MANAGED CARE HEMO.com PRESENTS

HEMOPHILIA

Clinical Updates and Cost Management Solutions

Jointly provided by

National Hemophilia Foundation
for all bleeding disorders

Impact Education

Medical Education Resources

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Held in conjunction with

AMCP MANAGED CARE & SPECIALTY PHARMACY ANNUAL MEETING 2019

MARCH 25–28 SAN DIEGO

Assessing the Clinical Benefits and Appropriate Use of Current and Emerging Hemophilia Treatment Options

Shannon Carpenter, MD, MS
Professor of Pediatrics, UMKC School of Medicine
Hematology/Oncology, Director Kansas City Regional Hemophilia Treatment Center
Director, Anticoagulation Management Program
Children's Mercy Hospital

Disease Overview

Hemophilia is a genetic disorder preventing blood from clotting normally.
The primary symptom is uncontrolled, often spontaneous, bleeding in different areas of the body.

Hemophilia results from a **missing or deficient protein** needed for blood clotting.

The two main forms are **hemophilia A** (factor VIII deficiency) and **hemophilia B** (factor IX deficiency

5,000

Hemophilia A occurs in **1 in 5,000** live male births. Hemophilia A is about four times as common as hemophilia B

The number of people with hemophilia in the United States is estimated to be about **20,000** individuals

Internal bleeding, which often occurs in the space around joints and in muscles, frequently causes pain and swelling. **Left untreated, bleeding can lead to permanent, painful joint disease and in some cases, death.**

Data & Statistics on Hemophilia. CDC website: https://www.cdc.gov/ncbddd/hemophilia/data.html. Accessed February 2019
What is hemophilia? Hemophilia Federation of America: https://www.hemophiliafed.org/understanding-bleeding-disorders/what-is-hemophilia. Accessed February 2019.

Clinical Features of Hemophilia

Severity of bleeding tendency depends on the factor level

Mild (>5%)	Moderate (1-5%)	Severe (<1 %)
▪ Bleed only after severe injury, trauma, or surgery ▪ May not be diagnosed until adulthood	▪ Bleed after injury, surgery ▪ May have occasional, spontaneous bleeding	▪ Frequent, spontaneous bleeding ▪ Diagnosis made in early childhood

Clinical Features of Hemophilia

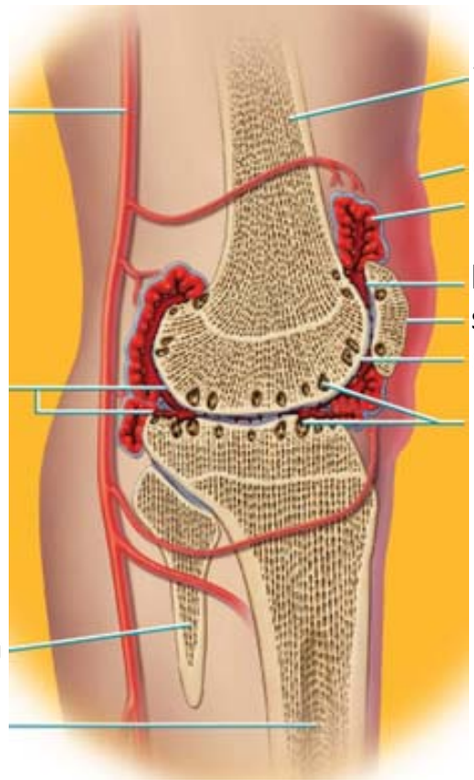
Joint Bleeds (Hemarthrosis)

Blood in joint

Inflammation

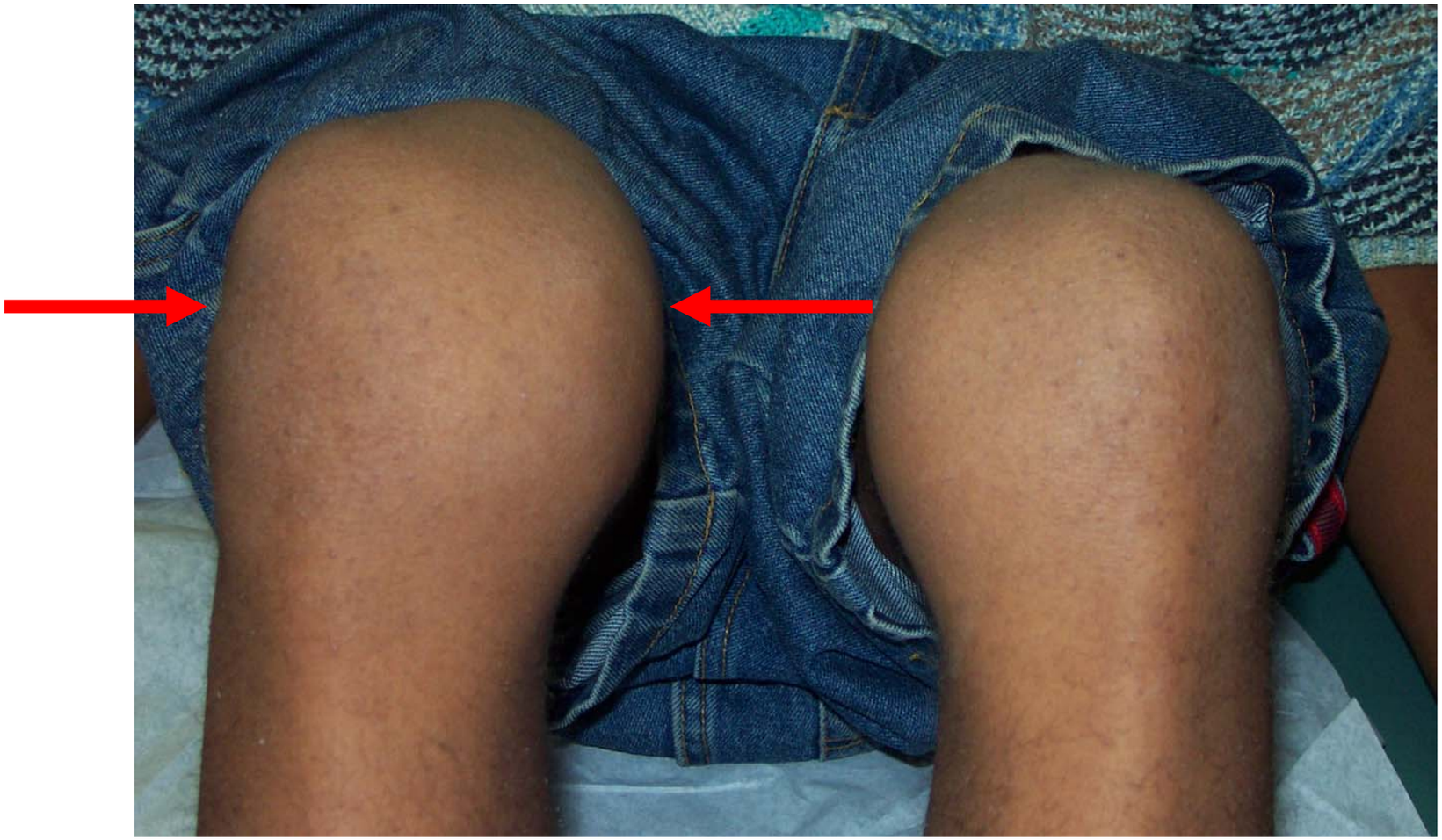
Synovitis

Recurrent bleeding



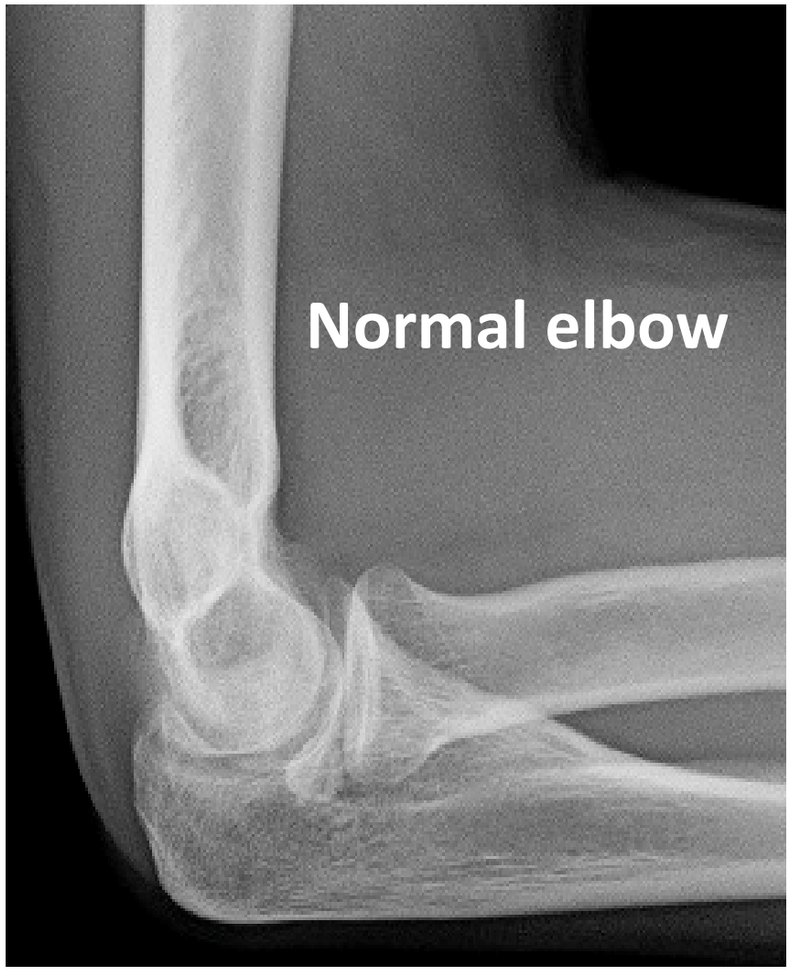
Clinical Features of Hemophilia

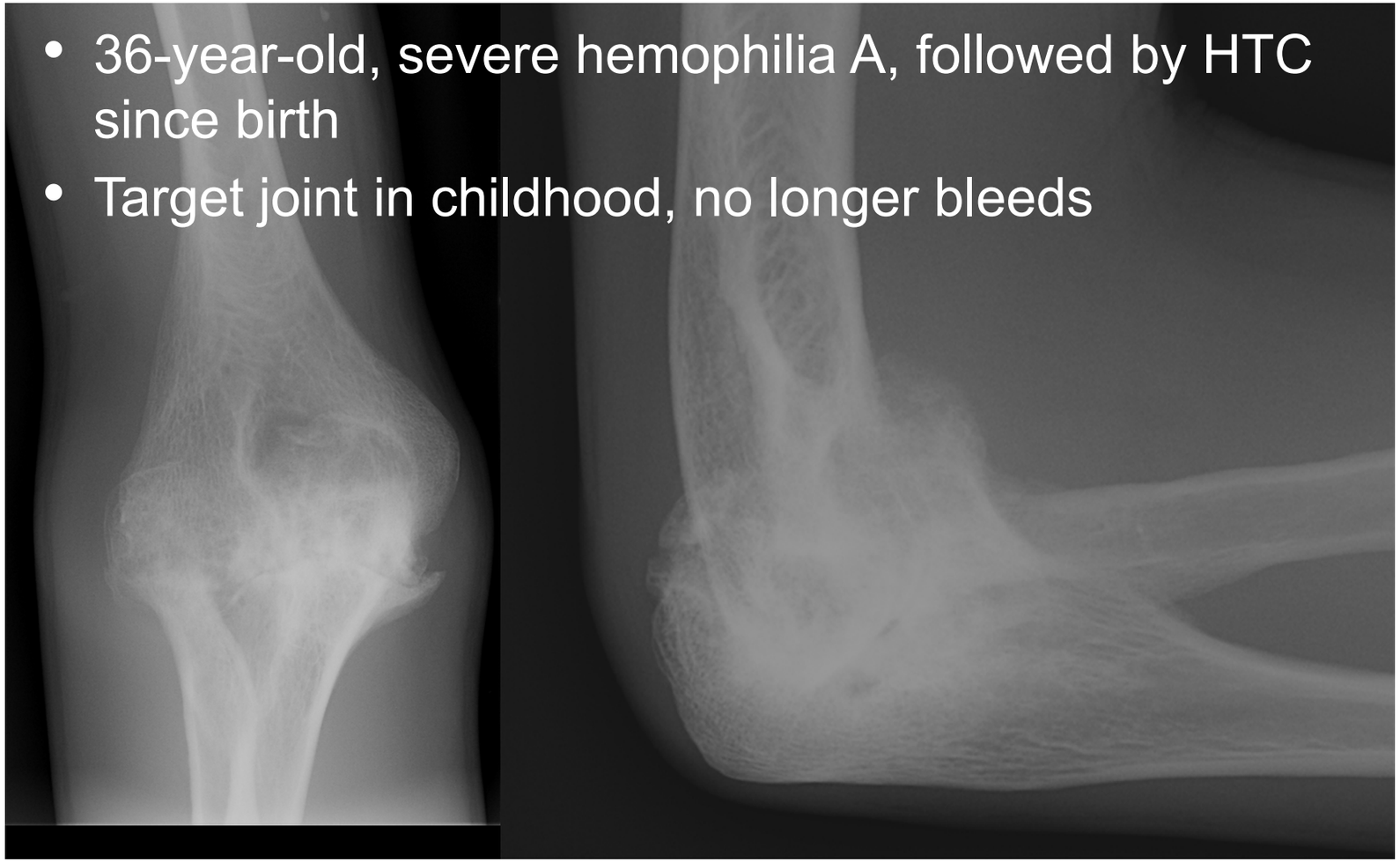
Joint Bleeds (Hemarthrosis)



Clinical Features of Hemophilia

Joint Bleeds (Hemarthrosis)

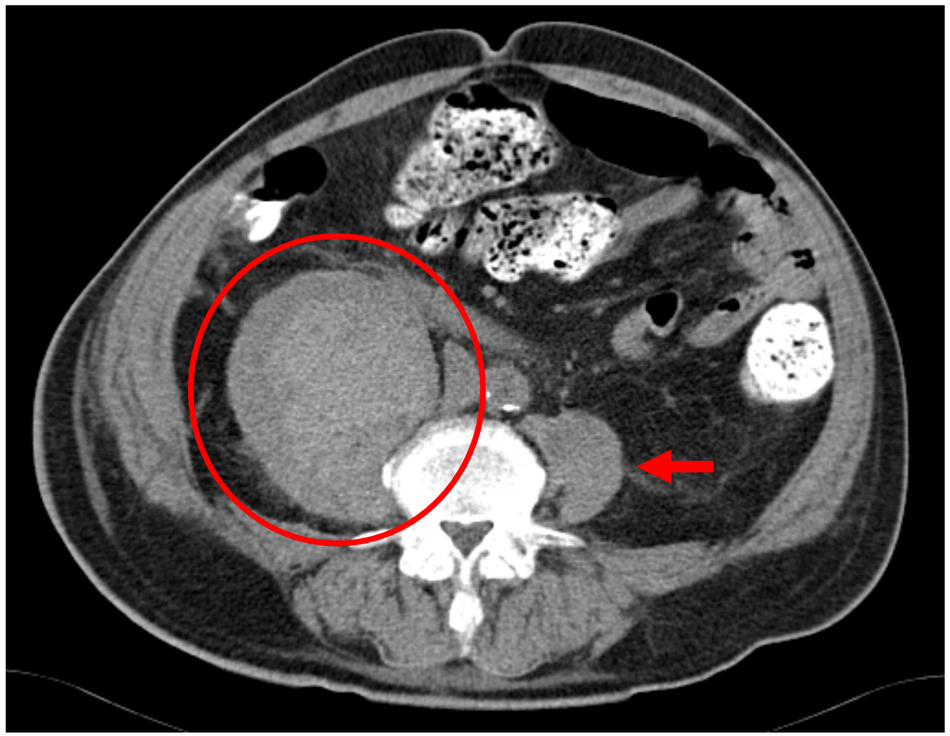


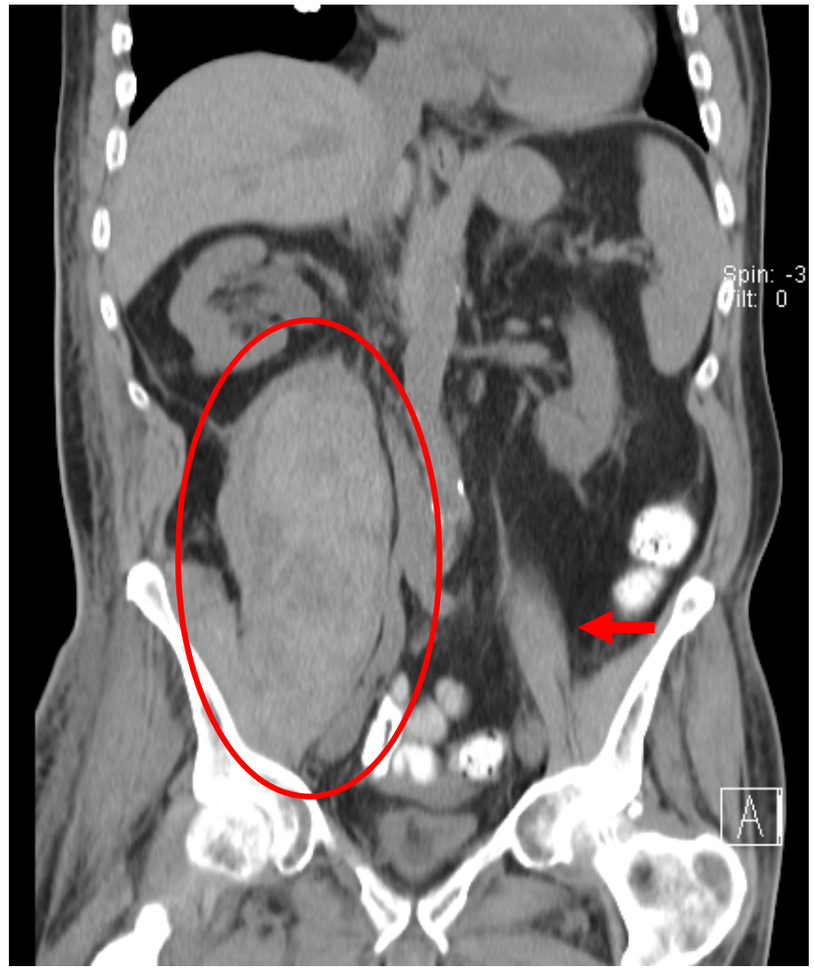


- 36-year-old, severe hemophilia A, followed by HTC since birth
- Target joint in childhood, no longer bleeds

