HEMOPHILIA

Treatment Recommendations and Cost Management for Managed Care and Specialty Pharmacy

Jointly provided by

National Hemophilia Foundation
for all bleeding disorders

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AMCP Academy of Managed Care Pharmacy®

Held in conjunction with AMCP Managed Care & Specialty Pharmacy Annual Meeting 2018

Evolving Clinical Practice Guidelines and Treatment Recommendations

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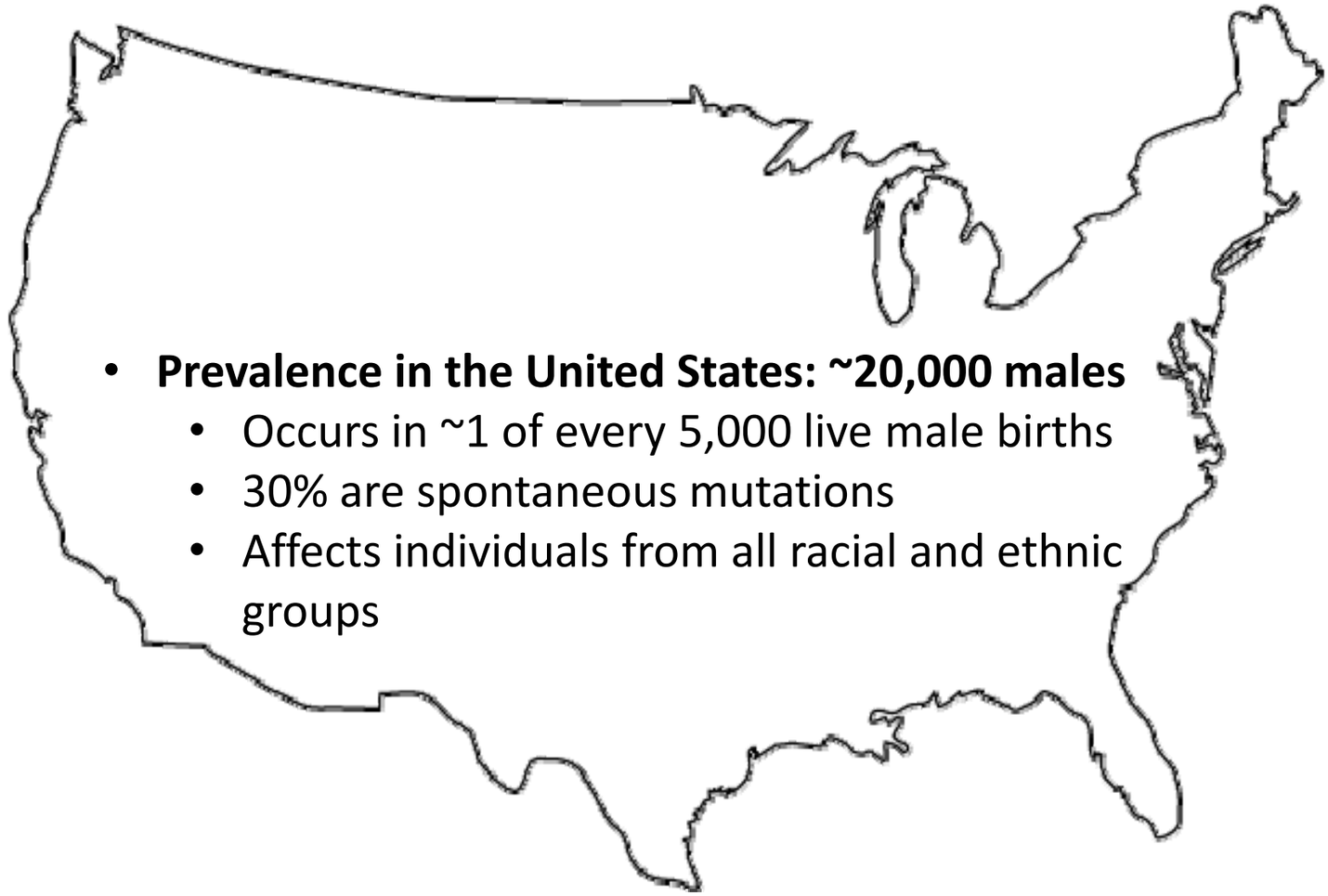
Hemophilia Defined

- X-linked recessive bleeding disorder leading to spontaneous bleeding and bleeding following trauma or surgery
  - Typically expressed in males; female carriers may have symptoms
  - Characterized by a deficiency of Factor VIII (hemophilia A) or Factor IX (hemophilia B)
    - Hemophilia A ~4x more common



- **Prevalence in the United States: ~20,000 males**
  - Occurs in ~1 of every 5,000 live male births
  - 30% are spontaneous mutations
  - Affects individuals from all racial and ethnic groups

Hemophilia facts. Centers for Disease Control and Prevention Web site. http://www.cdc.gov/ncbddd/hemophilia/facts.html. Accessed March 2018.
Types of Bleeding Disorders. National Hemophilia Foundation Web site. https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders. Accessed March 2018.

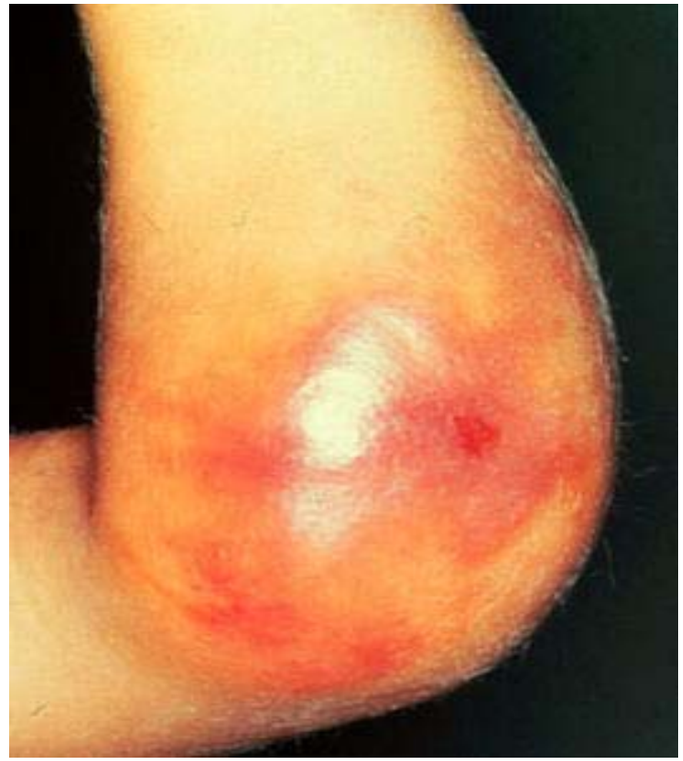
Clinical Classification

Classification (% of affected patients)	Mild (30%- 40%)	Moderate (10%)	Severe (50%-70%)
FVIII or FIX activity	6% – 40%	1% – ≤5%	<1%
Pattern of bleeding episodes	Uncommon	~4–6 per year	~2–4 per month
Cause of bleeding episodes	Major trauma, Surgery	Minor trauma	Spontaneous

Adapted from McPherson RA. Pincus MR. Henry's Clinical Diagnosis and Management by Laboratory Method. 21st edition. Table 38-4. St. Louis, MO: Elsevier Health Sciences; 2007.

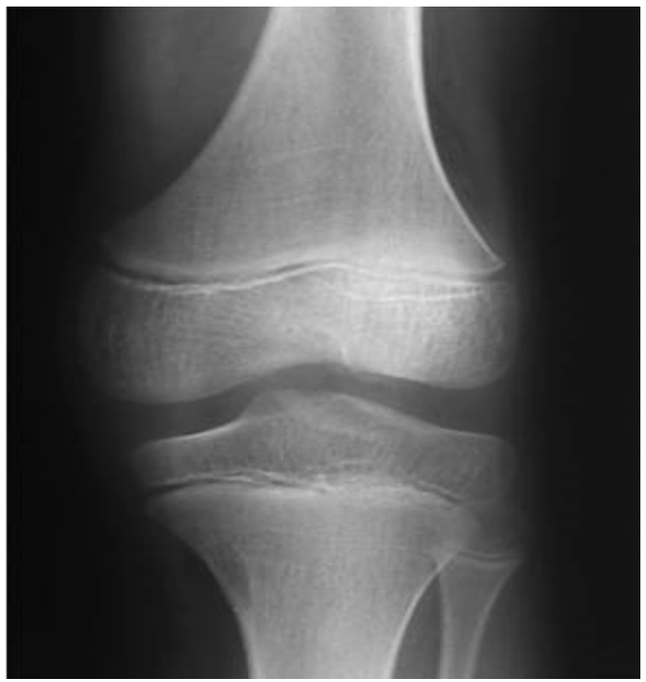
Clinical Manifestations and Disease Complications

- Clinical manifestations include bleeding into joints (hemarthrosis), muscles, soft tissues, and other locations
- Long-term sequelae often occur if bleeding not prevented, including arthritis/arthropathy, chronic pain, muscle atrophy, and loss of mobility or even disability
- Severe bleeds or those in specific locations can be life-threatening

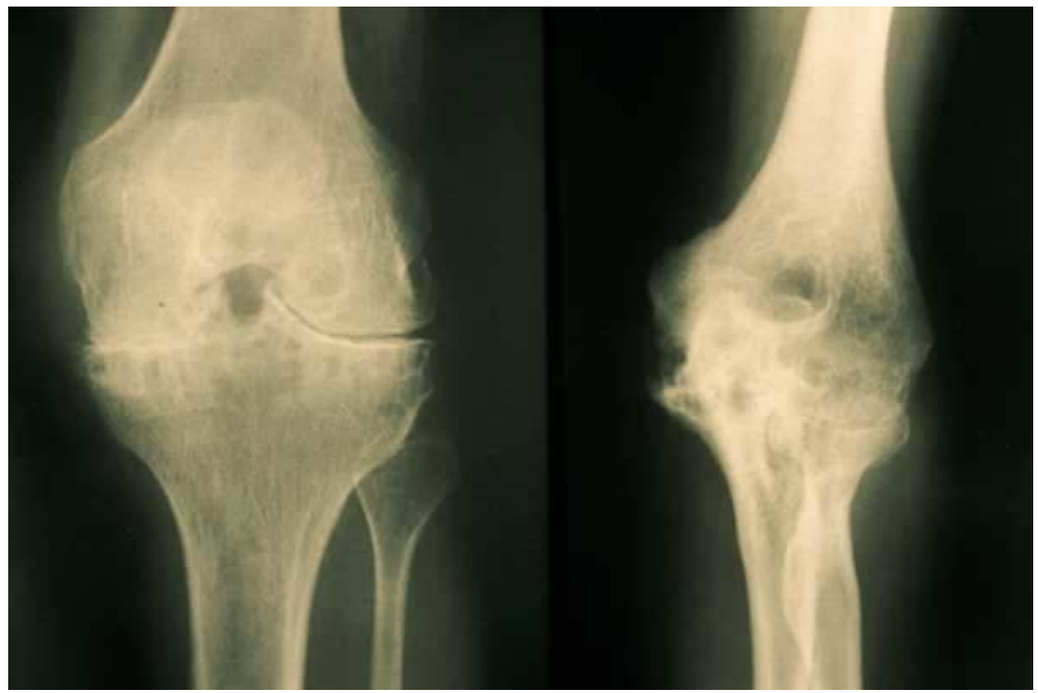


Narrowing of Knee Joint Space

Normal



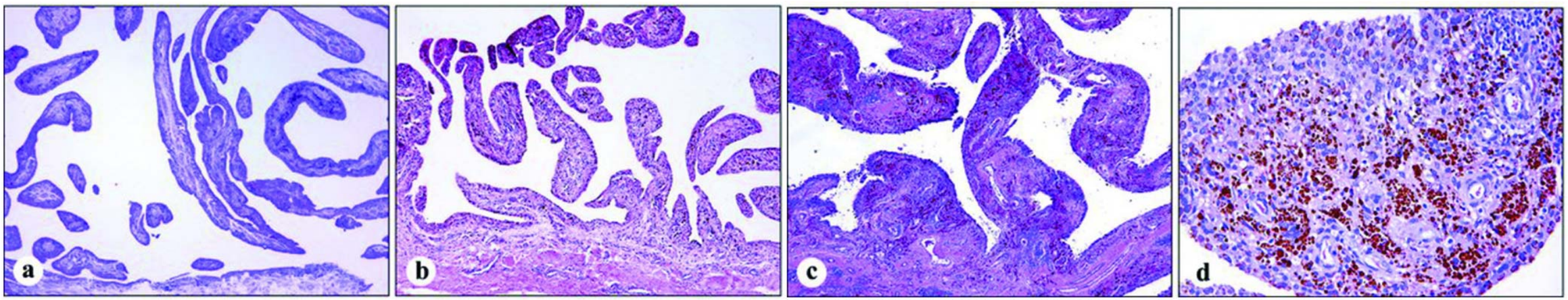
Hemophilic Arthropathy



Synovitis Pathophysiology

Normal synovium is thin, white, and not very vascular

With repeated bleeds synovium hypertrophies and becomes villous with neovascularization



Morbidity of Hemarthrosis, Synovitis, and Arthropathy

If joint bleeds are left untreated, chronic hemarthrosis and synovitis develop

Chronic synovitis leads to a chronic inflammatory condition in the joint making recurrent bleeding more common

Recurrent bleeding induces cartilage destruction and arthritis

Arthropathy is a major cause of morbidity in patients with hemophilia

- ***As few as 1 to 2 bleeds can trigger changes in the synovium and cartilage that eventually result in arthropathy***

Treatment: Considerations and Options

Considerations

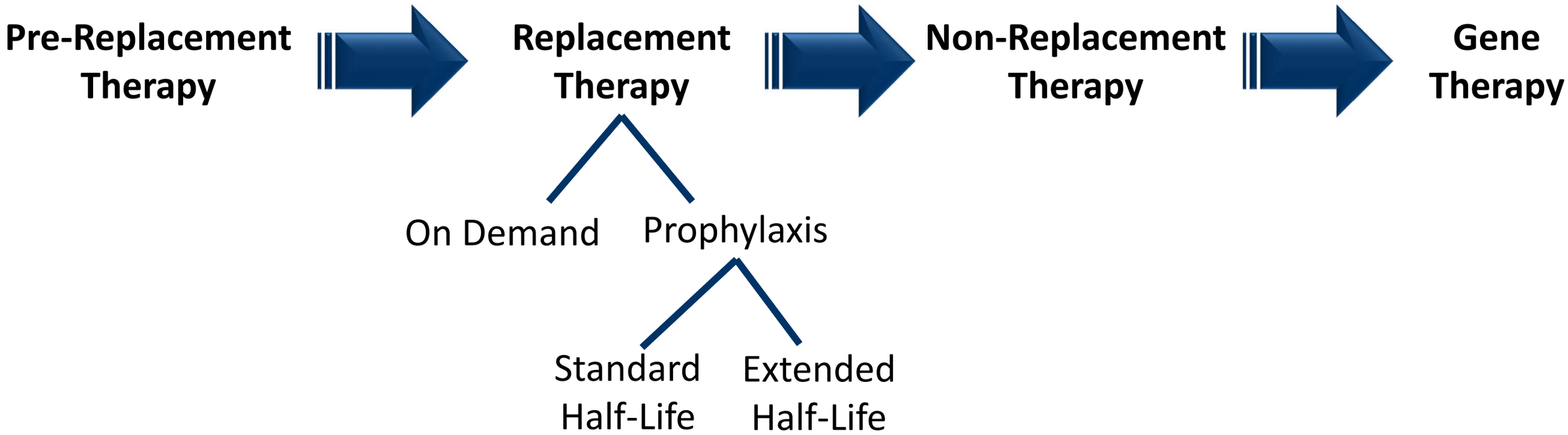
- Goal
  - Rapid and effective replacement of missing coagulation factor
- Approach
  - Comprehensive hemophilia treatment center (HTC) staffed by a multidisciplinary team of experts who care for patients with bleeding disorders
- Strategies
  - Episodic or “on-demand” factor replacement
  - Prophylaxis

Options

- Replacement of missing clotting protein
  - Factor VIII and IX
- DDAVP (IV, intranasal) in mild FVIII deficiency
- Adjunctive therapies
  - Antifibrinolytic agents
    - Amicar/Lysteda
  - Supportive measures
    - “RICE” – rest, ice, compression, and elevation
    - Immobilization

Hemophilia facts. Centers for Disease Control and Prevention Web site. http://www.cdc.gov/ncbddd/hemophilia/facts.html. Accessed March 2018.
Types of Bleeding Disorders. National Hemophilia Foundation Web site. https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders. Accessed March 2018.

