000 affected individuals in the United States today.

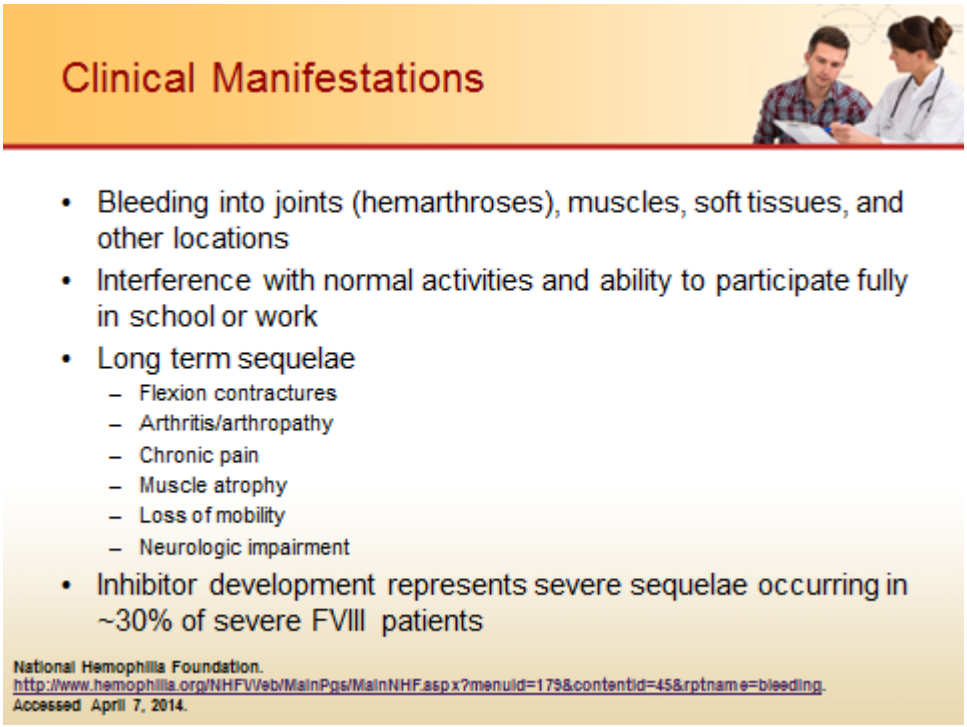
The majority (80-85%) of individuals with hemophilia are comprised of FVIII deficiency while hemophilia B constitutes 15-20% of the population. Hemophilia B is also known as Christmas disease. Clinically the two forms of hemophilia are quite similar.




**Slide 10: Detection/Diagnosis**

Detection and diagnosis may differ in those individuals where a known family history of hemophilia is present as compared to those where there is no family history. In those with a prior history of hemophilia there is an emphasis on carrier identification, most accurately performed through mutational analysis. In women of child bearing age, pre-conception counseling affords an opportunity to educate these women on optimal care practices for both them and a potentially affected fetus, including fetal sexing, prenatal diagnosis, and delivery. Testing of at-risk male infants is optimally performed at birth via cord blood testing – this requires coordination between the Hemophilia Treatment Center, or HTC, patient, and obstetrician. Again, female carriers may have factor levels in the mild deficiency range requiring specific hemostatic interventions at delivery or during the post-partum period.

In individuals without a prior history of hemophilia, the diagnosis of an affected individual most often occurs due to abnormal bleeding at birth or during the post-natal period. Bleeding due to circumcision occurs in approximately 50% of patients with severe disease. Bleeding with injections or interventions may also occur. The most catastrophic bleeding in newborns is intracranial hemorrhage, occurring in up to 4% of the affected population; importantly this issue may be higher in those without a family history due to lack of awareness of the potential diagnosis and how bleeding may be impacted by delivery. Infants and toddlers may present with abnormal bruising or joint bleeds as they become mobile.




**Slide 11: Clinical Manifestations**

Characteristic bleeding events that occur in patients with hemophilia include joint, deep tissue, or muscle bleeds. Other sites can be involved including the central nervous system, the gastrointestinal tract, and other deep tissues. Bleeding events that occur into joints are termed hemarthroses.

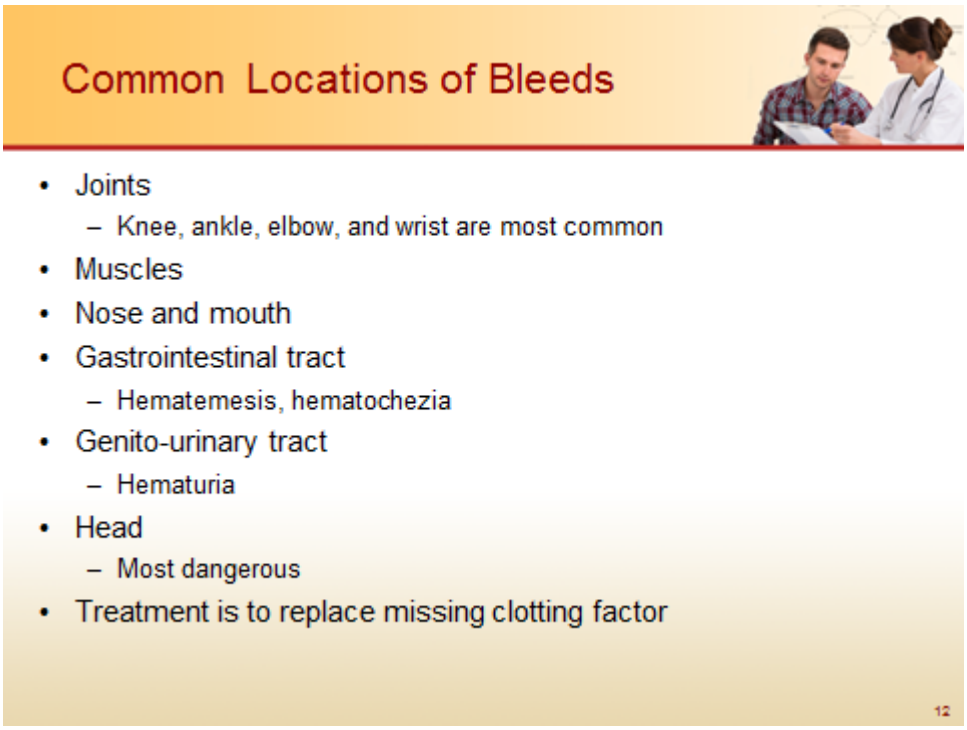
Both acute and repeated bleeds impact an individual's ability to participate in normal activities including school, sports, play, or work. Family functioning can also be affected. Parents of children with chronic diseases are at increased risk of loss of time from work. In addition,

unaffected siblings may have their psychosocial functioning impacted. Children with hemophilia are at-risk of being overprotected with resultant impact on independence and psychosocial functioning.

Repetitive bleeding into joints leads to joint disease that may progress to end stage arthropathy, which is often associated with interference with function and disability. This level of joint disease often leads to chronic pain and ambulatory challenges and negatively impacts an individual's quality of life by interfering with every day activities and ability to work and/or perform in school. For example, a patient with severe joint disease in their knee or ankle may find it difficult to stand for long periods of time or maneuver up and down stairs. This in turn leads to restrictions in the types of work and activities that individual can perform.

Ultimately, the ability of a person with hemophilia with significant joint disease to find their place in the work force is diminished. Therefore, the total societal effect must be considered and include individual productivity, use of public programs, and ability to become an active functioning member of the work force. It is in the best interest of the individual and society to have patients who are most able to achieve optimal individual outcomes.

Another important consequence of hemophilia is the development of an inhibitory antibody, termed an inhibitor. These specific sequelae are discussed later in more depth. However, the prevalence of inhibitor development is more common in FVIII deficiency or hemophilia A where it occurs in approximately 20-30% of the severely affected population. Inhibitors are uncommon in hemophilia B, even in severe disease, with a prevalence rate of about 1-4%.



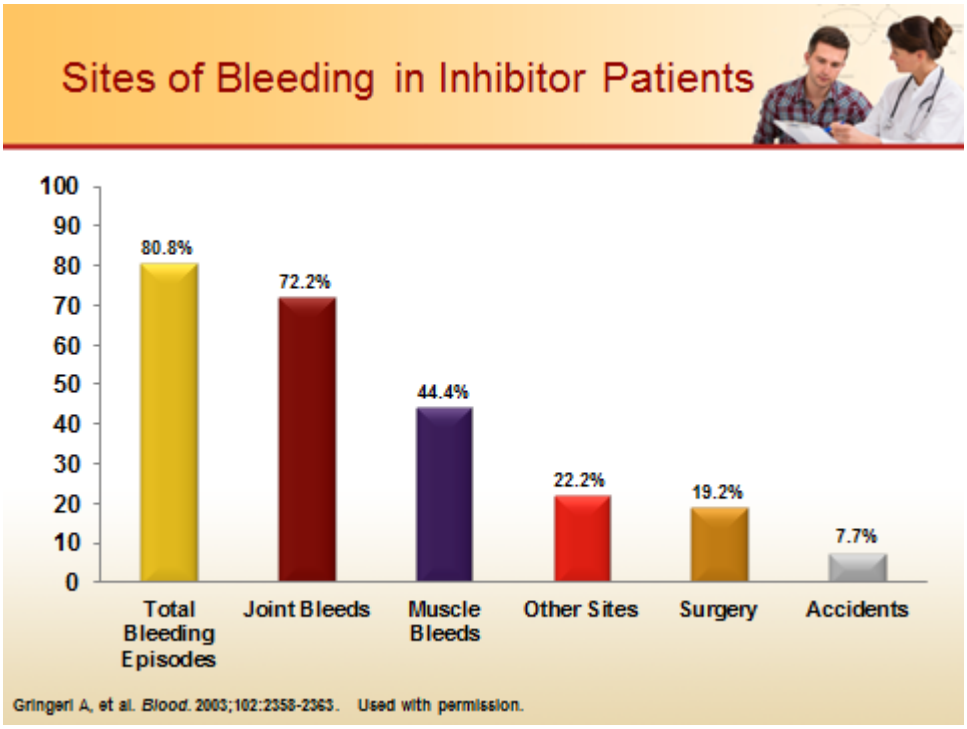

**Slide 12: Common Locations of Bleeds**

The potential for acute and long term consequences of bleeding events depends on the location and severity of the bleed. Certain locations are considered "critical" with the potential for a bleeding episode to become life- or limb-threatening. For example, a small amount of bleeding into the central nervous system can result in significant sequelae. Due to this, pregnant females who are known carriers have established delivery plans to protect the potentially affected infant from birth injury and central nervous system hemorrhage.

The most common area of bleeding in hemophilia is the joints. When blood leaks into the joint, it has a small confined space in which it accumulates. Accumulated blood stretches the capsule, which is highly innervated and results in significant pain and reduced range of motion. In addition, blood contains substances that cause inflammation. An inflammatory reaction in the joint contributes to acute and chronic pain and development of joint disease.

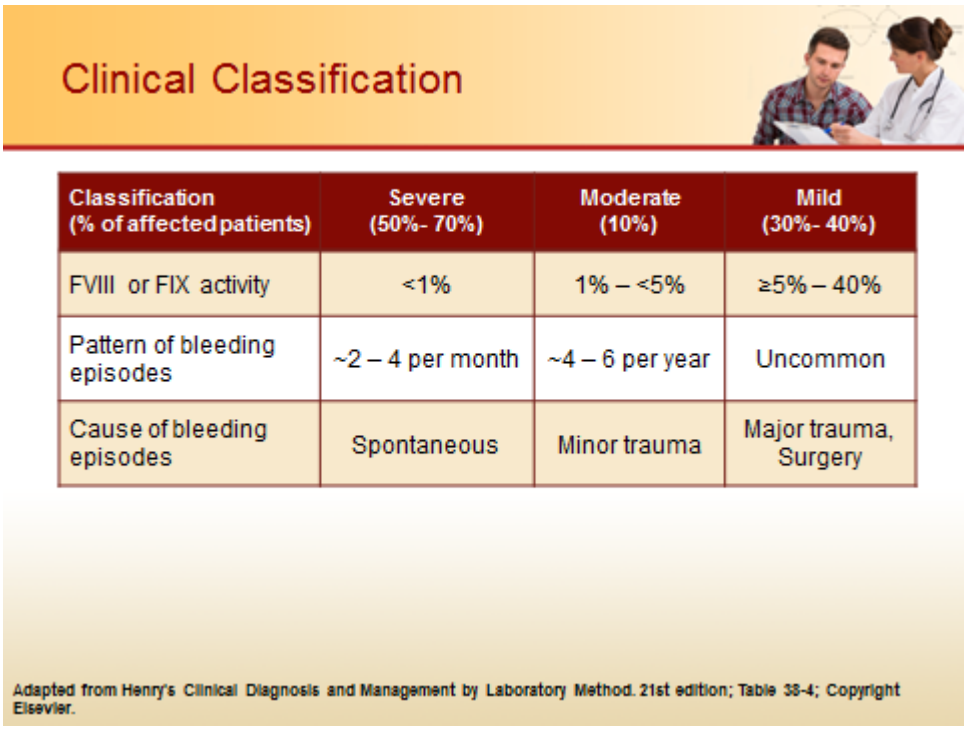
Other common sites of bleeding include the muscles, nose and oral cavity, the gastrointestinal tract as well as other areas.

Today, safe, effective treatments are available including genetically engineered replacement products that minimize the risk of blood-borne viral transmission. These products are utilized to replace the missing or deficient clotting factor to a hemostatic level for bleeding episodes. Repeated infusion may be required based upon the severity of disease, and the site and extent of the bleeding episode.




**Slide 13: Sites of Bleeding in Inhibitor Patients**

A report by Dr. Gringeri in the journal *Blood* in 2003 demonstrated that approximately 70% of all bleeding episodes experienced by hemophilia patients occurred in the joints, 44% in the muscles, 19% related to surgery, and almost 8% to accidents. Twenty-two percent of bleeds occurred in a variety of other areas as previously mentioned.



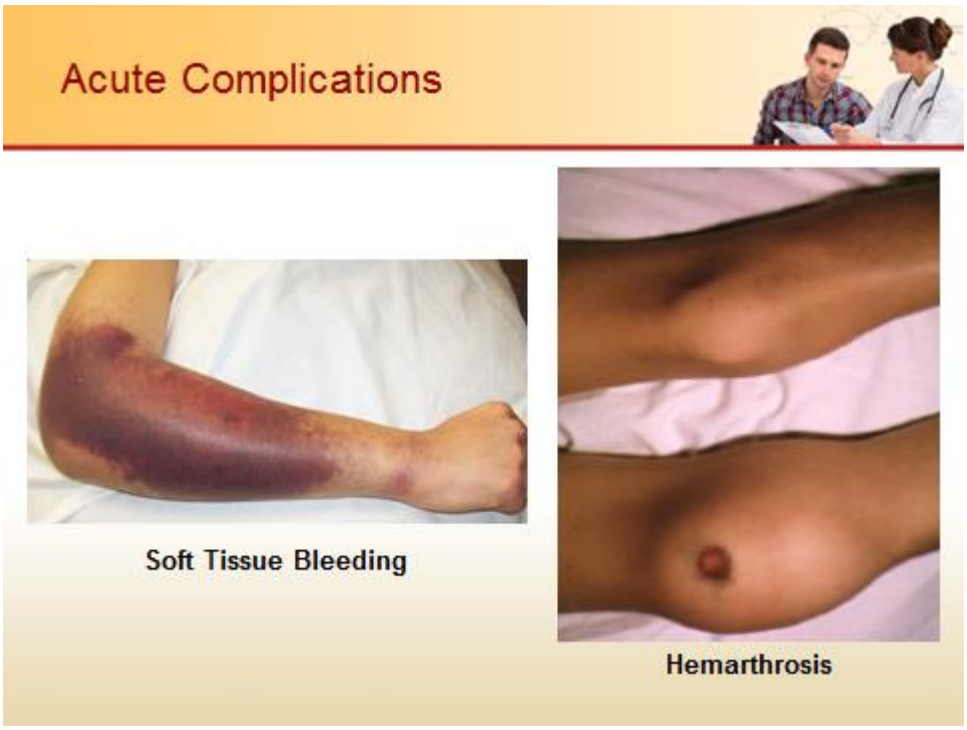

**Slide 14: Clinical Classification**

Hemophilia is divided into three categories based on the level of the deficient clotting factor detectable in the patient's blood. We divide patients into severe, with a clotting factor level of <1%; moderate, with a clotting factor level of 1% to <5%; and mild with a clotting factor level of 5% to 40%. A patient's clinical history often allows the hematologist to place them into one of these categories based upon the frequency and types of bleeding experienced.

Patients with severe hemophilia bleed approximately two to four times monthly and their bleeding episodes are often characterized as spontaneous. Spontaneous bleeding is due to the normal stress of everyday activity that precipitates micro-bleeding progressing in patients with hemophilia to clinically evident hemorrhagic episodes.

In moderate deficiency states, patients experience approximately four to six bleeding episodes yearly, often in association with minor injury.

Patients with mild deficiency bleed infrequently and usually only in association with injury, trauma, intervention, or surgery.