Clinical Features of Hemophilia

Deep Muscle Bleeds

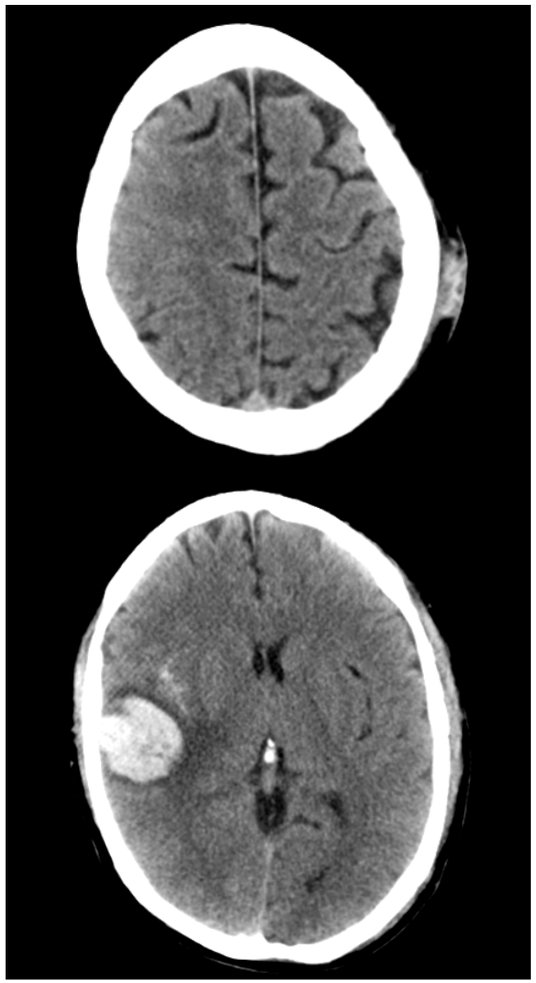




- 52-year-old with severe hemophilia B
- Spontaneous bleed

Clinical Features of Hemophilia

Intracranial Bleeds



Inhibitors in Congenital Hemophilia

- Some hemophilia patients have a physiologic response to exogenous factor VIII or factor IX products and react to these products as foreign proteins
- Infusion of factor concentrate to prevent or treat bleeding triggers an immune response
- Antibodies (“inhibitors”) directed against factor VIII or factor IX neutralize the procoagulant effect and render standard treatment ineffective

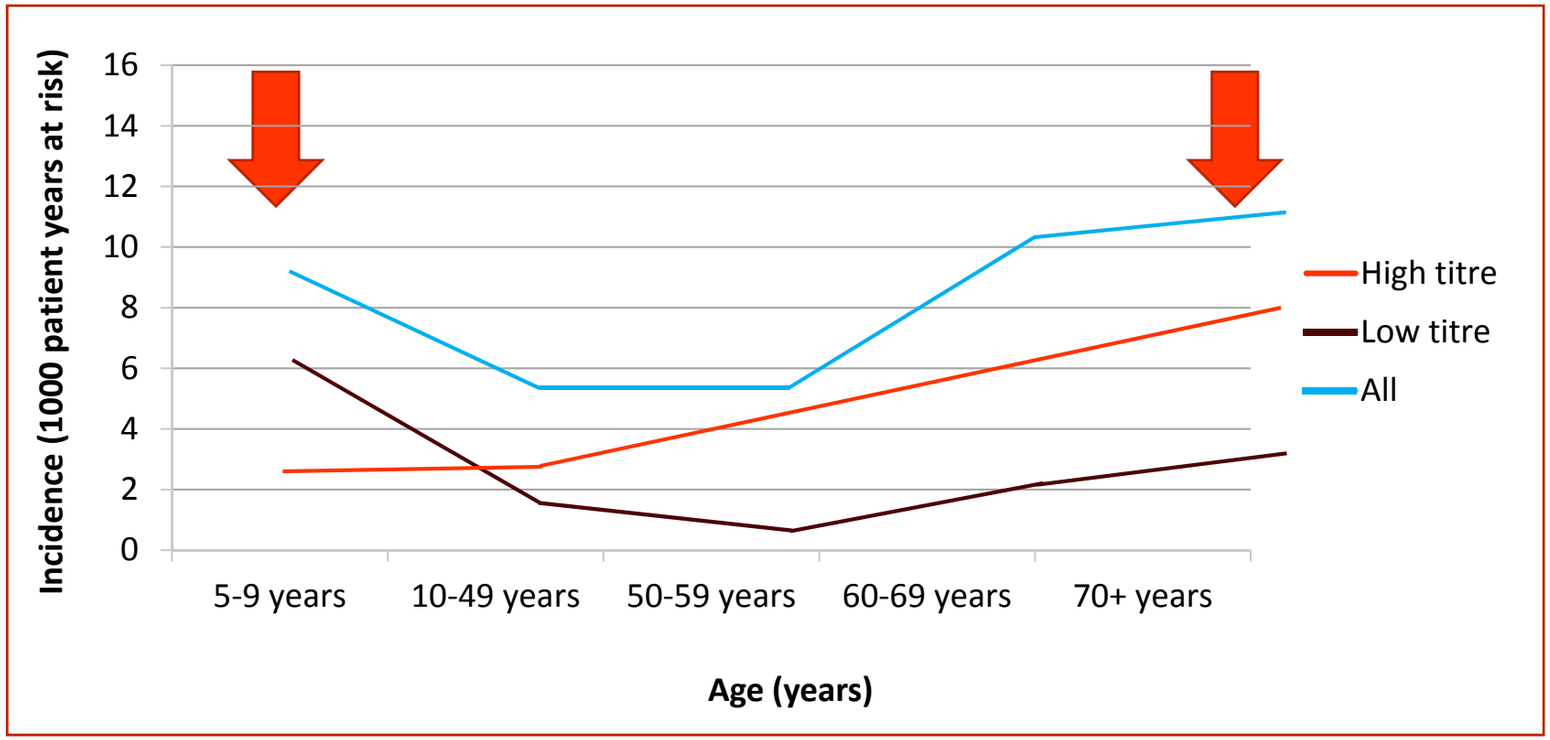
Inhibitors in Congenital Hemophilia, cont.

- Development of inhibitors is currently the most serious complication of factor replacement therapy
  - Typically seen in those with severe hemophilia (hemophilia A ~30%, hemophilia B <5%)
  - May also occur in those with mild or moderate hemophilia, usually after intense factor exposure related to trauma or surgery
- *Clinical presentation:*
  - *Bleeding more difficult to control*
  - *Devastating joint disease and disability*
  - *Major clinical and economic challenges*

Inhibitors. Hemophilia Federation of America: https://www.hemophiliafed.org/understanding-bleeding-disorders/complications/inhibitors. Accessed February 2019.

Factor VIII Inhibitors

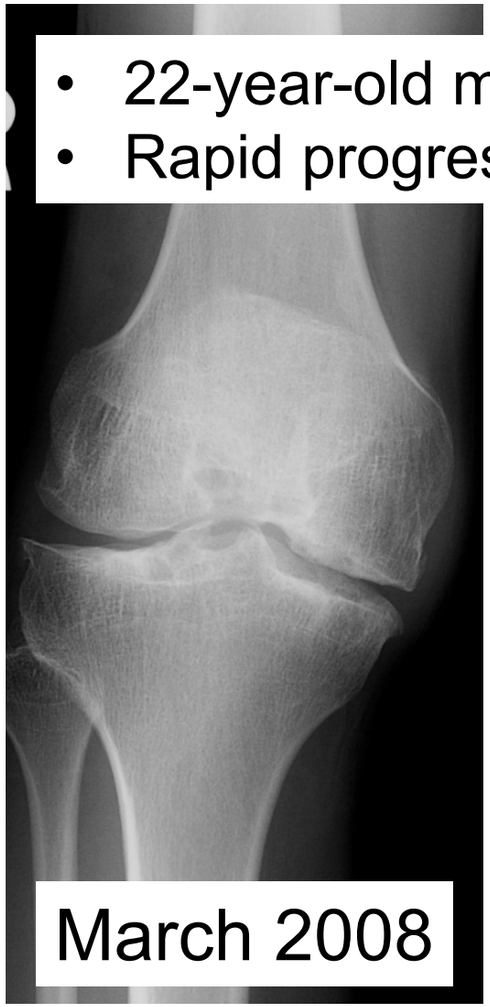
- Previously thought that almost all inhibitors in those with severe hemophilia A developed after only a few exposures, earlier in life
- Now, it is known that inhibitors arise throughout lifespan, with a bimodal risk

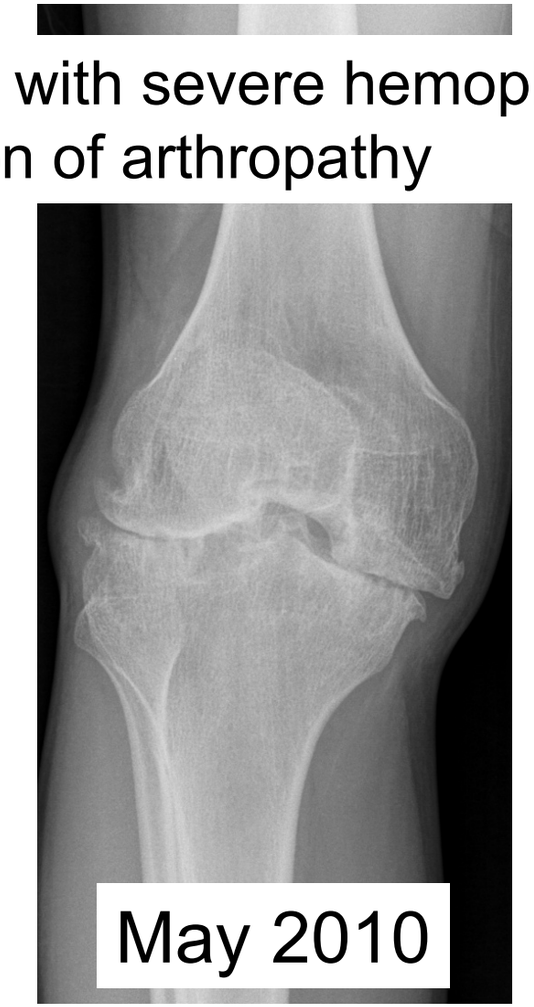


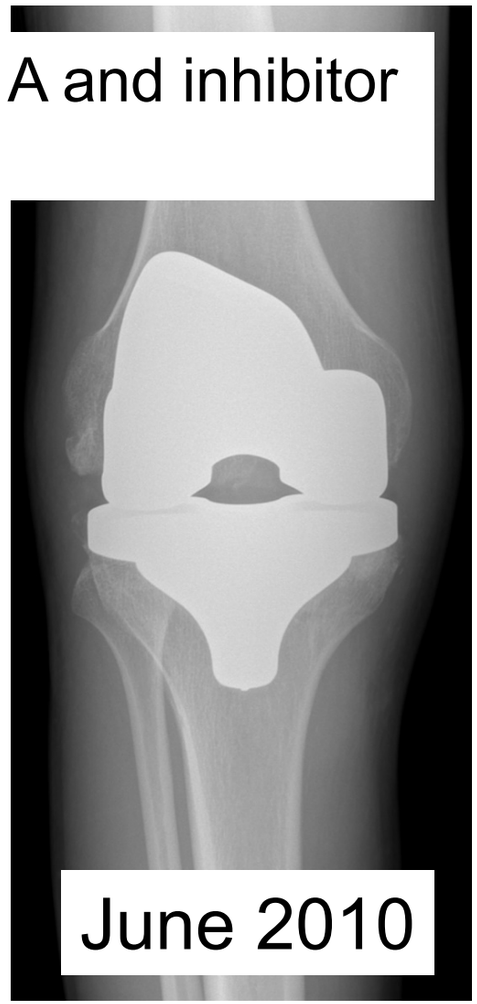
Hay CR, Palmer B, Chalmers E, et al. *Blood*. 2011;117(23):6367-70.

Clinical Features of Hemophilia with Inhibitor

- 22-year-old male with severe hemophilia A and inhibitor
- Rapid progression of arthropathy







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Inhibitors in Congenital Hemophilia

Unique Treatment Challenges

- Standard factor replacement therapy ineffective
- Traditional inhibitor-specific therapies only have 75%-90% efficacy in stopping acute bleeds
- High degree of variability in response between patients and bleeding episodes
- Prophylaxis is less well established, less effective, high burden due to frequent large infusion volume
- No established routine method of lab monitoring
- Risk of thrombosis
- Immune tolerance therapy only ~70% successful

Treatment of Hemophilia

Factor Replacement Therapy

- Plasma-derived concentrates – 1960s
- HIV / AIDS era – 1980s
- Recombinant factor products – 1990s

1st generation 2nd generation 3rd generation	*Removal of human / animal proteins* *Smaller infusion volume*
4th generation	*Potentially less immunogenic (?)*

- Equivalent efficacy, same dosing schedules

Factor Replacement Therapy

On-Demand

- Treatment of bleeds when they occur
- Good at stopping bleeds after they start, but does not prevent bleeds

Prophylaxis

- Regular administration of factor to prevent bleeds form occurring
- Goal is elimination of all bleeds
- Pioneered in Sweden (1958); standard of care since 1990s

Prophylaxis to Prevent Bleeding

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

Severe Patients

(<1% factor activity)

- Average 30-35 bleeds/year
- Likely develop chronic arthropathy from repeated bleeds into the joints unless treated with effective prophylactic factor replacement therapy

Mild & Moderate Patients

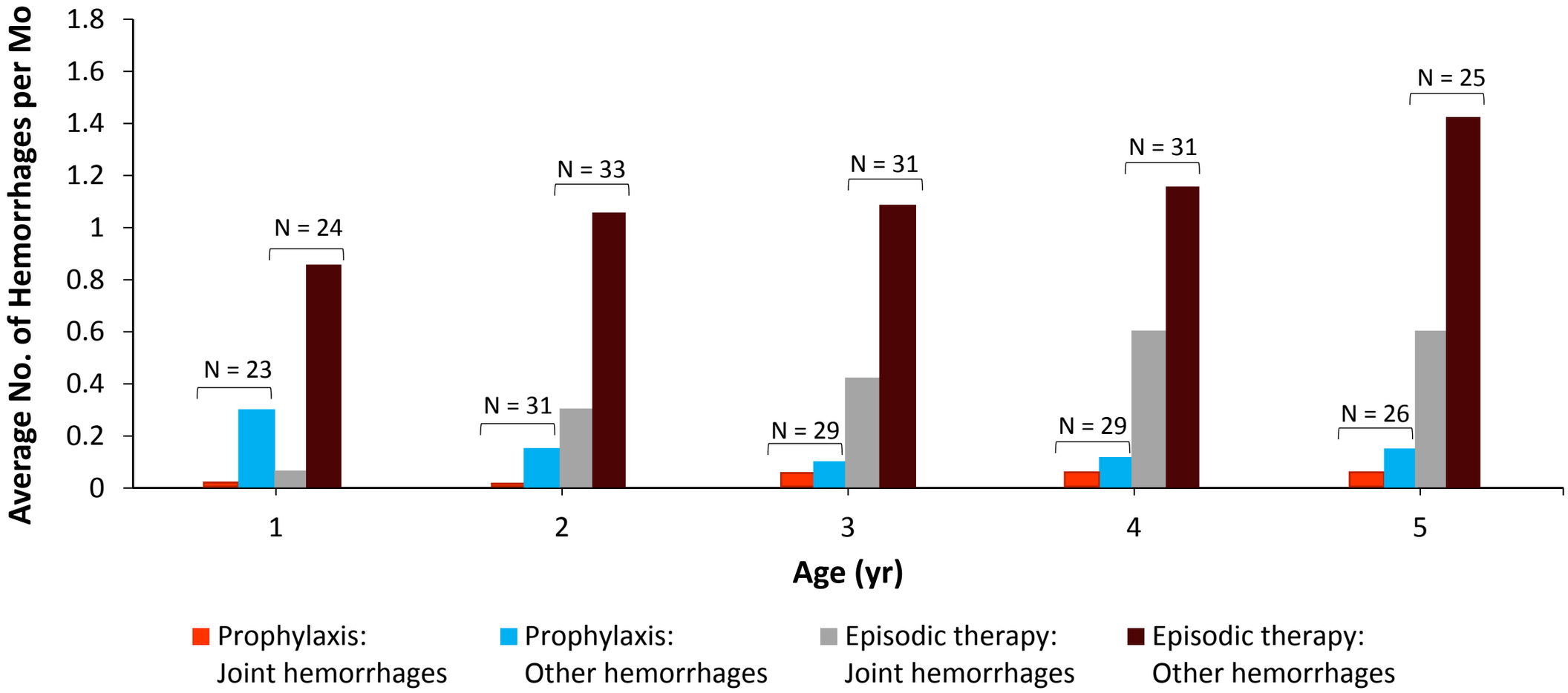
- Less likely to develop chronic arthropathy

Establishing the Case for 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)

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



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

Factor Replacement Therapy

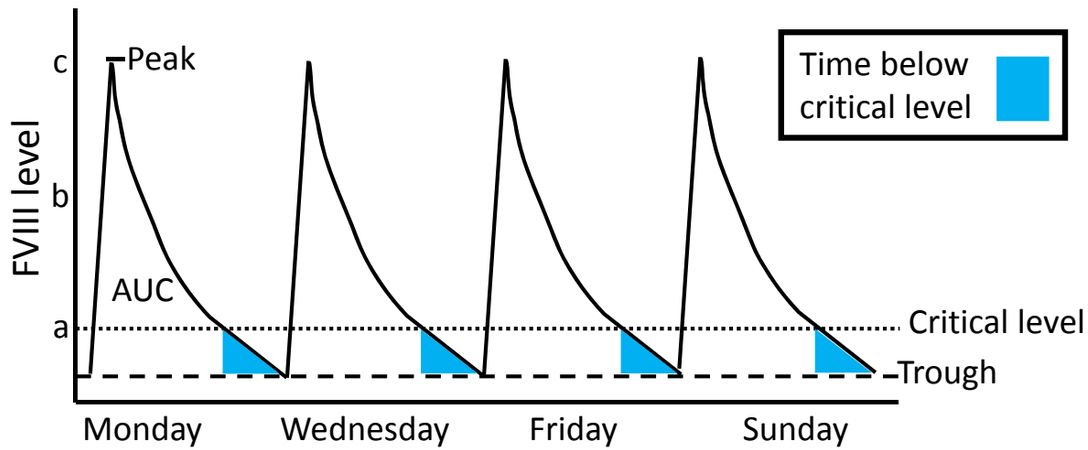
Prophylactic Treatment

Benefits

- Proven to decrease bleeds and prevent joint damage
- Improves functional status and QoL
- May delay progression of arthropathy
- Protection from traumatic and unexpected bleeds

Challenges

- Requires frequent intravenous infusions
- Venous access
- Peaks / troughs
- Maintaining adherence long-term



Mahdi AJ, Obaji SG, Collins PW. *Br J Haematol*. 2015;169(6):768-76.