Current and Future Approaches to Care



Pipe SW. New Therapies for Hemophilia. 2016(1);650-6. American Society of Hematology Web site. http://asheducationbook.hematologylibrary.org/content/2016/1/650.full. Accessed March 2018.

Factors VIII and IX

	FVIII	FIX
Intravenous infusion (IV push or continuous)	a	a
Dose	**20-50+ units/kg body weight**	**20-100+ units/kg body weight**
Half-life	**8-12 hours**	**18-24 hours**
Expected change in plasma factor activity with each unit/kg infused	**+2%**	**+1%**

*Depending on level of purity

Types of Bleeding Disorders. National Hemophilia Foundation Web site. https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders. Accessed April 2018.

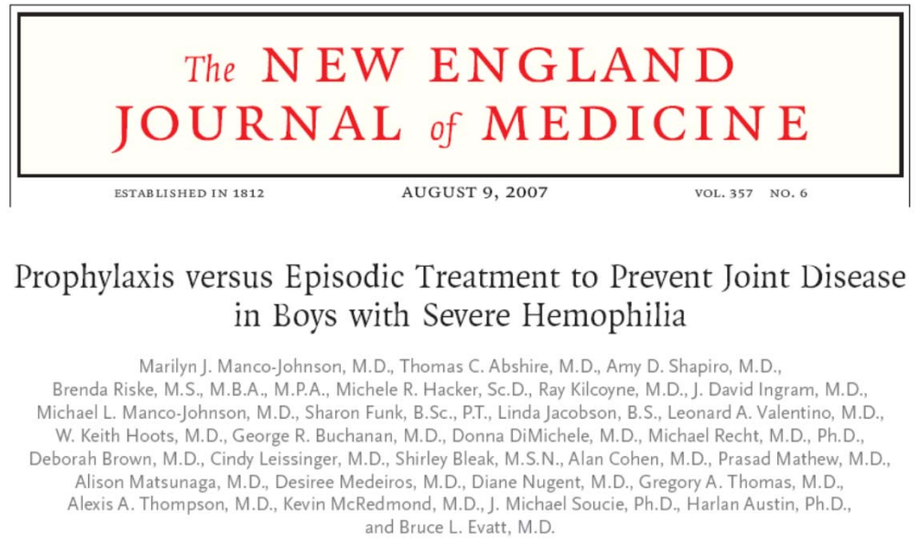
Prophylaxis to Prevent Bleeding

- ***Aim:*** ***Prevention of arthropathy and improvement in quality of life***

Severe Patients (<1% factor activity)	• **Average 30-35 bleeds/year and will inevitably develop chronic arthropathy unless treated with effective prophylactic factor replacement therapy**
Mild & Moderate Patients	• **Less likely to develop chronic arthropathy**

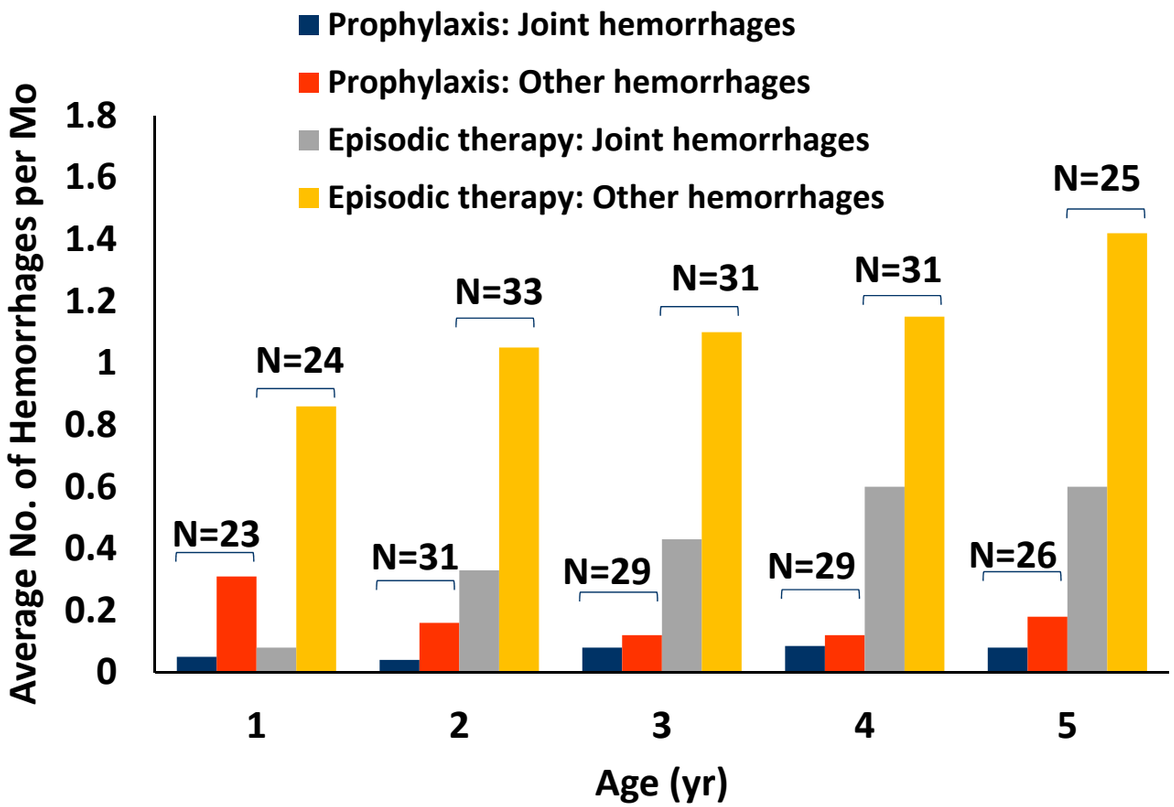
Establishing the Case: Prophylaxis in Children

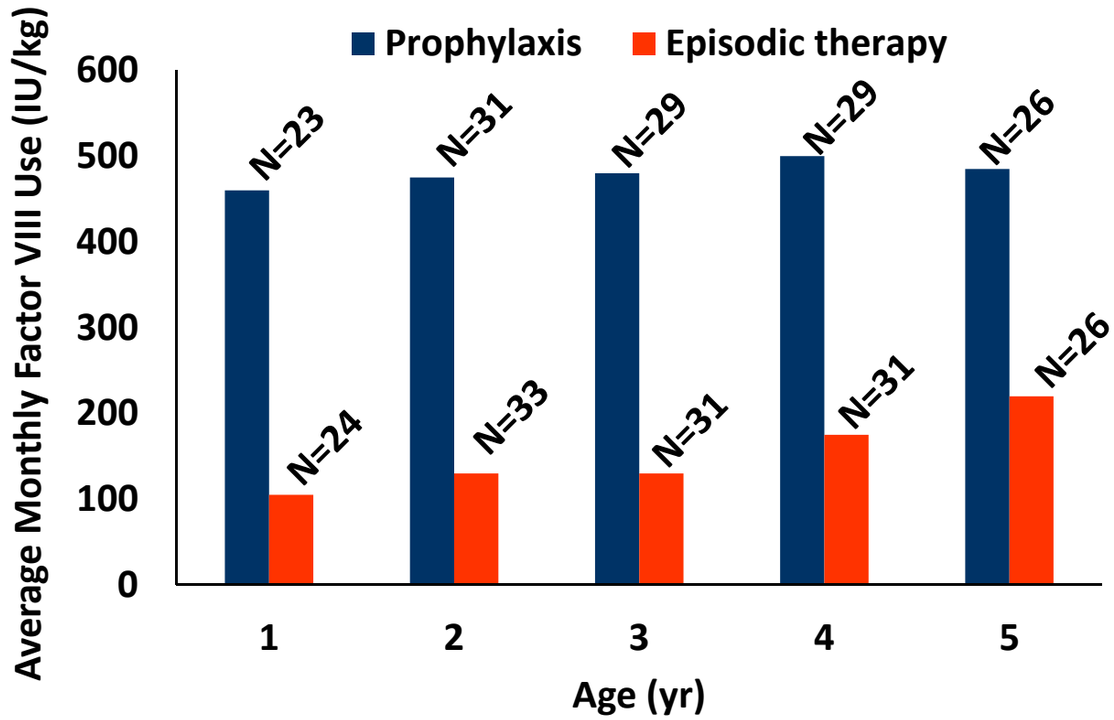
- In the Joint Outcome Study, 65 boys aged <30 months were randomly assigned to one of the following groups:
  - prophylaxis (n=32) with rFVIII
  - enhanced episodic therapy (n=33)
- At 6 years of age, normal index-joint structure on MRI was found in:
  - 93% of those in the prophylaxis group
  - 55% of those in the episodic-therapy group (*P*=0.006)
- Relative risk of MRI-detected joint damage with episodic therapy as compared with prophylaxis was 6.1 (95% CI, 1.5-24.4)
- Mean annual numbers of joint and total hemorrhages were higher at study exit in the episodic-therapy group than in the prophylaxis group (*P*<0.001 for both comparisons)



Manco-johnson MJ, Abshire TC, Shapiro AD, et al. *N Engl J Med*. 2007;357(6):535-44.

Childhood Prophylaxis in Severe Hemophilia A is Associated with Fewer Bleeding Episodes and Increased Factor Utilization





Manco-johnson MJ, Abshire TC, Shapiro AD, et al. *N Engl J Med*. 2007;357(6):535-44.

Response to Prophylaxis Studies

1994

- Medical and Scientific Advisory Council (MASAC) of NHF recommended prophylaxis as the optimal therapy for individuals with severe hemophilia

Prophylaxis has also been endorsed by the following organizations:

- World Health Organization
- World Federation of Hemophilia

2009

- More than one-third of all patients, regardless of age or severity, were on prophylaxis
- 57% of patients with *severe disease*, regardless of age, were on prophylaxis

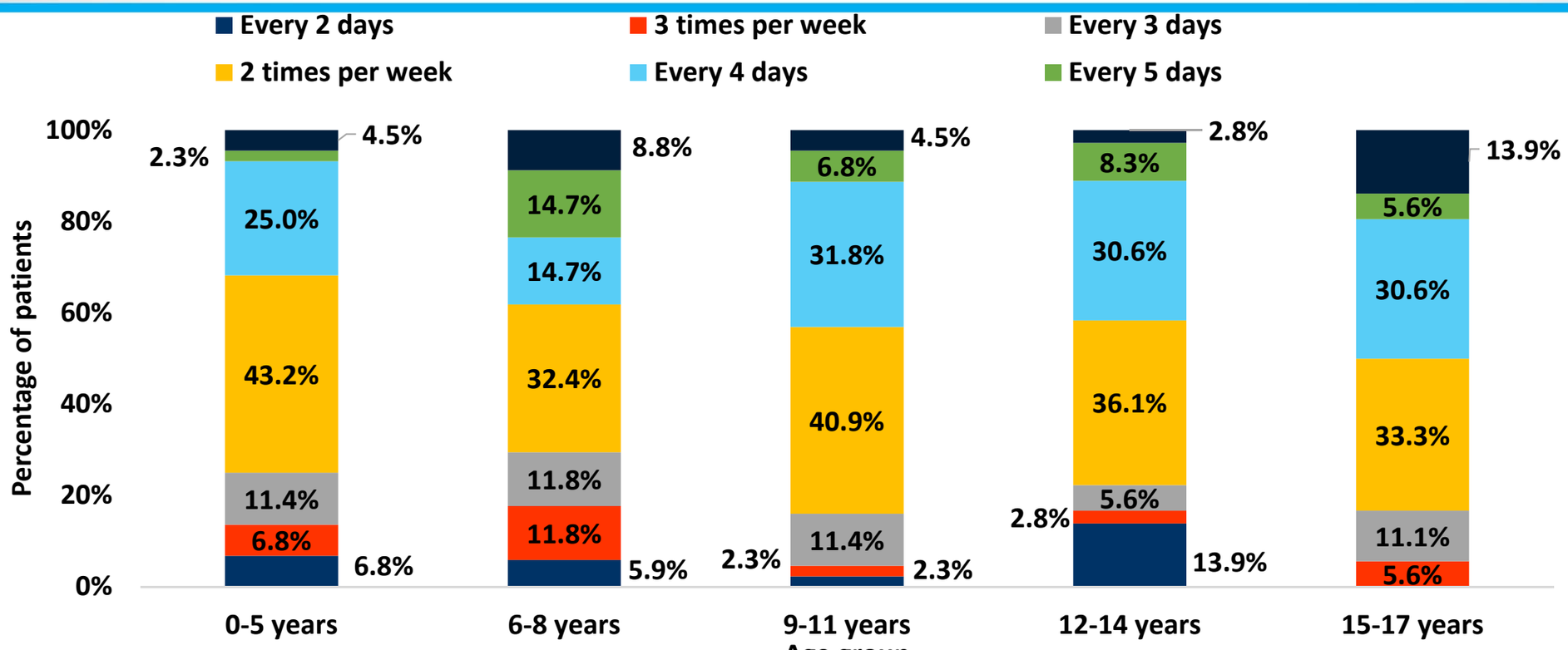
Report on the Universal Data Collection Program. Centers for Disease Prevention and Control Web site. https://www.cdc.gov/ncbddd/blooddisorders/udc/documents/report-udcprogram_january2005-december-2009_jan-2014.pdf. Published January 2014. Accessed April 2018.

Examining the Role of Longer-Acting Factor Replacement Products in Prophylaxis

- Half-life of standard hemophilia therapies requires frequent injections
  - Factor VIII – three times per week to every other day
  - Factor IX – two to three times per week
- Benefits of replacement products with longer half-life include
  - Reduced frequency of administration
  - Ability to achieve higher trough levels in certain clinical situations
  - Potentially improved adherence
- Long-acting rFVIII and rFIX have FDA approval
  - Several additional long-acting agents currently in development
- Data are available demonstrating the following in clinical application:
  - Prophylactic rFVIIIFc and rFIXFc infusion interval by age group
  - Mean medication possession ratio (MPR) before and after initiation of prolonged half-life therapy by hemophilia type and age
  - Reduction in infusion frequency with rFVIIIFc for patients previously using FVIII 3 times per week

Franchini M, Mannucci PM. *Orphanet J Rare Dis*. 2012;7:24. http://www.ojrd.com/content/7/1/24. Accessed April 2018.