**Slide 15: Acute Complications**

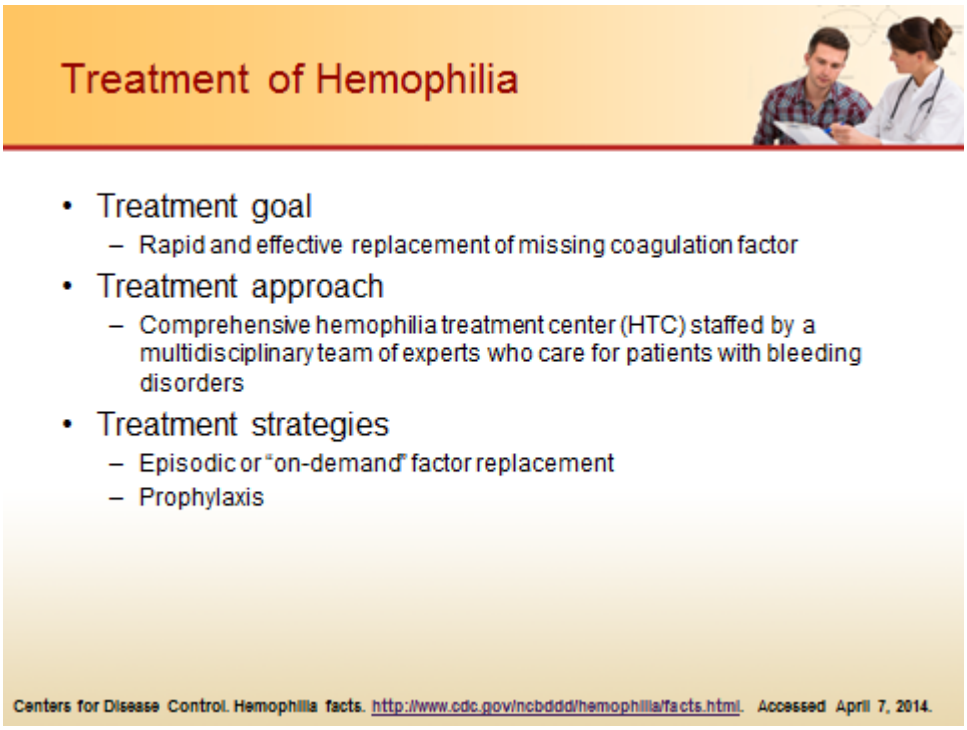
This slide demonstrates a visual representation of a significant soft tissue bleed and hemarthrosis. Repeated bleeding within the joints can initially lead to a condition known as synovitis. Following an intra-articular bleed, the breakdown of erythrocytes results in the deposition of cytoplasmic iron into the synovium, the membrane that lines the joint, and chondrocytes of the articular cartilage. Recurrent intra-articular bleeding triggers inflammation of the synovium leading to synovial hypertrophy. A hypertrophied synovium is more easily injured and likely to bleed. This initiates a vicious cycle of bleeding, chronic synovitis, and re-bleeding. As synovitis develops, the synovium becomes clinically palpable and the joint may remain permanently swollen even in the absence of pain. Inflammation of the synovium ultimately destroys cartilage and bone as it is associated with elevated concentrations of hydrolytic enzymes in the synovial fluid. Pain and arthritis develop.

Treating these bleeds before they advance to this stage is an important goal of HTC care providers.


**Slide 16: Long-Term Complications**

Eventually the patient develops hemophilic arthropathy as demonstrated here. The synovitis has resulted in cartilage degeneration, bone erosion, and advanced arthropathy with stiffness, chronic pain, and limited range of motion. In the most severe cases, bones may fuse resulting in a completely non-functional joint. In addition, muscle wasting occurs. Other associated conditions often include osteopenia, decreased ability to perform activities of daily living and participate in gainful employment, and a decreased quality of life. Late-stage hemophilic arthropathy may require orthopedic surgery to alleviate pain and restore function. A variety of orthopedic procedures may be utilized and are dependent upon the desired goal, age of the patient, presence of osteopenia, specific affected joint, and stage of joint disease. The ability to achieve normal function depends upon a variety of factors including muscle wasting and contracture, compliance with the prescribed post-operative physical therapy program, and the current capabilities of prosthetic devices.

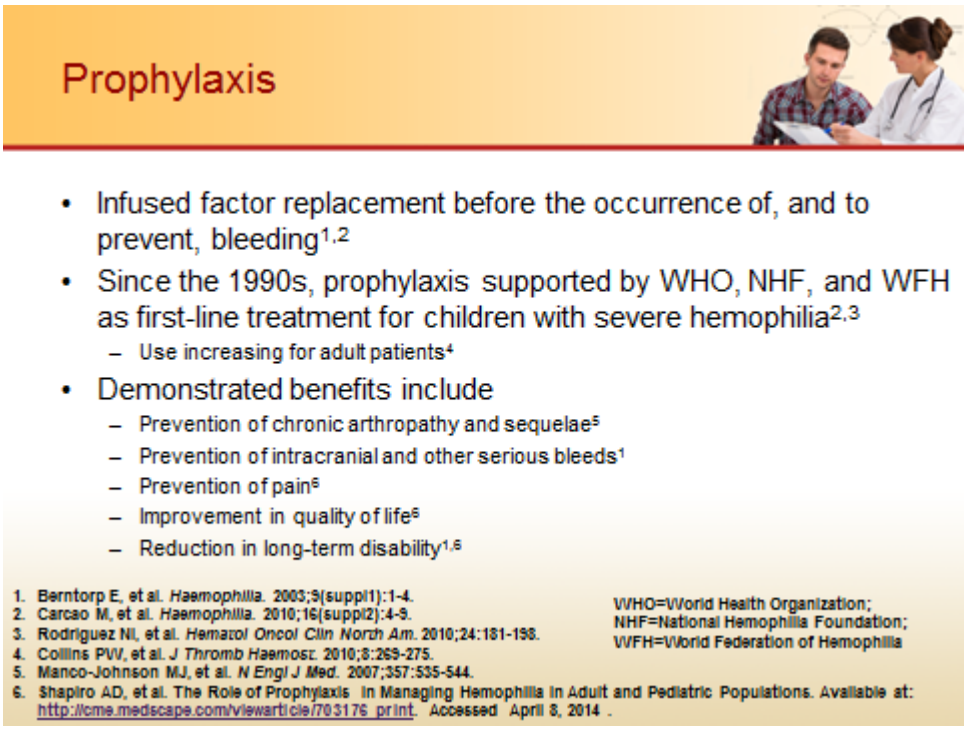
The picture on the right depicts a Volkmann's contracture due to a compartment syndrome with resultant nerve damage.




**Slide 17: Treatment of Hemophilia**

The goal of hemophilia treatment is rapid and effective replacement of the missing coagulation factor using plasma derived or genetically engineered replacement products. The treatment of bleeding episodes, once experienced, is defined as "on-demand" or "episodic" treatment, while treatment of patients with infusions to prevent bleeding episodes is defined as "prophylaxis".

Hemophilia is a rare disorder and those who are affected are best managed through highly trained specialists located within the national federal network of Hemophilia Treatment Centers, or HTCs. HTCs are also staffed by a multidisciplinary team expert in these disorders. Outcomes for patients with hemophilia have been demonstrated by the Centers for Disease Control and Prevention, or CDC, to be significantly improved when patients are cared for within the HTC network.

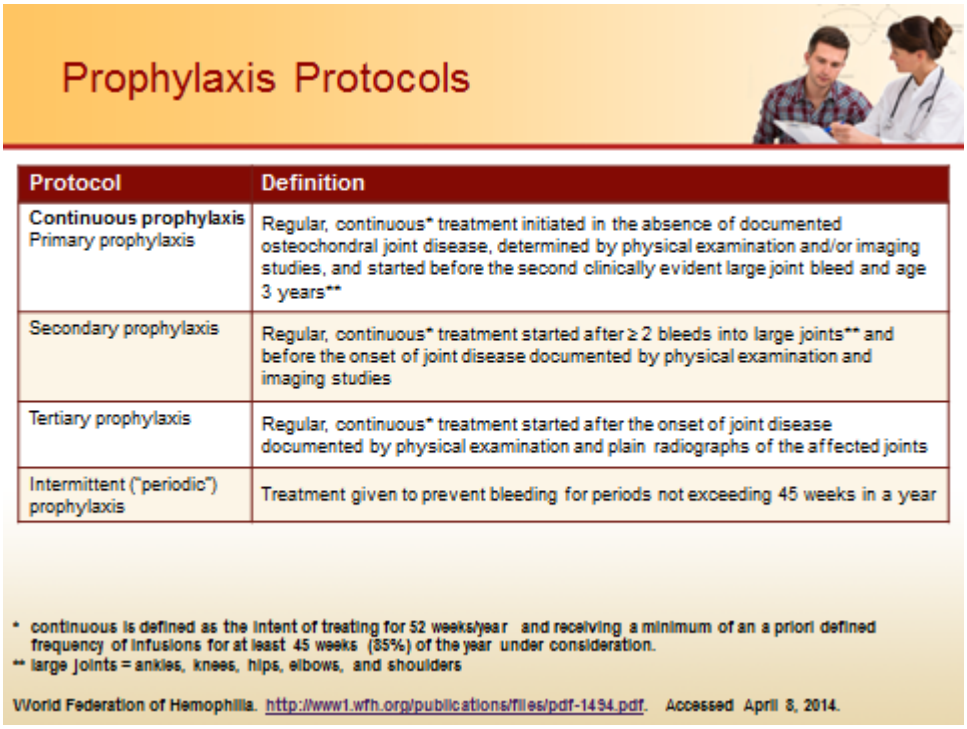



**Slide 18: Prophylaxis**

Presently available data demonstrate that bleed prevention from an early age enables the affected individual to avoid or reduce the clinical impact of musculoskeletal impairment from hemophilic arthropathy. In addition, there are associated improvements in non-physical bleeding consequences including improved psychosocial development and quality of life. Psychosocial development is enhanced through the use of prophylaxis by allowing patients to participate in physical activities, improving their general health, their sense of well-being, and their interaction with peers. Additionally, prophylaxis improves school attendance and decreases absenteeism, allowing patients the opportunity to achieve their academic potential.

Patients treated with prophylaxis are more able to actively participate in society and have better employment opportunities throughout their lifespan. This improves their overall quality of life. When evaluating prophylaxis, a lifetime perspective is required to assess treatment related long-term outcomes and cost effectiveness. Joint outcome, disability, labor force participation, health care cost for hospitalization, rehabilitation, physiotherapy, orthopedic interventions, and overall quality of life must be considered when assessing outcomes in hemophilia.

Prophylaxis in the appropriate patient population is the recommended treatment regimen and is supported by the World Health Organization, National Hemophilia Foundation, and World Federation of Hemophilia.




**Slide 19: Prophylaxis Protocols**

Prophylaxis is defined as the administration of clotting factor concentrate in the absence of bleeding to prevent bleeding episodes. Prophylaxis is further subdivided.

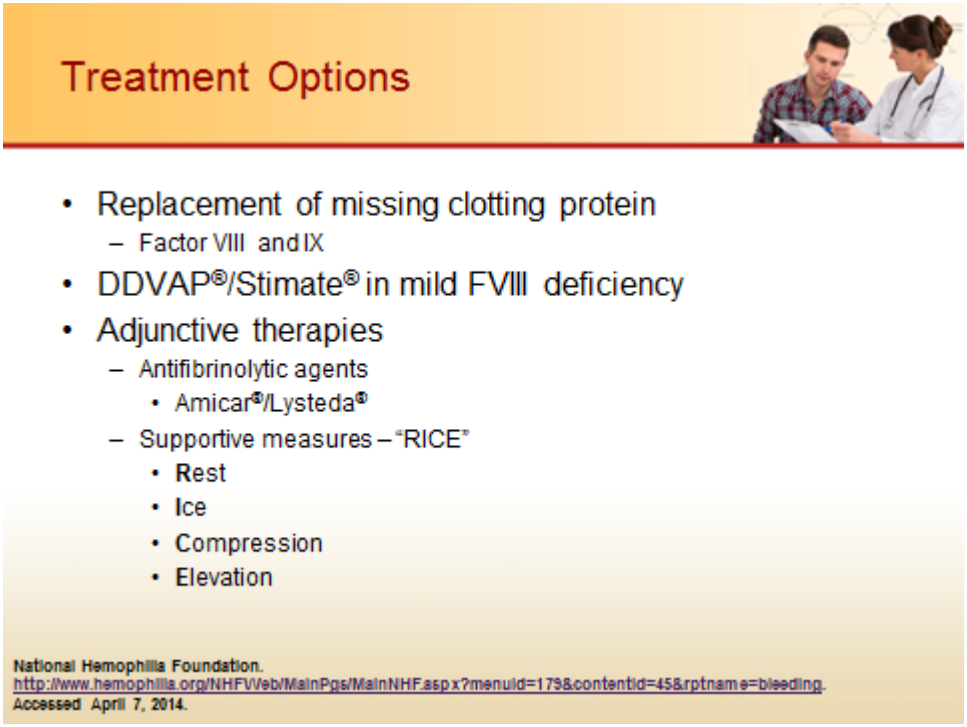
Primary prophylaxis is defined as continuous regular treatment initiated in the absence of documented osteochondral joint disease, determined by physical examination and/or imaging studies, and started before the second clinically evident large joint bleed and age 3 years. Continuous is defined as the intent of treating for 52 weeks per year and with patients receiving a minimum of an a priori defined frequency of infusions for at least 45 weeks, or 85%, of the year under consideration.

Secondary prophylaxis is regular, continuous treatment started after two or more bleeds into large joints and before the onset of joint disease documented by physical examination and imaging studies.

Tertiary prophylaxis is regular, continuous treatment started after the onset of joint disease documented by physical examination and plain radiographs of the affected joints.

Intermittent or periodic prophylaxis is treatment given to prevent bleeding for periods not exceeding 45 weeks in a year.

Large joints are defined as ankles, knees, hips, elbows, and shoulders.

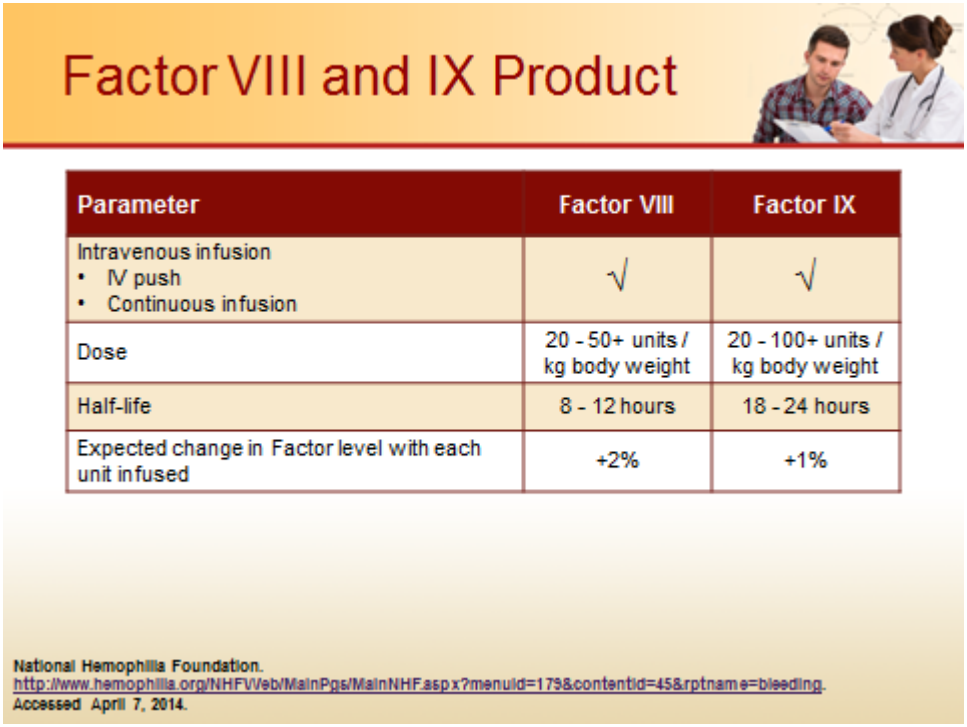



**Slide 20: Treatment Options**

The mainstay of therapy for patients with hemophilia without inhibitors is replacement of the deficient clotting factor protein to a level that will achieve, and maintain, hemostasis required to either treat or prevent bleeding episodes.

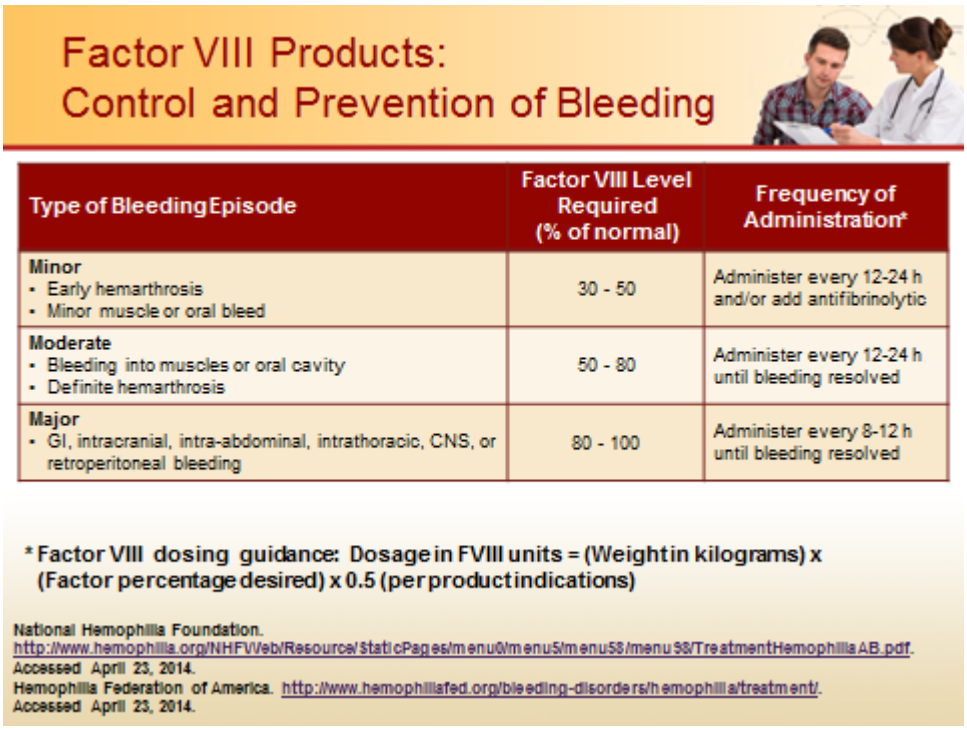
In addition, other agents and supportive care measures are utilized for treatment of hemophilia including DDAVP® and Stimate®. These are utilized in mild FVIII deficiency and for some forms of Von Willebrand Disease. Antifibrinolytic agents are useful adjunctive therapies, especially for procedures or bleeding events involving mucous membranes. These agents prevent

clot lysis and allow adequate healing to occur. Other supportive measures commonly utilized for bleeding episodes include ***R***est, ***I***ce, ***C***ompression, and ***E***levation, termed ***RICE***.