Hemophilia Treatment Landscape

Present and Future

	Factor Replacement Products		Non-Factor Replacement Products				
	Standard Half-Life Products	Extended Half-Life Products	Emicizumab	Fitusiran	Concizumab	BAY 1093884	PF-06741086
MOA	Replacement of FVIII / FIX		FVIII mimetic	Reduce AT	Anti-TFPI		
Indications	• Hemophilia A or B • Without inhibitors • On-demand and prophylaxis		• Hemophilia A • With and without inhibitors • Prophylaxis	• Hemophilia A or B • With and without inhibitors • Prophylaxis			
Dosing	• Intravenous • 2x/week • 3x/week • Q.O.D.	• Intravenous • 2x/week • Q 3-5 d • Q 7-14 d	• Subcutaneous • Every 1 to 4 weeks				
Safety Concerns	Inhibitors		Thrombosis TMA	Thrombosis	??		

Hemophilia A Treatment Landscape

2014	2015	2016	2017	2018	2019	2020 – 2023
pdFVIII	pdFVIII	pdFVIII	pdFVIII	pdFVIII	pdFVIII	pdFVIII
Recombinate	Recombinate	Recombinate	Recombinate	Recombinate	Recombinate	Recombinate
Kogenate	Kogenate	Kogenate	Kogenate	Kogenate	Kogenate	Kogenate
Helixate	Helixate	Helixate	Helixate	Helixate	Helixate	Helixate
Advate	Advate	Advate	Advate	Advate	Advate	Advate
Xyntha	Xyntha	Xyntha	Xyntha	Xyntha	Xyntha	Xyntha
Novoeight	Novoeight	Novoeight	Novoeight	Novoeight	Novoeight	Novoeight
Eloctate	Eloctate	Eloctate	Eloctate	Eloctate	Eloctate	Eloctate
	Adynovate	Adynovate	Adynovate	Adynovate	Adynovate	Adynovate
	Nuwiq	Nuwiq	Nuwiq	Nuwiq	Nuwiq	Nuwiq
		Kovaltry	Kovaltry	Kovaltry	Kovaltry	Kovaltry
		Afstyla	Afstyla	Afstyla	Afstyla	Afstyla
			Emicizumab	Emicizumab	Emicizumab	Emicizumab
				BAY 94-9027	BAY 94-9027	BAY 94-9027
					N8-GP	N8-GP
						Fitusiran
						Concizumab
						BAY 1093884
						PF-06741086

Notes:

- Individual plasma derived products not listed
- Some products may become unavailable (e.g. Helixate)
- Based on anticipated approval dates

Treatment of Hemophilia

Major Unmet Needs

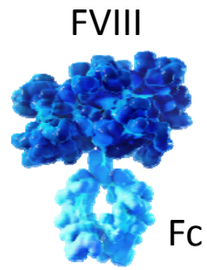
- Maintaining adherence over decades
- Reducing the burden of prophylaxis
- Innovative therapies for non-inhibitor patients
- Innovative therapies for inhibitor patients
  - Effective prophylaxis
  - More consistent bleed management

Addressing Unmet Needs

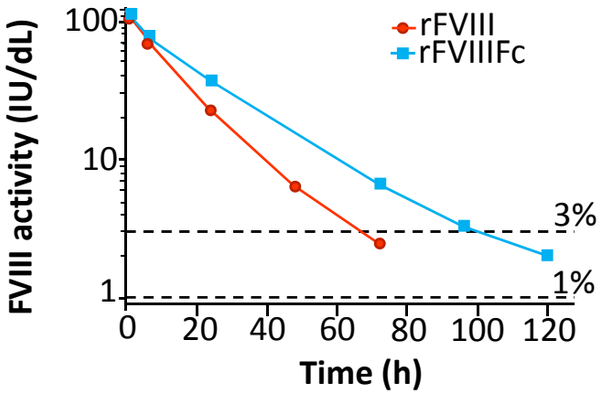
Potential interventions for optimizing outcomes

- Extended half-life (EHL) factor products
- Personalized prophylaxis
- Emerging therapies

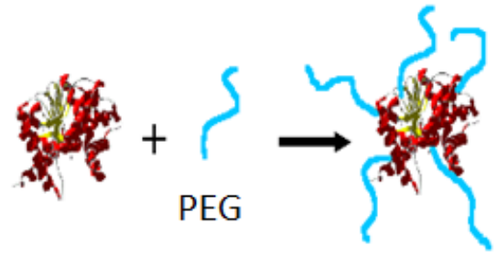
Extended Half-life (EHL) Factor Products



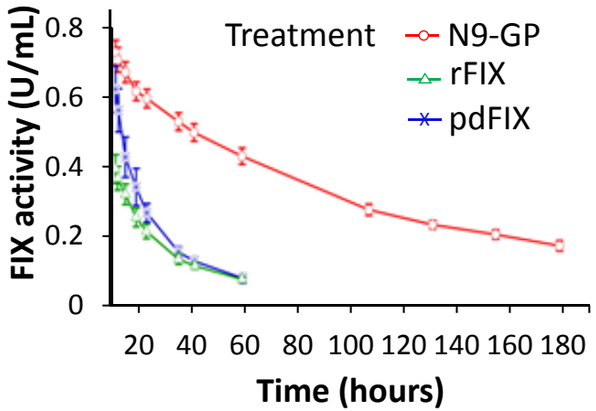
Fc fusion



Mahlangu J, Powell JS, Ragni MV, et al. *Blood*. 2014;123(3):317-25.

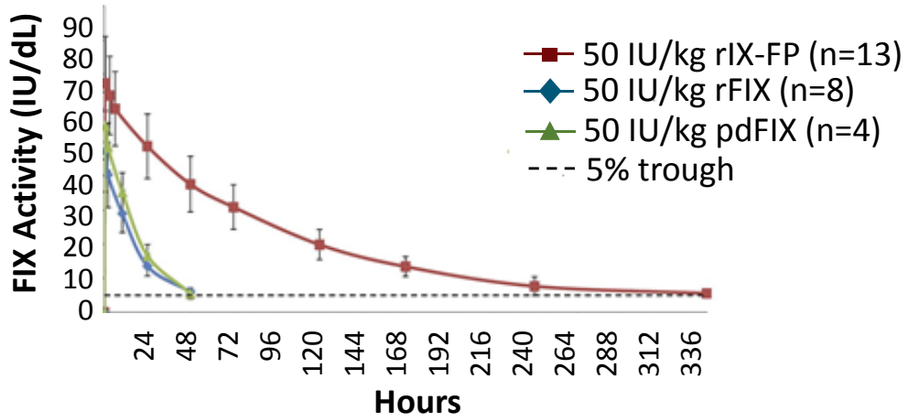


PEGylation



Negrier C, Knobe K, Tiede A, Giangrande P, Møss J. *Blood*. 2011;118(10):2695-701.

Albumin fusion



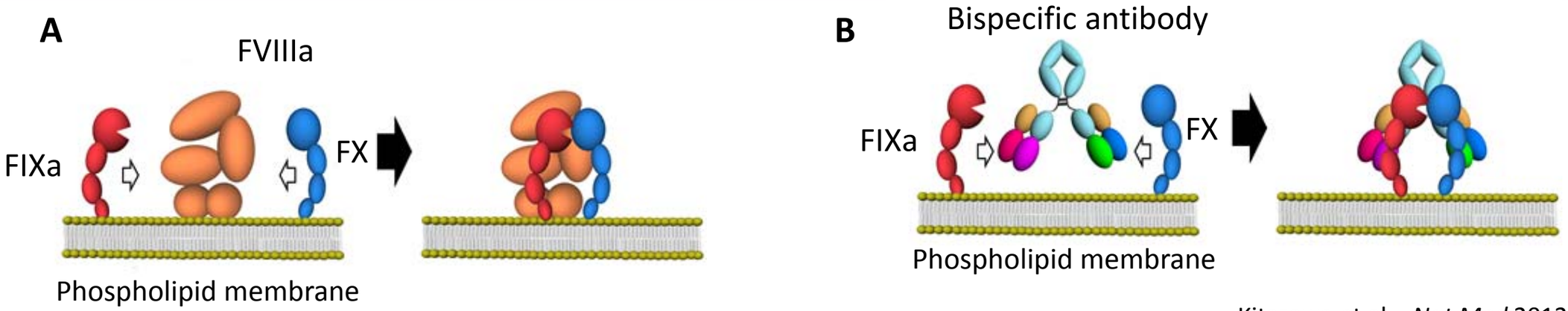
Santagostino E, Negrier C, Klamroth R, et al. *Blood*. 2012;120(12):2405-11.

Half-life Prolongation

- **Factor VIII: moderate; dosing every 2-3 days → every 3-7 days**
- **Factor IX: dramatic; dosing 1-2 x per week → once every 1-2 weeks**

Dunn A. The long and short of it: using the new factor products. *Hematology Am Soc Hematol Educ Program*. 2015;2015:26-32.

Emicizumab-kxwh



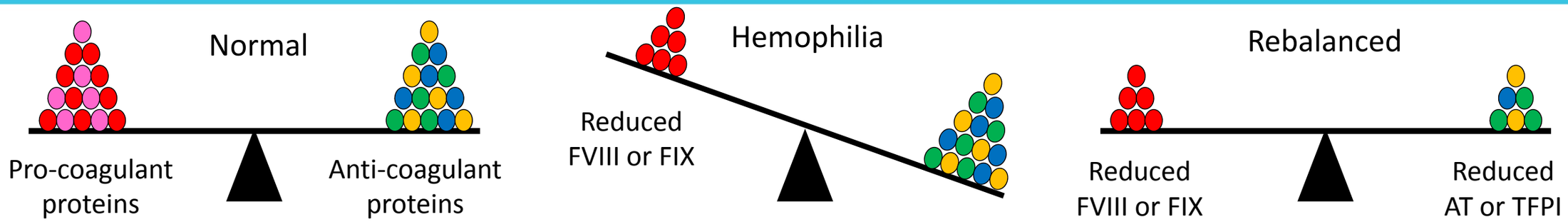
Kitazawa et al., *Nat Med* 2012

- Approved in November 2017 based on data from two clinical trials: an adult and adolescent trial (HAVEN 1) and a pediatric trial (HAVEN 2)
- Recommended dose of 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly
- Impressive reduction in bleeding seen in inhibitor patients on prophylaxis
- For prophylaxis, not acute bleed management

Oldenburg J, Mahlangu JN, Kim B, et al. *N Engl J Med.* 2017;377(9):809-818.

Emerging Therapies

Fitusiran and TFPI inhibitors



What we know so far…

- 3 TFPI inhibitors in development; fitusiran farther along
- Studied in hemophilia A and B, with and without inhibitors
- Subcutaneous dosing at 1 to 4 week intervals
- Early phase clinical trial results promising
- For prophylaxis, not acute bleed management

Hartmann J, Croteau SE. *Am J Hematol*. 2016;91(12):1252-1260.
Pasi KJ, Rangarajan S, Georgiev P, et al. *N Engl J Med*. 2017;377(9):819-828.

Emerging Therapies
Fitusiran and TFPI Inhibitors

Looking forward…

- Fitusiran clinical trial put on hold September 2017 due to a fatal thrombotic event (cerebral venous sinus thrombosis) in a non-inhibitor patient (clinical trial re-opened in December 2017)
- Concerns about the unknowns associated with manipulating regulatory pathways
- Concerns also about management of breakthrough bleeds and use in other procoagulant states (e.g. cancer, sepsis, trauma)
- Anticipated approval ~2020 – 2023

Hartmann J, Croteau SE. *Am J Hematol*. 2016;91(12):1252-1260.
Pasi KJ, Rangarajan S, Georgiev P, et al. *N Engl J Med*. 2017;377(9):819-828.

Emerging Therapies
Gene Therapy

- *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
- Anticipated to carry a cost potentially approaching $1 million per patient for a one-time treatment

Keown A. Gene Therapies for Hemophilia Could Hit $1.5 Million, Analysts Speculate. *Biospace*. https://www.biospace.com/article/gene-therapies-for-hemophilia-could-hit-1-5-million-analysts-speculate. Published May 7, 2018. Accessed February 2019.

The HTC/Comprehensive Care Model

- A hemophilia treatment center (HTC) is a federally recognized comprehensive care facility featuring a multidisciplinary team who are 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 individualized treatment plans
  - Preventive medicine
  - Access to multiple health care disciplines
  - Optimized care

Hemophilia Treatment Centers (HTCs). Centers for Disease Control Website. https://www.cdc.gov/ncbddd/hemophilia/HTC.html. Published September 2, 2015. Updated February 6, 2017. Accessed February 2019.

HTC Team Members

Core Team Members

- Patient/Family
- Hematologist
- Nurse
- Social Worker
- Physical Therapist

Additional Team Members

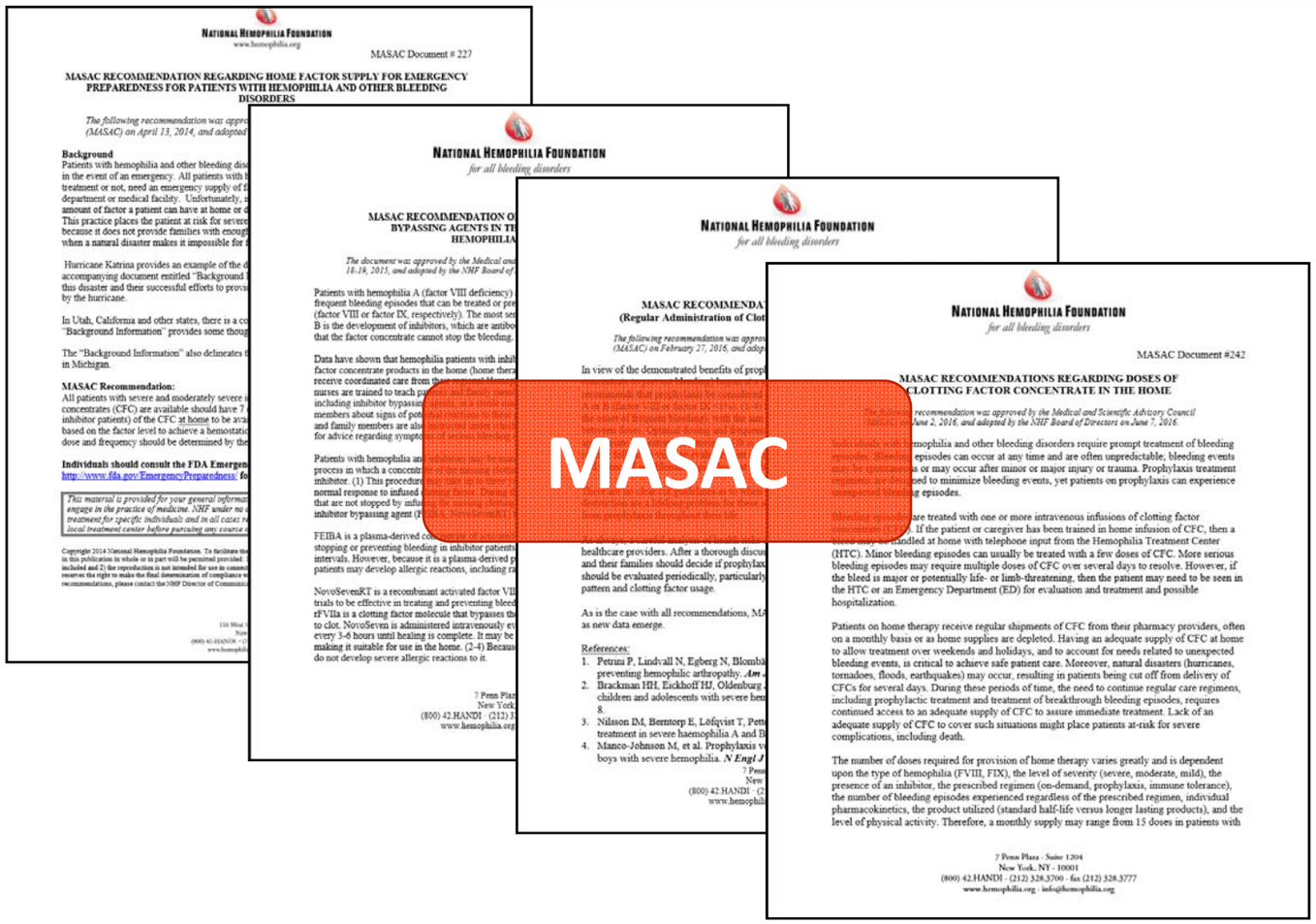
- Other physicians
  - Primary care
  - Orthopedics
  - Infectious disease
  - Obstetrics-gynecology
  - Hepatology
- Pharmacist
- Genetics
- Dental
- Nutritionist
- Educational/vocational counselors

Defining the Role of HTCs

- Coordinate state-of-the-art medical treatment for persons with hemophilia throughout their life span
- Education
- Research
- Outreach
- Emotional support
- Ensure optimal therapy for patient (age, activity level, medical background)
- Prepare patient and families for home treatment
  - Identifying candidates
  - Teaching concepts and skills
  - Oversight

HTCs provide care for patients, regardless of insurance status

Treatment Guidelines Promoting Evidence-based Care in the Management of Hemophilia



MASAC recommendations. National Hemophilia Foundations Web site. https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations. Accessed June 2016.