Prophylactic rFVIIIFc Infusion Interval by Age Group

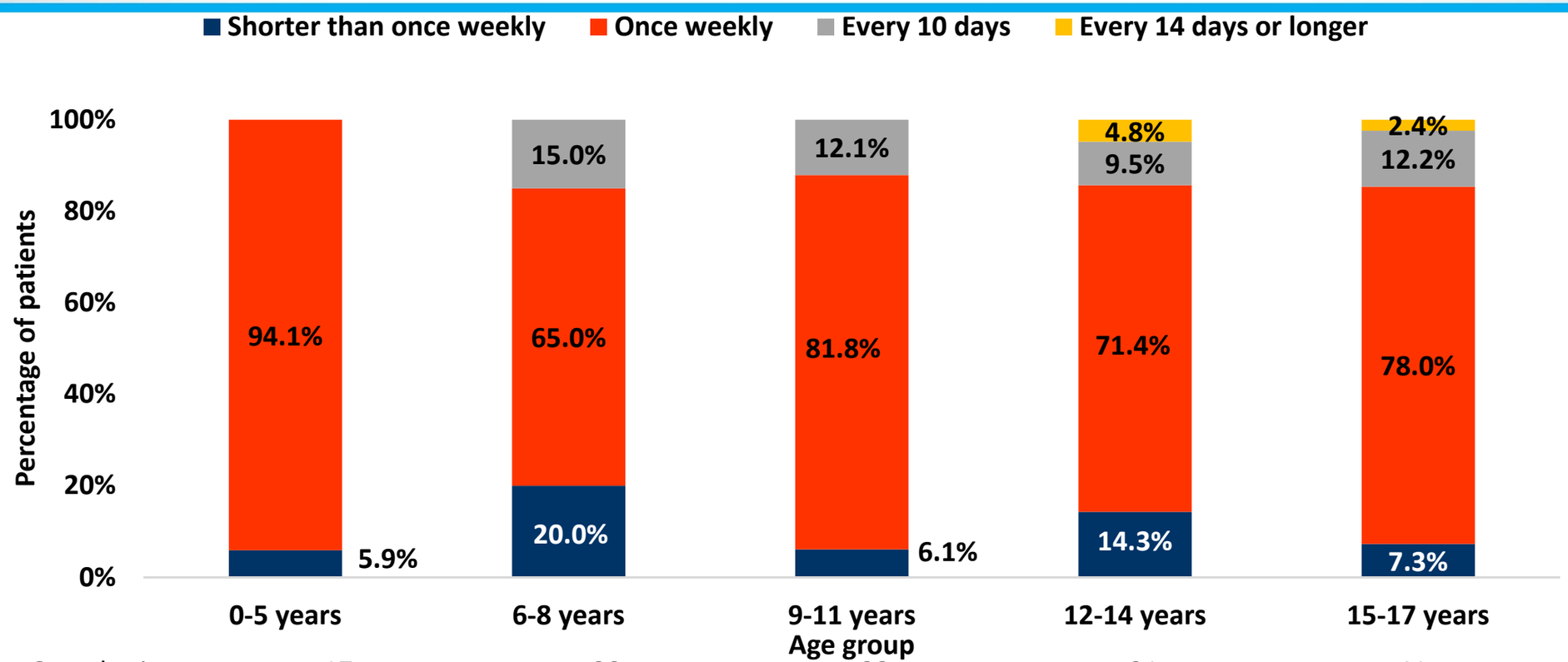


Sample size	n=44	n=34	n=44	n=36	n=36
Percentage of patients on a 2 times per week or longer dosing regiment	**75.0%**	**70.6%**	**84.1%**	**77.8%**	**83.3%**

***If a single patient had >1 infusion interval, the most recently prescribed infusion interval was used.**

Buckley BC. Real-World Dosing of RFVIIFC and RFIXFC in CHILDREN with Hemophilia. Oral presentation at Thrombosis and Hemostasis Societies of North America; April 14-16, 2016; Chicago.

Prophylactic rFIXFc Infusion Interval by Age Group

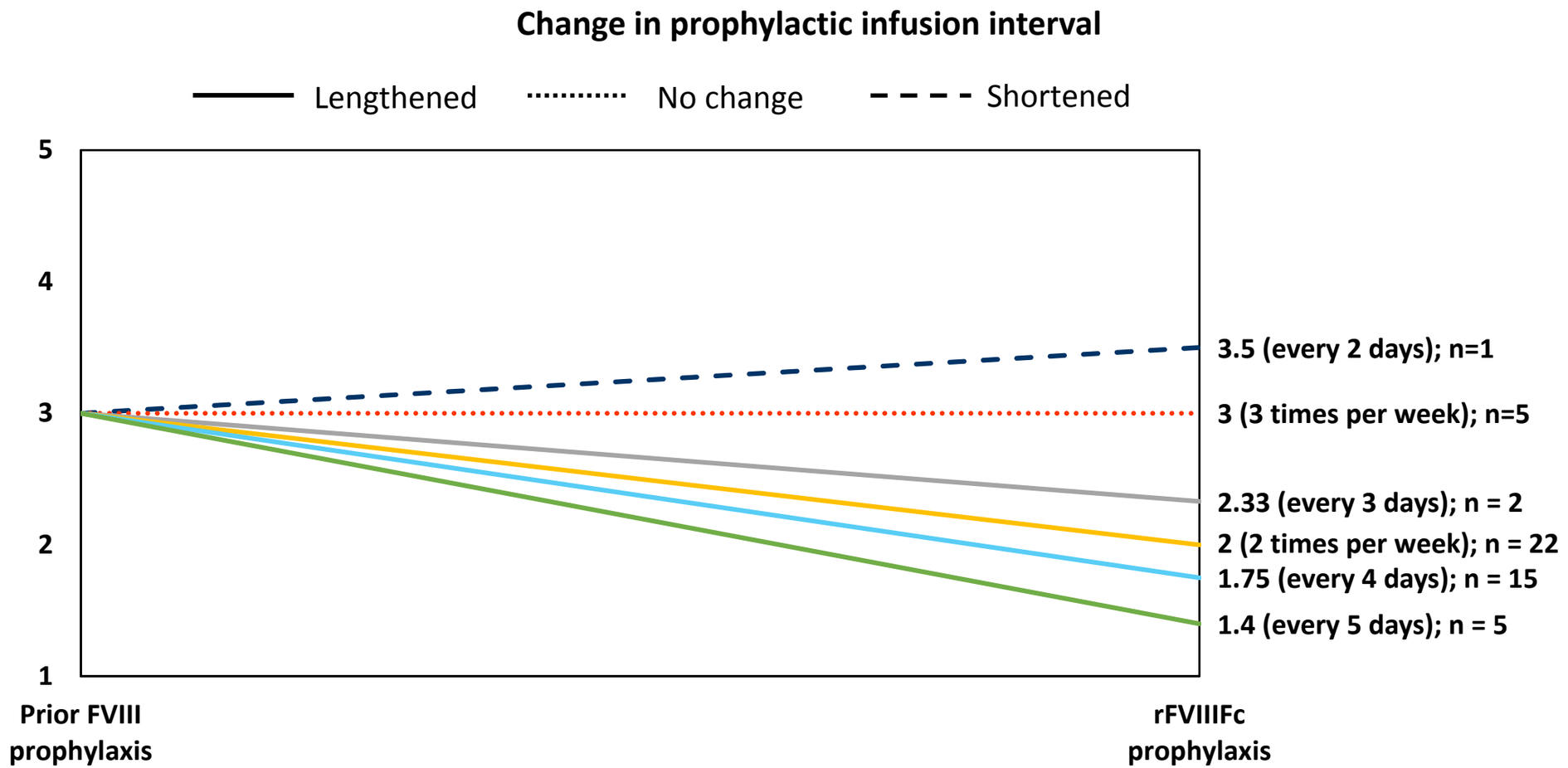


	0-5 years	6-8 years	9-11 years	12-14 years	15-17 years
Sample size	n=17	n=20	n=33	n=21	n=41
Percentage of patients on a 2 times per week or longer dosing regiment	94.1%	80.0%	93.9%	85.7%	92.7%

*If a single patient had >1 infusion interval, the most recently prescribed infusion interval was used.

Buckley BC. Real-World Dosing of RFVIIFC and RFIXFC in CHILDREN with Hemophilia. Oral presentation at Thrombosis and Hemostasis Societies of North America; April 14-16, 2016; Chicago.

Reduction in Infusion Frequency with rFVIIIFc for Patients Previously Using FVIII 3 Times per Week



[a] Excluded de-identified patient records for which prophylactic dose frequency was not known for both FVIII competitor product and rFVIIIFc.

[b] Includes only prophylaxis to prophylaxis switches.

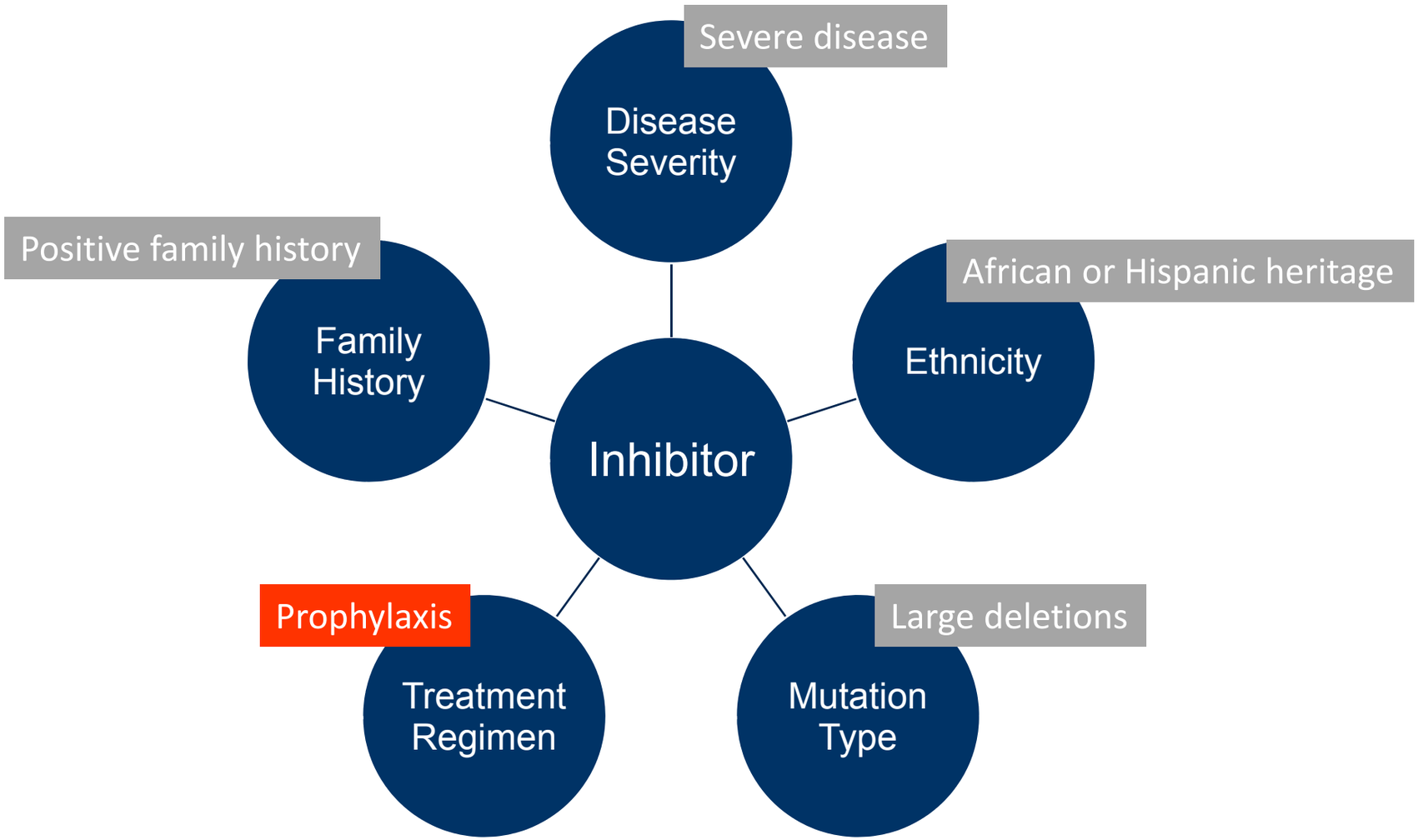
Nolan B, et al. *Haemophilia*. 2016;22:72-80.

Inhibitors

- Infusion of exogenous clotting factor can trigger an immune response
- IgG antibodies (inhibitors) directed against Factor VIII or IX protein that neutralizes the procoagulant effect of the infused factor[1]
- Incidence highest in patients with severe disease
  - Hemophilia A is 20-30%; Hemophilia B, 1-4%
- Typically develop early in life (median age 1.7 – 3.3 years)
- Greatest risk for inhibitor development occurs within the first 50 days of exposure to infused product[2]

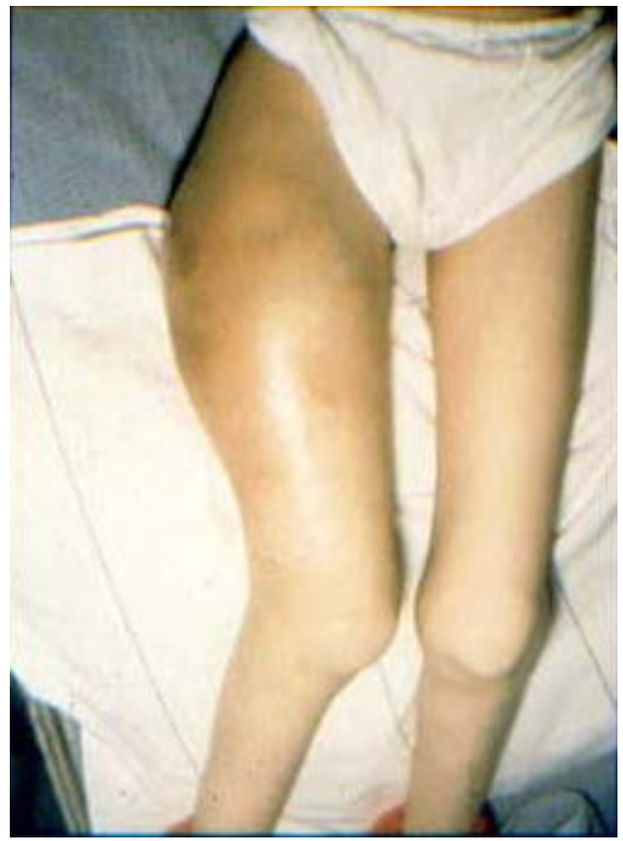
1. Hemophilia facts. Centers for Disease Control and Prevention Web site. http://www.cdc.gov/ncbddd/hemophilia/facts.html. Accessed April 2018.
2. Bray GL, Gomperts ED, Courter S, et al. *Blood*. 1994;83(9):2428-35.

Factors Contributing to Inhibitor Formation



Inhibitor Impact

- Failure of prophylaxis and on-demand therapy
- Difficulty controlling hemostasis
- Increased morbidity/mortality
- Decreased ability to perform needed or elective surgery
- Specific problems involved with FIX inhibitors



Management of Inhibitors

- Use of bypassing agents
  - Available bypassing agents:
    - Activated prothrombin complex concentrates (aPCC)
    - Recombinant FVIIa
  - Limitations include their unpredictable efficacy
  - Increasingly used prophylactically to prevent joint bleeding
    - In 78% of children and 28% of adults with inhibitors
- Prophylaxis with emicizumab-kxwh
  - Approved as a once weekly SC injection to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A with factor VIII inhibitors
- Immune Tolerance Induction (ITI)
  - Method to eradicate inhibitor
  - ~ 70% effective
- Total cost of treating inhibitors is significant
  - Short-term: More frequent bleeding, increased factor utilization
  - Long-term: Increased joint damage

1. Hemophilia facts. Centers for Disease Control and Prevention Web site. http://www.cdc.gov/ncbddd/hemophilia/facts.html. Accessed April 2018.

Emicizumab-kxwh is the First in a New Class of Non-factor Options for the Management of Inhibitors

- The approval of emicizumab-kxwh was based on data from two clinical trials: an adult and adolescent trial (HAVEN 1) and a pediatric trial (HAVEN 2)
- For patients receiving emicizumab-kxwh prophylaxis in HAVEN 1, the annualized bleeding rate (ABR) was 2.9 (95% CI; 1.7, 5.0) compared with 23.3 (95% CI: 12.3, 43.9) for patients not receiving prophylaxis corresponding to an 87% ABR reduction (95% CI: 72.3%, 94.3%), $P<0.0001$
- In HAVEN 2, the interim analysis ABR for emicizumab-kxwh-treated bleeds was 0.2 (95% CI: 0.1, 0.6) versus an ABR of 2.9 for all bleeds (treated + untreated) (95% CI: 1.8, 4.9)
- The recommended dose of emicizumab-kxwh is 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly

Oldenburg J, Mahlangu JN, Kim B, et al. *N Engl J Med.* 2017.