**Slide 21: Factor VIII and IX Product**

Clotting factor replacement therapies are administered intravenously most commonly by IV push but at times by continuous infusion in the hospital. Dosing is based upon the patient's weight, the desired level, and the volume of distribution of the infused product. Each clotting factor has a half-life that may necessitate repeated dosing to treat or prevent bleeding episodes. In general, for every unit per kilogram infused of FVIII an increase of 2% is anticipated; in FIX deficiency an increase of 1% is anticipated. Pharmacokinetics, including anticipated recovery and half-life, vary based upon age and may vary individually.



## Factor VIII Products: Control and Prevention of Bleeding

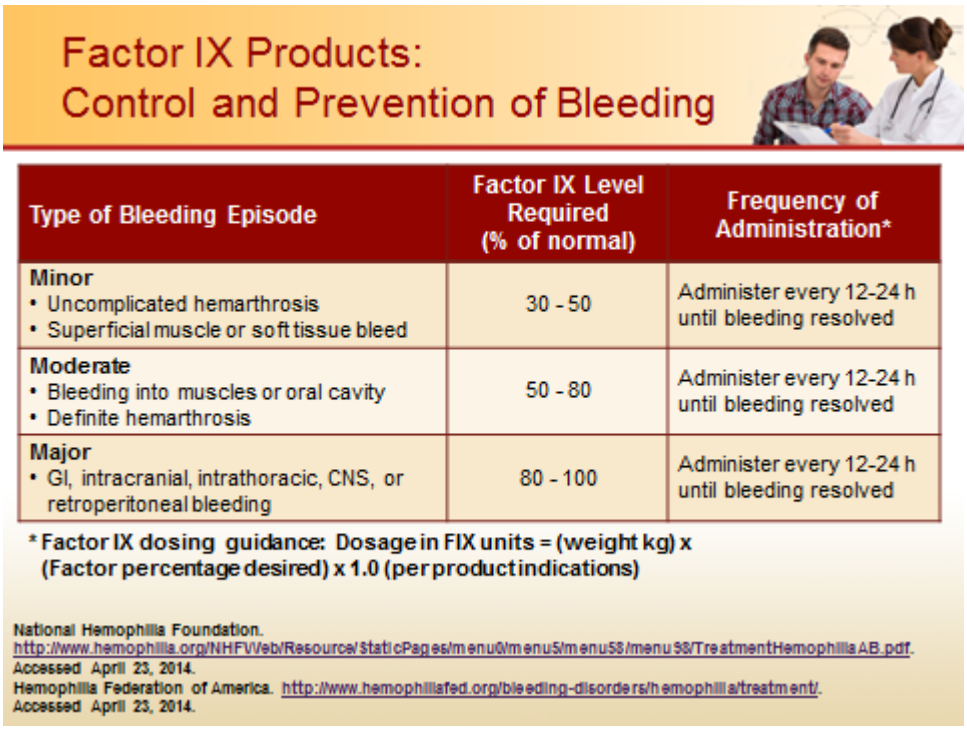
| Type of Bleeding Episode | Factor VIII Level Required (% of normal) | Frequency of Administration* |
|---|---|---|
| **Minor**<br>• Early hemarthrosis<br>• Minor muscle or oral bleed | 30 - 50 | Administer every 12-24 h and/or add antifibrinolytic |
| **Moderate**<br>• Bleeding into muscles or oral cavity<br>• Definite hemarthrosis | 50 - 80 | Administer every 12-24 h until bleeding resolved |
| **Major**<br>• GI, intracranial, intra-abdominal, intrathoracic, CNS, or retroperitoneal bleeding | 80 - 100 | Administer every 8-12 h until bleeding resolved |

* Factor VIII dosing guidance: Dosage in FVIII units = (Weight in kilograms) x (Factor percentage desired) x 0.5 (per product indications)

National Hemophilia Foundation. http://www.hemophilia.org/NHFWeb/Resource/StaticPages/menu0/menu5/menu58/menu98/TreatmentHemophiliaAB.pdf. Accessed April 23, 2014.
Hemophilia Federation of America. http://www.hemophiliafed.org/bleeding-disorders/hemophilia/treatment/. Accessed April 23, 2014.

**Slide 22: Factor VIII Products: Control and Prevention of Bleeding**

Coagulation factor concentrates are utilized to replace the deficient clotting factor to a hemostatic level required to treat a particular bleeding episode. This slide demonstrates general guidelines for the treatment of hemophilia A. Although these represent good initial general guidelines, the treatment of a specific bleeding episode requires knowledge of the patient's therapeutic response, their individual pharmacokinetics, their inhibitor status, and the severity of the bleed to determine the appropriate target level and duration of therapy. The treatment of hemophilia is complex and requires an expert with experience in these disorders.



## Factor IX Products: Control and Prevention of Bleeding

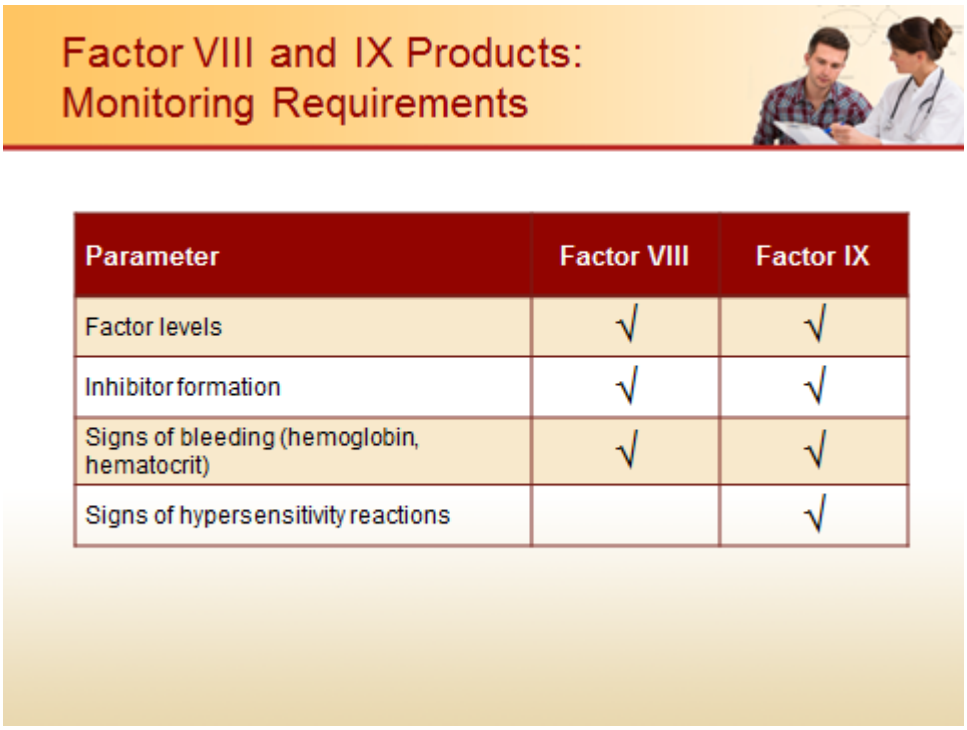
| Type of Bleeding Episode | Factor IX Level Required (% of normal) | Frequency of Administration* |
|---|---|---|
| **Minor**<br>• Uncomplicated hemarthrosis<br>• Superficial muscle or soft tissue bleed | 30 - 50 | Administer every 12-24 h until bleeding resolved |
| **Moderate**<br>• Bleeding into muscles or oral cavity<br>• Definite hemarthrosis | 50 - 80 | Administer every 12-24 h until bleeding resolved |
| **Major**<br>• GI, intracranial, intrathoracic, CNS, or retroperitoneal bleeding | 80 - 100 | Administer every 12-24 h until bleeding resolved |

*** Factor IX dosing guidance: Dosage in FIX units = (weight kg) x (Factor percentage desired) x 1.0 (per product indications)**

National Hemophilia Foundation. http://www.hemophilia.org/NHFWeb/Resource/StaticPages/menu0/menu5/menu58/menu98/TreatmentHemophiliaAB.pdf. Accessed April 23, 2014.
Hemophilia Federation of America. http://www.hemophiliafed.org/bleeding-disorders/hemophilia/treatment/. Accessed April 23, 2014.

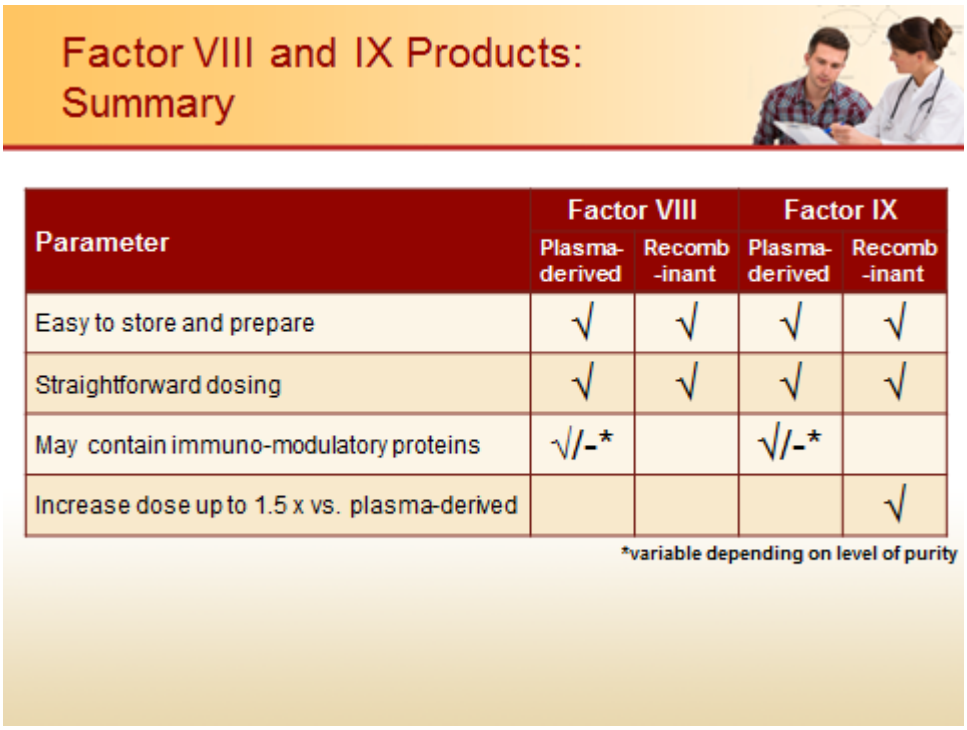
**Slide 23: Factor IX Products: Control and Prevention of Bleeding**

This slide shows therapy in hemophilia B or FIX deficiency. Although similar in general guidelines to FVIII deficiency, there are clearly differences in the number of units required and the expected half-life of infused products. Again, the treatment of a specific bleeding episode requires knowledge of the patient's therapeutic response, their individual pharmacokinetics, their inhibitor status, and the severity of the bleed to determine the appropriate target level and duration of therapy.




**Slide 24: Factor VIII and IX Products: Monitoring Requirements**

Monitoring of replacement therapy may be required in a variety of clinical situations and patient circumstances. Evaluation of other laboratory parameters such as hemoglobin or iron status should be considered based on site and extent of bleeding. In addition to obtaining specific factor assays after administration of replacement therapy, inhibitor formation must always be kept in mind and monitored for on a regular basis or as required by clinical response. Although rare, hypersensitivity reactions may occur with administration of replacement therapy – these are more commonly associated with inhibitor development in FIX deficiency. Hypersensitivity reactions should always prompt an evaluation for development of an inhibitor and should be reported as adverse events.

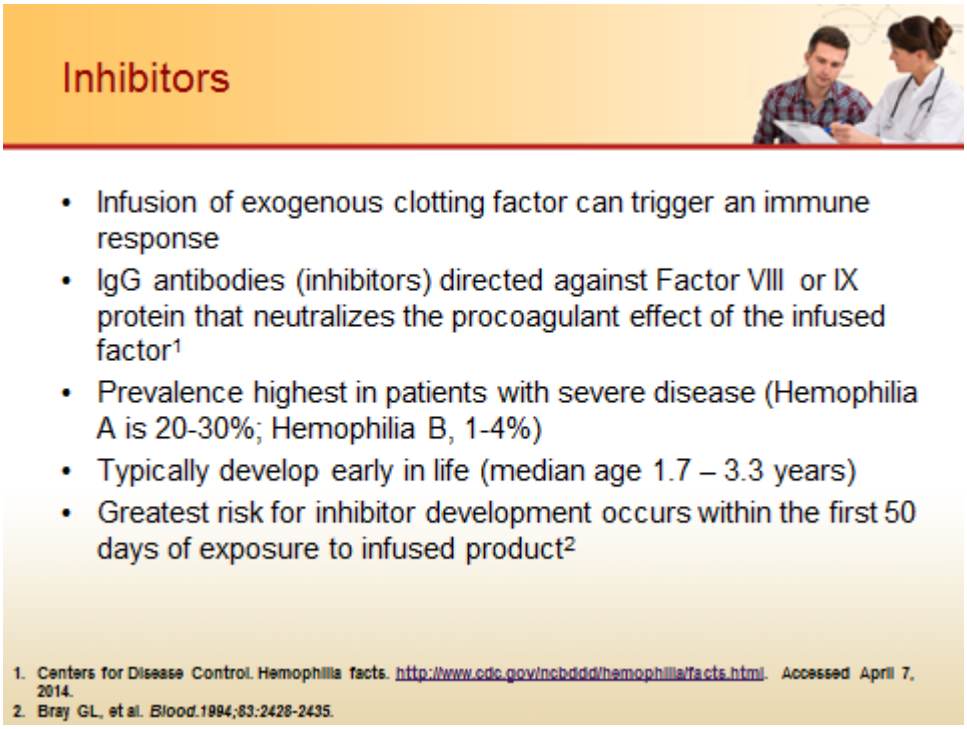



**Slide 25: Factor VIII and IX Products: Summary**

Presently, a variety of clotting factor replacement options exist for treatment of hemophilia. These replacement options may be divided into two major product categories: plasma derived, meaning manufactured from blood donors; and those that are recombinant or manufactured through genetic engineering. Currently available replacement therapies are relatively easy to store and prepare for administration. In general, dosing is fairly straightforward although knowledge of an individual's response and pharmacokinetics is important to guide treatment. Some plasma derived products may contain immune-modulating proteins and this should be considered especially in individuals with viral comorbidities. Standard half-life recombinant FIX concentrates have demonstrated an increased volume of distribution as compared to their plasma derived counterparts and this must be reflected when calculating doses.

It is important to note that these products are not licensed as generic, nor should they be treated as such. Further product sub-categorization for plasma derived products is based upon purity, including intermediate or high purity, which is dependent upon the number of other plasma proteins present in the concentrate.

Product choice for each patient is a crucial decision for both care providers and patients. The hemophilia population was affected during the late 1970s through the 1980s with a variety of viral blood borne infections including hepatitis B, hepatitis C, and HIV. Therefore, the risks and benefits for each product should be carefully discussed and weighed before a product is chosen. This decision is made by patients in conjunction with their care providers and should not be dictated by agencies whose primary concern is cost.

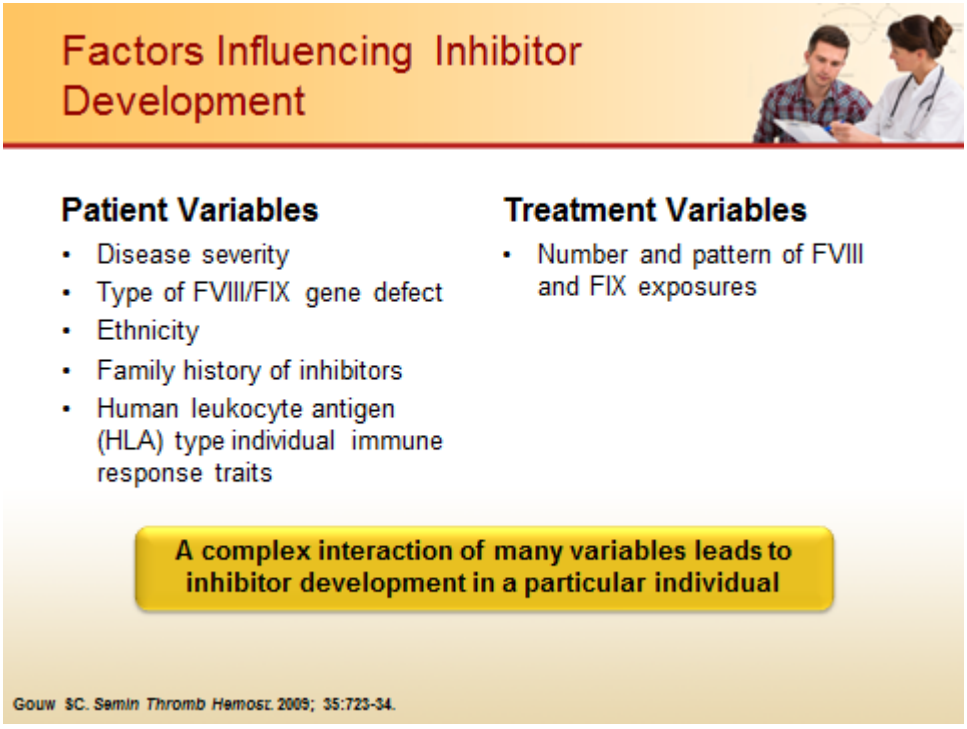



**Slide 26: Inhibitors**

Inhibitors are antibodies that develop after normal exogenous replacement factor exposure, either FVIII or FIX. The majority of inhibitory antibodies are immunoglobulin G. Most inhibitors develop early in life with a median patient age of 1.7 to 3.5 years of age. The highest risk for inhibitor development is within the first 50 exposure days. The median number of exposure days for inhibitor development documented in clinical trials of recombinant products is approximately nine. At 100 days, the risk of inhibitor development is very low, although not nonexistent. The prevalence of inhibitor development is more common in FVIII deficiency where it occurs in approximately 20-30% of the severely affected population. Inhibitors are uncommon in hemophilia B, even in severe disease, with a prevalence rate of about 1-4%.