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

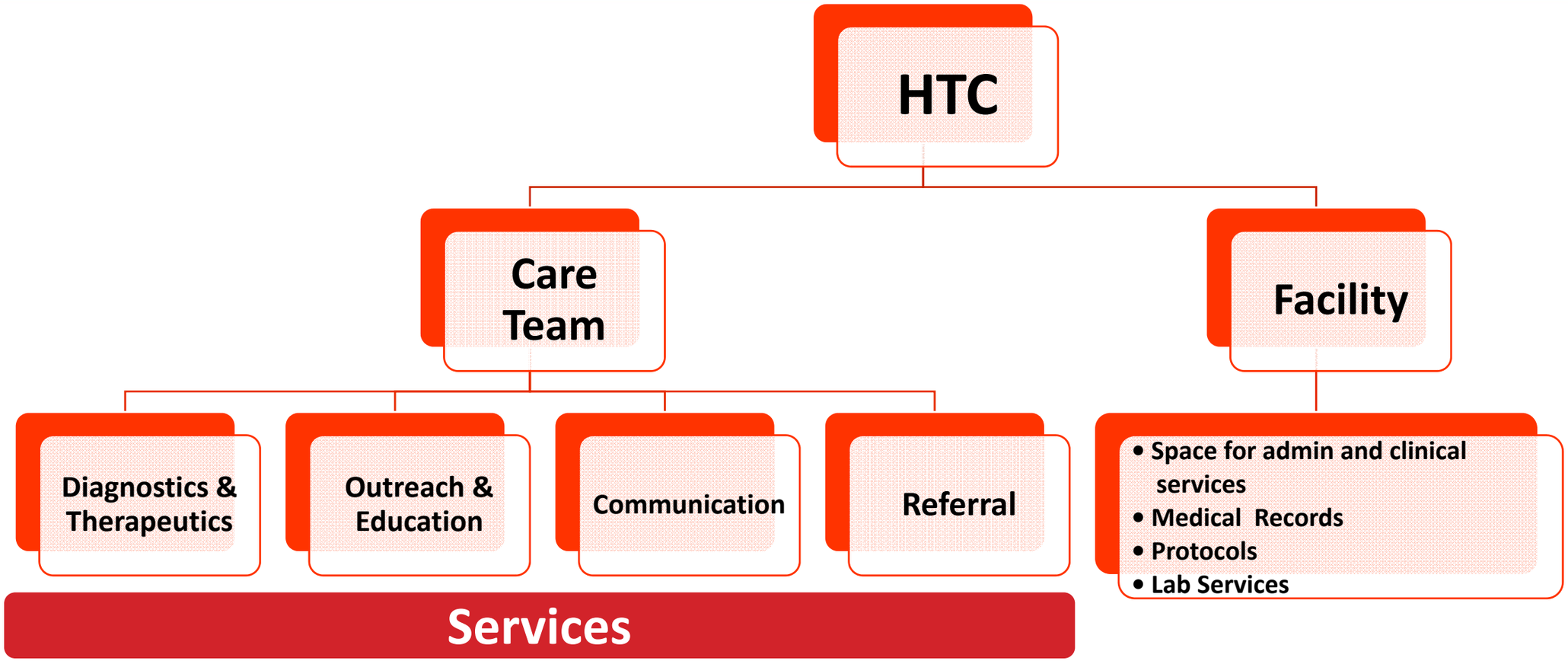
- This recommendation is even more pressing for individuals with inhibitors or individuals at risk for developing inhibitors

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



Standards and Criteria for the Care of Persons with Congenital Bleeding Disorders. MASAC #132. National Hemophilia Foundations Web site. https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations/Standards-and-Criteria-for-the-Care-of-Persons-with-Congenital-Bleeding-Disorders. Accessed February 2019.

Summary

- Hemophilia is a rare, inherited disorder preventing blood from clotting normally
  - The primary symptom is uncontrolled, often spontaneous, bleeding in different areas of the body
- Patients are typically treated with on-demand or prophylactic factor replacement therapy according to disease severity
- New and emerging treatments are beginning to address many of the barriers to effective prophylaxis, and offer hope to those with inhibitors
- Optimal use of these new treatments and tools for personalized prophylaxis has made clinical decision making much more complex
- Treatment guidelines and evidence-based recommendations assist in clinical decision-making, with multidisciplinary integrated care via an HTC being the gold standard model

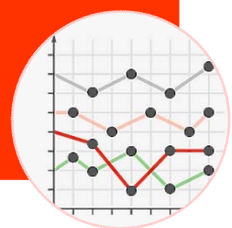
Medical and Pharmacy Benefit Management Strategies for Cost-Effective Hemophilia Care

Edmund Pezalla, MD, MPH
CEO
Enlightenment Bioconsult, LLC

Hemophilia Payer Snapshot

Epidemiology

- ~20,000 individuals nationwide
- Median age at diagnosis: 1-3 y, depending on severity



Treatment

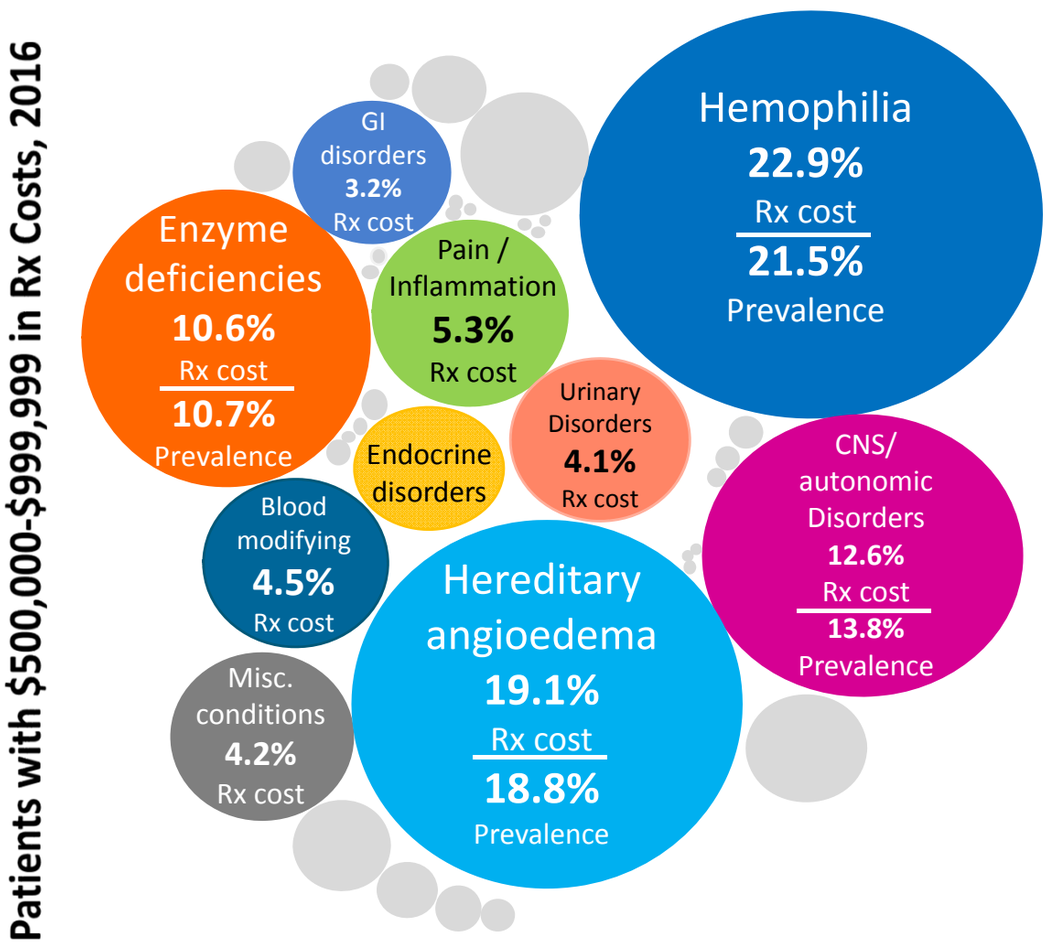
- 20+ available treatments
- Average annual cost of treatment for severe disease: $711,606
- Treatment costs can approach $4M or more

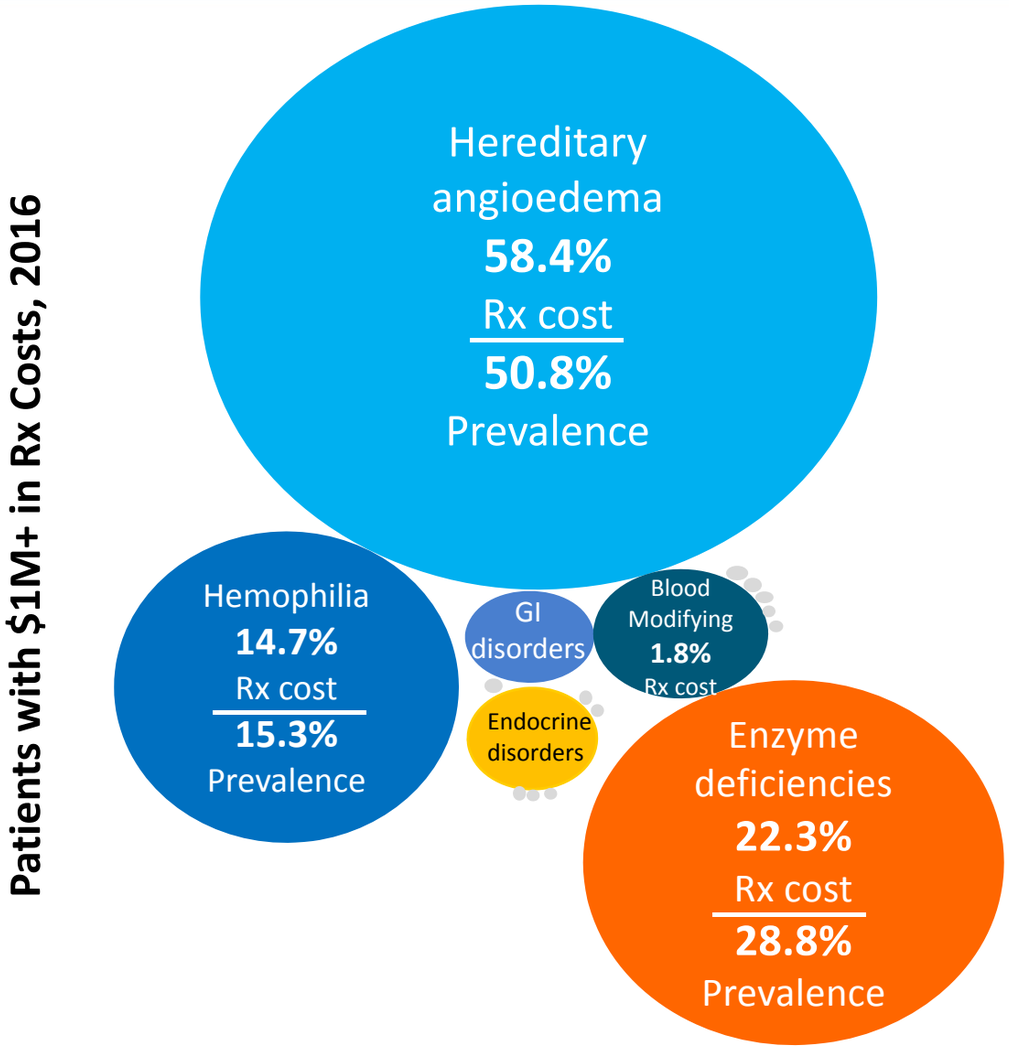
Morbidity

- Bleeding occurs most commonly in the joints and muscles
- Minor head or abdominal trauma can be life-threatening

Express Scripts. Super Spending: US Trends in High-Cost Medication Use. October 2017.

Members with Hemophilia Are Among the Very Highest Annual Rx Claimants





Express Scripts. Super Spending: US Trends in High-Cost Medication Use. October 2017.

Hemophilia Ranked Among the Top-10 High-Cost Claim Conditions for 2018

Total payments

31.8%
Top 3 conditions

51.8%
Top 10 conditions

Medical Condition	Rank 2014-2017	Rank 2013-2016	Stop-loss claim reimbursements 2014-2017: Total Reimbursements	Stop-loss claim reimbursements 2014-2017: % of total *
Malignant neoplasm (cancer)	1	1	$564.0M	18.9%
Leukemia , lymphoma, and/or multiple myeloma (cancers)	2	2	$234.7M	7.9%
Chronic/end-stage renal disease (kidneys)	3	3	$152.8M	5.1%
Congenital anomalies (conditions present at birth)	4	4	$115.2M	3.9%
Transplant	5	5	$103.3M	3.5%
Septicemia (infection)	6	7	$88.5M	3.0%
Complications of surgical and medical care	7	8	$78.2M	2.6%
Disorders relating to short gestation and low birthweight (premature birth)	8	6	$74.3M	2.5%
Liveborn **	9	13	$69.3M	2.3%
Hemophilia/bleeding disorder	10	12	$67.9M	2.3%
		Top 10 conditions	$1.58	51.8%
		Total stop-loss reimbursements	$3.08	

Sun Life Financial. 2018 Sun Life Stop-Loss Research Report.

*Percentage of total stop-loss claims reimbursements that Sun Life provided to its policyholders from 2014 to 2017.
**When the Liveborn diagnosis becomes a high-cost claim, it is often accompanied by additional diagnosis.

Payer and Employer Exposure to and Experience with Hemophilia Claims is Limited

Medical condition	Percentage of employers with at least one stop-loss claim for this condition
Malignant neoplasm (cancer)	50.7%
Leukemia , lymphoma, and/or multiple myeloma (cancers)	18.7%
Chronic/end-stage renal disease (kidneys)	16.3%
Congenital anomalies (conditions present at birth)	10.9%
Transplant	7.4%
Septicemia (infection)	11.8%
Complications of surgical and medical care	14.6%
Disorders relating to short gestation and low birthweight (premature birth)	6.3%
Liveborn **	5.1%
Hemophilia/bleeding disorder	3.2%

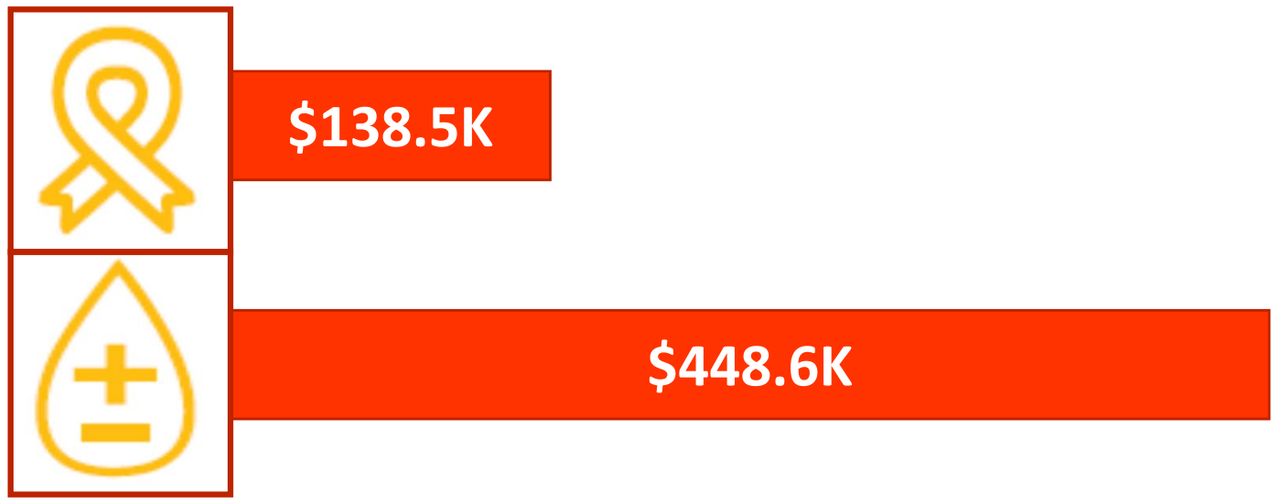
71.1%

Likelihood of a top 10 claim

Sun Life Financial. 2018 Sun Life Stop-Loss Research Report.

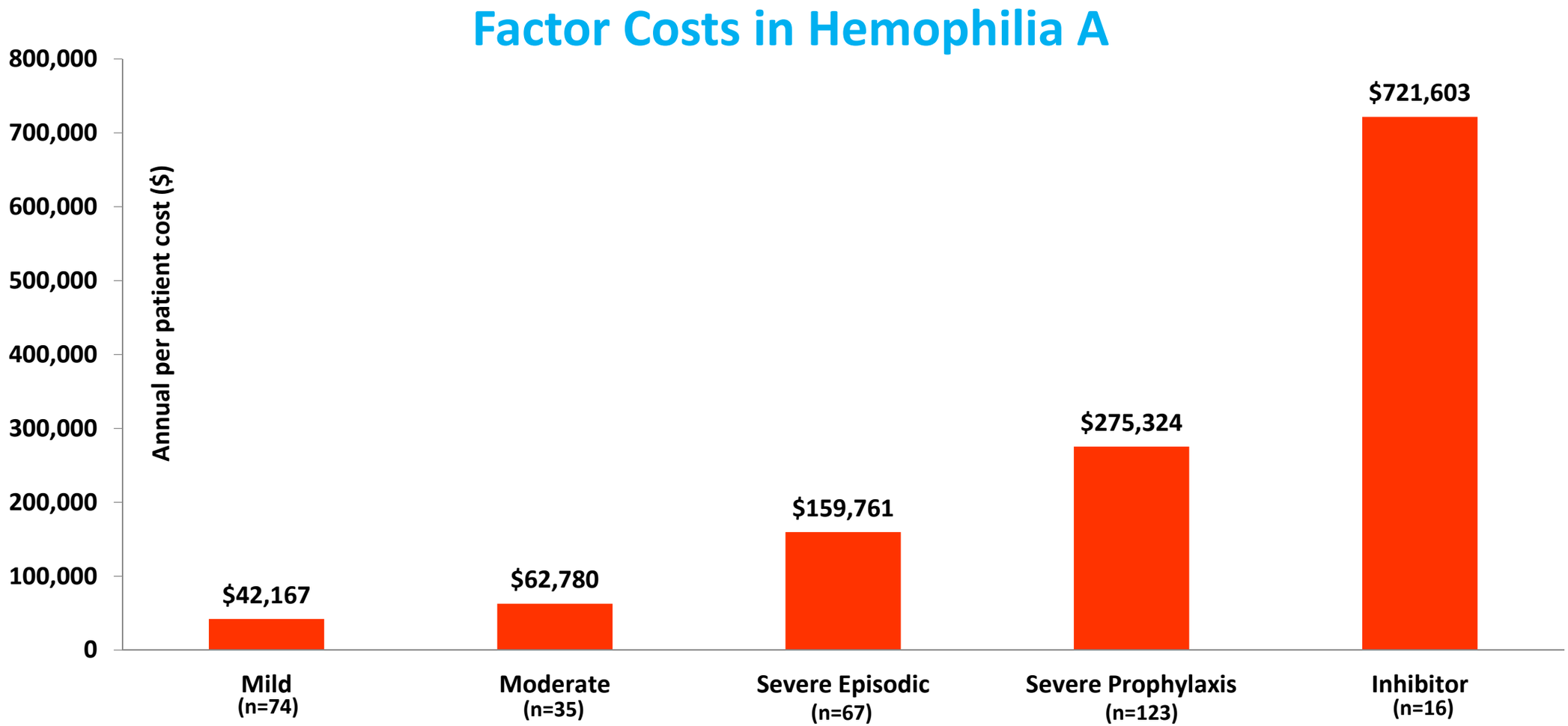
Despite Limited Prevalence, Hemophilia Accounts for Significant Share of Health Care Dollars

- Cancer is #1 high-cost claim condition based on both frequency and cost of cancer claims
- While hemophilia affects a much smaller number of people, the average treatment cost for hemophilia is >3x higher than average cost for cancer



Sun Life Financial. 2018 Sun Life Stop-Loss Research Report.