Other Non-factor Therapies are In Late-stage Development for Inhibitors and Other Hemophilia-related Indications

- Concizumab is a monoclonal antibody targeting tissue factor pathway inhibitor (TFPI) that can be administered SC
  - In a first human dose, phase 1, multicenter, randomized, double-blind, placebo-controlled trial escalating single IV (0.5-9000 µg kg(-1)) or SC (50-3000 µg kg(-1)) doses of concizumab were administered to healthy volunteers (n=28) and hemophilia patients (n=24)
  - A dose-dependent procoagulant effect of concizumab was seen as increased levels of D-dimers and prothrombin fragment 1 + 2
- Fitusiran is a SC administered investigational RNA interference (RNAi) therapeutic targeting the endogenous anticoagulant antithrombin (AT) as a means to improve thrombin generation and promote hemostasis in patients with hemophilia
  - In a Phase 1/2 extension study in hemophilia A and B patients, participants received SC administered, weekly or once-monthly weight-based dosing ranging from 225 to 1800 µg/kg or fixed doses of 80 mg fitusiran
  - Fitusiran dosing resulted in dose-dependent lowering of AT with a mean maximal AT lowering of 87±1% at the 80mg fixed dose and mean thrombin generation increase of 289% relative to baseline with AT lowering >75%
  - Exploratory analysis of bleed events showed a median annualized bleeding rate (ABR) of zero during the defined observation period

Waters EK, Sigh J, Friedrich U, Hilden I, Sørensen BB. *Haemophilia*. 2017;23(5):769-776.
Young G, et al. *Blood*. 2017;130(Suppl 1):85.

Gene Therapy Represents the Next Wave of Innovation in Hemophilia Research

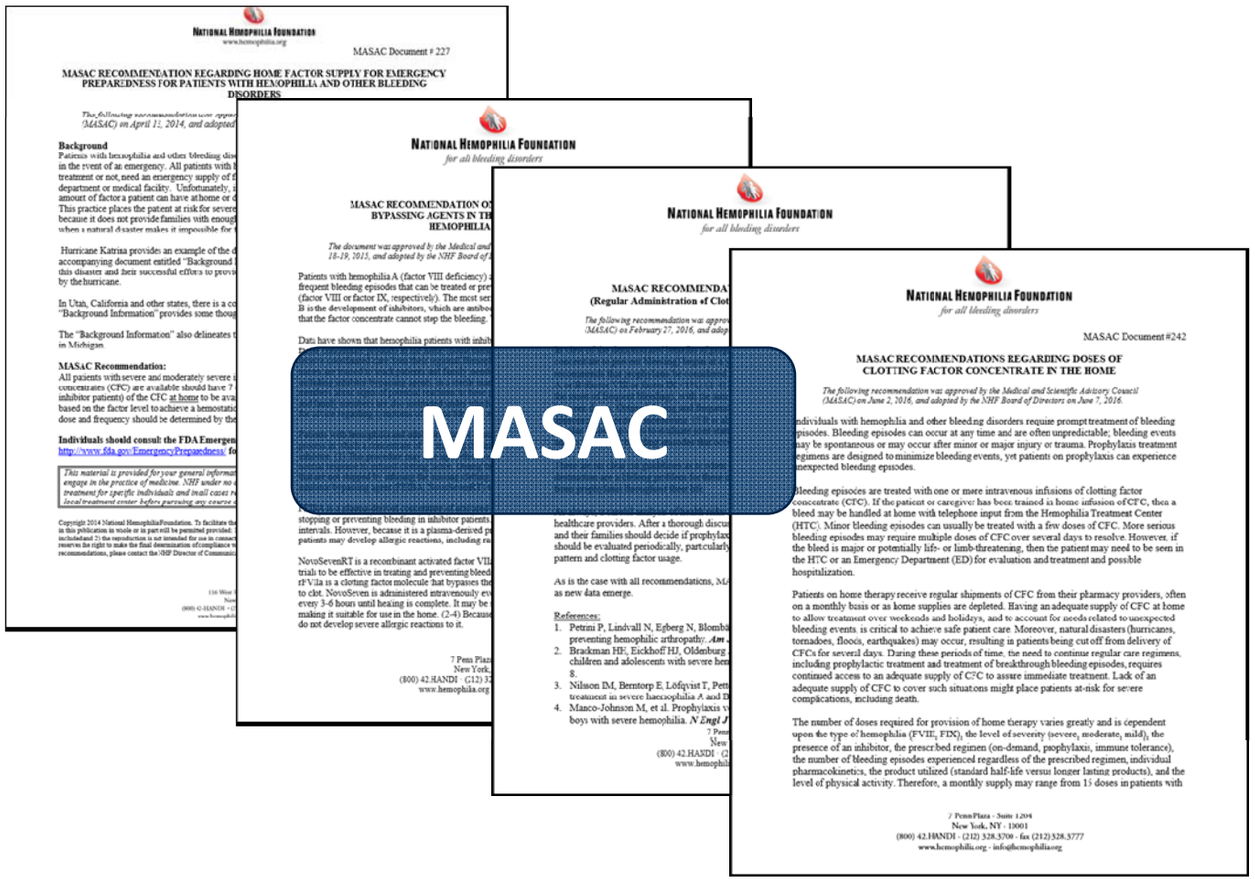
- Conventional therapy for hemophilia requires frequent intravenous infusions of the missing coagulation protein
  - To reduce dosing burden on patients with hemophilia and improve long-term outcomes, a persistent therapeutic affect through gene therapy has been the goal of specific teams of investigators.
- After a series of successes in small and large animal models, gene therapy success has been realized in humans by in vivo gene transfer to the liver using adeno-associated viral (AAV) vectors.
- Multiple, recent clinical trials have shown therapeutic, and in some cases at least temporarily curative, expression.
- Cellular immune responses against the virus have emerged as an obstacle in humans, potentially resulting in loss of expression.
  - Transient immune suppression protocols have been developed to blunt these responses.
- Gene therapies for hemophilia have progressed as far as phase 2b in the US and are anticipated to carry a cost potentially approaching $1 million per patient for a one-time treatment upon approval

Evolving Considerations in the Management of Hemophilia

- Prophylaxis
  - Target trough levels: Is 1% the best level?[1]
    - Cost: benefit ratio of targeted higher levels
    - Impact on patient outcomes and QoL
  - Impact of peak levels[2]
  - Applicable age groups – not just for pediatrics[3-4]
- Bleed treatment[5-6]
  - How long is hemostatic coverage required for healing and prevention of re-bleeding?
  - What is the best target peak level?
- What is the risk of cardiovascular disease in hemophilia?[7-9]
  - How does level of severity impact risk?
  - FVIII versus IX deficiency
  - Will prophylaxis in an older hemophilia population affect expression of underlying atherosclerotic disease?

1. Fischer K, Steen carlsson K, Petrini P, et al. *Blood*. 2013;122(7):1129-36.
2. Lindvall K, Astermark J, Björkman S, et al. *Haemophilia*. 2012;18(6):855-9.
3. Manco-johnson MJ, Sanders J, Ewing N, et al. *Haemophilia*. 2013;19(5):727-35.
4. Gringeri A, Lambert T, Street A, Aledort L. *Haemophilia*. 2012;18(5):722-8.
5. Simpson ML, Valentino LA. *Expert Rev Hematol*. 2012;5(4):459-68.
6. Sørensen B, Benson GM, Bladen M, et al. *Haemophilia*. 2012;18(4):598-606.
7. Fransen van de putte DE, Fischer K, Makris M, et al. *Thromb Haemost*. 2012;108(4):750-5.
8. Alesci S, Krekeler S, Seifried E, Miesbach W. *Haemophilia*. 2012;18(5):e364-5.
9. Konkle BA. *Am J Hematol*. 2012;87 Suppl 1:S27-32.

Treatment Guidelines Provide Evidence-based Recommendations for Delivery of Optimal Care



MASAC recommendations. National Hemophilia Foundation Web site. https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations. Accessed April 2018.
Pai M, Key NS, Skinner M, et al. *Haemophilia*. 2016;22 Suppl 3:6-16.

NHF-McMaster Guideline on Care Models

Integrated care model should be used over non-integrated care models

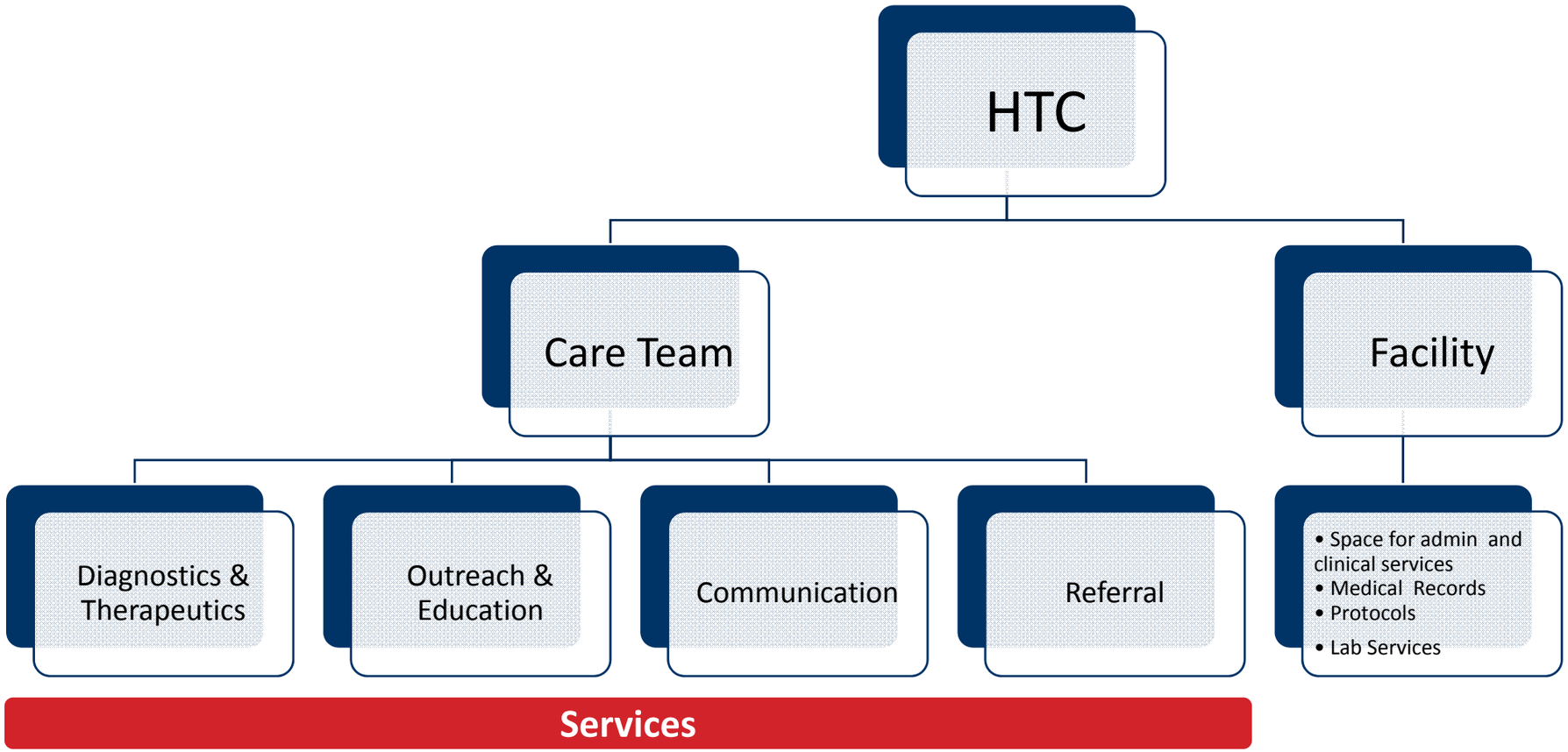
- This recommendation is even more pressing for individuals with inhibitors or individuals at risk for developing inhibitors

A hematologist, specialized hemophilia nurse, physical therapist, and social worker should be part of the integrated care team

- Round-the-clock access to a specialized coagulation laboratory is another key component of the integrated care model

Pai M, Key NS, Skinner M, et al. *Haemophilia*. 2016;22 Suppl 3:6-16.

MASAC #132: Standards and Criteria for the Care of Persons with Congenital Bleeding Disorders



MASAC recommendations. National Hemophilia Foundation Web site. https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations. Accessed April 2018.

The HTC Integrated Care Model

- A hemophilia treatment center (HTC) is a federally recognized comprehensive care facility featuring a multidisciplinary team of experts in the care of patients with bleeding disorders and whose staff spends a majority of their time caring specifically for these patients
- Key features:
    - Expertise in coagulation disorders
    - Development and provision of individual treatment plans
    - Preventive medicine
    - Access to multiple health care disciplines
    - Optimized care

Care at Comprehensive Treatment Centers Can Save Lives. CDC, 2009.

HTC Facilities. CDC, 2011.

Improving Hemophilia Outcomes Through Integrated Care

- Integrated care for hemophilia is defined as the continuous supervision of all medical (including factor replacement utilization) and psychological aspects affecting the patient and family
- Optimal treatment is based on:
  - Early detection and diagnosis
  - Prevention and early treatment of bleeding episodes and any complications, particularly hemophilic arthropathy
  - Detection and management of inhibitors
  - Psychosocial and educational support
  - Monitor for treatment-related comorbidities
  - Coordination of care with other providers and payers involved in management of the patient

Ruiz-Sáez A. *Hematology*. 2012;17 Suppl 1:S141-3.

Summary

- Hemophilia is characterized by significant morbidity, with clinical manifestations including bleeding in the joints (hemarthrosis) and muscles
  - Long-term complications include joint destruction, muscle atrophy, and decreased quality-of-life
- Prophylactic factor replacement may avoid or reduce musculoskeletal impairment from hemophilic arthropathy and enhances quality-of-life
  - Longer-acting factor products have been approved in recent years and play a role, specifically in prophylaxis
- Inhibitor development is the most severe complication of hemophilia treatment and has significant clinical and economic consequences
  - Emerging non-factor therapies represent a potential new option for the management of inhibitors
- Current guidelines and recommendations recognize the value of the HTC model for improving clinical and economic outcomes via multidisciplinary, integrated care

Challenges and Opportunities in the Optimal Management of Hemophilia

Michael Zeglinski, RPh
Senior Vice President, Specialty Pharmacy
OptumRx®/BriovaRx®