Inhibitors are categorized into three main groups; high-responding, low-responding, and transient. The level of inhibitors is measured in Bethesda units. Patients with high-responding inhibitors (≥5 Bethesda units at any time) represent 30-50% of those with inhibitors, while low-responding inhibitors (<5 Bethesda units despite repeated exposure) comprise approximately 30%, and transient inhibitors <15%. Regardless of type, an inhibitor can affect therapy and negatively impact outcomes. Patients with high-responding inhibitors are the most vulnerable population.

Inhibitors neutralize the activity of the infused product making standard replacement therapy often ineffective and result in difficulty achieving hemostasis. Therefore, bleeding episodes in patients with inhibitors are prolonged and as a result, the morbidity they experience is increased. Alternative hemostatic therapies are often required.




**Slide 27: Factors Influencing Inhibitor Development**

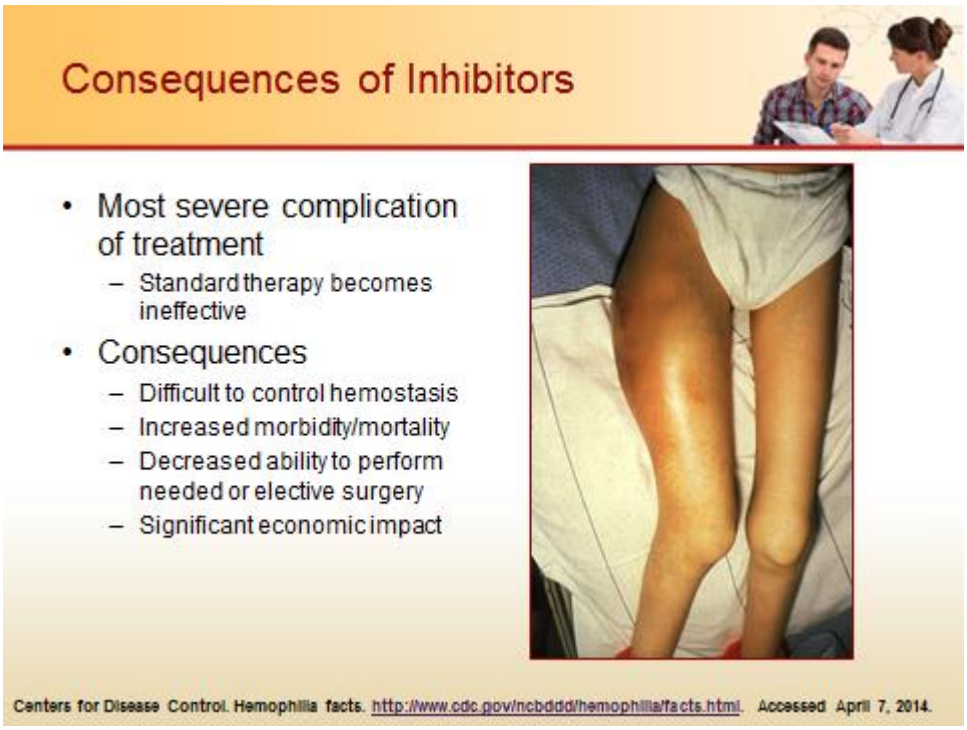
A variety of issues are known to impact inhibitor development including the severity of disease, with inhibitors occurring more frequently in those with severe as compared to moderate or mild disease; the type of genetic alteration causing the hemophilia has been shown to impact its rate of occurrence with those changes resulting in deletions or protein absence representing higher risk;

ethnicity is important as inhibitors are almost twice as common in individuals of color; a positive family history of inhibitors increases risk in an individual patient; and finally differences in human leukocyte antigen (HLA) types and polymorphisms in individual immune response genes also impact inhibitor expression as reported in the genes coding[§] for *IL-1*, *IL-2*, *IL-10*, *TNFA*, *TGFβ*, and *CTLA-4*. The majority of genetic markers identified to date are known to be involved in various B and/or T cell-mediated mechanisms and several of the genes code for molecules involved in intracellular signaling pathways, many of which may interact with one another.

In addition, environmental factors exist that impact inhibitor expression including the number and pattern of exposures especially in relationship to the presence of what the immune system sees as danger signals.

Based on the findings to date, it is clear that the pathophysiologic immune process is complex and impacted by both genetic and non-genetic variables.

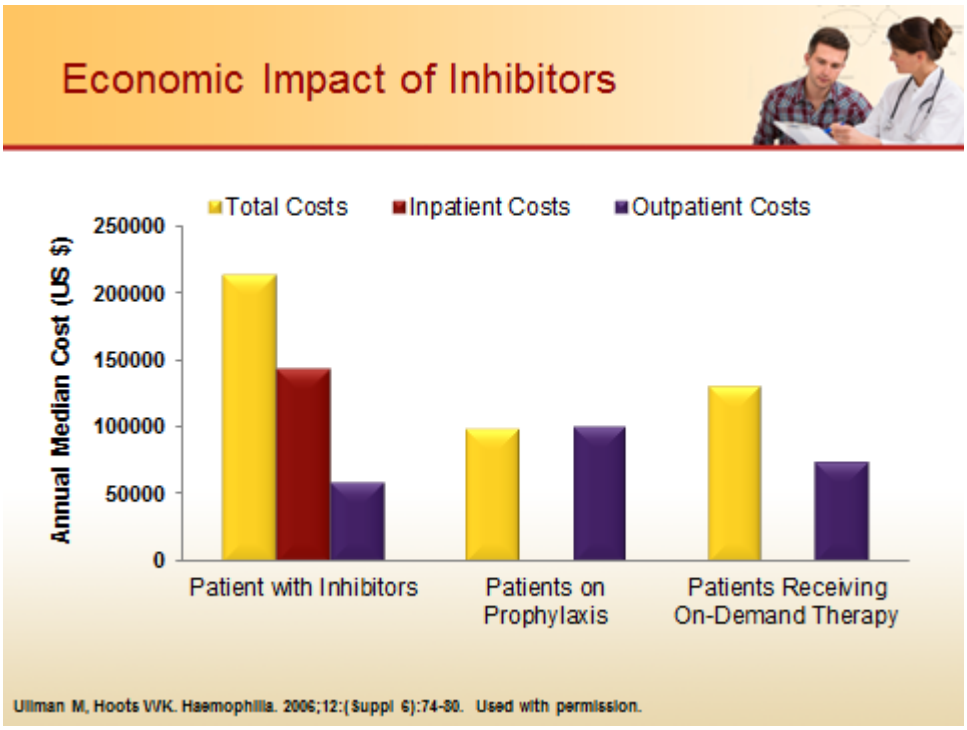
[§] IL: Interleukin; TNFA: Tissue Necrosis Factor Alpha; TGFβ: Transforming Growth Factor Beta; CTLA-4: Cytotoxic T-Lymphocyte Antigen 4




**Slide 28: Consequences of Inhibitors**

The consequence of inhibitor development is the failure of normal replacement therapy and need for use of alternative hemostatic agents. These alternative agents are called “bypassing therapies” and often achieve cessation of bleeding. Patients with inhibitors have the highest rate of morbidity and mortality within the hemophilia population. There is a decreased ability to perform needed or elected surgery in these patients because of the difficulty achieving consistent and reliable hemostasis. The cost of care for patients with inhibitors is far greater than for hemophilia patients without inhibitors. Patients with inhibitors may require very frequent therapy for months or years depending upon the regimen utilized; therapy administered to eradicate the inhibitor is called immune tolerance induction.

Interestingly, although inhibitors in the FIX deficient population are far less common as compared to the FVIII deficient population, they do present specific problems that pose an even greater risk of morbidity. These problems include the development of anaphylactic reactions in association with exposure to FIX protein and development of nephrosis with immune tolerance programs used to eradicate the inhibitor.



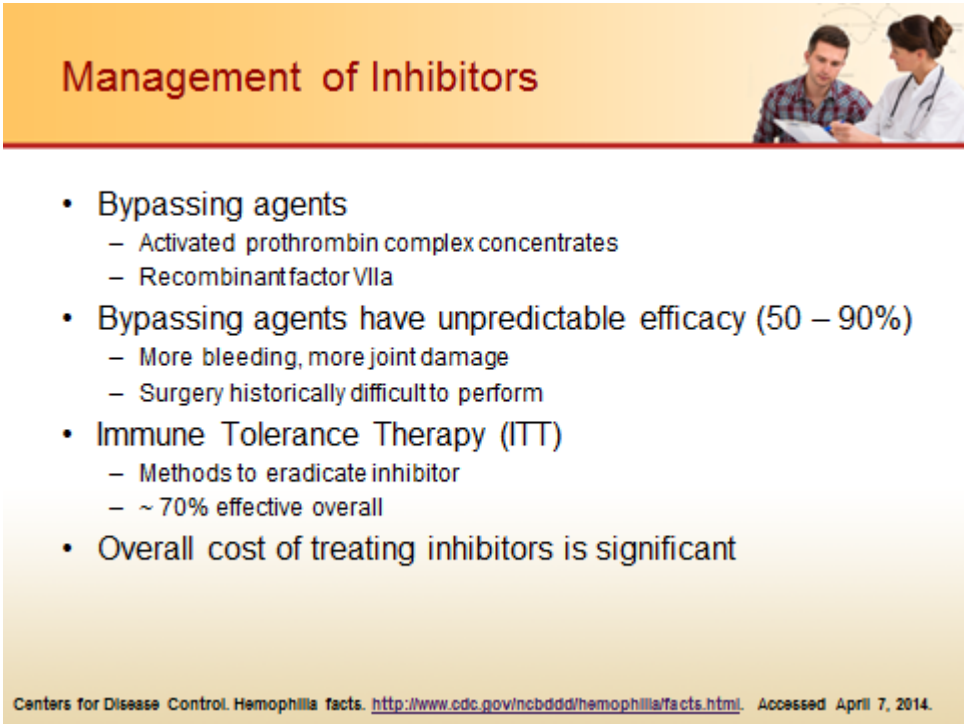

**Slide 29: Economic Impact of Inhibitors**

It is important to emphasize the financial burden that is associated with the development of inhibitors in hemophilia. Patients with inhibitors commonly represent cost outliers for both HTCs and their insurers. Patients with inhibitors have total costs that are comprised of the cost of bypassing agents, immune tolerance induction therapy regimen costs, inpatient cost due to hospitalization for severe or recalcitrant bleeds, or need for orthopedic interventions.

Overall, patients without inhibitors treated with prophylaxis have the majority of their financial burden comprised of cost of concentrate with little allocated towards hospitalization or other issues.

Patients treated with on-demand therapy have an increased percentage of their financial burden comprised of other costs beyond concentrate including rehabilitation, orthopedic interventions, intermittent hospitalizations, etc. It is interesting to note that the costs of patients utilizing on-demand therapy were higher in their population than those associated with the use of prophylaxis.

The cost of hemophilia-related care and the impact of unusually expensive, or outlier, patients on these costs cannot be underestimated. Specifically inhibitor patients exhibit the highest costs with wide variability. There is little debate that the health care costs of hemophilic patients with high-responding inhibitors are overall higher and more variable than those of non-inhibitor patients. A report by Ullman and Hoots compared the variation and range in health care expenditures among patients with inhibitors and those without, through data gathered during a 24-month period in 1995-1997 from a prospectively created cohort as part of a broader cost and utilization study conducted at a large HTC. The authors concluded that although the use of outpatient factor replacement products was not significantly greater or more expensive among inhibitor patients, their hospital-related costs greatly increased overall expenditures. Among their patient cohort, the overall costs associated with inhibitor patients were not only higher in absolute monetary terms, but also in terms of the variability.




**Slide 30: Management of Inhibitors**

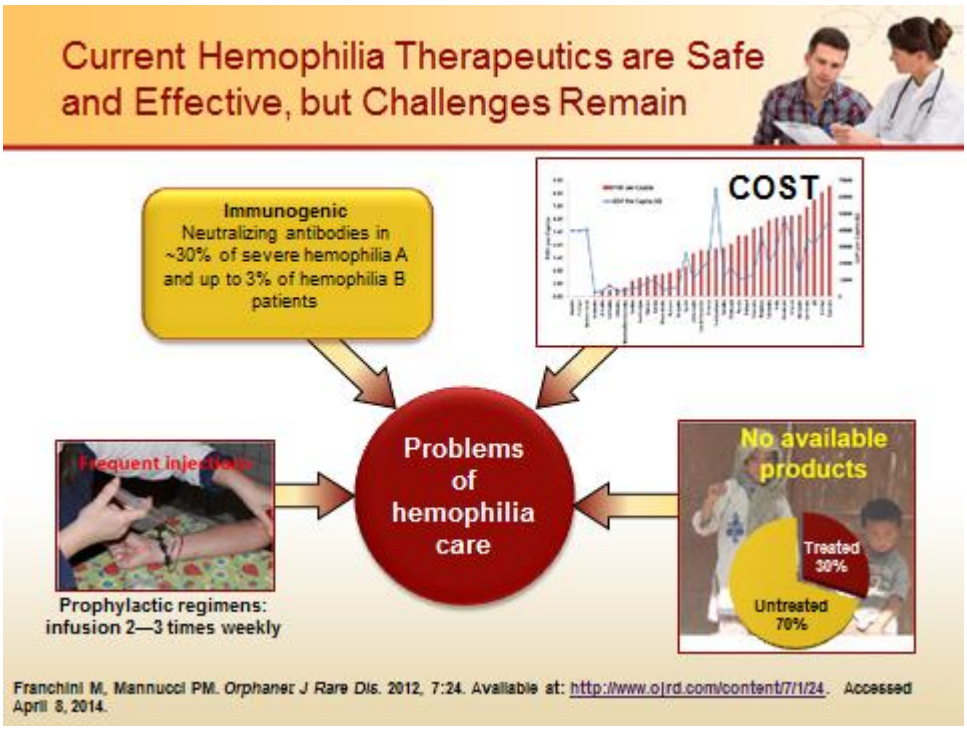
Bleeding episodes in patients with inhibitors are difficult to treat and treatment products and schemas are different as compared to their non-inhibitor patient counterparts. The majority of treatment utilized in patients with inhibitors is on-demand therapy. The products utilized are

termed bypassing agents, with the two presently available products including recombinant activated factor VIIa (rFVIIa, NovoSeven®) and activated prothrombin complex concentrate (aPCC, FEIBA®, a plasma derived product). Bypassing therapies achieve hemostasis through an alternate route. Although largely effective, the predictability of a response is not equal to standard replacement therapy utilized in patients without inhibitors. Not all patients respond reliably to either of the bypassing agents and therefore it is important to recognize that individual patient response is variable for each product and each bleeding episode. Bleeding episodes in the same patient may not respond to one specific agent uniformly. Choice in the use of bypassing products is required and treatment of bleeding events in inhibitor patients necessitates the expertise of skilled HTC care providers.

Prophylaxis in inhibitor patients has been performed with bypassing agents and has had some demonstrated success in suppression of bleeding events. There have been some recently published reports for both rFVIIa and aPCC with prophylaxis.

In addition, other inhibitor treatment modalities include methods to attempt to eradicate the inhibitor, termed immune tolerance induction regimens. Immune tolerance protocols may be difficult to accomplish, often take considerable time, and require significant consumption of expensive medical resources. Importantly, if the inhibitor is eradicated, the patient may then be able to utilize standard replacement therapy. These standard replacement therapies are easier to administer and achieve more reliable hemostasis as compared to bypassing products, making immune tolerance an important therapeutic option.

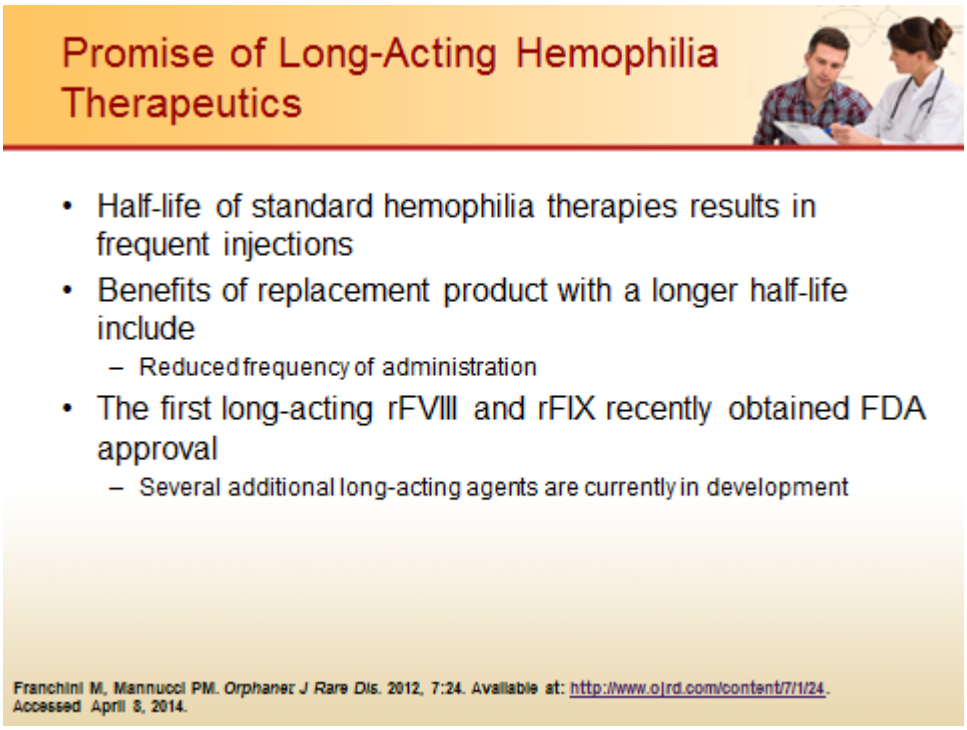
Again, there is significant financial burden associated with the development of inhibitors in hemophilia.