Prophylaxis and Inhibitors Contribute Significantly to Annualized Factor Costs



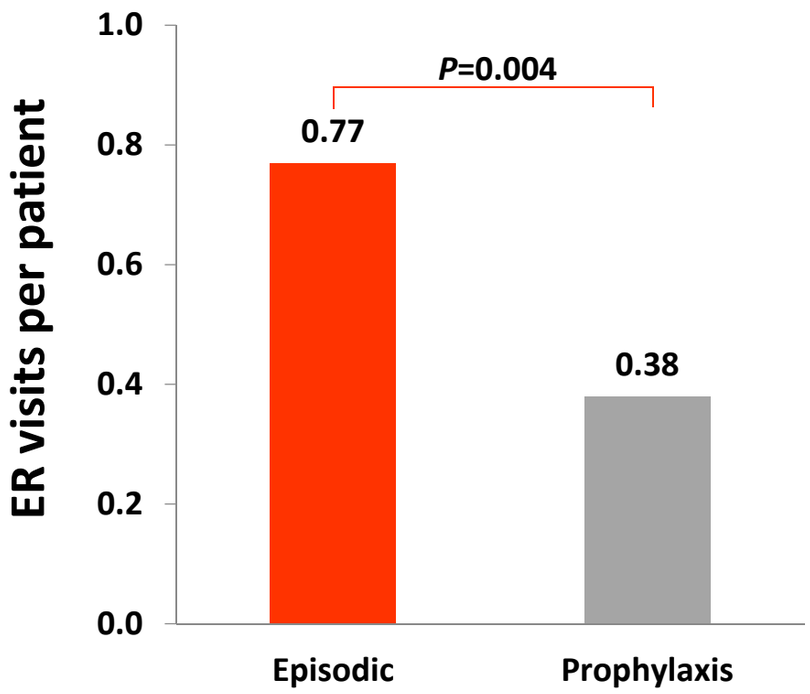
Reference prices: Medicare Average Sales Price.
Data from Hemophilia Utilization Group Study (HUGS); 2011.

Guideline-derived Care with Prophylaxis Can Decrease Overall Healthcare Utilization

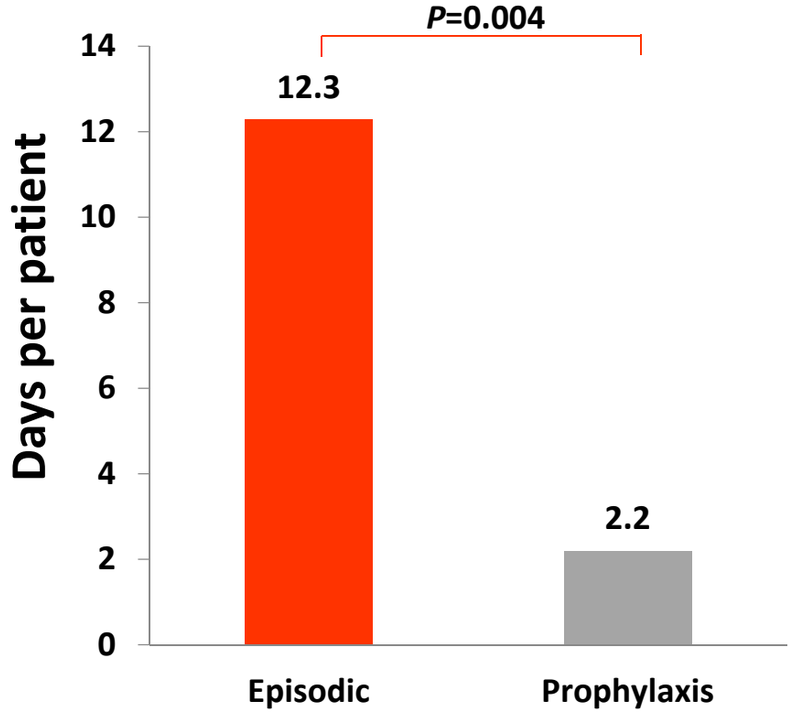
Healthcare Utilization in Severe Hemophilia

(n=205); HUGS data 2011

Annual Number of ER Visits



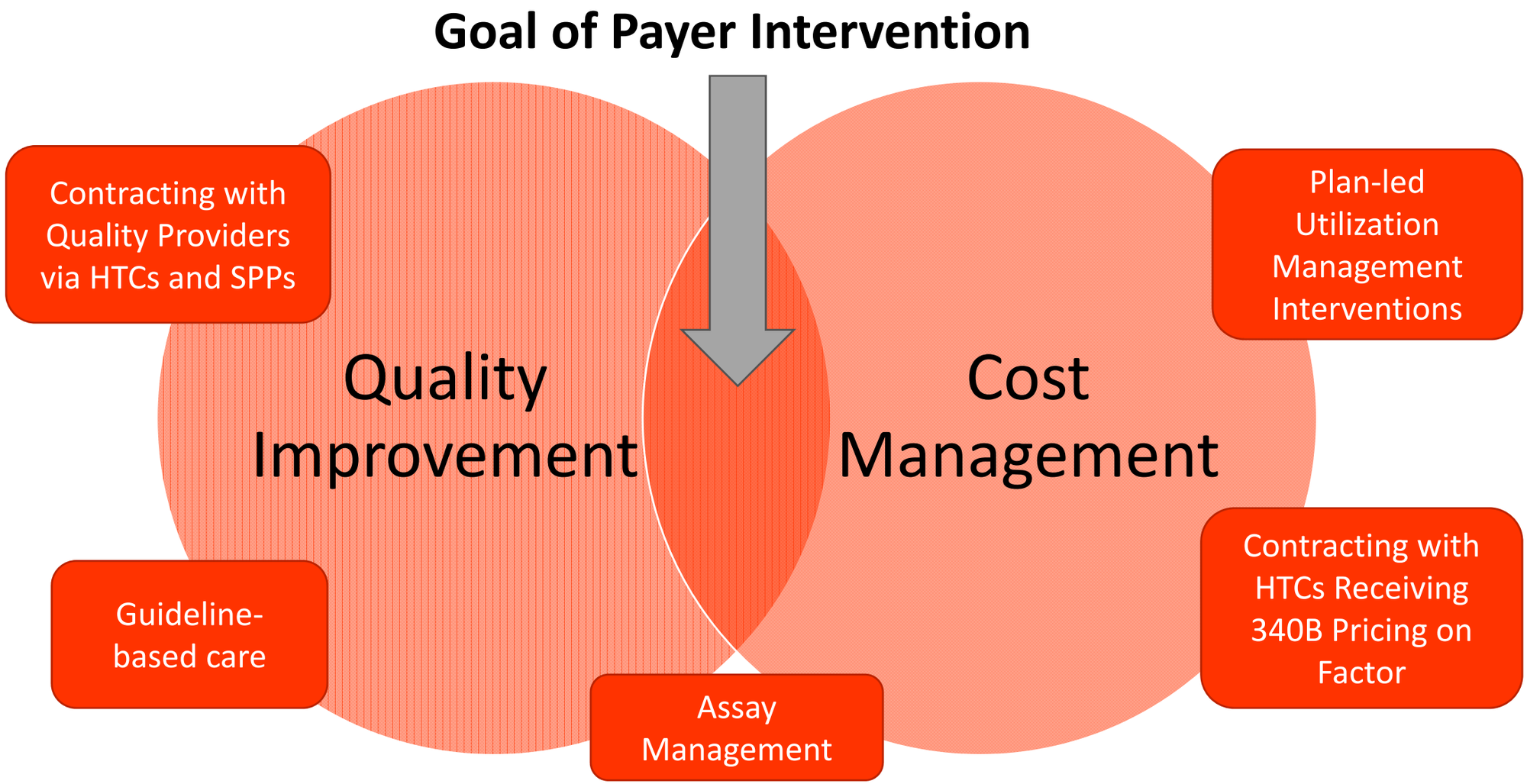
Length of Hospital Stay*



**Only applies to patients who had a hospitalization*

Data from Hemophilia Utilization Group Study (HUGS); 2011.

Payer Management Interventions to Improve Care Quality and Manage Disease Costs



Current Trends in Managing Specialty Drug Costs

- Benefit Design
- Formulary and Clinical Policy
- Innovative Contracting
- Clinical and Economic Drug Evaluation

Redefining Benefit Design

- Some plans have attempted to redefine covered benefits to exclude gene and cell therapy products
  - This may not be an effective long-term strategy but in the short-term it allows plans to scrutinize the requests for treatment more thoroughly
- Patient out-of-pocket
  - Continued growth in high deductible plans
  - Additional co-insurance payments (e.g. adding a second or third specialty tier)

Health Care Purchasers Are Driving these Approaches

- A National Business Group on Health (NBGH) survey of 170 large employers representing coverage of 19 million employees and their dependents noted the following:
  - Nearly half of all companies cited delivery system changes, such as using narrow network delivery models (e.g., accountable care organizations), direct contracting, and high-performance networks, to shift healthcare costs.
  - Nearly 60% plan to use the aforementioned strategies by 2021
  - However, fewer employers (30%) plan to offer consumer-directed—or high-deductible—health plans as the only option for their employees compared to 39% in 2018

NBGH. https://www.businessgrouphealth.org/news/nbgh-news/press-releases/press-release-details/?ID=348

Current Environment of Copay Assistance

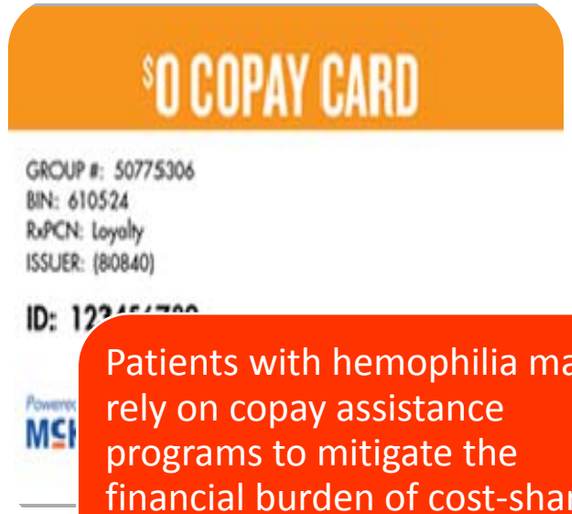
- While copay cards have some positive benefits for patients (improves access, affordability, and compliance), some plan sponsors believe they increase costs via the following:
  - Assisting beneficiaries to expend their accumulators more quickly can remove barriers to unnecessary testing/procedures by limiting patients' stake
  - Potentially incentivizing patients to utilize non-preferred drugs that are less cost-effective
- In response to these issues and as a way to drive greater savings for plan sponsors, two new specialty copay card programs were introduced in 2017: accumulator adjustment and copay allowance maximization
  - However, when applied to high-cost/high-value drugs, these programs may create a barrier to patients' utilization of necessary and potentially life-saving therapies

Cleveland Research Company, 2017.

Copay Assistance Mitigates Patient Cost Burden in Chronic Disease, but Accumulator Adjustment Programs Reintroduce Financial Barriers to Access

For patients with complex, chronic conditions like hemophilia, finding the right therapy can be a long and difficult journey

- Adherence results in decreased health care service utilization



Patients with hemophilia may rely on copay assistance programs to mitigate the financial burden of cost-sharing

- A significant proportion of patients now only have high-deductible plan options
- Copay assistance programs are offered by all manufactuers of specialty drug products

Copay Accumulator Programs interfere with a vital lifeline for patients with chronic conditions necessitating specialty drugs

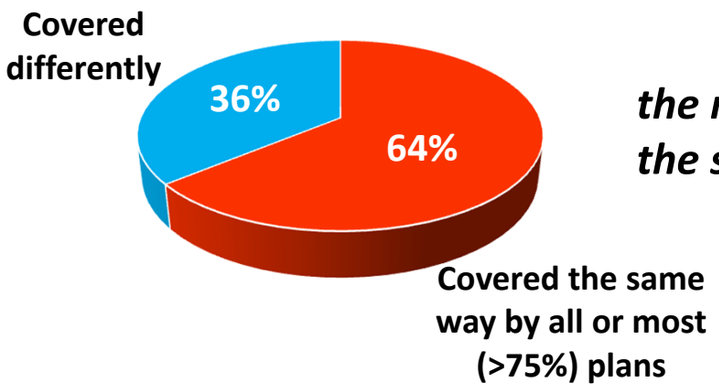
- Accumulator adjustment and copay allowance maximization negate the benefits of copay assistance programs and reintroduce financial barriers to care

Formulary and Clinical Policy

- Completely closed formularies are becoming more common
  - NDC block until review
  - Increasing number of excluded drugs
- Narrowing the number of preferred or covered products
- More restrictive policies/PA criteria: going beyond the label to consider clinical trial inclusion/exclusion
  - Restricted patient population
  - Stopping rules for nonresponse
  - More rigorous re-authorization criteria

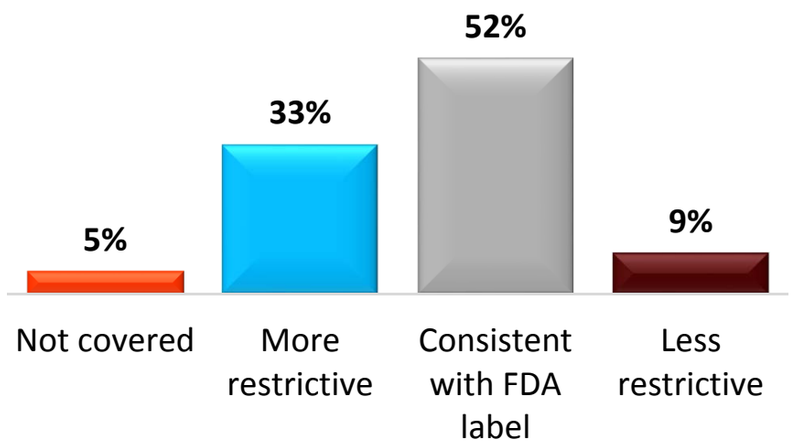
Tufts Study on Restrictive Coverage

Across 3,417 decisions addressing coverage for 302 drug indication pairs…



the majority were covered the same way…

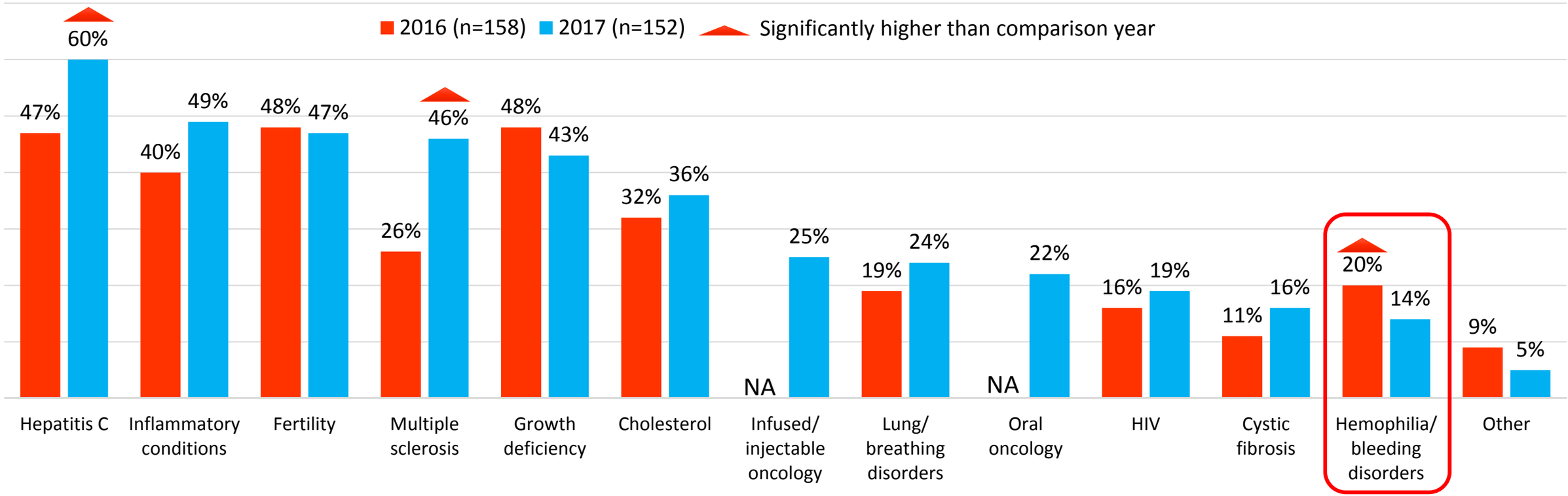
and specifically the decisions were…



- Health plans restricted coverage of drugs indicated for cancer less often than they did coverage of drugs indicated for other diseases
- Using multivariate regression, it was found that several drug-related factors were associated with less restrictive coverage, including indications for orphan diseases or pediatric populations, absence of safety warnings, time on the market, lack of alternatives, and expedited FDA review

Chambers JD, et al. *Health Affairs*. 2018;37:1041-1047.