Hemophilia Challenges and Opportunities for Managed Care Stakeholders

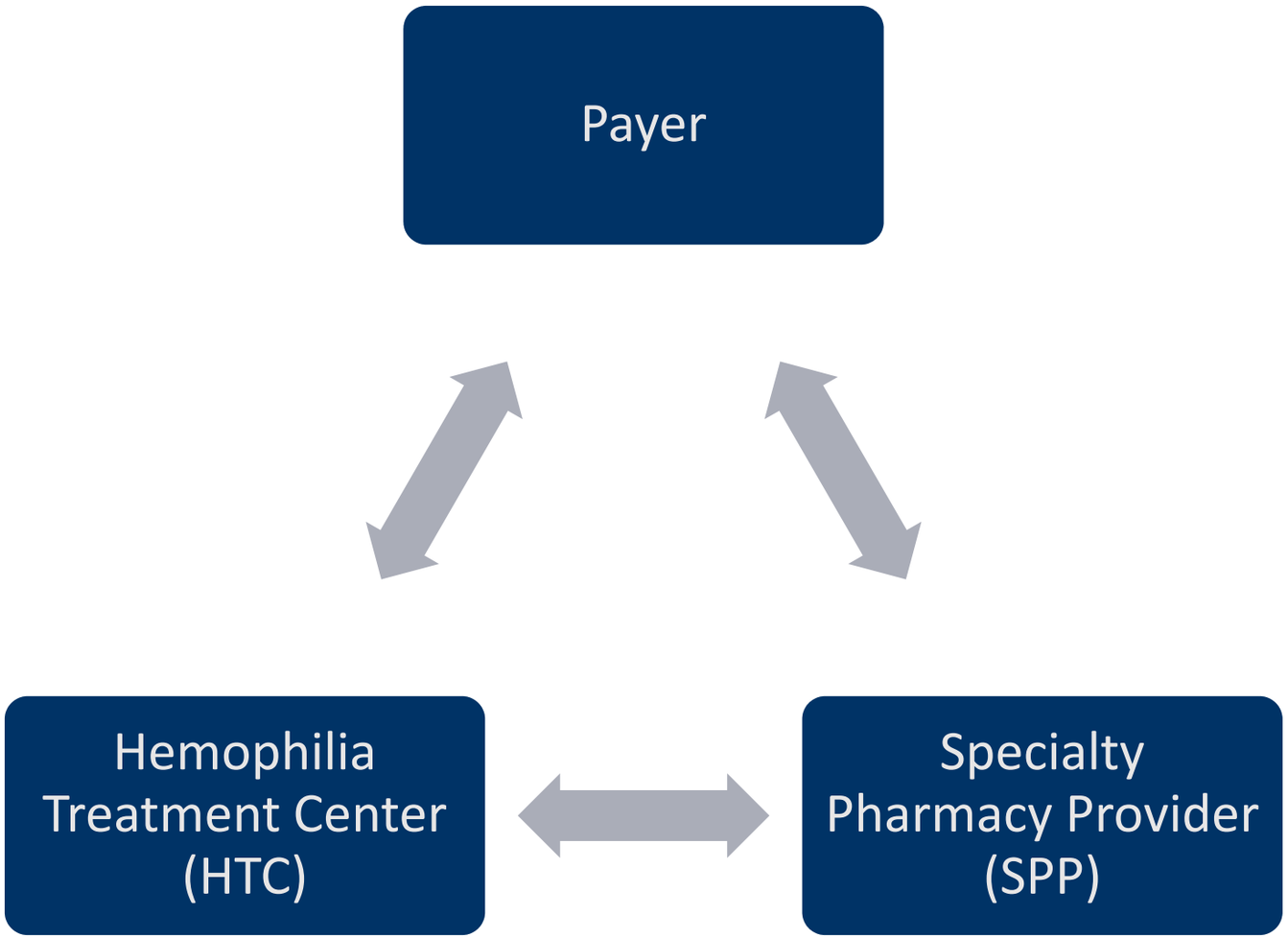
Challenges

- Factor costs dominate total cost of care
- Potential impact of cost-sharing on patients' adherence
  - Cost-sharing is increasing in response to growing health care costs
- Potential of investment in care today to achieve improved long-term clinical outcomes and cost savings
  - Short-term care approaches for patients with inhibitors can yield long-term cost savings

Opportunities

- Capitalizing on capabilities of, and enhancing relationships with, HTCs, SPPs, and NHF
  - Collaboration to achieve higher quality and more cost-effective care
- Encouraging care consistent with best clinical practices
  - Apply evidence-based guidelines, ie, MASAC Quality of Care Recommendations
- Better understanding of needs and coordination of care between HTCs, community hematologists, SPPs, and payers

Opportunities Exist for Collaboration between Payers, HTCs, and SPPs



HTC Integrated Pharmacies and SPPs Can Provide an Array of Services for Patients with Bleeding Disorders

Services Designed to Improve the Overall Quality of Care and Manage Disease-Related Costs

Disease Management and High-touch Pharmacy Services

Integrated HTC Pharmacy and SPP Services

- Home delivery of factor
- Coordination of nursing services
- Assay management
- Patient education/on-demand consultation
- Treatment logs
- Monitoring bleeding episodes as needed/requested

Outcomes

- Improved access to care/home therapy
- Reduced variance in dispensed dose
- Improved adherence
  →Reduced bleeding complications
  → Reduced ER visits/hospitalizations/ hospital LOS

LOS=length of stay

Specialty Pharmacy Providers Offer Broad Spectrum of Services

SPP may offer different areas of expertise, as well as varying geographic capabilities and services:

Full-service specialty pharmacies

- Support several chronic specialty conditions and may or may not have disease-specific areas of expertise

Hemophilia specialty pharmacies

- Focus exclusively on serving patients with bleeding disorders and possible comorbidities

Advanced therapy specialty pharmacies

- Focus on limited, specific specialty area/conditions

Infusion specialty pharmacies

- Focus on conditions requiring infused medications

Specialty Pharmacy Can Play an Integral Role in Improving Quality and Managing Costs

Patient

- Access to appropriate site of service
- Holistic care model to address clinical and socioeconomic elements

Outcomes

- Promoting adherence
- Focused on high-quality care

Payer

- Demonstrate quality care services via data sharing
- Meet network requirements for inclusion
- Controlling spend via coordination and quality of care

Issue Brief: Specialty Drugs—Issues and Challenges. America's Health Insurance Plans Web site. https://www.ahip.org/wp-content/uploads/2015/07/IssueBrief_SpecialtyDrugs_7.9.15.pdf. Published July 2015. Accessed March 2018.

Home-based Care Initiatives Have Been Adopted Across Many Health Care Settings

- 72% of respondents to a recent survey have implemented a home-based care program
- Ongoing care management was the principal goal of home care for 46% of respondents
- Priority populations for home care included the frail elderly and homebound (69%), the medically complex (69%), and individuals recently discharged from the hospital (68%)
- Primary task during the visit for 81% of respondents was patient and caregiver education, with an emphasis on medication reconciliation (80%)

N=107 organizations; 37% hospitals or health systems; 16% health plans; 16% case management organizations; 10% physician practices; 9% home health providers, 22% "other"

Home Visits in 2017. HINtelligence Report. The Healthcare Intelligence Network Web site. http://www.hin.com/library/HomeVisits2017.pdf. Published February 2017. Accessed April 2018.

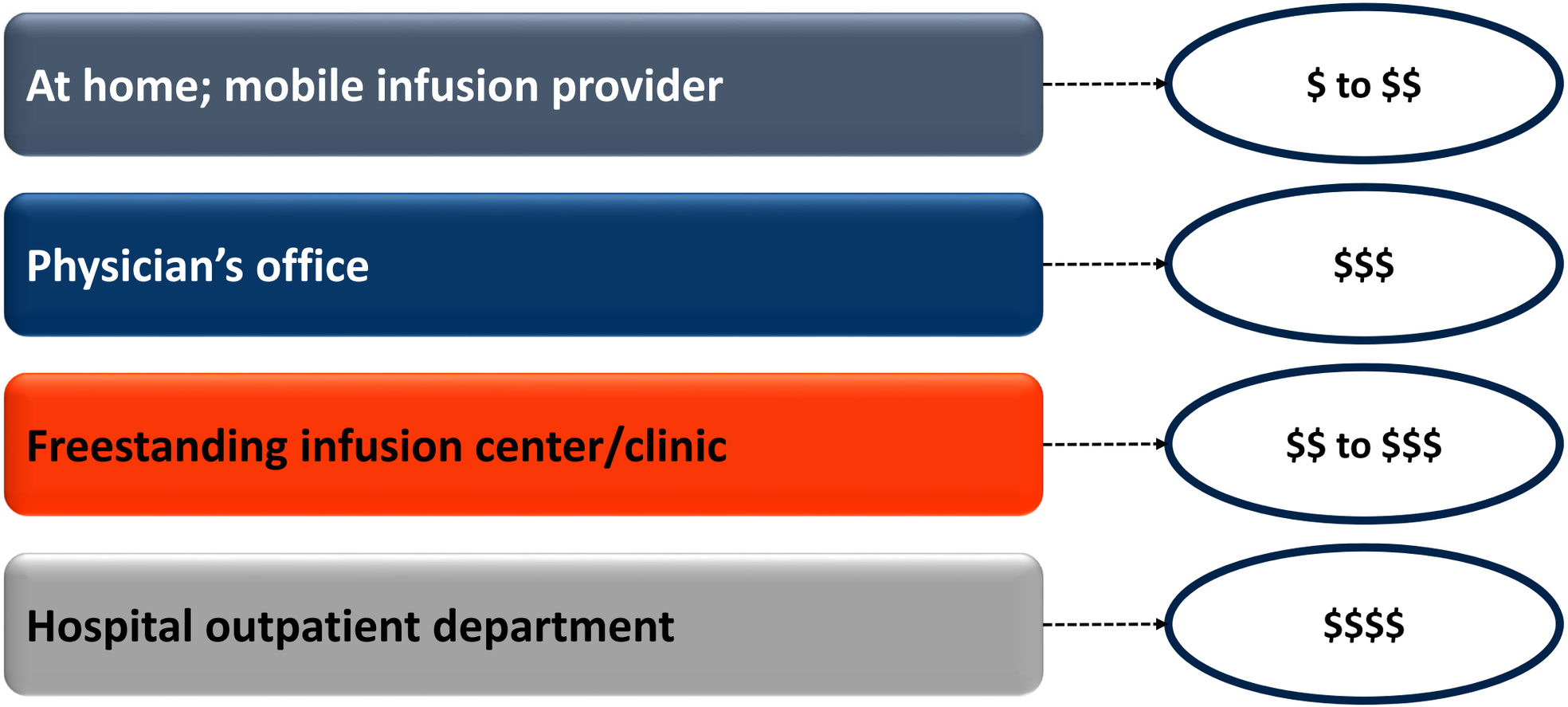
Perceived ROI of Home-based Care is High

- 10% report ROI from home visits falling between 2:1 and 3:1, with 5% reporting home visit-related ROI >5:1
- 87% report increased medication adherence as a result of home visits
- 70% reported reduced hospital readmissions and in ER visits attributed to home visits

N=107 organizations; 37% hospitals or health systems; 16% health plans; 16% case management organizations; 10% physician practices; 9% home health providers, 22% “other”

Home Visits in 2017. HINtelligence Report. The Healthcare Intelligence Network Web site. http://www.hin.com/library/HomeVisits2017.pdf. Published February 2017. Accessed April 2018.

Home Infusion: Lower Cost Site of Care that is Vital in the Management of Hemophilia



Consequences of a Lack or Delays in Access to Factor

- Causes delayed response time to treat bleeding episode
  - Available guidelines recommend immediate treatment of bleeding episodes and the utilization of home-based care whenever possible
  - HTC integrated pharmacies and external SPPs strive to provide the most immediate treatment possible
- Increased morbidity can result in increased long-term cost
  - Lack of immediate treatment may result in further complications and increased factor utilization to resolve bleeding episodes, increasing costs
- Increased mortality

Srivastava A, Brewer AK, Mauser-bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19(1):e1-47. Accessed online April 2018 at World Federation of Hemophilia Web site https://www1.wfh.org/publication/files/pdf-1472.pdf.

Who Keeps Factor At Home?

- Severe patients
  - For prophylaxis treatment
  - Emergency doses should be kept at home for breakthrough bleeding, in addition to the prophylactic doses
- Moderate-to-severe patients
  - Treating on-demand
  - Emergency doses
- Mild/moderate patients
  - Those who do not have local access to clotting factor/live a great distance from treatment facility
  - Moderate patients who experience easily precipitated or increased number of spontaneous bleeds
  - Emergency doses

Providing Clotting Concentrate in the Home Setting

- MASAC Recommendation 188
  - Specialty pharmacy providers should be:
    - Knowledgeable about bleeding disorders, factor, and ancillary supplies
    - Able to keep a full range of factor and supplies on hand
    - Able to fill orders within 48 hours
    - Able to fill orders within 12 hours in emergency situations, with a goal of 3 hours where logistically possible

MASAC Recommendation 242

- The number of doses required in the home depends on a variety of factors, including the number of breakthrough bleeding events anticipated based on past number of such bleeds

MASAC=Medical and Scientific Advisory Committee of the National Hemophilia Foundation

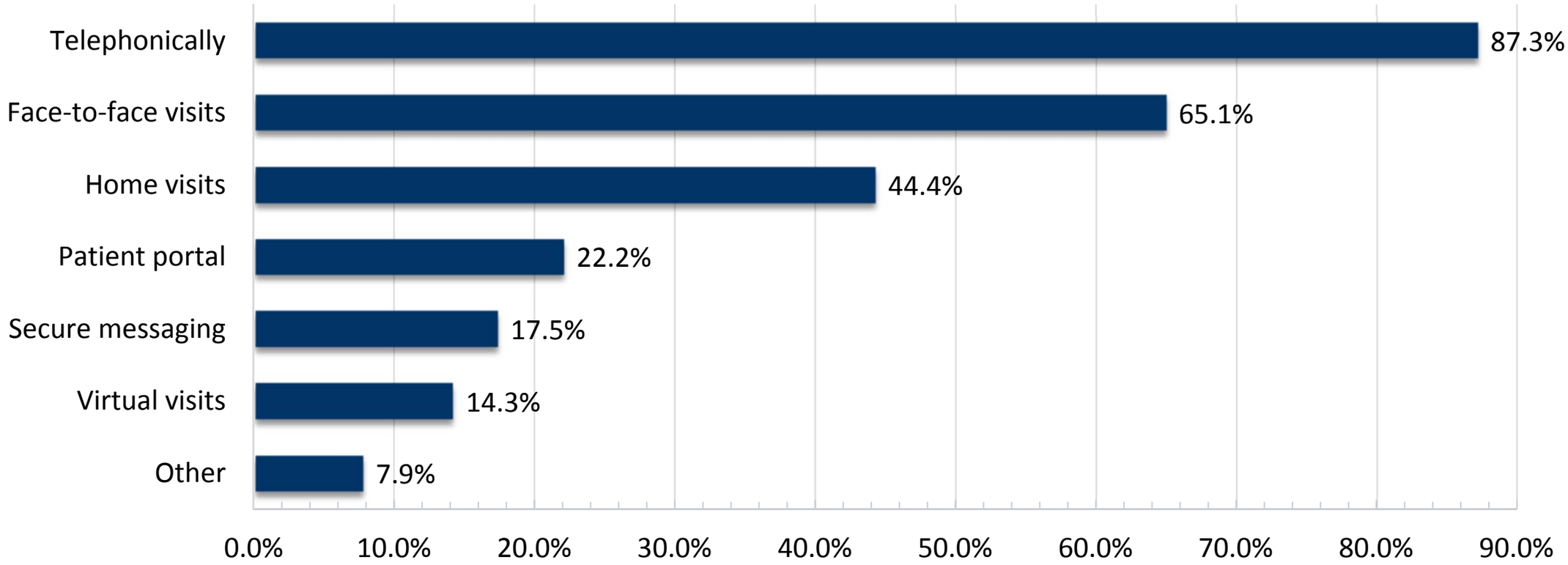
Challenges and Opportunities Related to Home Infusion

Gold Standard in Hemophilia Care: *Teach patients/caregivers to self-infuse/infuse*

Advantages	**Disadvantages**
Ability to infuse on a regular schedule (prophylaxis) without disruptions in work and school	Difficulty obtaining venous access
Prompt treatment of bleeding episodes when they occur ▪ Current recommendations: Within 1-3 hours of onset of bleeding	Patient/caregiver availability
Ability to travel with confidence	Requires patient/caregiver to take full responsibility for each treatment; inappropriate response to bleeds
Decreased health care-related cost and patient-related impact ▪ Cost of medical facility ▪ Cost of nursing care ▪ Travel costs ▪ Time away from school/work	Potentially inadequate supply of factor and ancillary supplies in certain scenarios
Patient autonomy	Reduced provider oversight

Remote Strategies are Increasingly Common in Chronic Disease Interventions, Particularly Telephonic Management

How is chronic care management conducted?



N=110 organizations; 28% hospitals, 17% health plans, 13% physician practices, 13% disease management or health coaching organizations, 12% independent practice associations (IPAs), and 15% "other"

Chronic Care Management in 2017. HINtelligence Report. The Healthcare Intelligence Network Web site. http://www.hin.com/library/ChronicCareManagement2017.pdf. Published April 2017. Accessed April 2018.

By Leveraging Technology, Telehealth Continues to Gain Popularity

- Health care organizations using telehealth rose from 63% in 2015 to 74% in 2018
  - 35% have engaged a third-party provider to manage telehealth functions
- Virtual provider visits topped the list of telehealth applications for 2018
  - Adoption of virtual visits jumped from 45% to 61%
- Medicare use for telehealth reached 53% this year up from 47% in 2015

N=73 organizations; 19% hospitals or health systems, 12% employers, 8% physician organizations, 6% either health plans, primary care, or specialists, and 38% “other”

Telehealth and Remote Patient Monitoring in 2018. HINtelligence Report. The Healthcare Intelligence Network Web site. http://www.hin.com/library/TelehealthRemoteMonitoring2018.pdf. Published February 2018. Accessed April 2018.