**Slide 31: Current Hemophilia Therapeutics are Safe and Effective, but Challenges Remain**

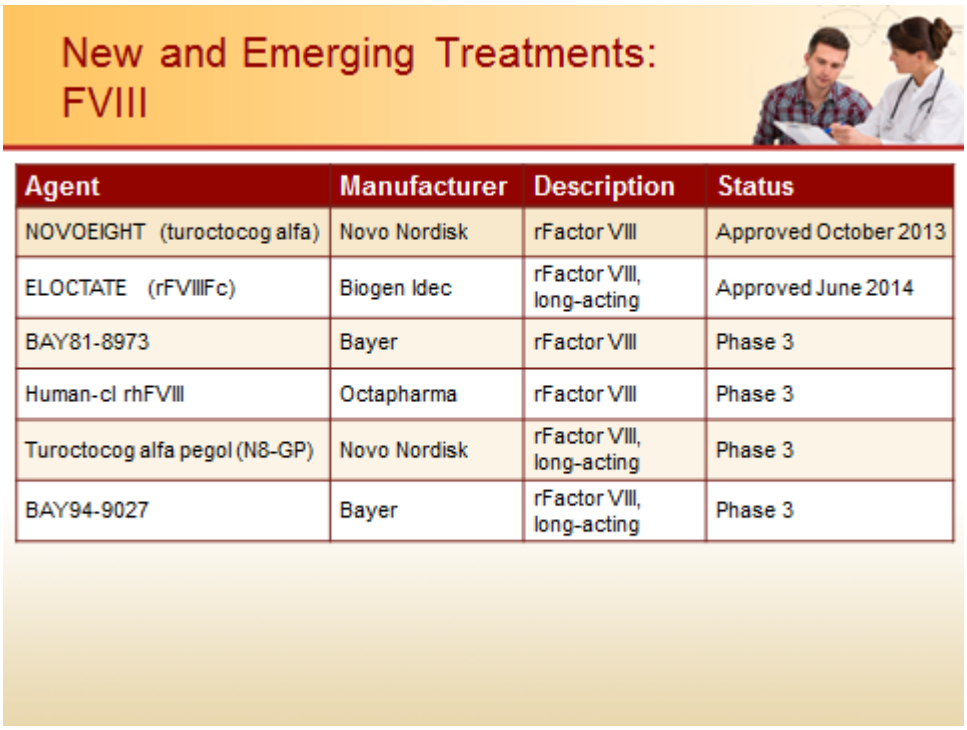
In summary, achieving optimal care and outcomes for the hemophilia patient population requires a balance with careful weighing of benefits, risks and costs. The cost of care for hemophilia is significant; HTCs can decrease the cost of care and help achieve optimal outcomes. Prophylaxis decreases joint disease and serious bleeding episodes and yields an increased ability to participate in normal activities and to perform academically. Therefore, prophylaxis may reduce the long-term cost of care while improving quality of life.

HTCs have been proven to be the disease specific expert in the management of this uncommon condition. Access to, and use of an HTC is required to manage this rare disorder. Disease management should only be performed through the HTC with coordinated support from health plans as needed. The use of restricted formularies at pharmacy benefit managers (PBMs), and prior authorization for every dispensation can negatively impact care and affect outcomes.




**Slide 32: Promise of Long-Acting Hemophilia Therapeutics**

The half-life of most replacement therapies necessitates frequent injections, often a burden in the most vulnerable populations. There clearly exist benefits to products that might exhibit a longer half-life as compared to standard therapies including decreased frequency of administration – an especially important attribute to pediatric patients treated with prophylaxis. The first long acting recombinant factors VIII and IX recently obtained U.S. Food and Drug Administration (FDA) approval and several long-acting agents are currently in development.




| Agent | Manufacturer | Description | Status |
|---|---|---|---|
| NOVOEIGHT (turoctocog alfa) | Novo Nordisk | rFactor VIII | Approved October 2013 |
| ELOCTATE (rFVIIIFc) | Biogen Idec | rFactor VIII, long-acting | Approved June 2014 |
| BAY81-8973 | Bayer | rFactor VIII | Phase 3 |
| Human-cl rhFVIII | Octapharma | rFactor VIII | Phase 3 |
| Turoctocog alfa pegol (N8-GP) | Novo Nordisk | rFactor VIII, long-acting | Phase 3 |
| BAY94-9027 | Bayer | rFactor VIII, long-acting | Phase 3 |

**Slide 33: New and Emerging Treatments: FVIII**

The past few years have witnessed the development of many new replacement products for the treatment of hemophilia. Some of these new products for treatment of FVIII deficiency recently approved or currently in clinical trials are shown on this slide. A new rFVIII product, NovoEight®, was approved in October 2013, and has a pharmacokinetic profile similar to another serum-free rFVIII preparation, Advate®. The first long acting rFVIII, ELOCTATE™, Fc Fusion Protein, was approved in June 2014 and has a 1.5 fold increase in half-life as compared to other rFVIII concentrates.


| Agent | Manufacturer | Description | Status |
|---|---|---|---|
| Rixubis | Baxter | rFactor IX | Approved June 2013 |
| ALPROLIX (rFIXFc) | Biogen Idec/Sobi | rFactor IX, long-acting | Approved March 2014 |
| IB1001 | Cangene | rFactor IX | Phase 3 |
| C255238539 | Novo Nordisk | rFactor IX | Phase 3 |
| rIX-FP | CSL Behring | rFactor IX, long-acting | Phase 3 |
| NN79 (N9-GP) | Novo Nordisk | rFactor IX | Phase 3 |

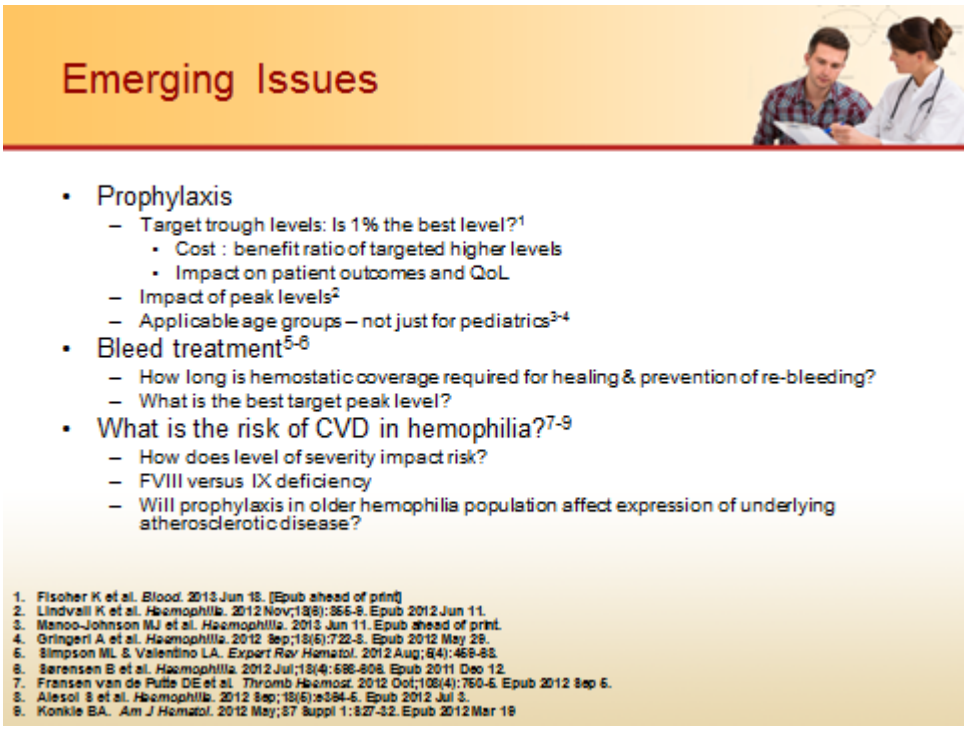
**Slide 34: New and Emerging Treatments: FIX**

Here are shown recently approved products for treatment of FIX deficiency as well as products still in clinical trials. A new rFIX product, Rixubis®, was approved in June 2013, and has a half-life of 25 hours, compared to 18 hours for its competitor rFIX product, BeneFIX®. The first long acting rFIX, Alprolix™, Fc Fusion Protein, was approved in March 2014 and has a 3 to 5 fold increase in half-life as compared to other recombinant or plasma derived FIX concentrates.


| Agent | Manufacturer | Description | Status |
|---|---|---|---|
| OBI-1 | Baxter (from Inspiration) | Porcine Factor VIII | Phase 3; BLA submitted December 2013 |
| BAY 86-6150 | Bayer | rFactor VIIa | Phase 3 |
| LR769 | rEVO Biologics | rFactor VIIa | Phase 2/3 |

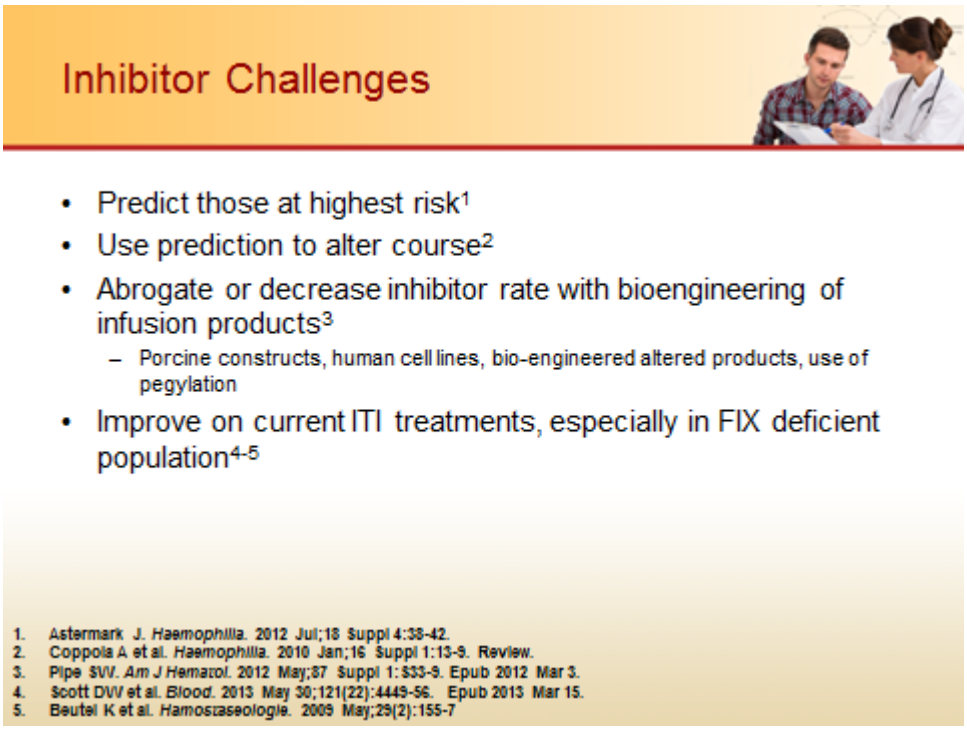
**Slide 35: New and Emerging Treatments: Inhibitors**

This table presents three products in clinical trials for the treatment of inhibitors, including one porcine FVIII product as well as two new rFVIIa products.




**Slide 36: Emerging Issues**

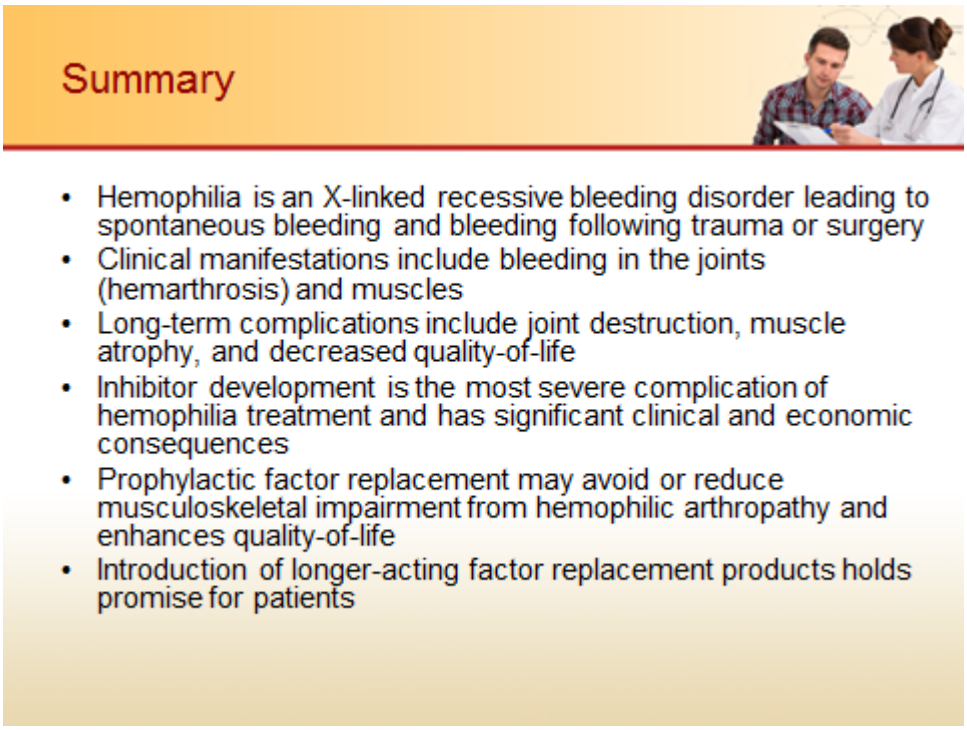
Despite these many advances in hemophilia care, we continue to face emerging issues that require us to challenge our current paradigms of care and investigate new treatment avenues. A listing of some of these emerging issues includes determining the most appropriate trough level in patients treated with prophylaxis and the cost benefit ratio and impact on outcomes and quality of life associated with higher trough levels such as 5% or higher. Issues such as optimal bleed treatment still remain to be defined including the optimal length of therapy required for healing and prevention of re-bleeding and the required target peak level to assist in the process. As our patients with hemophilia have been able to lead longer more productive lives, other medical issues such as the emergence of cardiovascular diseases have emerged. We are trying to define how hemophilia severity impacts the risk of development of cardiovascular disease as well as whether its rate is similar or different in hemophilia A versus B. In addition, as we utilize prophylaxis for adult patients we are concerned that intermittent hemostatic normalization may affect the expression of underlying atherosclerotic disease especially as many of these patients are currently optimally managed in terms of primary preventive measures to prevent these sequelae.




**Slide 37: Inhibitor Challenges**

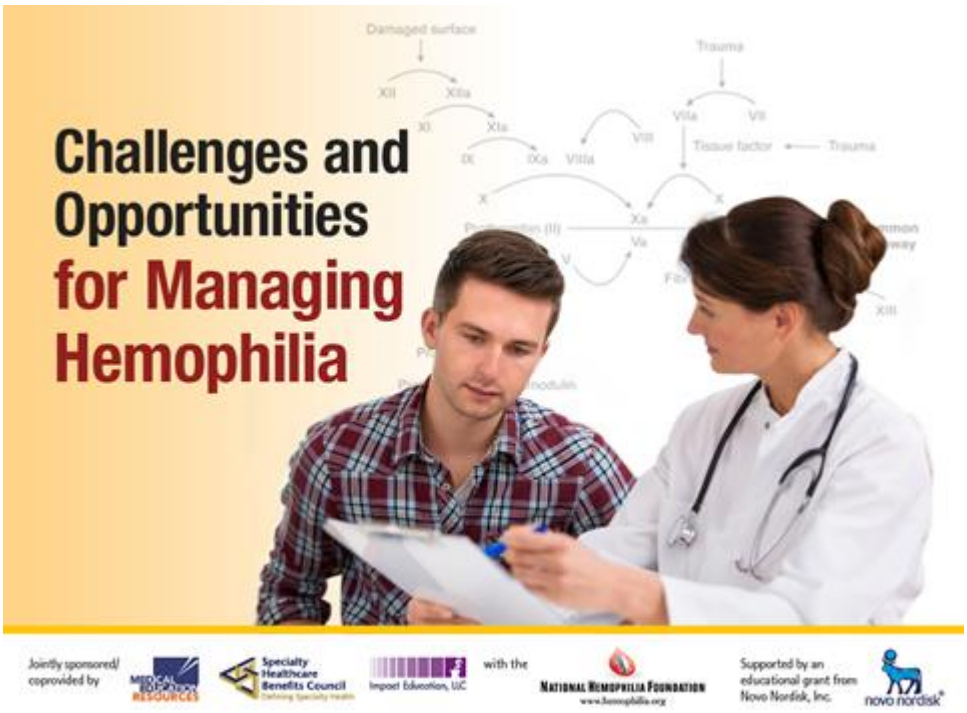
Challenges also remain for inhibitors, which continue to be one of the most severe sequelae associated with hemophilia. Despite increased knowledge of risk factors that impact the expression of inhibitors, we are still unable for any individual patient to predict those at highest risk or use a prediction score to alter the course of inhibitor emergence. As product bioengineering advances there may be avenues to explore that abrogate or decrease the rate of inhibitor expression. This remains to be evaluated as we see porcine constructs, use of human cell lines, specifically engineered products to modify the most immunogenetic sequences or use of pegylation or Fc fusion.