Formulary Exclusion Classes

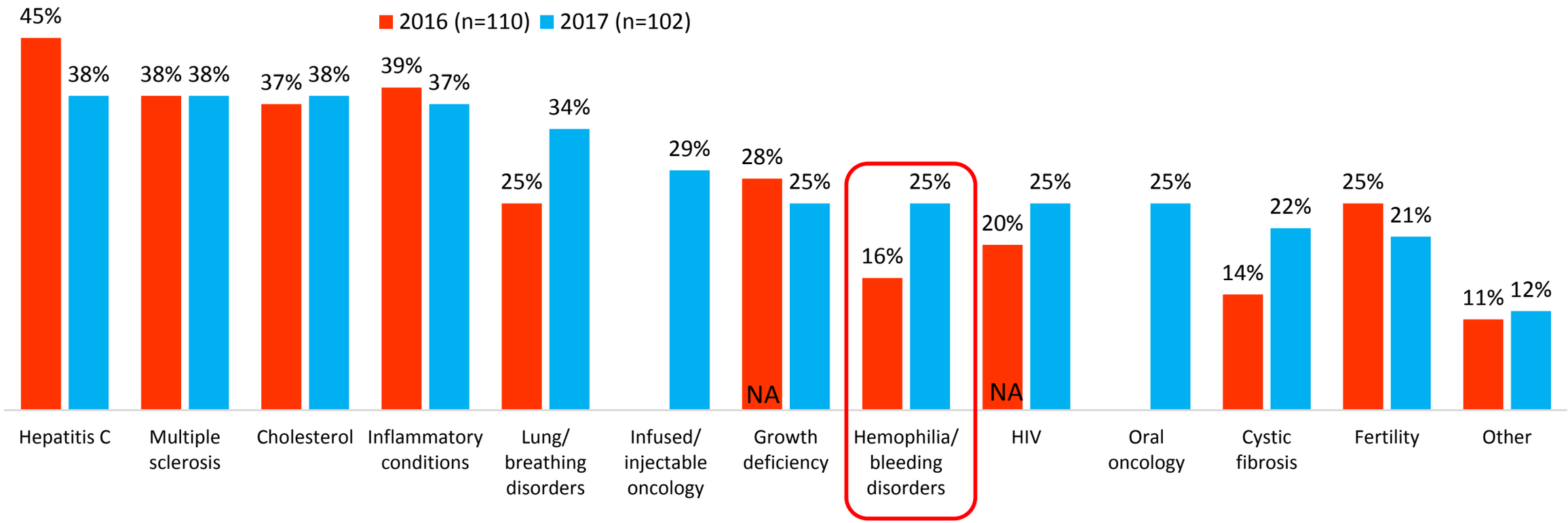


Base: Respondents who have formulary exclusions in place. Multiple responses allowed. NA = not asked.

N=299 employer-based plans of all sizes

Pharmaceuticals Strategies Group. Trends in Specialty Drug Benefits. 2018.

Classes Under Consideration for Formulary Exclusion



Base: Respondents who are considering formulary exclusions. Multiple responses allowed. NA = not asked.

N=299 employer-based plans of all sizes

Pharmaceuticals Strategies Group. Trends in Specialty Drug Benefits. 2018.

Innovative Contracting

- Outcomes-based contracts
- Contracts with refunds if patient does not stay on drug for a sufficient period of time
- Limits on plan liability (e.g. if costs exceed expected amounts or number of patients exceed projections)

Contracting Approaches

Drug

- Formulary positioning
  - Multiple specialty tiers
  - Closed formularies
  - Step therapy

Provider

- Narrow networks
- Reimbursement issues
  - Role of the HTC and 340B pricing
- Accreditation
- Credentialing

Traditional vs. 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

Tighter assay management and minimized bleeding episodes/ ER utilization are a logical fit for such arrangements

Increasing Data & Complexity

Long G, et al. *J Med Econ*. 2014;17:883-893.

Value-Based Contracting in Action for Rare, High-Cost Diseases

- Patisiran was recently approved to treat polyneuropathy caused by hereditary transthyretin-mediated (hATTR) amyloidosis
- To help payers cope with the $450,000 annual list price of patisiran, the manufacturer is working with commercial insurance plans to offer value-based contracts for the therapy
- The Contracts will tie the level of reimbursement to patient outcomes:
  - If patisiran delivers the same benefits in real-world practice that it did in clinical trials, the manufacturer will receive a higher level of reimbursement
  - If the drug does not perform as well, the manufacturer will receive lower reimbursement

Value-Based Arrangements (VBAs) May be More Common Than Previously Thought

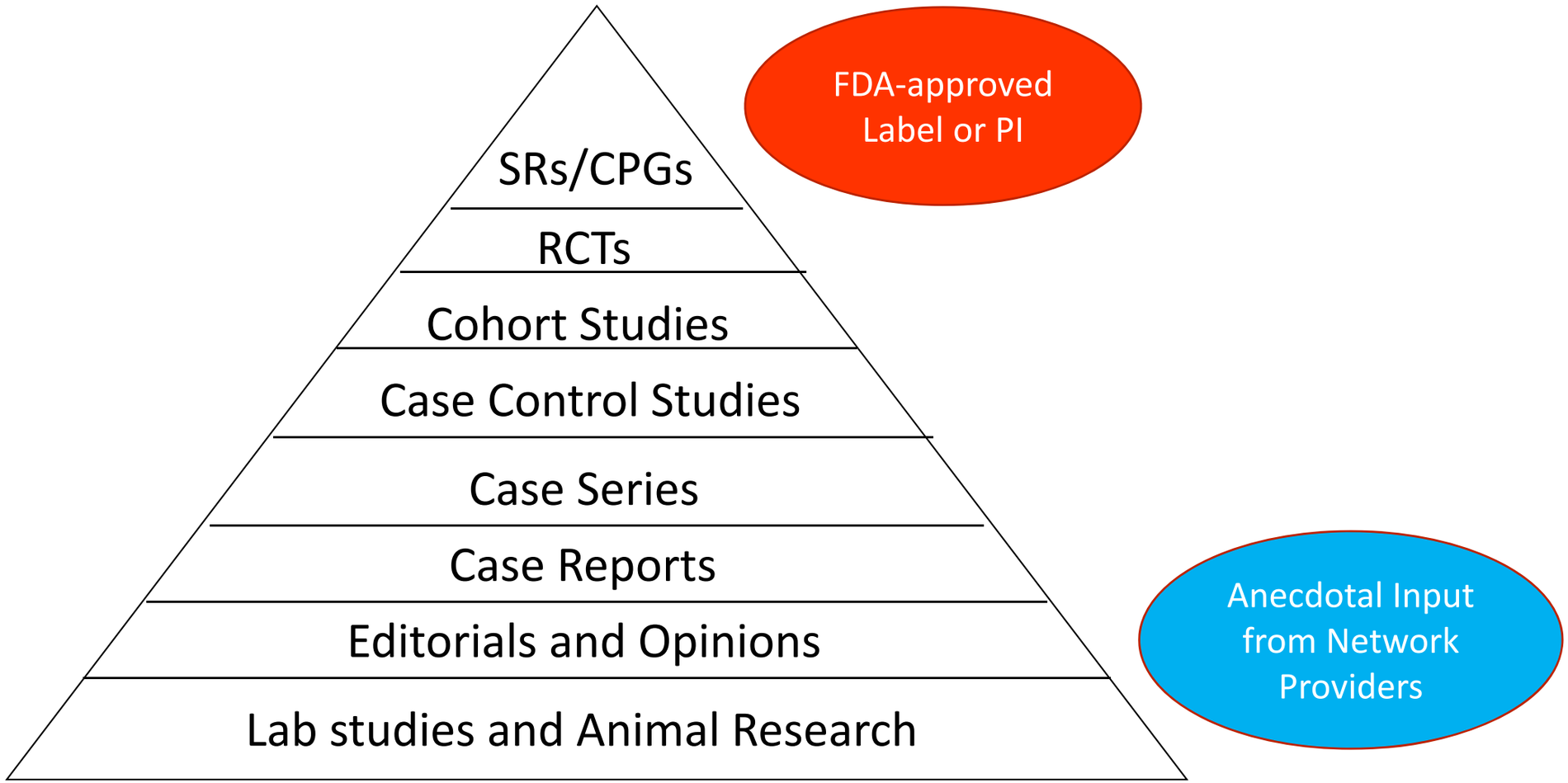
- A survey was administered to a sample of senior representatives from payer organizations and biopharmaceutical manufacturers
- Of the 25 respondents, only 1 manufacturer and 4 payers reported not having explored or negotiated any VBAs
- Questionnaire results from 11 biopharmaceutical manufacturers and 9 payers who had experience with VBAs were analyzed:
  - More than 70% of VBAs implemented between 2014 and 2017 were not publicly disclosed
  - Manufacturers and payers reported that approximately 33% and 60% of early dialogues translate into signed VBA contracts, respectively
- These findings suggest that the true prevalence and impact of VBAs may be underestimated since the majority are not publicly disclosed

Mahendraratnam N, et al. *Am J Manag Care.* 2019;25(2):70-76.

Health Technology Assessment/Drug Review

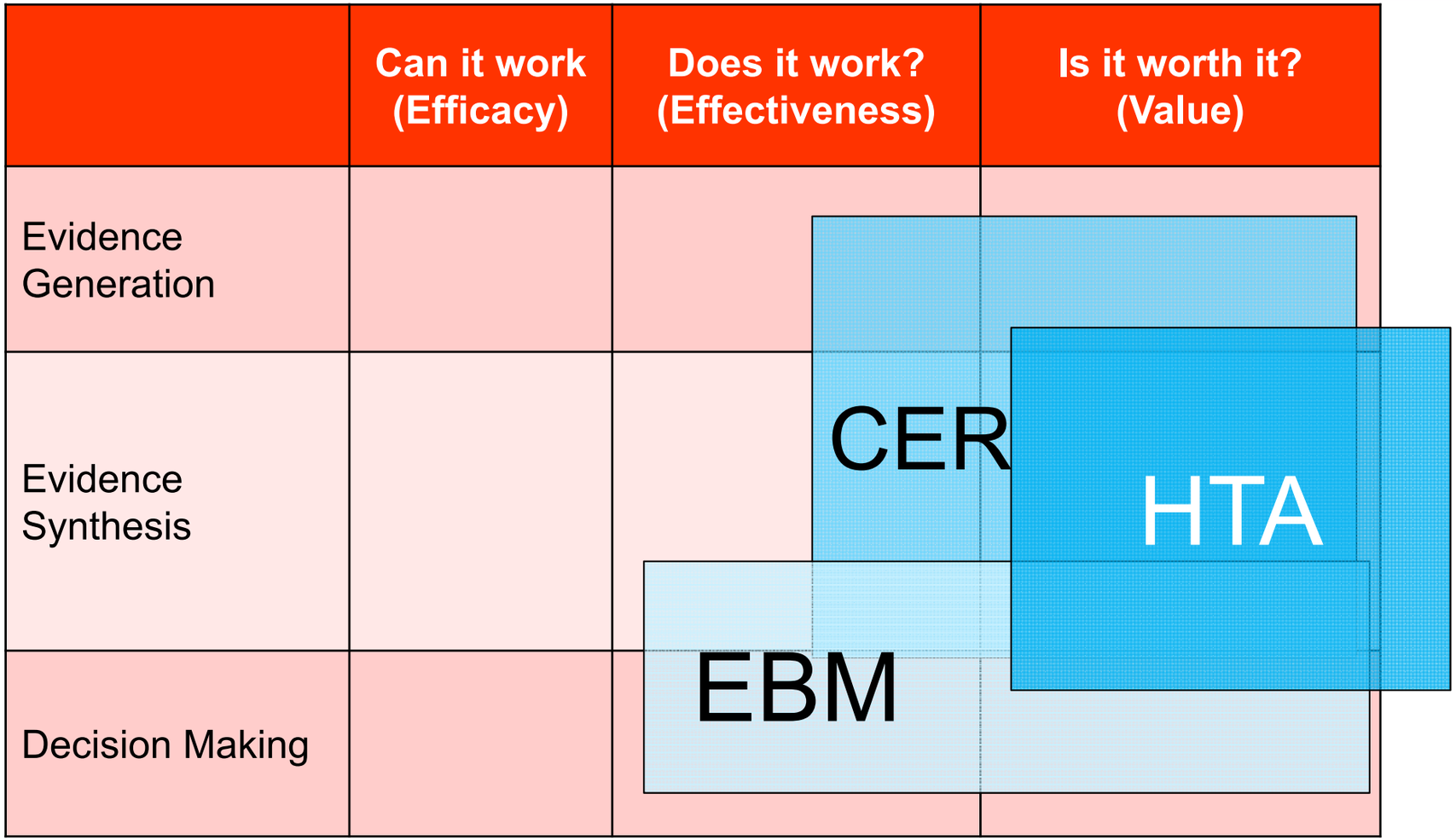
- Payers are demonstrating more interest in Institute for Clinical Effectiveness Research (ICER) reviews and the potential for use of Cost Effectiveness Analysis
- Drug evaluation, contracting, etc. are contributing to large discrepancies between plan coverage and coverage policies

Drug Evaluation: Evidence Hierarchy



PI=package insert; SRs=systematic reviews; CPGs=clinical practice guidelines; RCTs=randomized controlled trials

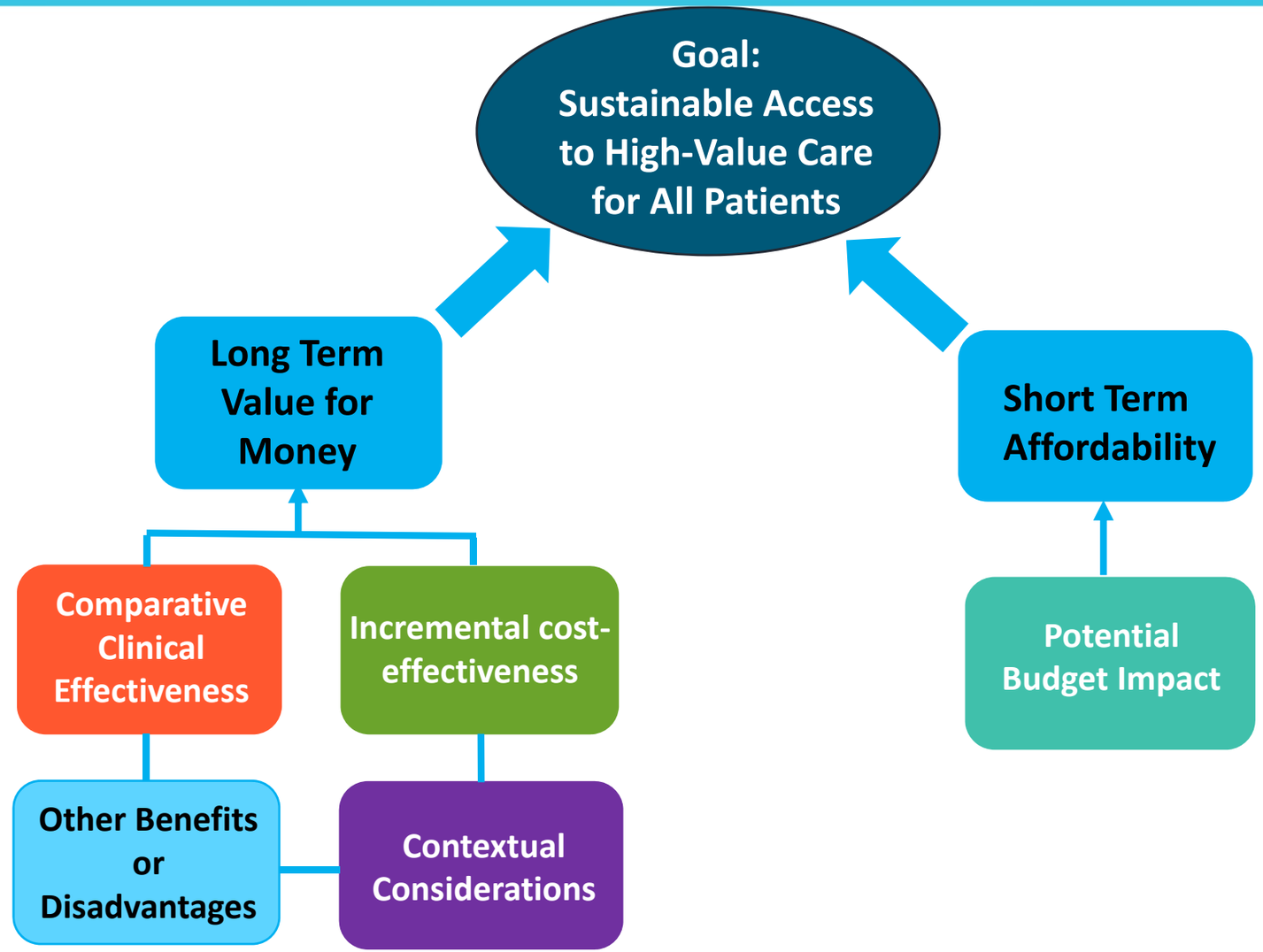
Relationship and Functions of CER, HTA, and EBM in Drug Evaluation



CER=comparative effectiveness research; HTA=health technology assessment; EBM=evidence-based medicine.

Luce BR, et al. *Milbank Q*. 2010;88;256-276.