The Perceived ROI of Telehealth Initiatives is High

- 91% of respondents to a recent survey report that telehealth has improved access to care for served populations
- 71% attribute a drop in hospital readmissions to telehealth initiatives
- 69% experienced an increase in organizational efficiency as a result of telehealth implementation

N=73 organizations; 19% hospitals or health systems, 12% employers, 8% physician organizations, 6% either health plans, primary care, or specialists, and 38% “other”

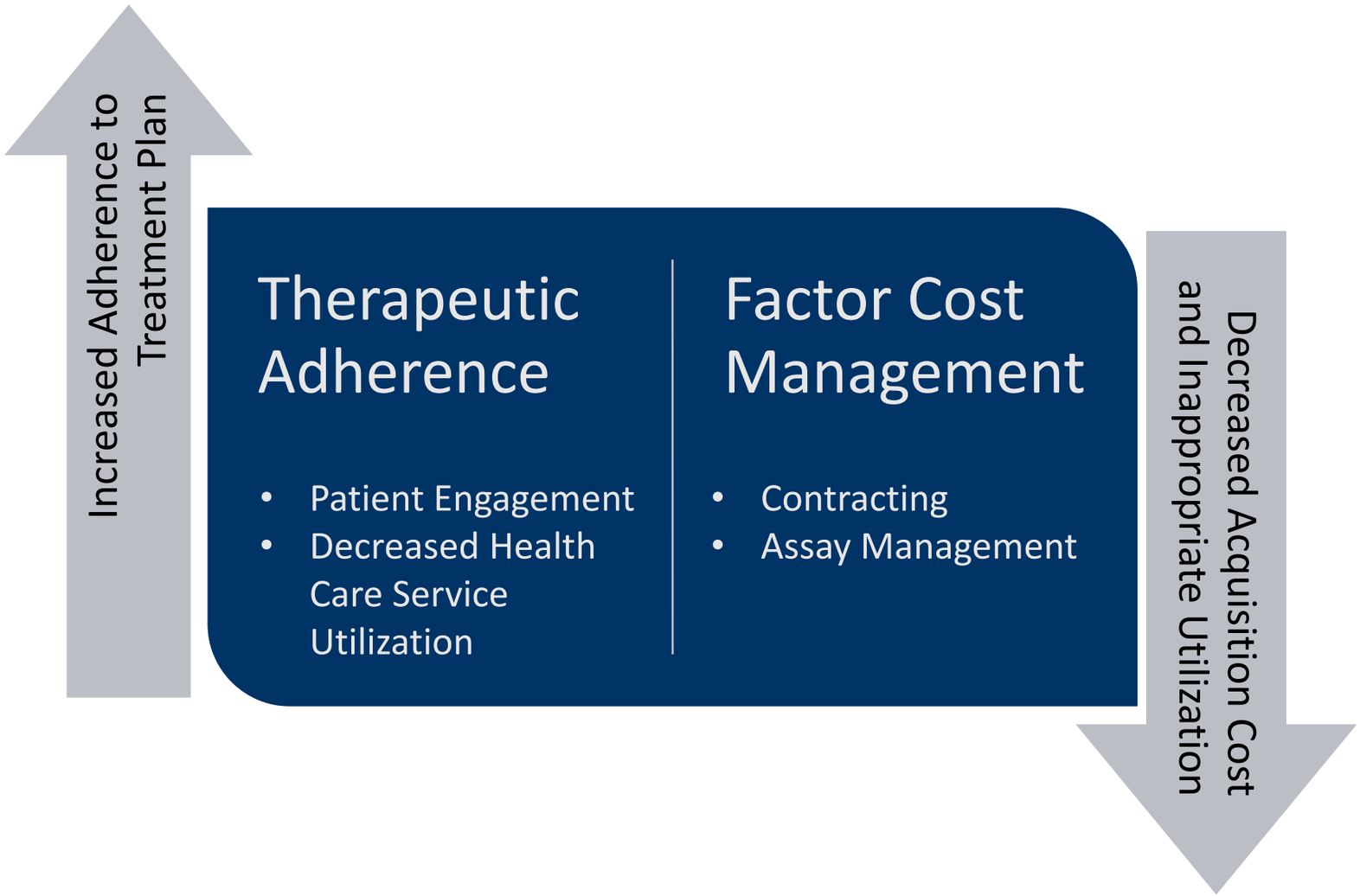
Telehealth and Remote Patient Monitoring in 2018. HINtelligence Report. The Healthcare Intelligence Network Web site. http://www.hin.com/library/TelehealthRemoteMonitoring2018.pdf. Published February 2018. Accessed April 2018.

Summary

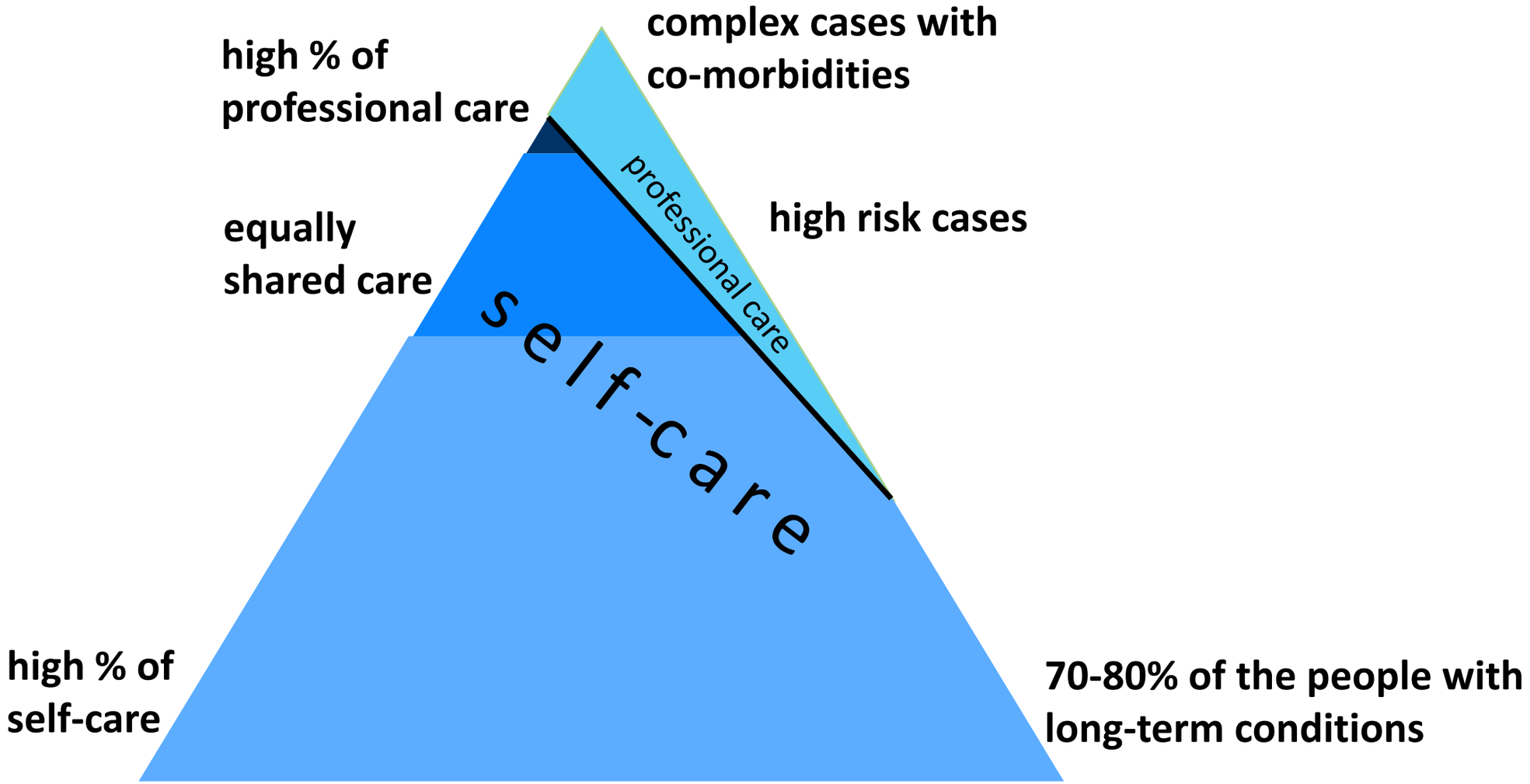
- Collaboration between payers, SPPs, and HTCs is necessary to address the challenges and leverage the opportunities in hemophilia management
- SPPs provide a wide breadth of services in the management of hemophilia, the most noteworthy being those pertaining to home infusion and patient education
- Home-based care initiatives are widespread in chronic care management, but telephonic monitoring and telehealth initiatives are gaining traction

Patient Adherence Strategies and Factor Cost Management: Recommendations for Managed Care Pharmacy

Therapeutic Adherence and Factor Cost Management Represent Two Key Areas of Hemophilia Pharmacy Management



With the Exception of the Most Complex and Severe Cases, Self-Care Comprises the Largest Share of Chronic Disease Management



Kennedy A, Rogers A, Bower P. *BMJ*. 2007;335(7627):968-70.

Patient Engagement Has Been Termed "The Blockbuster Drug of the Century"

- Patients can play an integral role in improving the quality, safety, and cost of health care interventions
- Furthermore, the importance of patient engagement as an essential component of high-quality health care has been recognized worldwide
- The parameters shown to be influenced by patient engagement is extensive include the following:
  - Improved clinical outcomes (improved treatment adherence, faster recovery, and reduced mortality rates)
  - Reduced health care resource utilization (fewer hospitalizations, ER visits, etc)
  - Improved service quality

Chase D. Patient engagement is the blockbuster drug of the century. *Forbes.* https://www.forbes.com/sites/davechase/2012/09/09/patient-engagement-is-the-blockbuster-drug-of-the-century/#5eaa75b56381. Published September 9, 2012. Accessed March 2018.

Patient Engagement Strategies are Widespread and Focus on Patient and Caregiver Education

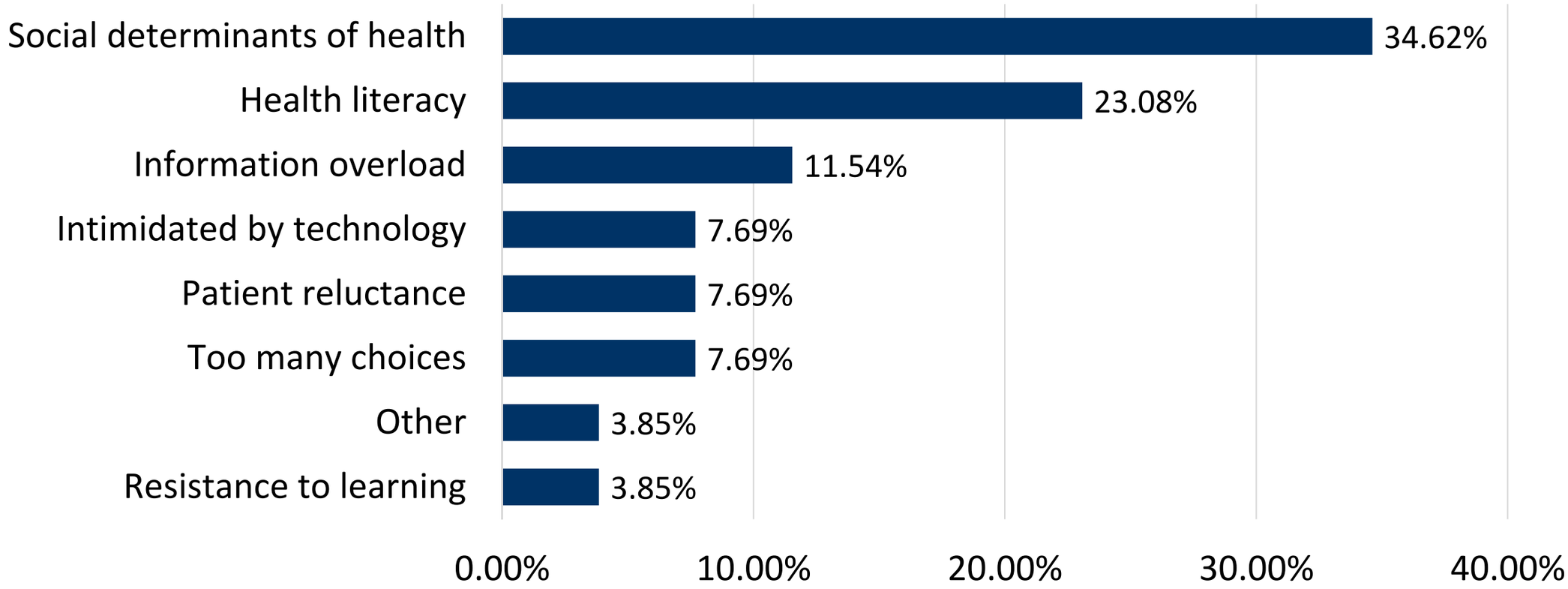
According to a recent survey…

- 71% created formal patient engagement programs, with 45% of the remaining slated to launch a program in the coming year
- 63% mine clinical data analytics to risk-stratify individuals for engagement efforts
- 37% employ social determinants of health (SDOH) screenings of patient populations to target individuals for patient engagement interventions
- To improve engagement, 75% respondents focus on education of patients, family and caregivers
- ~20% rate education as the most effective engagement tool, closely followed by telephonic outreach (13%) and home visits (13%)
- On the technology side, a patient-centered platform or portal anchors 63% of patient engagement initiatives

N=75 organizations; 30% hospitals or health systems, 25% population health, 12.5% physician practices, 5% health plans, and 30% “other”

Patient Engagement in 2017. HINtelligence Report. The Healthcare Intelligence Network Web site. http://www.hin.com/library/PatientEngagement2017.pdf. Published September 2017. Accessed April 2018.

Barriers to Patient Engagement



N=75 organizations; 30% hospitals or health systems, 25% population health, 12.5% physician practices, 5% health plans, and 30% “other”

Patient Engagement in 2017. HINtelligence Report. The Healthcare Intelligence Network Web site. http://www.hin.com/library/PatientEngagement2017.pdf. Published September 2017. Accessed April 2018.

Engaging the Patient: Techniques

Using specific methods demonstrate empathy
and empower patients to be stewards of their own care

- Shared Decision-making
  - An approach that de-emphasizes “adherence” as the primary goal
  - Focuses on a prophylaxis plan that is customized by the clinicians in conjunction with the patients and aligned with patient priorities
- Motivational Interviewing
  - Collaborative, patient-centered form of information exchange to facilitate constructive patient communications and address a patient’s motivation for change
  - Important when working with patients who are non-adherent with their treatment regimen or have fears about having to infuse themselves or their children

Shared Decision-making

Foster Approach that Meet the Patients Where They Are and Encourages Introspection

Gue D, Squire S, Mcintosh K, et al. *J Multidiscip Healthc.* 2015;8:527-34.

Motivational Interviewing Techniques

Scenario	Technique	Example
General Medication Nonadherence	Elicit-Provide-Elicit	"Can you tell me what you know about how clotting factor replacement works and how you're supposed self-administer it?" [Patient response] "Yes, most of that is true, but you must be careful not to miss doses or you may experience a bleed."
	Decisional Balance	"Would you mind listing the pros and cons of infusing regularly as well as the pros and cons of not infusing?" [Patient obliges] "It looks like the benefits outweigh the disadvantages in the long-run, wouldn't you agree?"
Medication Nonadherence Related to Perceived Ineffectiveness	Reflective Listening	"It sounds like you're a little annoyed that you have to infuse three times per week and don't see any concrete benefit from it. Unfortunately, you won't necessarily get the 'proof' that your prophylaxis is working until you *don't* infuse and experience a bleed."
	Validation	"I can totally understand your frustration. You have to take time out of your busy life to infuse factor and your life goes on with no noticeable difference. The fact is, this treatment provides long-term benefits for bleed prophylaxis and joint health."
Medication Nonadherence Related to Adverse Events	Open Questions	"Tell me about what side effects are bothering you the most… And how are the injection site reactions effecting your daily activities?" [Patient responds] "Well unfortunately, that's a completely normal reaction you're having. Have you considered alternating arms? They may become less burdensome if you're not regularly infusing in the same arm."