Although immune tolerance induction has been used in clinical practice for more than 30 years and is often successful, it is not uniformly successful, it is expensive, and clinical management of those who remain with inhibitory antibodies is complicated. There is a compelling need for improved prediction models, identification of how these models might translate into interventional methods and overall less expensive and more effective methods to induce tolerance.




**Slide 38: Summary**

In summary, hemophilia is an X-linked recessive bleeding disorder that results in spontaneous bleeding and bleeding following injury or surgery. The clinical manifestations of hemophilia include bleeding into the joints, termed hemarthrosis, and muscles. Long-term complications include joint destruction, muscle arthropathy, and decreased quality of life. Inhibitor development remains the most severe complication of hemophilia treatment and has significant clinical and economic consequences. Prophylactic factor replacement regimens may prevent or reduce musculoskeletal impairment from hemarthropathy and enhance quality of life of the affected population. The introduction of longer-acting factor replacement products holds promise to decrease the burden of care experienced by the population.

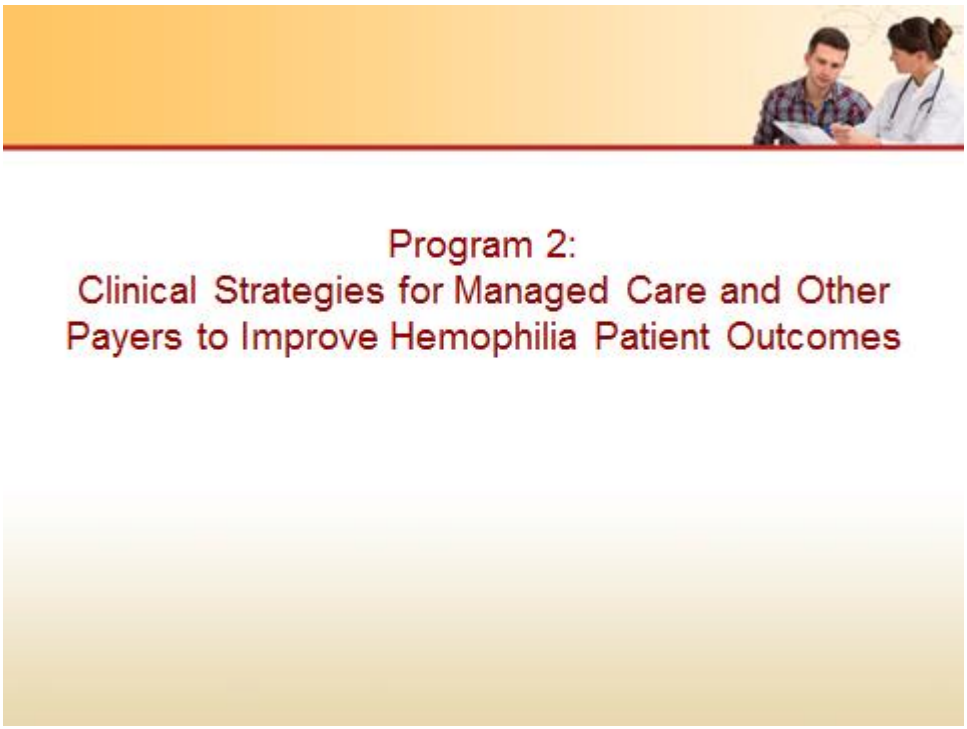



**Slide 39: Challenges and Opportunities for Managing Hemophilia**

This concludes Program 1 of Track 1, entitled Current Practices and Approaches to Care: An Update.

# Program 2:

# Clinical Strategies for Managed Care and Other Payers to Improve Hemophilia Patient Outcomes

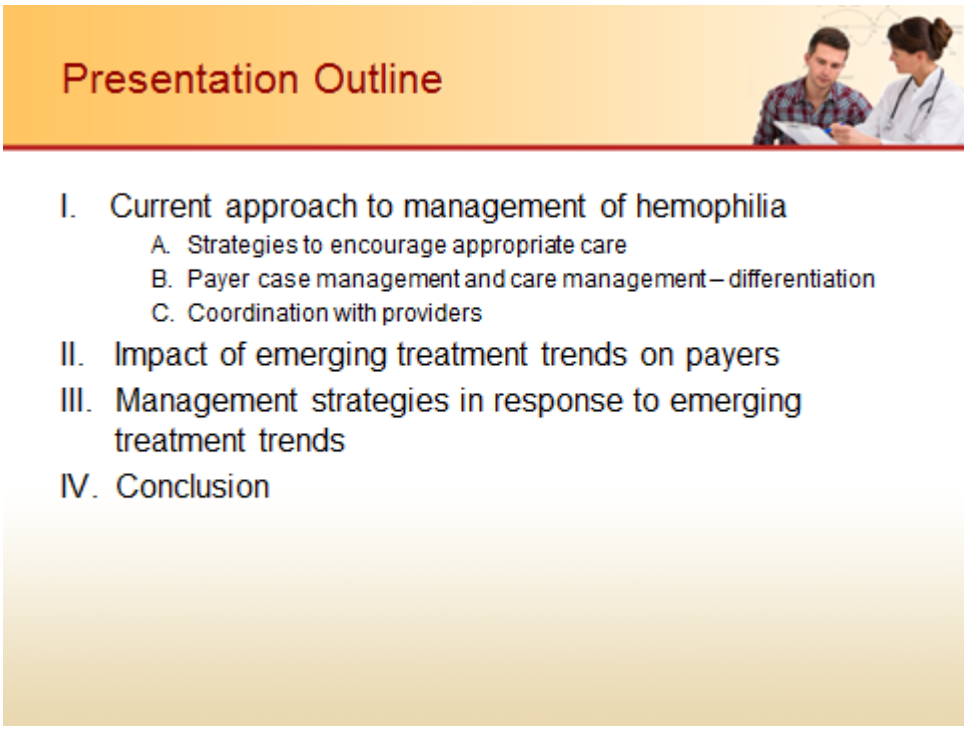



**Slide 40: Program 2: Clinical Strategies for Managed Care and Other Payers to Improve Hemophilia Outcomes**

The second presentation of Track 1 is entitled Clinical Strategies for Managed Care and Other Payers to Improve Hemophilia Outcomes, and represents the payer perspective on hemophilia management.


**Slide 41: Program Faculty**

The faculty for this presentation is Dr. Celynda Tadlock, Vice President of Pharmacy Business Development at Aetna, Inc., and President of Coventry Prescription Management Services. Support staff for this presentation includes Joe Eichenholz, Executive Director of the Specialty Healthcare Benefits Council, and Marla Feinstein and Michelle Rice, from the National Hemophilia Foundation's Public Policy Team.




**Slide 42: Presentation Outline**

From a payer perspective, hemophilia providers are all working toward a common goal: to ensure provision of high quality care, cost-effective care for this population. There are a number of opportunities that are available to leverage the resources that we have at our disposal, such as the Hemophilia Treatment Centers, or HTCs, as a reference, the expertise of specialty pharmacies, and the knowledge base of the National Hemophilia Foundation, or NHF.

There are also opportunities for payers serve as liaisons to integrate and streamline much of the important care and resources that these entities provide.

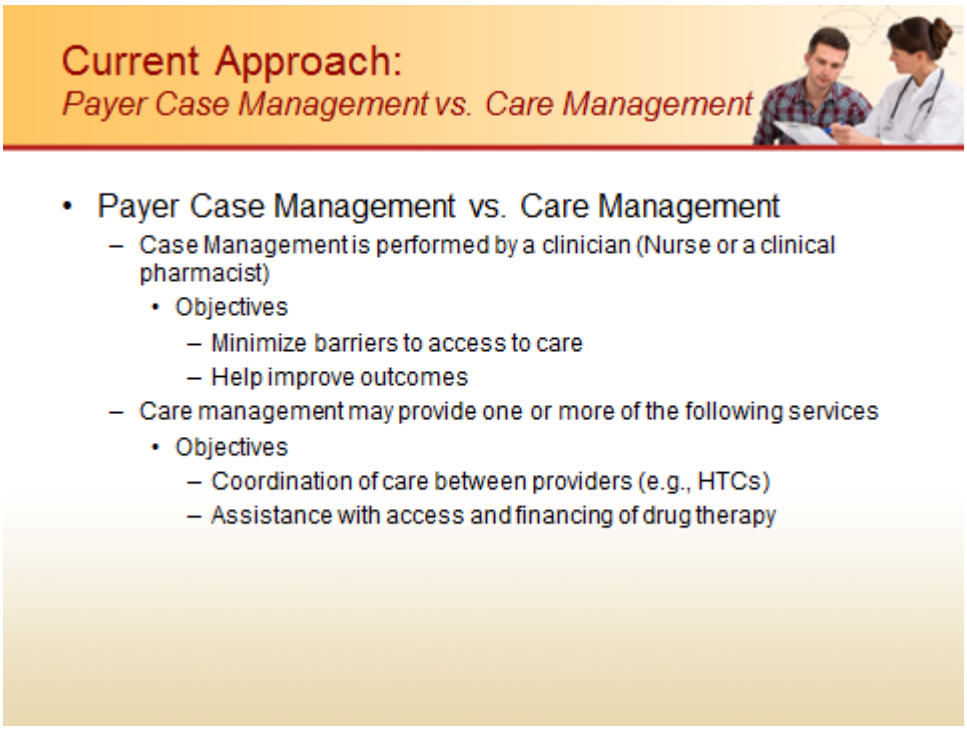
In this presentation, we are going to cover the current approach to the management of hemophilia. We will then look at the impact of emerging trends on payers. Finally, we will look at management strategies in response to those emerging trends.


**Slide 43: Current Approach: *Encourage Appropriate Use***

Managed care has a small number of tools that can be utilized to manage both the cost and the quality of care in the hemophilia population. Prior authorization, case management, and coordination with the HTCs and the specialty pharmacy are some of the most common tools that are available.

Prior authorization has the objective not to restrict care, but to encourage appropriate care by verifying the patient's diagnosis and communicating the severity of the patient's disorder, which can help determine the appropriateness of various treatment options from the standpoint of their efficacy, their safety, the out-of-pocket costs for the patients, as well as the cost to the health system.

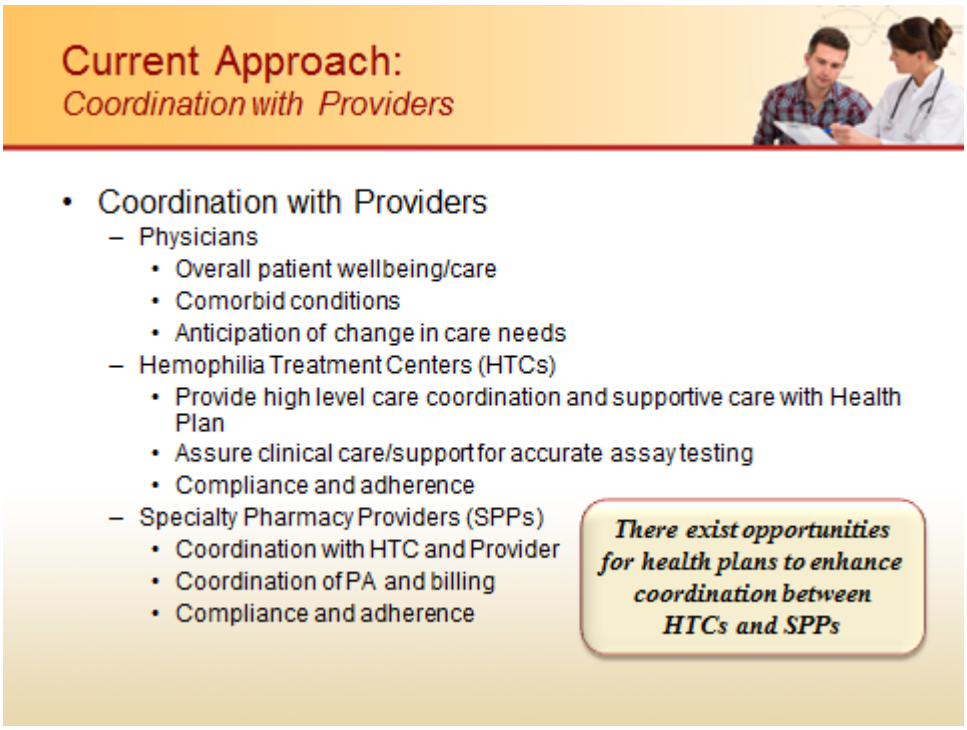
The goal of payers is to support providers in the delivery of the most appropriate care possible in this population.




**Slide 44: Current Approach:** ***Payer Case Management versus Care Management***

Case management and care management are tools that are commonly used by payers. Some of these services can be insourced within the managed care unit of the payer organization, or many times they can be outsourced to specialty pharmacies or to other organizations that have the expertise in hemophilia on staff that can provide these services through nurses or clinical pharmacists.

The primary objectives of case management and care management programs are to help minimize barriers to care, educate about the disease state, coordinate care between providers, and provide education to the patient's family regarding benefit coverage and out-of-pocket expenditures, financing, and financial responsibility.

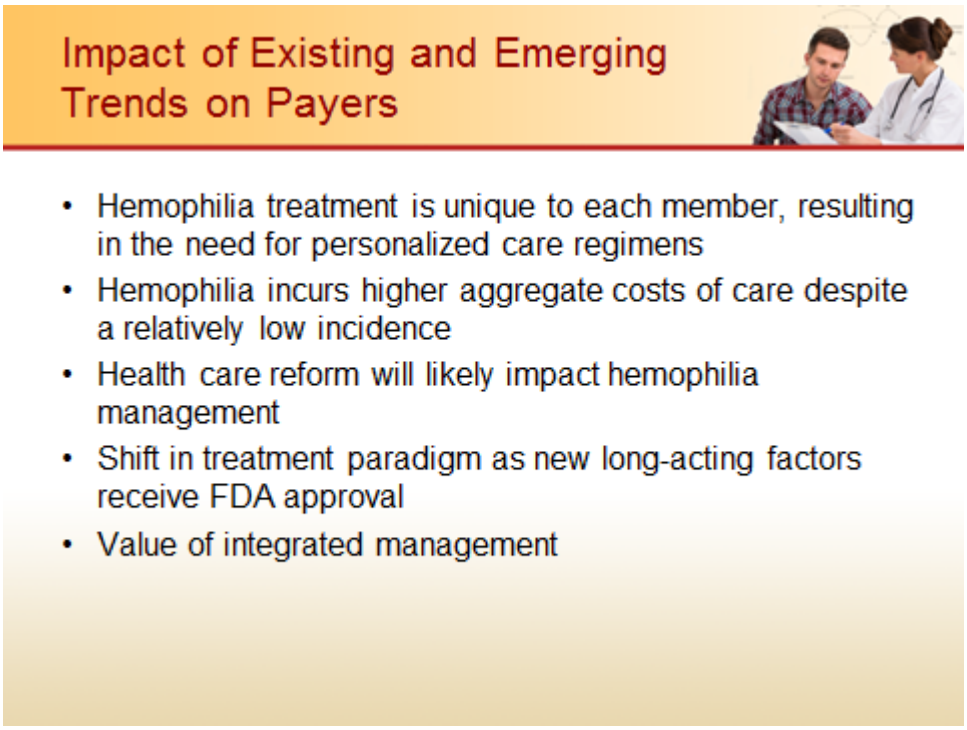



**Slide 45: Current Approach: *Coordination with Providers***

Coordination with physicians, HTCs, and specialty pharmacies is another very important tool that payers can use. Providers play a critical role in this coordination by preparing written treatment plans that have the expected dosages and the dose intervals for the factor products.

Communication with the HTCs is imperative to understand how a patient is doing and to anticipate what changes might be needed in therapy as the patient progresses through the disease or through different stages of life and necessary treatment.

The coordination of treatment plans with HTCs or specialty pharmacies that might be delivering product can help facilitate the prior authorization approval request. As noted at the bottom of the slide, despite all the best of intentions for communication and coordination, there still exist many opportunities to enhance that coordination.




**Slide 46: Impact of Existing and Emerging Trends on Payers**

Now we are going to examine some of the emerging trends. We know that hemophilia is a unique condition and it does result in a need for personalized treatment regimens. A patient who is 4 years of age is not going to require the same treatment as a patient that is 40 years of age. We also know that the aggregate cost for hemophilia is high despite the very low incidence. Most of the dollars are associated with costs of clotting factor concentrate.