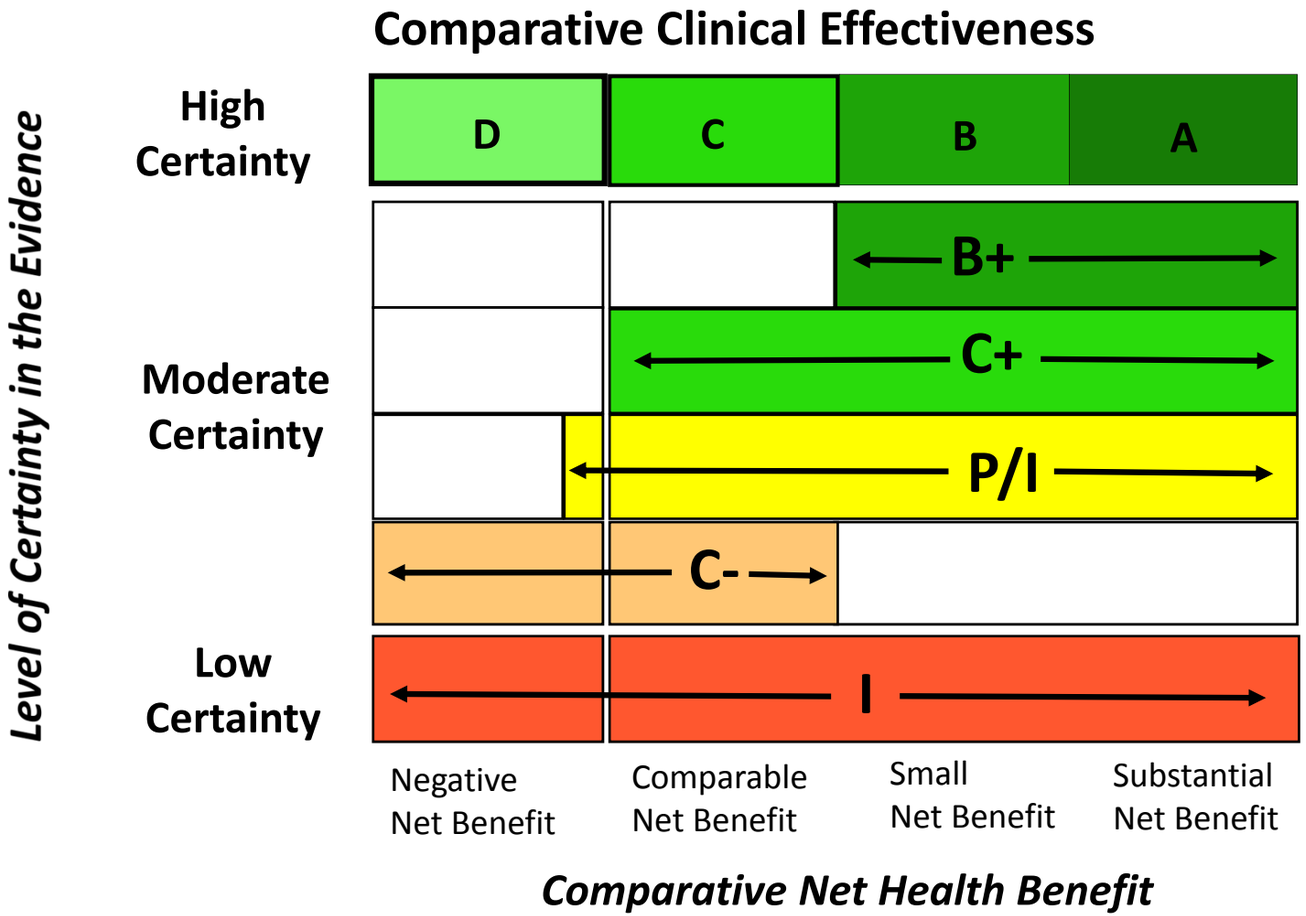
The Institute for Clinical and Economic Review (ICER) Approach



ICER. ICER Value Framework. January 2018.

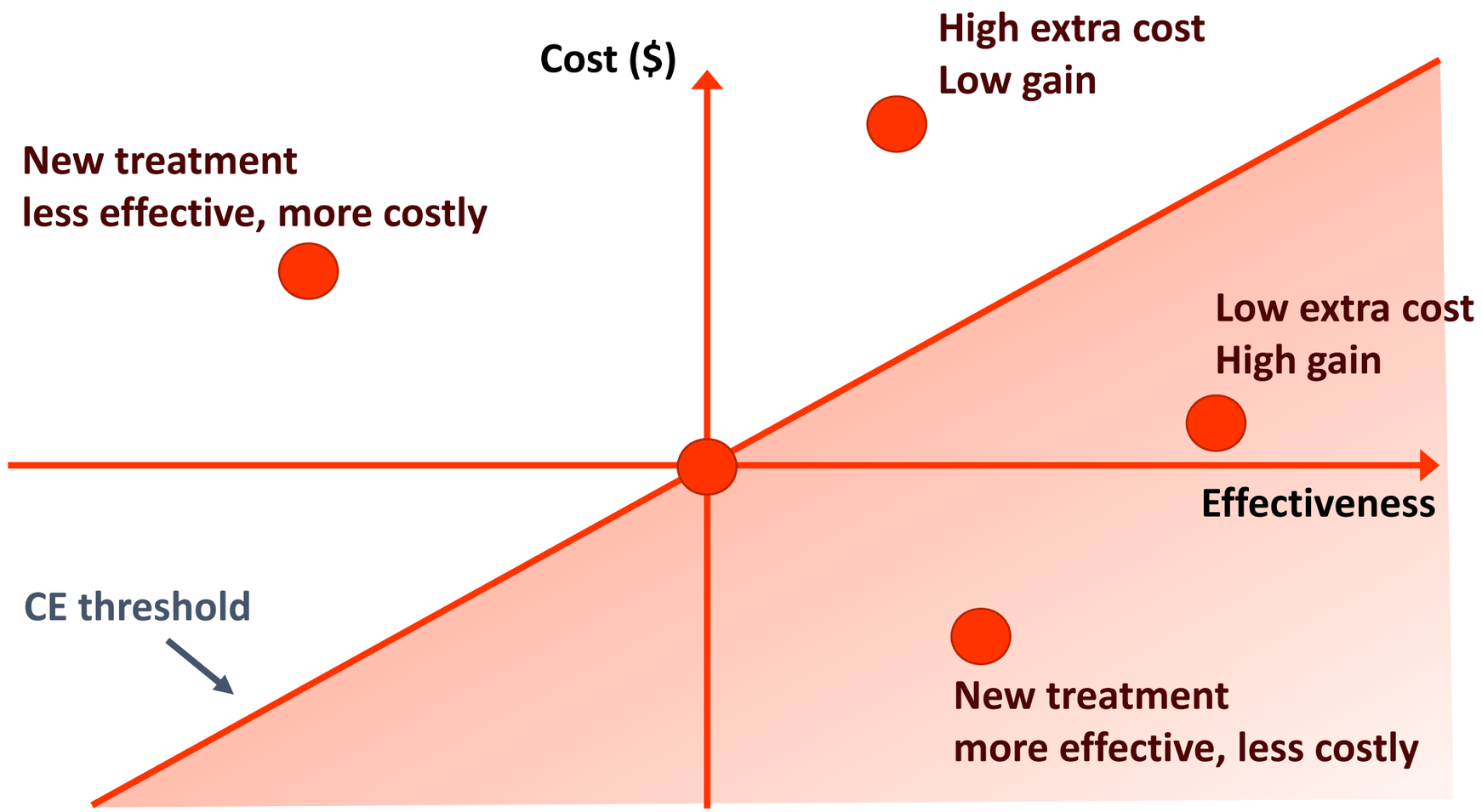
ICER Approach: Clinical Effectiveness

ICER EBM Matrix



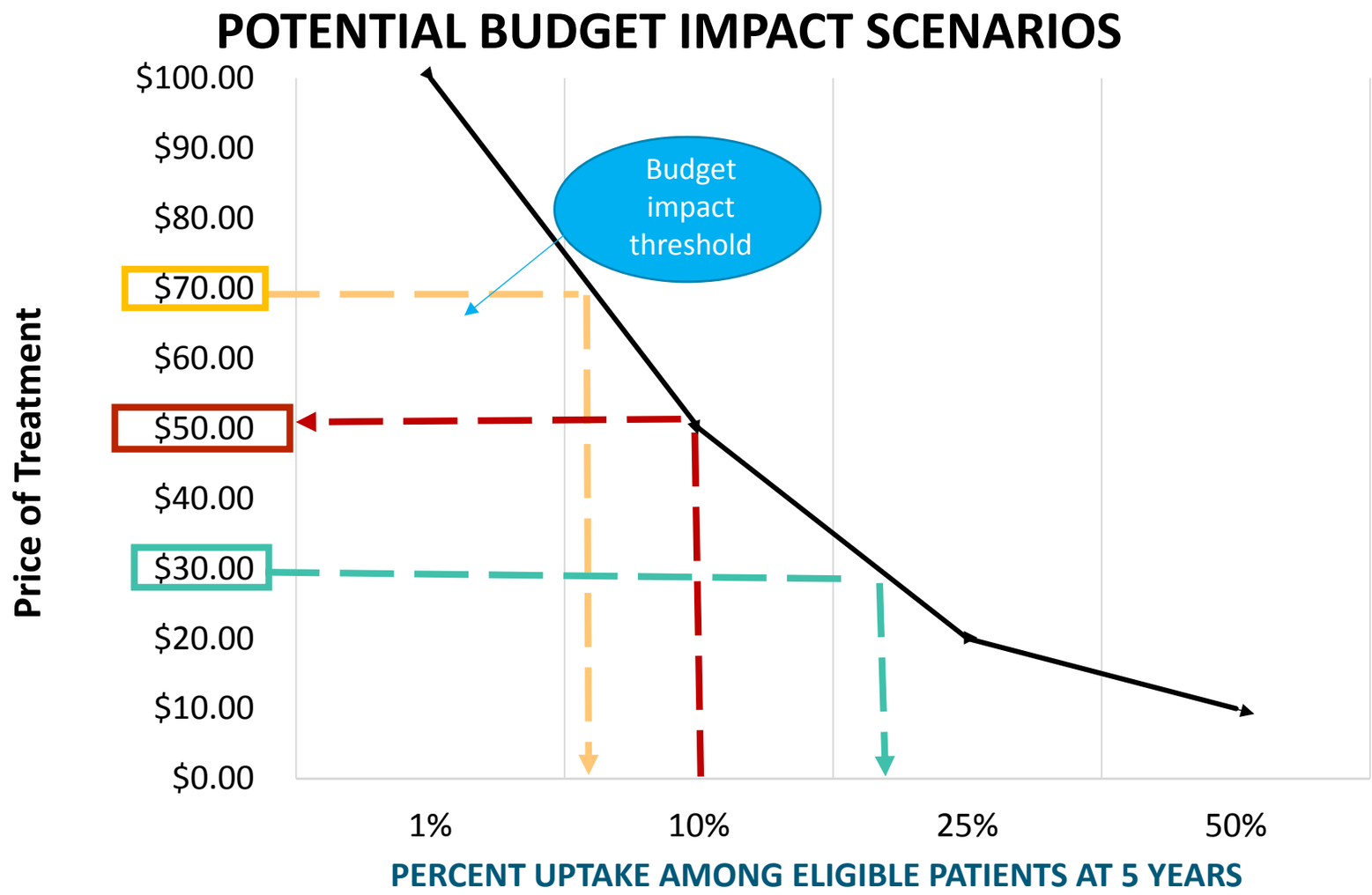
ICER. ICER Value Framework. January 2018.

ICER Approach: Incremental Cost-Effectiveness



ICER. ICER Value Framework. January 2018.

ICER Approach: Budget Impact



ICER. ICER Value Framework. January 2018.

Use of ICER Reports by Payers

- At what point were ICER reports used in the formulary decision process?
  - 75% inform or validate the payer's own analysis
  - 69% used during research process
  - 56% used during the P&T review phase
  - 33% use during coverage policy development

May 2015 Survey of AMCP eDossier Users (N=99)

Lising A. *J Manag Care Pharm*. 2016;Suppl N 10-a.

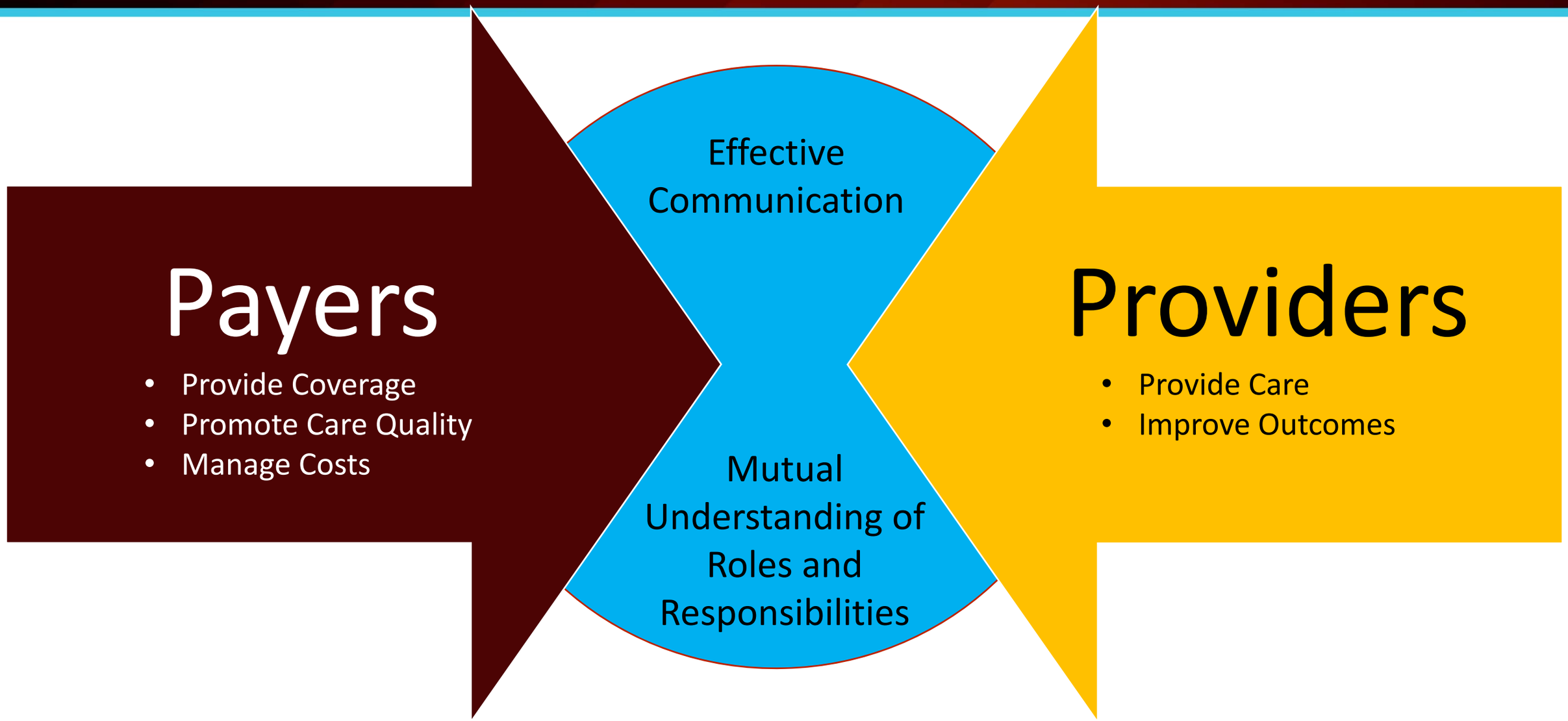
Summary

- Despite extremely limited prevalence, hemophilia accounts for a significant share of heath care expenditures
  - The vast majority of these direct expenditures are the result of specialty drug costs, with prescription factor replacement therapy averaging >$700,000 per patient /per year
- The ultimate goal of payer interventions is to manage these costs in a manner that promotes high-quality care and is sustainable for the health care system
- Benefit design, formulary and clinical policy, innovative contracting, and clinical and economic drug evaluation have all played an increased role in managing the specialty drug spend in recent years
- A key challenge of applying these drug management initiatives is striking a balance between cost-savings and member access

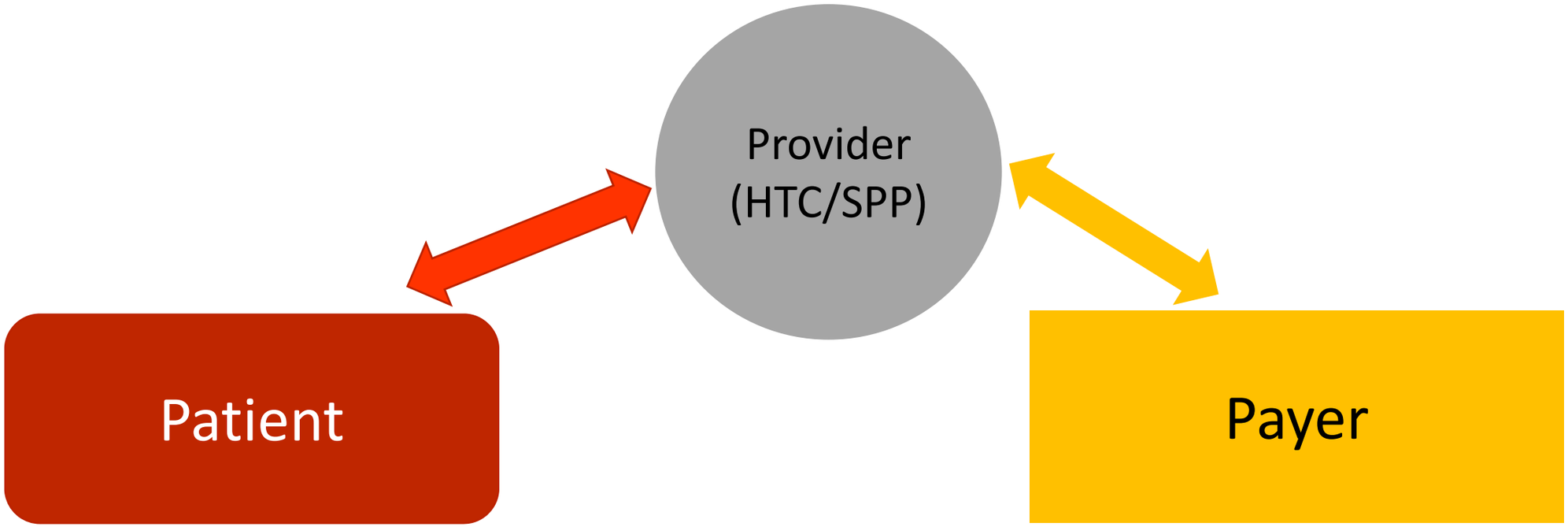
Hemophilia Treatment Center Care Coordination and Communication Strategies to Enhance Patient Outcomes

Jeffrey Dunn, PharmD, MBA
Vice President, Clinical Strategy and Programs and Industry Relations
Magellan Rx Management

Payers and Providers Share Similar Goals Despite Disparate Points of View



Providers are Tasked with Communicating with Patients and Payers to Facilitate Optimal Outcomes



- Concerns regarding disease and its management
- Bleed monitoring
- Maintaining adherence

- Coverage considerations, prior authorizations, appeals, etc.
- Value of the comprehensive care model
- Data related to outcomes and assay management
- Contracting

Payers Should Be Educated and Informed about the Value of the HTC Comprehensive Care Model