Miller WR, Rollnick S. *Motivational Interviewing: Helping People Change*. Third Edition. 2012; New York, NY: Guildford Press; 2012.

Engaging the Patient: Tactics

For infusions and/or bleeds

Patient logs/diaries

For education and administration as needed

24/7 pharmacy on-call support and in-home nursing

Ongoing consultation

Regularly scheduled or follow-up calls

Hotlines or messaging systems

To reach the dedicated clinical team directly for pharmacy reorders, questions, or clinical consultation

Common Adherence Issues Reported with Hemophilia Treatment

- Inappropriate dose: under- or over-dosing of factor
- Delay of >3 hours before treating
- Not using rest, ice, compression, and elevation (RICE)
- Inappropriate timing of-prophylaxis dosing
- Not maintaining immune tolerance regimen
- Mismanagement of factor and supply inventory
- Venous access difficulties
- Failure to keep scheduled HTC visits
- Psychosocial issues

Coordination between the medical care team and either the HTC integrated pharmacy or SPP is vital to mitigating issues and improving outcomes

Innovative Tools and Resources Can Promote Engagement and Adherence

Live Multimedia

Live video education and counseling sessions with pharmacist

Web-based Tools & Mobile Apps

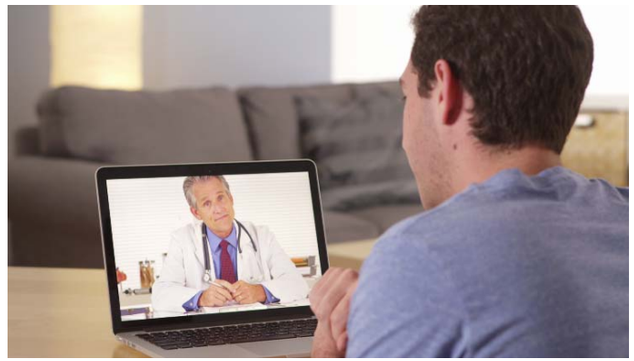
Easily accessible information to connect patients with education tools and community resources

Written Patient Information Guide

Written resources to promote understanding of condition and treatment

Community Resources

Educational and instructional videos designed to engage patients in disease management and treatment

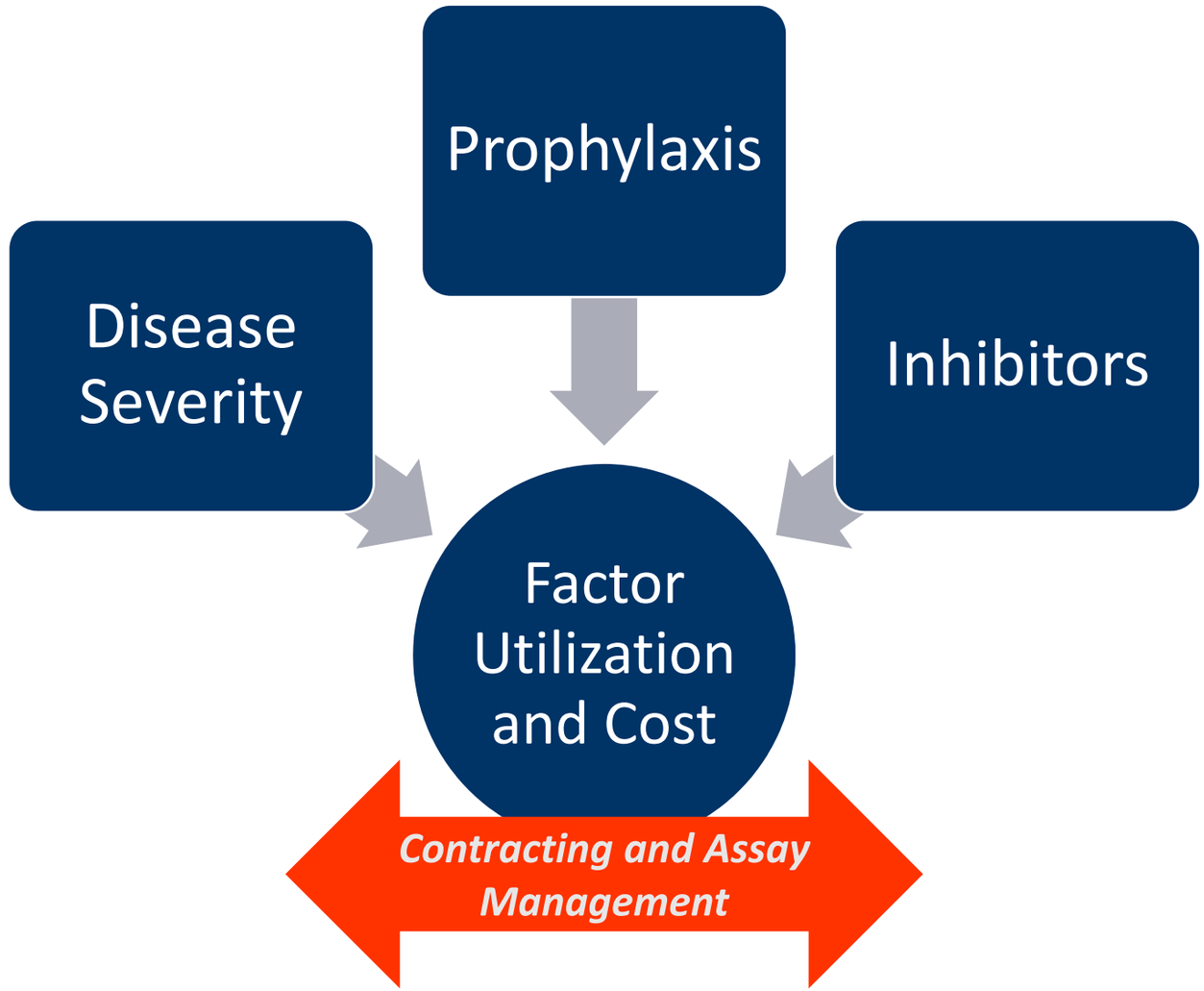


Important Components of Hemophilia Patient Education Messaging

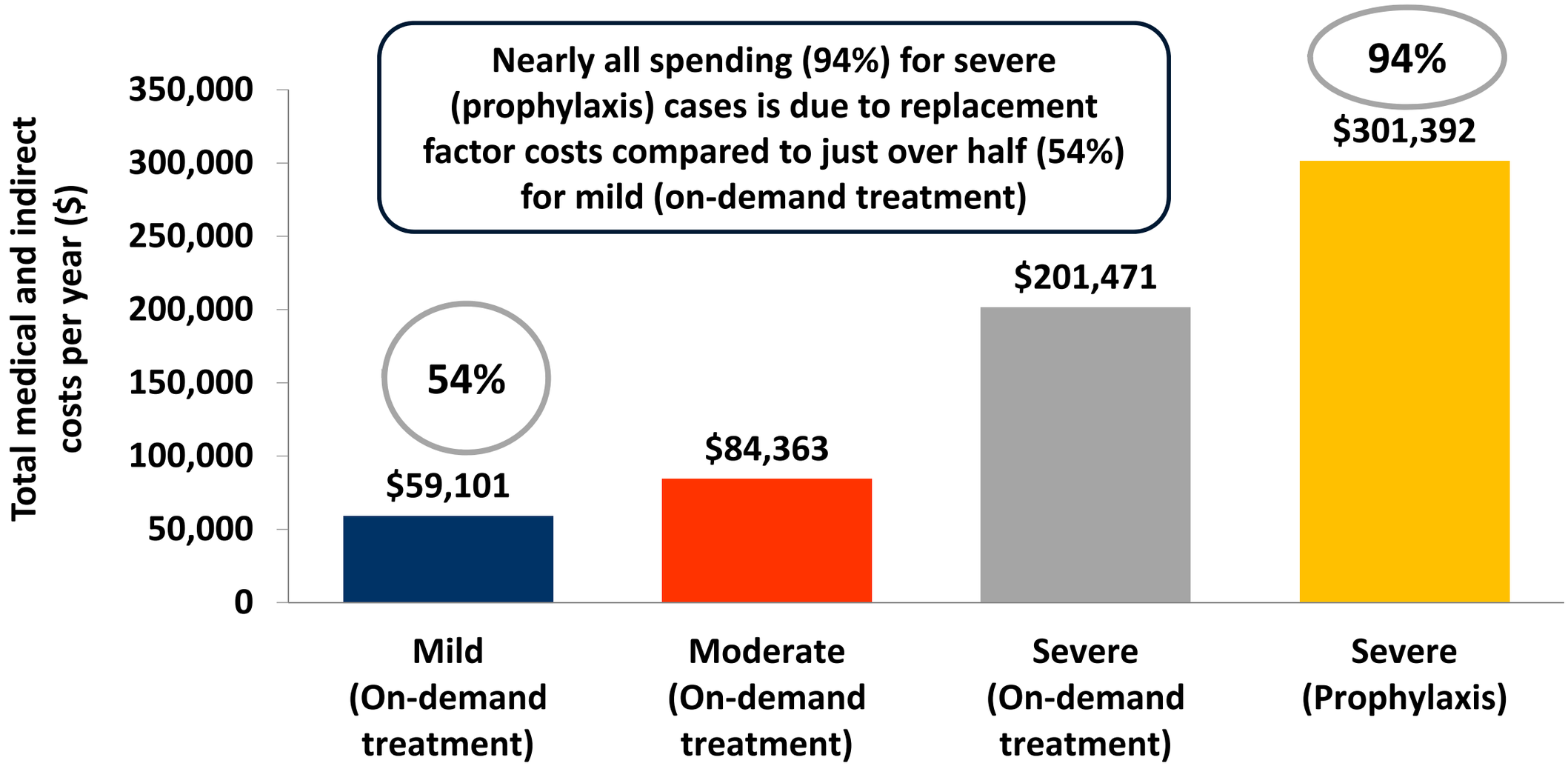
- Highlighting the importance of adherence
- Self-administration technique and training
- Preparing for and coping with adverse events
- Clotting factor concentrate storage
- Identification and immediate treatment for breakthrough bleeding

Bauer KA. *Am J Manag Care*. 2015;21(6 Suppl):S112-22.

Factor Cost Management Requires a Multifaceted Understanding of Elements Influencing Specialty Utilization and Expenditures

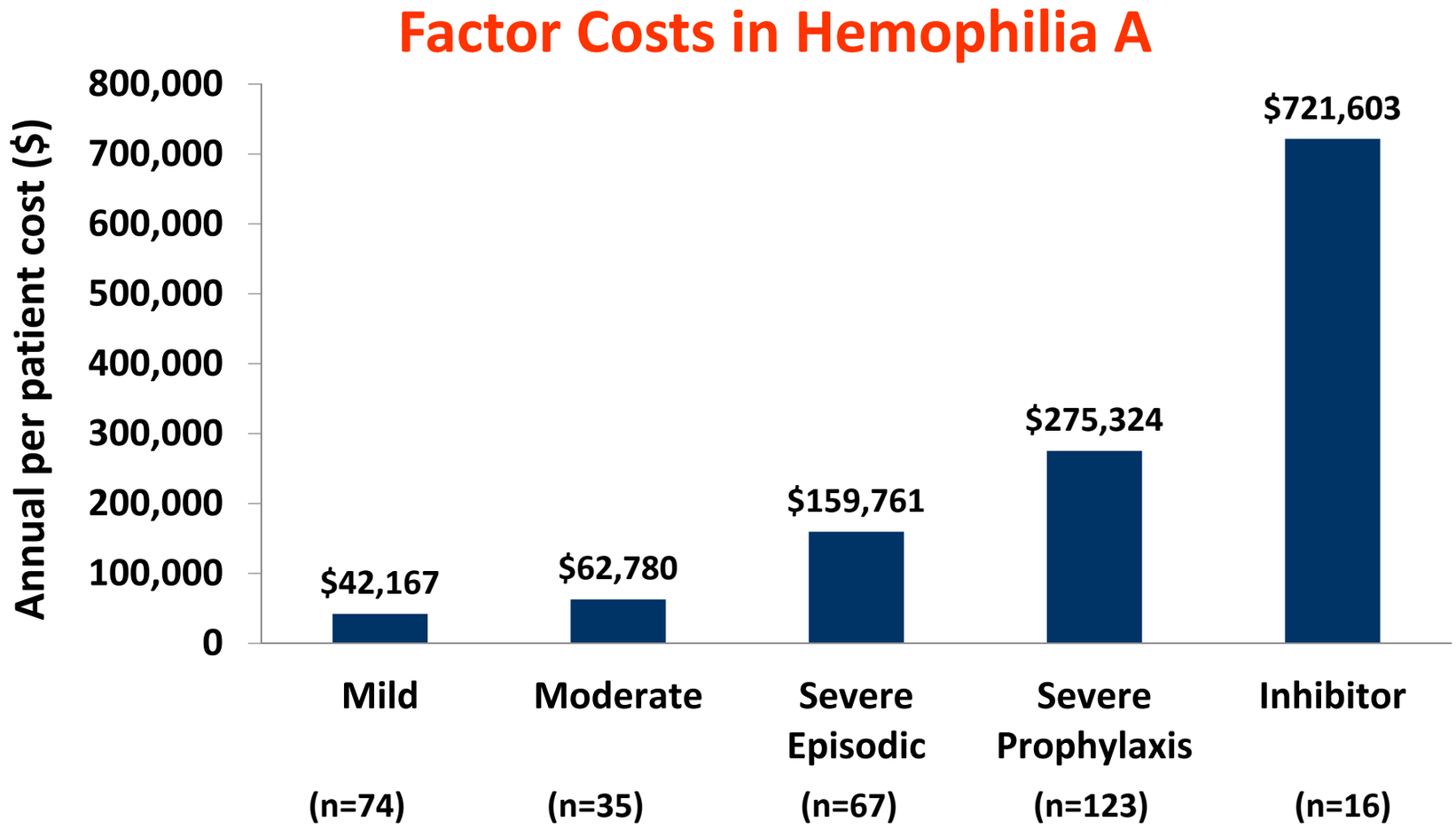


Disease Severity and Treatment Approach Determines Factor Utilization



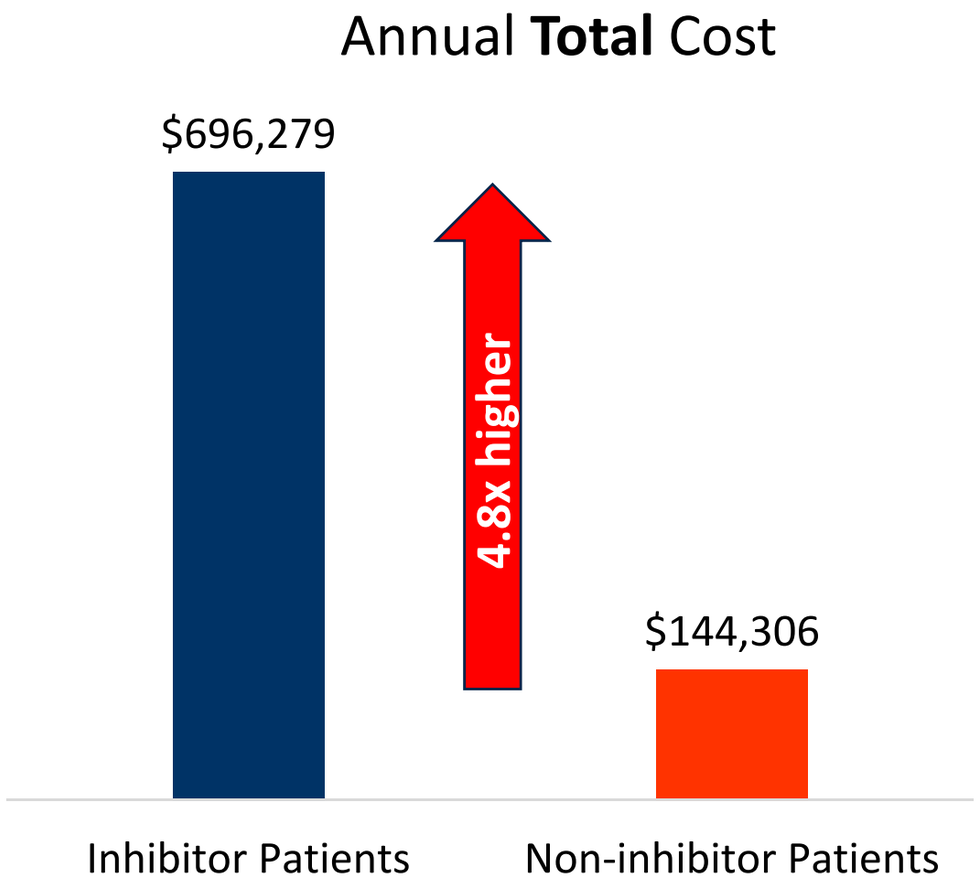
Zhou ZY, Koerper MA, Johnson KA, et al. *J Med Econ*. 2015;18(6):457-65.