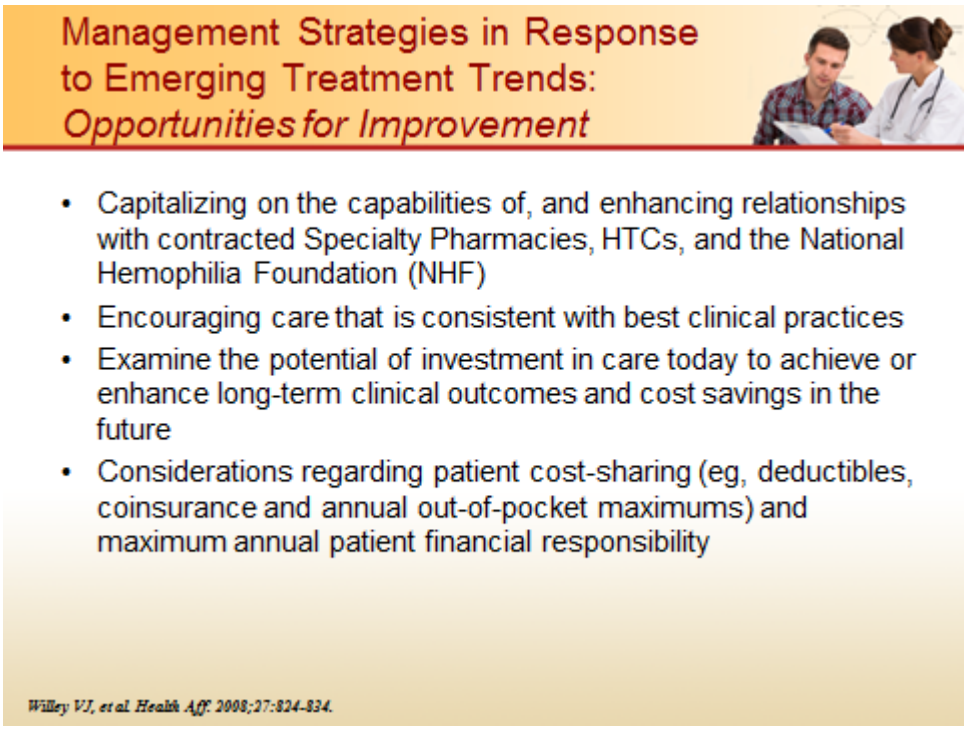
Even in comparison to cost incurred for an emergency room visit or hospital admission, the cost of factor is dominant. This is especially true, as seen from the physician's perspective, for patients with inhibitors or patients that have a major bleed. Those patients are going to require larger doses of clotting factor concentrate or different medications to overcome inhibitors, which are costly.

Healthcare reform will likely impact hemophilia management; payers are paying particular attention to the potential impact of the elimination of lifetime expense caps. It is possible that patients will change insurance plans less frequently and thus there will be less churn in patients' health insurance. Additionally, accountable care organizations are becoming established and will in the future take on more risk than the traditional managed care type payer.

Track 1 Program 1 included information on the long-acting factor products that have recently been approved or that we expect to be released in the near future. Patients will certainly need to be evaluated in light of those products and the best possible treatment regimens must be determined.

There is a value to integrated management which payers must remain cognizant of as accountable care organization models evolve. Currently, accountable care organizations are not taking on as much risk as some managed care organizations would like. We certainly need to make sure that consistent data is available to both Accountable care organizations and managed care organizations for the development of more extensive risk-sharing and risk-bearing arrangements in the future

The ability to track pharmacy and medical data and outcomes is extremely important. Managed care organizations have had the advantage of being able to warehouse data over time and analyze it to better understand clinical and economic risks. Accountable care organization-type practice models need this capability as well. Again, as we start to see shifts to accountable care organization payer-type models, it is essential that we make sure those organizations have the data and the information that they really need to be successful.




**Slide 47: Management Strategies in Response to Emerging Treatment Trends:**

***Opportunities for Improvement***

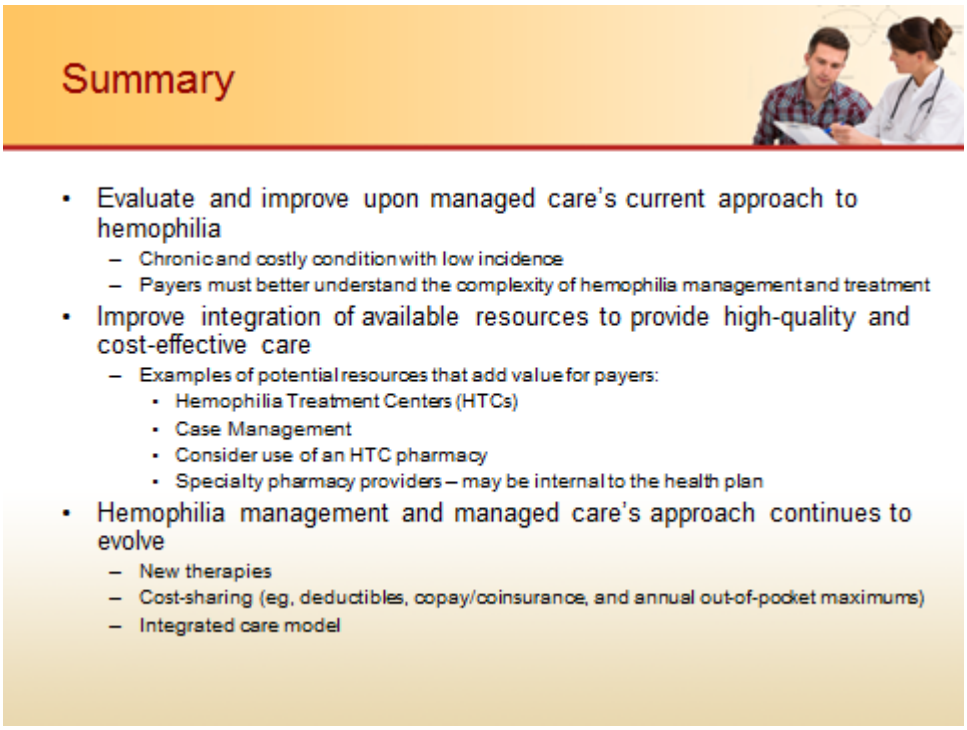
We should focus now on the opportunities for improvement. Enhancing the relationships between specialty pharmacies, providers, the NHF, and HTCs is important. Hemophilia education should be shared with those that are providing the case management services and those that are making decisions around the benefits and coverage for these patients.

As people realize what the HTCs and the NHF can do, by increasing this dialogue, we should take advantage of those interactions to further improve the quality of the care that is delivered.

Hemophilia is a disease where quality care tends to be the most cost effective care. The payers that are encouraging care that is consistent with best clinical practices such as prophylactic therapy, which was discussed in Track 1 Program 1, are encouraging that high quality care. It does require the use of data from clinical trials, evidence based guidelines, and a real world perspective that we can gain from the hemophilia treatment experts. Investment today will help improve the long-term clinical outcomes and save dollars for the future.


**Slide 48: Management Strategies in Response to Emerging Treatment Trends: *Opportunities for Improvement* (continued)**

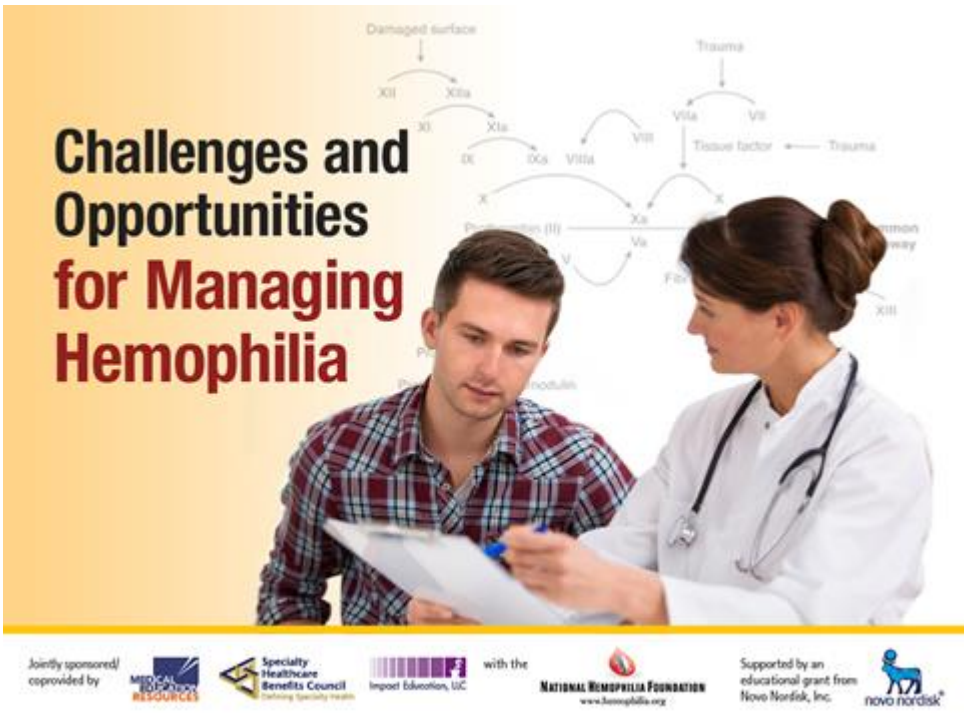
There are potential roles for specialty pharmacy providers with this increased coordination that we should briefly discuss. There is also the ability to leverage the data from HTCs. We also have some payer organizations that are exploring telemedicine to eliminate a barrier to care for those patients without easy access to an HTC. We want to make sure that those patients can be accessed through telemedicine so that HTC expertise can be shared with a larger number of patients in the population.




**Slide 49: Summary**

In summary, it is important that we evaluate and improve upon managed care's current approach to hemophilia. It is also important that we improve the integration of those available resources and data.

As hemophilia management and managed care payers' approaches continue to evolve, we must consider the value of new treatments on the horizon and monitor cost shares. We must focus on this integrated care model and ask how do we really share the information and data with those that most need the information to support patient care?

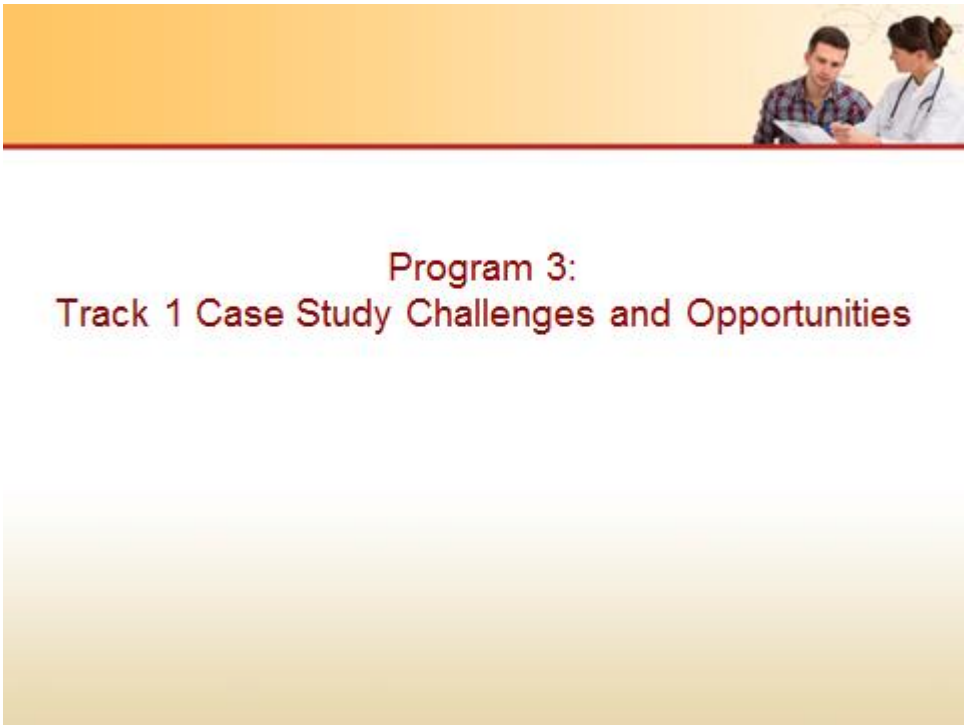



**Slide 50: Challenges and Opportunities for Managing Hemophilia**

This concludes Program 2 of Track 1, entitled Clinical Strategies for Managed Care and Other Payers to Improve Hemophilia Outcomes.

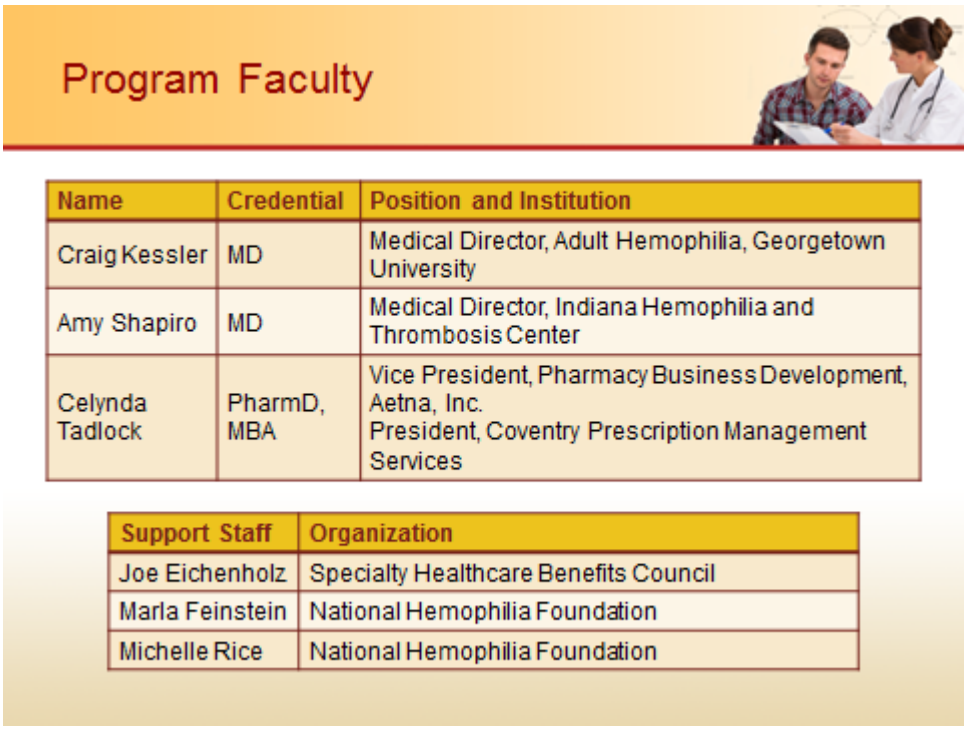
# Program 3:

# Track 1 Case Study Challenges and Opportunities



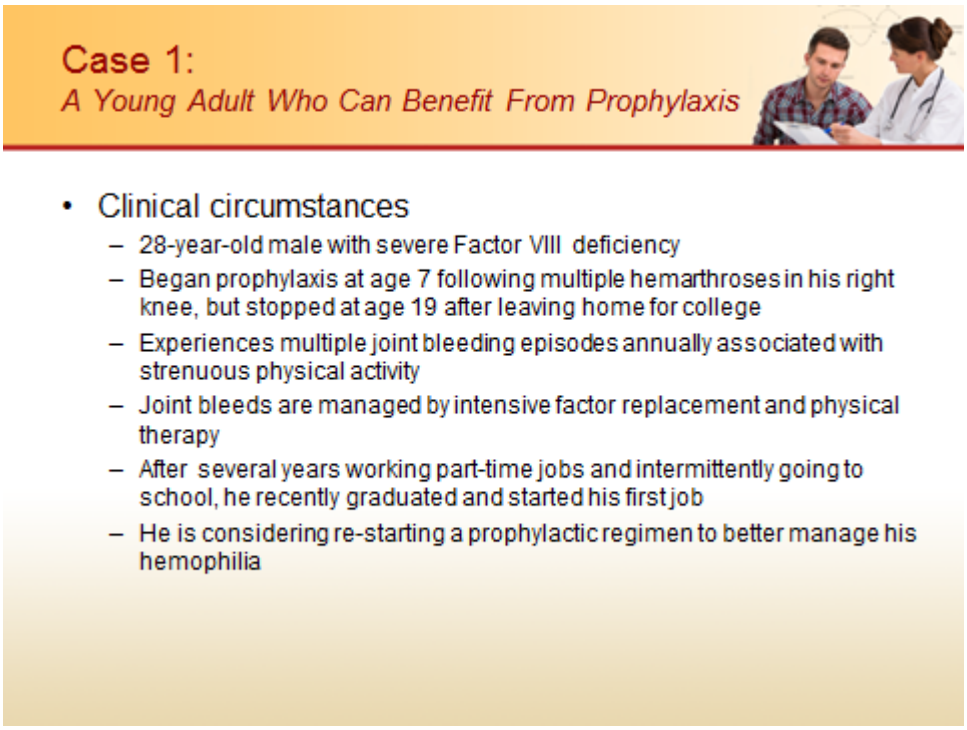

**Slide 51: Track 1 Case Studies Challenges and Opportunities**

Now that we have had a clinical and payer update, let us examine two real world cases.




**Slide 52: Program Faculty**

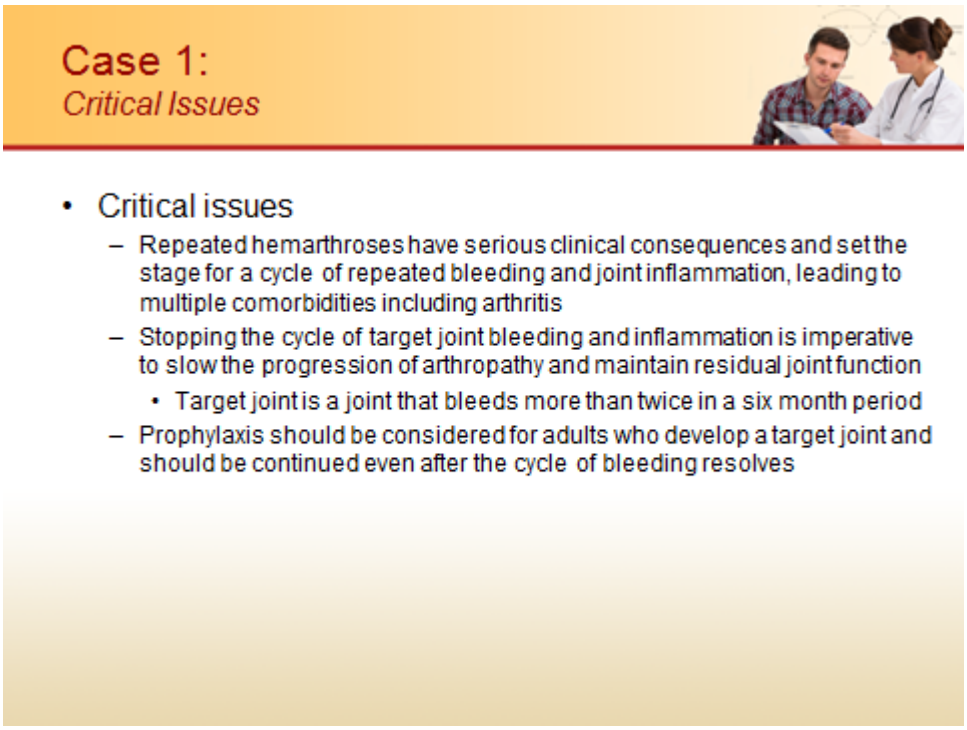
The faculty for this presentation includes Dr. Craig Kessler, Medical Director of Adult Hemophilia at Georgetown University; Dr. Amy Shapiro, Medical Director of the Indiana Hemophilia and Thrombosis Center; and Dr. Celynda Tadlock, Vice President of Pharmacy Business Development at Aetna, Inc., and President of Coventry Prescription Management Services. Support staff for this presentation includes Joe Eichenholz, Executive Director of the Specialty Pharmacy Benefits Council, and Marla Feinstein and Michelle Rice, from the National Hemophilia Foundation's Public Policy Team.




**Slide 53: Case 1: *A Young Adult Who Can Benefit From Prophylaxis***

The first case is a young adult male, 28 years old, who has severe FVIII deficiency. Recall that in severe hemophilia, his clotting factor activity level is less than 1%. He began prophylaxis at age 7 after multiple hemarthroses, or joint bleeds, into his right knee. Then, as we often see, he turned 19 and stopped prophylaxis after leaving for college.

While in college, he begins to experience more joint bleeds, particularly associated with strenuous physical activity. He treats himself with intensive factor replacement and physical therapy. After several years working part time post-graduation, he started his first full-time job. He is now considering re-starting a prophylactic regimen to manage his hemophilia.

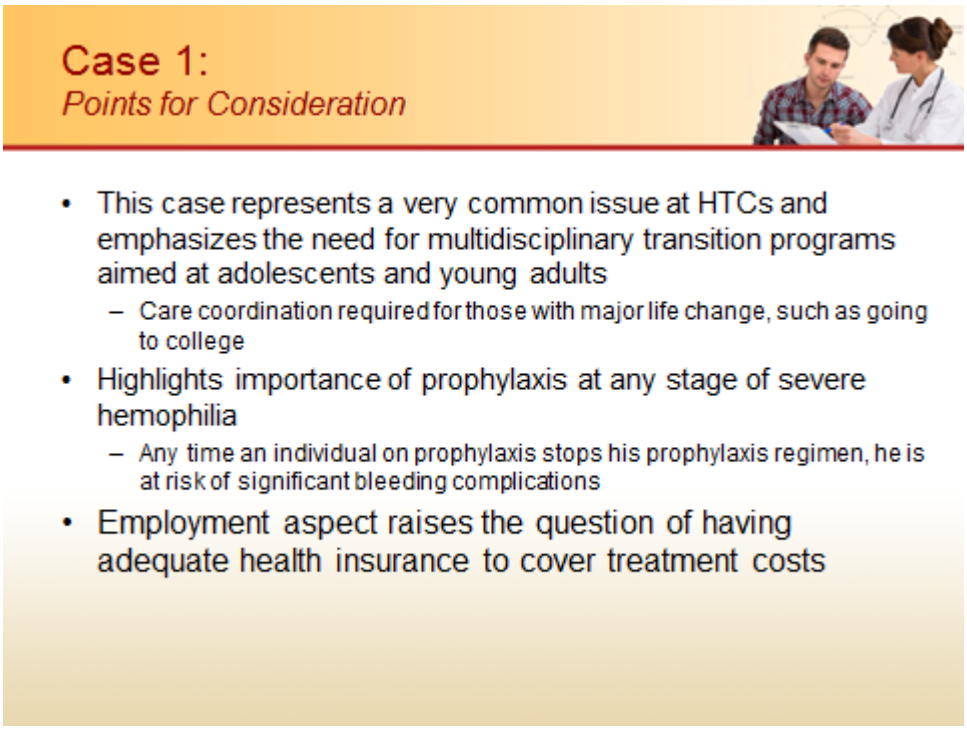



**Slide 54: Case 1: *Critical Issues***

The issue for this gentleman is that he's had repeated joint bleeds. These have serious consequences. They set the stage for a repetitious cycle of one bleed begets more bleeds. He has an extreme amount of inflammatory pain in the target joints, which are now causing additional problems in other joints that have been compensating for the limited range of motion in the target joints. He is going to start having more bleeds in those other joints as well.

The definition of a target joint is a joint that bleeds more than twice in a six month period of time. Once these joints develop bleeding complications, they are very difficult to reverse.

There must be something to stop the cycle of target joint bleeding and inflammation. Prophylaxis should be considered for adults who develop a target joint and should be continued even after the cycle of bleeding resolves.

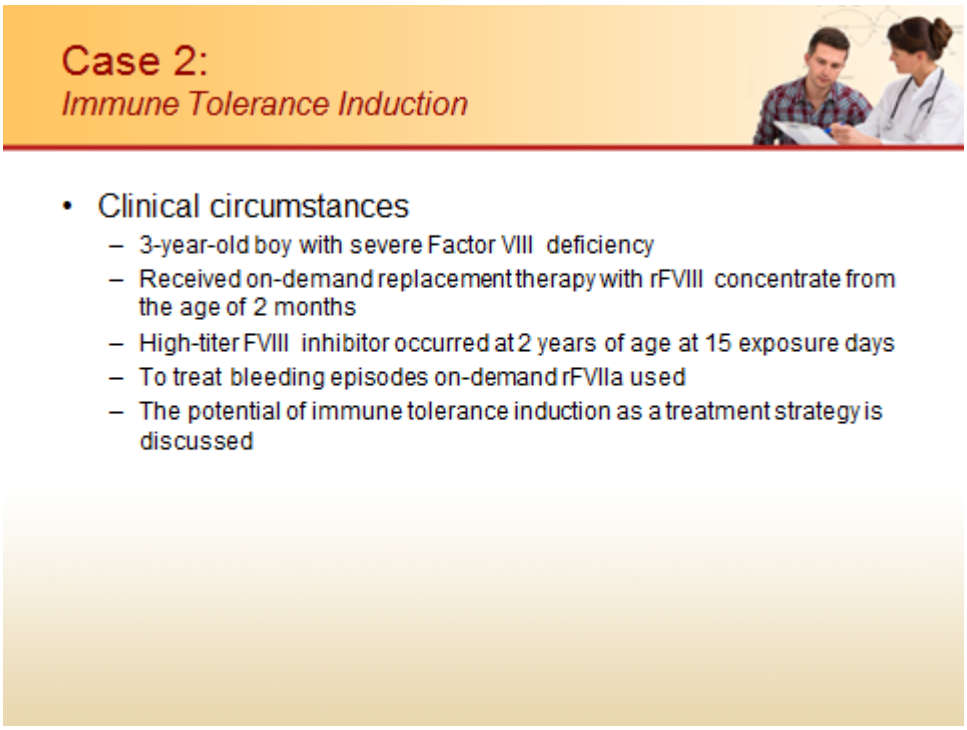



**Slide 55: Case 1: *Points for Consideration***

This case study raises a number of important points for consideration. First, this case represents a very common issue at Hemophilia Treatment Centers and emphasizes the need for multidisciplinary transition programs aimed at adolescents and young adults, and the special care coordination required for those with a major life change, such as going to college.

The case also highlights the importance of prophylaxis at any stage of severe hemophilia. As in this example, any time an individual with severe hemophilia utilizing prophylaxis stops his prophylaxis regimen, he is at risk of significant bleeding complications.

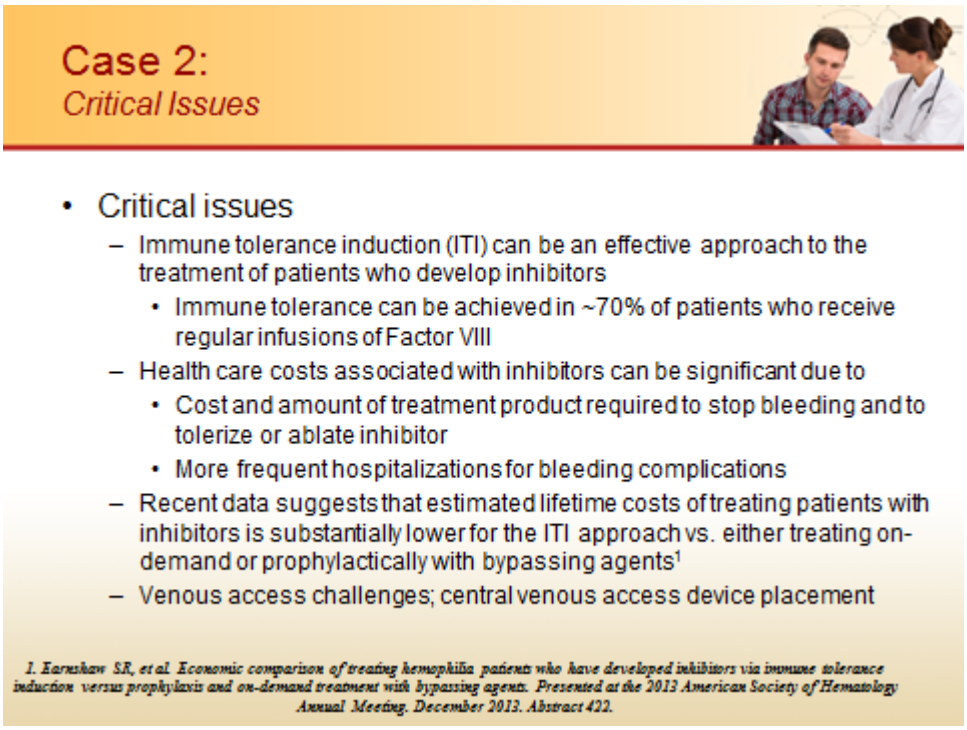
Finally, the employment aspect of this case raises the question of patients having adequate health insurance through their employer to cover hemophilia treatment costs. This is a critical consideration for patients in any employment decision.




**Slide 56: Case 2: *Immune Tolerance Induction***

The second case describes a 3-year-old boy with severe FVIII deficiency. He has received episodic replacement therapy with recombinant FVIII concentrate from the age of 2 months. He developed a high titer inhibitor at 15 exposure days. An exposure day is any day that you receive clotting factor concentrate. If an individual with severe FVIII deficiency infuses himself two to three times per week throughout his active life after he becomes a toddler, then 15 exposure days is very soon into the treatment that he will develop an inhibitor.

To prevent bleeding episodes, the boy receives on-demand rFVIIa, NovoSeven®, which is a bypassing agent. The potential of immune tolerance induction to try to eradicate the inhibitor is then discussed.



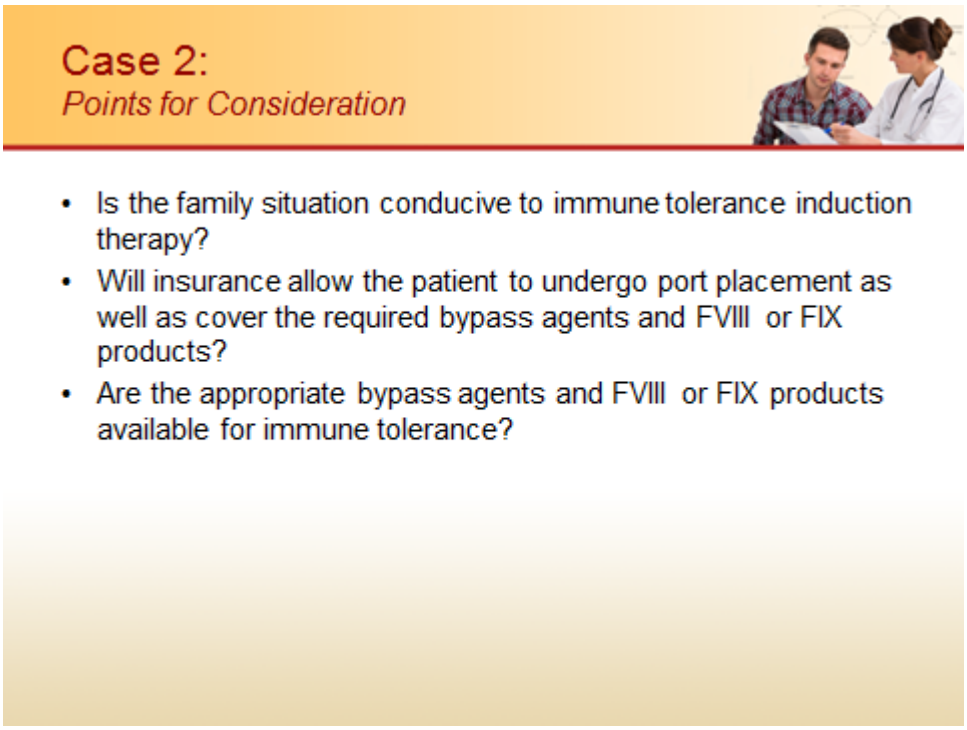

**Slide 57: Case 2: *Critical Issues***

Immune tolerance is a critical issue. It eradicates the inhibitor in approximately 70% of patients, particularly if it is initiated early on after recognition that the inhibitor has developed. However, immune tolerance is a very expensive way of treating these patients, upwards of a million dollars per year because of the clotting factor required.

These patients also require more frequent hospitalizations for bleeding complications.

In spite of the high costs, there are recent data to suggest that the estimated lifetime costs of treating patients with inhibitors is substantially lower for the immune tolerance induction approach versus either treating on-demand or prophylactically with bypassing agents.

Venous access can also present a challenge in young children as you have to stick them every day in order to prevent the inhibitor from neutralizing the clotting factor replacement. Oftentimes, this will require a surgical procedure to place a central venous access device, or a port, to make regular venous access easier for the parents. Importantly, ports present problems themselves, such as clotting and infection. So if parents are going to embark on immune tolerance in a young child, it is a real family commitment of person time, effort, and expense.

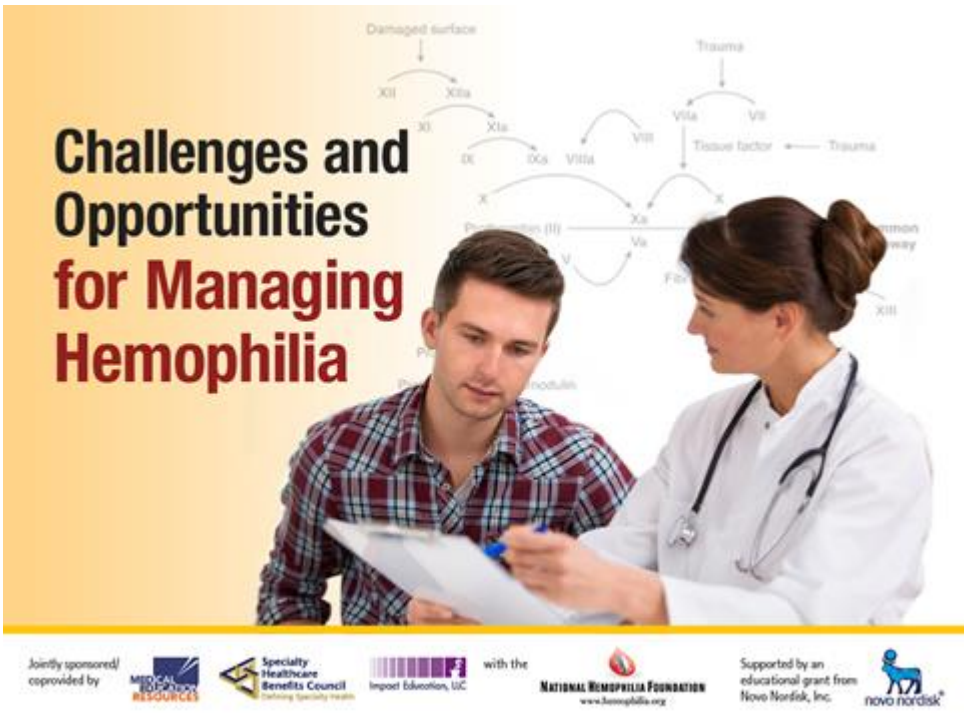



**Slide 58: Case 2: *Points for Consideration***

This case brings to light a few points for consideration. While immune tolerance induction therapy may be considered best practice, it is not always feasible or practical practice for a given family. Some families don't have the desire or the cohesiveness to manage such an intensive treatment regimen in a young child. It does require analysis of the patient and the family situation on the part of the clinician to make an informed decision about prescribing the treatment.

In families where immune tolerance induction therapy is deemed appropriate, it must then be determined whether the patient's insurance will allow the patient to undergo port placement as well as cover the required bypass agents and FVIII or FIX products.

Finally, availability of the required products must be taken into consideration. Most specialty pharmacies will be able to order these and have them in stock when needed; however, supply should be confirmed in advance in order to ensure treatment continuity.




**Slide 59: Challenges and Opportunities for Managing Hemophilia**

This concludes Track 1, Clinical Overview, of the Challenges and Opportunities for Managing Hemophilia 2014 Continuing Education Series. Please continue to the next track or visit the Specialty Healthcare Benefits Council at www.SHBC.us to complete the Track 1 post-test and evaluation and receive the appropriate amount of continuing education credit hours. Thank you for your time and attention.