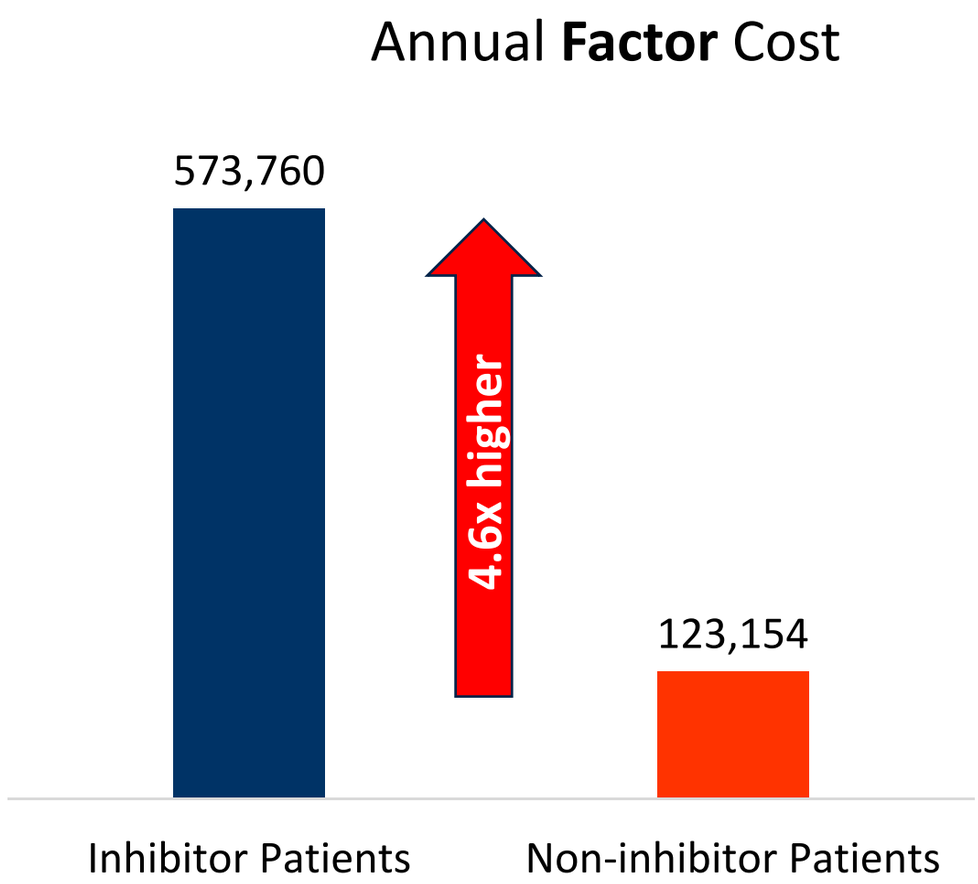
Prophylaxis and Inhibitors Contribute Significantly to Annualized Factor Costs



Reference prices: Medicare Average Sales Price.
Data Source: Hemophilia Utilization Group Study (HUGS); 2011.

Inhibitors Have Been Characterized Among the Most Costly Complications of Chronic Diseases

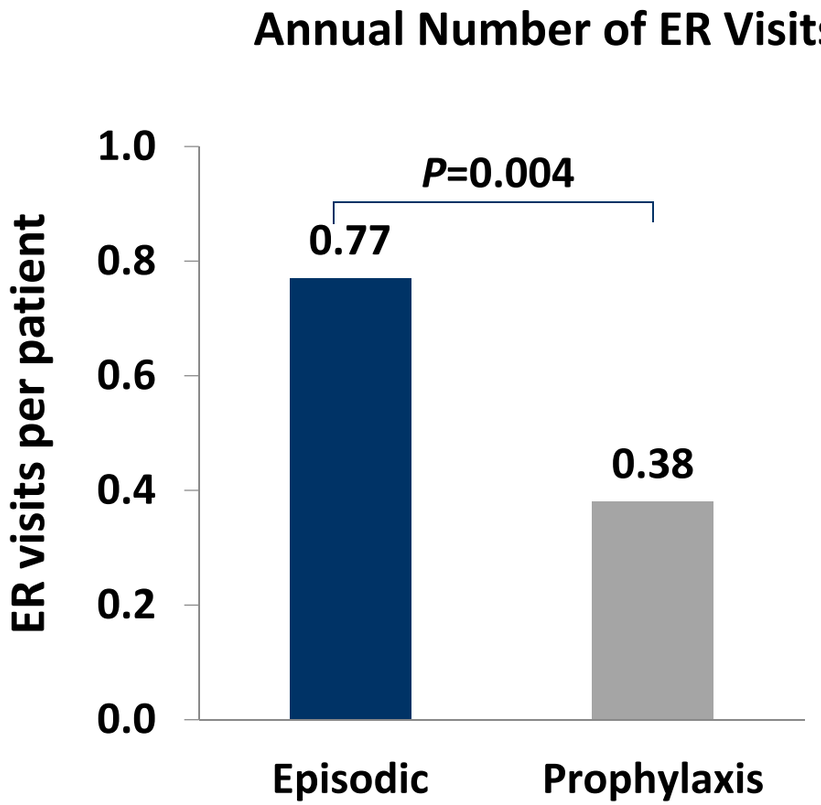


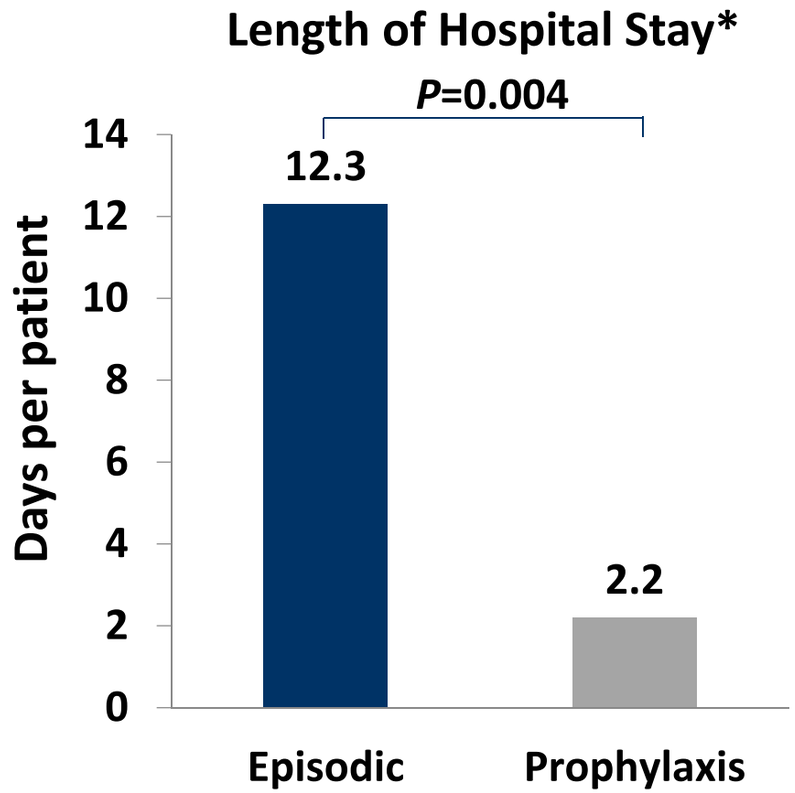


Guh S, Grosse SD, Mcalister S, Kessler CM, Soucie JM. *Haemophilia*. 2012;18(2):268-75.

Evidence-based Care with Prophylaxis Can Decrease Overall Health Care Utilization

Health Care Utilization in Severe Hemophilia
(n=205); HUGS data 2011





**Only applies to patients who had a hospitalization*

Data Source: Hemophilia Utilization Group Study (HUGS); 2011.

Contracting Approaches

Drug	Provider

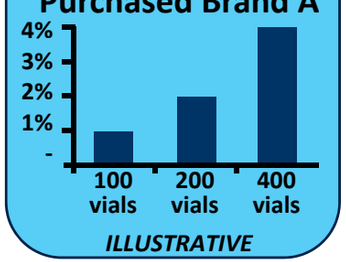
• Formulary positioning
  • Multiple specialty tiers
  • Closed formularies
  • Step therapy
	• Narrow networks
	• Reimbursement issues
	  • Role of the HTC and 340B pricing
	• Accreditation
	• Credentialing

Traditional Versus Potential Value-based Contracting in Hemophilia

Traditional Contracting

Flat, Volume or Share-Based

Concessions may depend on volume or share



Value-Based Contracting

Indication-Based

Rebate specific to an indication

Regimen-Based

Rebate paid when two products used in combination

"Outcomes" Based

Concessions depend on how 'well' the drug works for a patient/cohort

Assay management is a logical fit for such arrangements, but care must be taken to participate in "real" assay management contracting scenarios rather than merely contractual scenarios

Increasing Data & Complexity

Long G, Mortimer R, Sanzenbacher G. *J Med Econ*. 2014;17(12):883-93.

Factor Rx: Large Variances In Total Factor Units Dispensed Can Occur

Patient: John Doe

Infuse 1800 to 2000 units prn

or

Infuse 2000±5% units prn

Each Rx has potential for large variances built in

Assay sizes vary from lot to lot

Factor is manufactured in a range of unit or assay sizes

Low range

~250 IU

Mid range

~500 IU

High range

~1000+ IU

Both HTC integrated pharmacies and external specialty pharmacies should be transparent regarding dosage dispensing

Factor Rx: Assay Management

- Assay Management: Process of filling the prescription as closely to the prescribed target dose (more inventory = more assay sizes available)
- Cost to the payer: Depends on the total # of units actually dispensed
- MASAC #188 : Recommends dispensing within ±5%-10% of prescribed target dose, barring extenuating circumstances

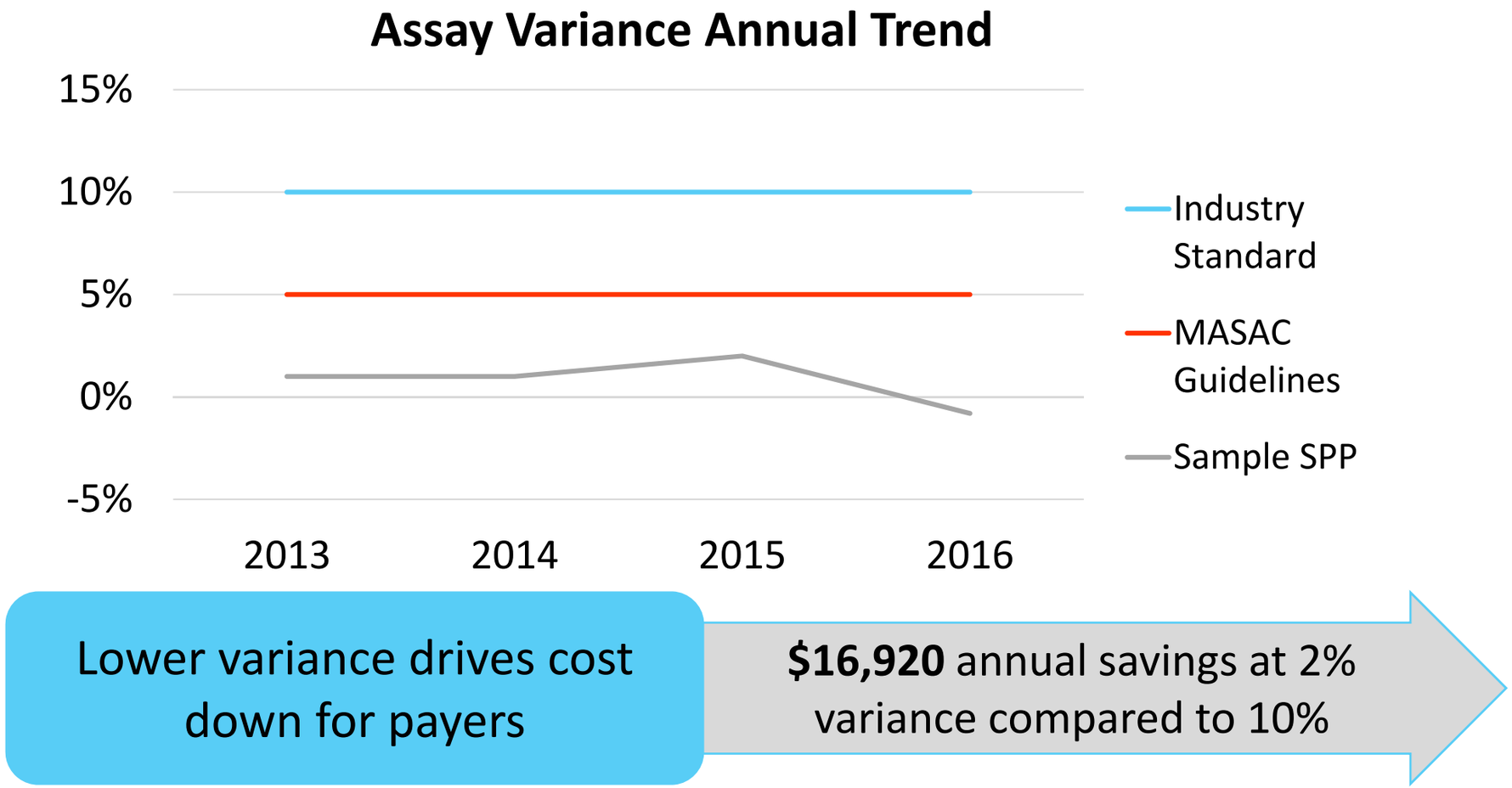
John Doe: Prescription Options

Infuse 1800 to 2000 units prn
or
Infuse 2000±5% units prn

Available Assays:
875 IU **1000 IU** **1100 IU**

Potential Dose Arrangements:
875 + 1100 vial = 1975 IU
1000 x 2 vials = 2000 IU

Assay Prescription Management Results: Annual Trend



MASAC recommendations regarding standards of service for pharmacy providers of clotting factor concentrates for home use to patients with bleeding disorders. http://www.hemophilia.org/sites/default/files/document/files/masac188.pdf. Accessed April 2018.

Summary

- Therapeutic adherence and factor cost management represent two key areas of hemophilia pharmacy management
- Patient engagement efforts focused on education and shared decision-making can enhance therapeutic adherence and encourage patients to be stewards of their own care
- Factor cost management in hemophilia is founded on the principles of contracting and assay management, which can decrease specialty drug acquisition costs and encourage appropriate utilization

HEMOPHILIA

Treatment Recommendations and Cost Management for Managed Care and Specialty Pharmacy

Jointly provided by

National Hemophilia Foundation
for all bleeding disorders

Impact Education

PIM Postgraduate Institute for Medicine
Professional Excellence in Medical Education

This activity is supported by independent educational grants from Novo Nordisk, Inc., CSL Behring, and Shire.

AMCP Academy of Managed Care Pharmacy®

Held in conjunction with AMCP Managed Care & Specialty Pharmacy Annual Meeting 2018