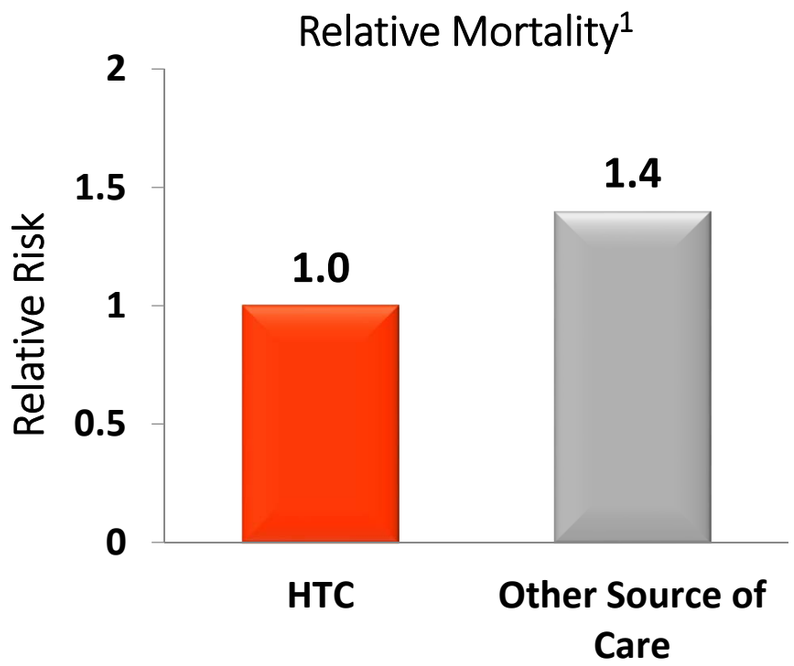
Improving Outcomes Through an Integrated, Comprehensive Care Approach

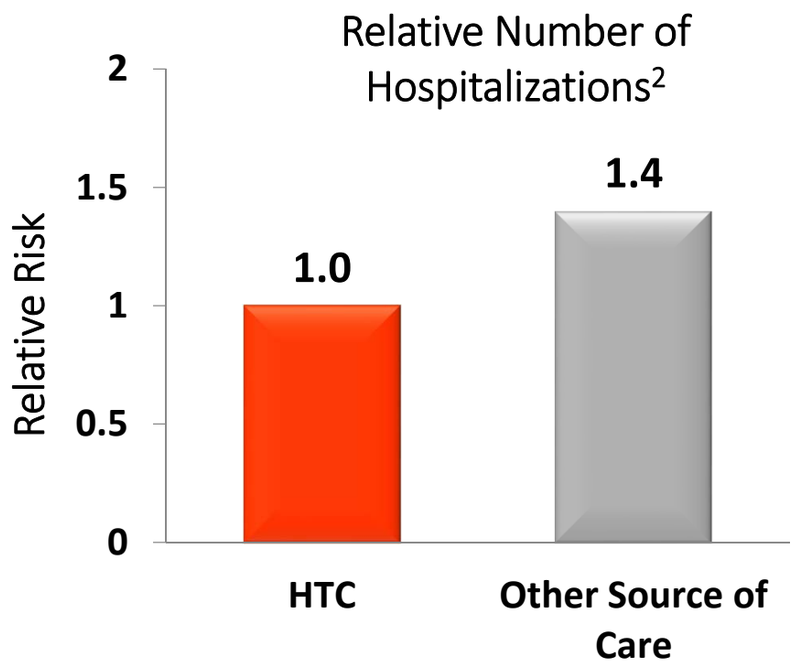
- Comprehensive care for hemophilia is defined as the continuous supervision of all medical (including factor replacement utilization) and psychosocial aspects affecting the patient and his family
- Optimal treatment is based on:
  - Early diagnosis
  - Prevention and early treatment of bleeding episodes 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-Saez A. *Hematology*. 2012;17(supp1):S141-143.

Reduced Morbidity and Mortality Derived via HTC-delivered Care

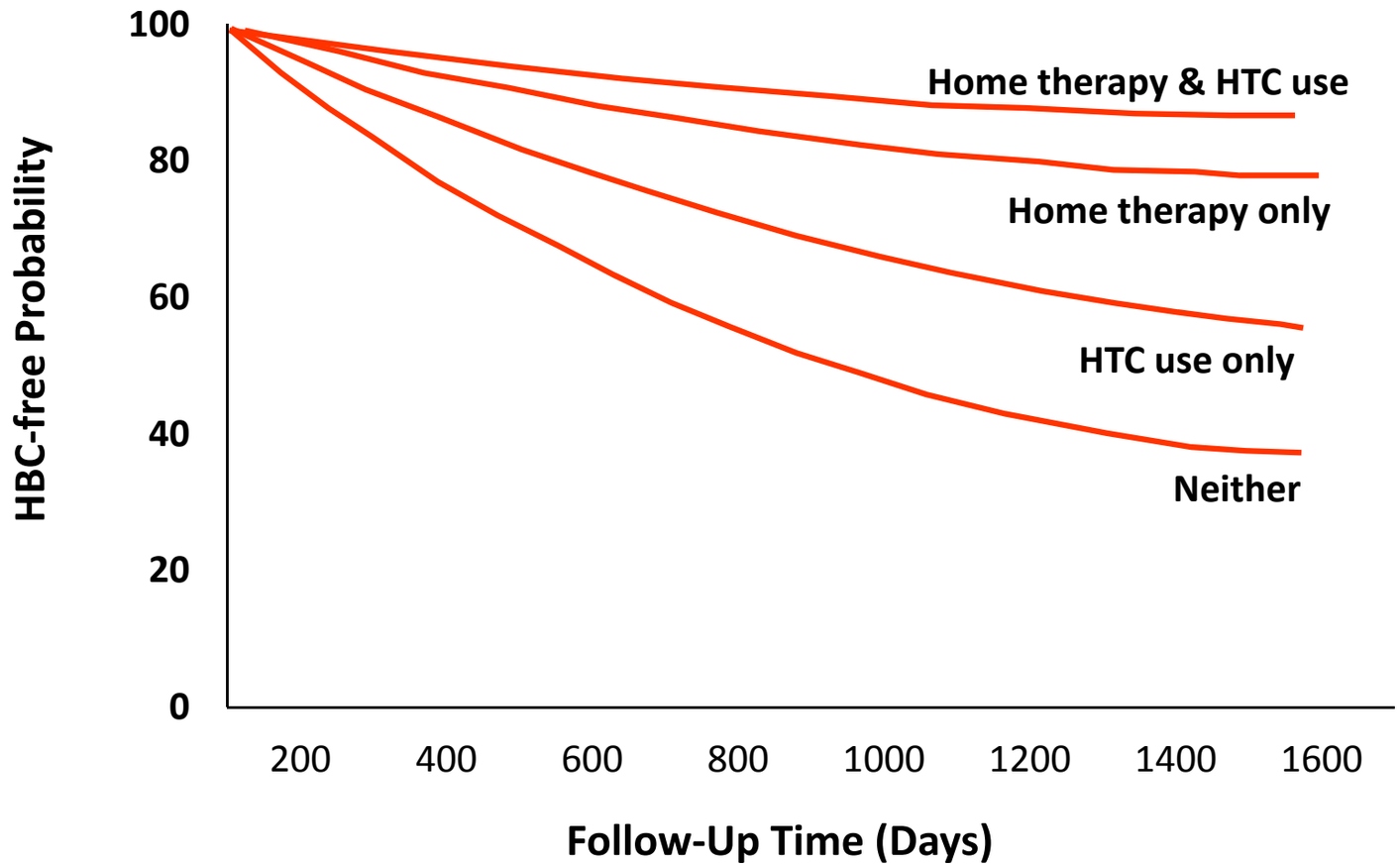
Patients Receiving Care at an HTC show 40% Reduction in Mortality and Hospitalization





1. Soucie JM, Nuss R, Evatt B, et al. *Blood*. 2000;96(2):437-42.
2. Soucie JM, Symons J, Evatt B, et al. *Haemophilia*. 2001;7(2):198-206.

HTC Care Minimizes Hospitalizations for Bleeding Complications



HBC=hospitalization for bleeding complications.

Soucie JM, Symons J, Evatt B, et al. *Haemophilia*. 2001;7(2):198-206.

Therapeutic Adherence and Factor Cost Management Represent Two Key Areas of HTC/SPP-derived Value

Opportunities to Engage Patients with Bleeding Disorders Supporting Patient Care

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 Meets the Patient Where They Are and Encourages Introspection

Gue D, et al. *J Multidiscipl Health*. 2015;8:527-534.

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 City: Guildford Press.

Tactics to Improve Adherence

For infusions and/or bleeds

For education and administration as needed

Regularly scheduled or follow-up calls

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

Data Tracking Tools Can Offer Cost Savings and Patient Adherence

- The Audaire platform, currently in pilot phase, collects information that combines the following information into actionable reports and notifications:
  - Prescription
  - Dispensation
  - Pharmacy and/or clinic touch points
  - Reported bleeds/exacerbations
  - Self or assisted medication administration information

NHF. https://www.hemophilia.org/Newsroom/NHF-Community-News/NHF-and-Partners-Announce-Innovative-Infusion-Logging-Tool

Data Tracking Platform: Process

Pharmacy

- Dispensation is recorded in the platform, under patient's profile, capturing specific assay, NDC, and lot #
- Places a label on each box of medication with number associated with patient and dispensing information

Patient

- Downloads mobile application (one-time action)
- Self-administers drug and instantly logs activity via mobile application (data cannot be changed by patient)

Real-time Logging

- The information is transferred instantly from the smartphone application into the platform
- Data transfer and database are HIPAA and Hitech compliant

Reports/Notifications

- Pharmacy has instant access to patient activity log, bleeds/exacerbations, notification system, and recording of patient touch points
- Detailed reporting available for pharmacy to provide to Payer or Third Party Administrators via electronic reports (Excel or Adobe) or electronic feed directly to payer

NHF. https://www.hemophilia.org/Newsroom/NHF-Community-News/NHF-and-Partners-Announce-Innovative-Infusion-Logging-Tool

Data Tracking Platform: Benefits

Community Member

- Pharmacy provides dispensation/dosing information pre-loaded for the patient, thus community member only responsible for scanning infusions and recording bleeds
- Ability to review their infusion and bleeding history and review with clinic and pharmacy to be more engaged in their care
- No cost to participate or access their own secure information

Payer, Pharmacy Benefits Manager (PBM), Employer Benefits Consultants (EBC)

- Review assay management stats and compare across multiple pharmacies in its network
- Ability to show value to payers of adherence and coordination with pharmacies and clinics

Pharmacy/Clinic

- Higher level of patient engagement that also allows patients to be more involved with their care
- Tracking medication adherence and being able to be proactive with customizable notification system
- Greater level of compliance with payer reporting requirements for maintaining and expanding network contracts

NHF. https://www.hemophilia.org/Newsroom/NHF-Community-News/NHF-and-Partners-Announce-Innovative-Infusion-Logging-Tool

An Array of Pharmacy Services can Support Patients with Bleeding Disorders

340B and Specialty Pharmacy Services Designed to Improve the Overall Quality of Care and Manage Disease-Related Costs

Disease Management and High-touch Pharmacy Services

Integrated HTC Pharmacy 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

340B History and Implications

History

Federal grant funding per HTC averages $35,000 annually, with variable state funding; these alone are inadequate to support services

340B program created in 1992 provides discounts on facility outpatient prescription drugs to select "safety net" providers, including HTCs

PHS pricing allows HTCs to reach more patients, provide more services, and support a multidisciplinary team at reduced cost

Implications

- Lower drug acquisition costs through 340B purchasing can result in savings over other sites of dispensation
- 340B funds daily operations and patient services of HTCs
- Proposed limitations on covered entities and evolving health care legislation place both the 340B program and the sustainability of HTCs in jeopardy

NHF Policy Statement: Hemophilia Treatment Center Participation in the 340B Drug Discount Program. National Hemophilia Foundation Website. https://www.hemophilia.org/sites/default/files/document/files/NHF-Position-Statement-Regarding-Hemophilia-Treatment-Center-Participation-in-the-340B-Drug-Discount-Program.pdf. Published July 30, 2015. Accessed July 2018.

Most HTCs Support Care Coordination and Case Management Almost Entirely with 340B Income

These high-touch services and rigorous oversight frequently lead to improved therapeutic adherence and clinical outcomes

N=31 HTCs with established 340B programs

Hemophilia Treatment Center Services	# of Encounters
Telephone Triage Urgent/Emergent	
Annual Mean Encounters per HTC	1,968
Annual Total Encounters 29 HTC	57,072
Medical Care Coordination	
Annual Mean Encounters per HTC	2,088
Annual Total Encounters 30 HTC	62,640
Care Management/Psychosocial/Vocational	
Annual Mean Encounters per HTC	960
Annual Total Encounters 30 HTC	28,800
Patient Education	
Annual Mean Encounters per HTC	516
Annual Total Encounters 30 HTC	15,480

Trujillo M, et al. Presented at the WFH 2016 World Congress, July 24-28, 2016, Orlando, FL.

Sample Case Study

Background

- Patient: 32-year-old male (110 kg)
- Diagnosis: mild hemophilia A with a high titer inhibitor
- Patient was being treated outside the HTC and received his factor from a specialty pharmacy prior to transitioning to an HTC.
- Patient requests to receive his factor from HTC pharmacy after transitioning his care

Physician prescribes

- Infuse factor VIII 125u/kg (+/-10%) daily and PRN for breakthrough bleeds
  - Dispensation (+/-10%) ranges
    - Low - 12,375 u
    - Target - 13,750 u
    - High - 15,125 u
- Infuse NovoSeven (VIIa) 8,000 mcg daily and PRN for breakthrough bleeds

Sample Case Study: Initial Cost Analysis

- Assay Management Factor VIII

Specialty pharmacy dispensed 5%-10% ***above*** target per month

HTC integrated pharmacy dispensed 1%-4% ***below*** target per month

- Cost Management Factor VIII and Factor VIIa
  - HTC dispensed factor VIII at $0.26 per unit below specialty pharmacy*
  - HTC dispensed factor VIIa at $0.60 per unit below specialty pharmacy*

*Pricing varies across HTCs. Each HTC negotiates own contracts.

Sample Case Study: Initial Cost Analysis (cont.)

- HTC dispensation **saved the plan $143,935 per month** for factor VIII through more aggressive assay management and shared savings from the 340B in-house pharmacy*
- HTC dispensation **saved the plan $144,000 per month** for factor VIIa using shared savings from the 340B in-house pharmacy*

*Pricing varies across HTCs. Each HTC negotiates own contracts.

Sample Case Study: Cost Analysis of Medical Management

Within months of transitioning the patient care to the HTC, through testing and education, the physician was able to alleviate the patient's concerns regarding appropriate dosing that would prevent complications with managing his inhibitor.

Prescriptions were changed to:

–Infuse Factor VIII 75u/kg daily and PRN for bleeding episodes.

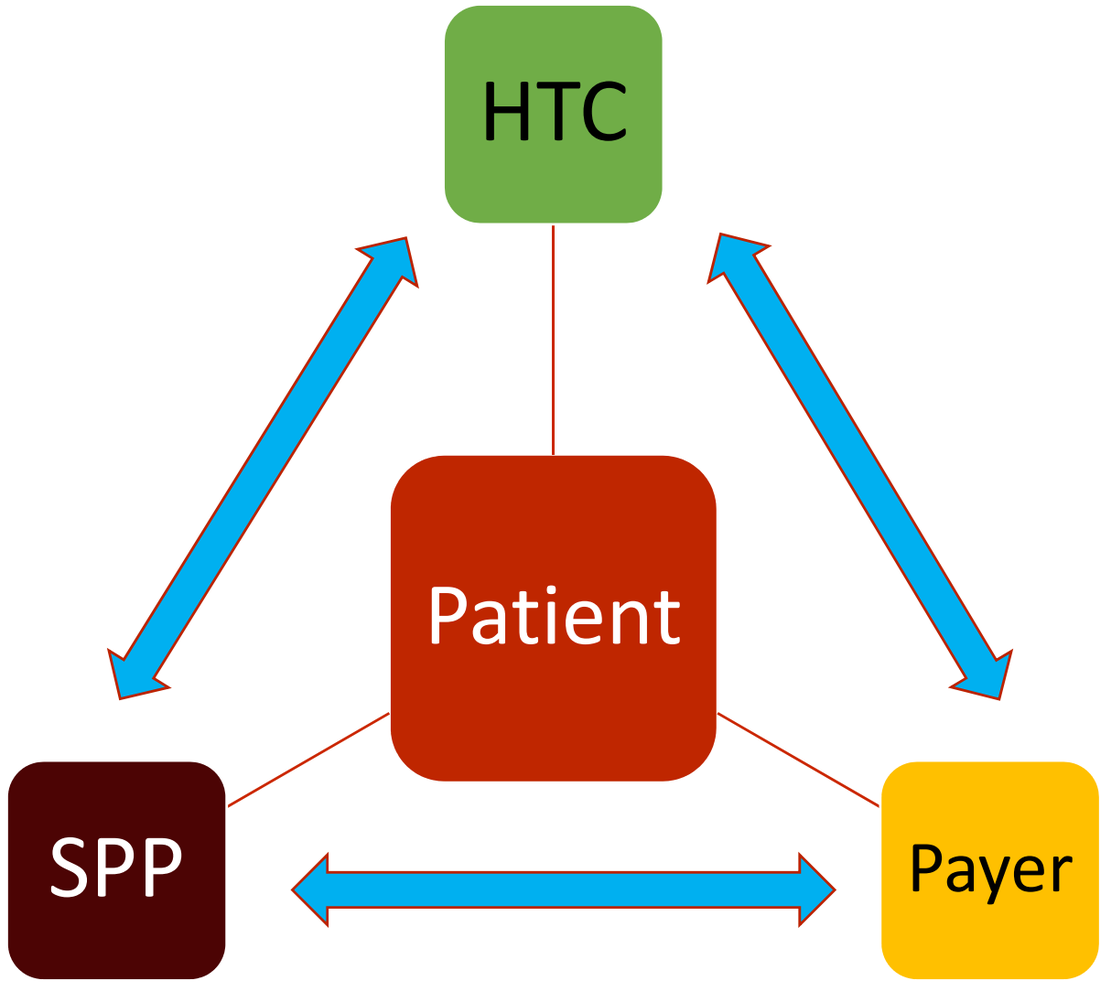
–Infuse Factor VIIa 8,000 mcg PRN as needed for bleeding episodes.

Expert medical management and recommended testing accounted for **saving the plan an additional $460,000*** through:

1. lowering daily factor VIII units by 75%
2. eliminating high cost daily factor VIIa infusions previously 240,000 mcg per month to an average of 32,000 mcg per month

*Pricing varies across HTCs. Each HTC negotiates own contracts.

Collaboration Among SPPs, HTCs, and Payers is Critical for Optimal Patient Care and Cost Management



Best Practices to Improve Collaboration Between HTCs and Payers

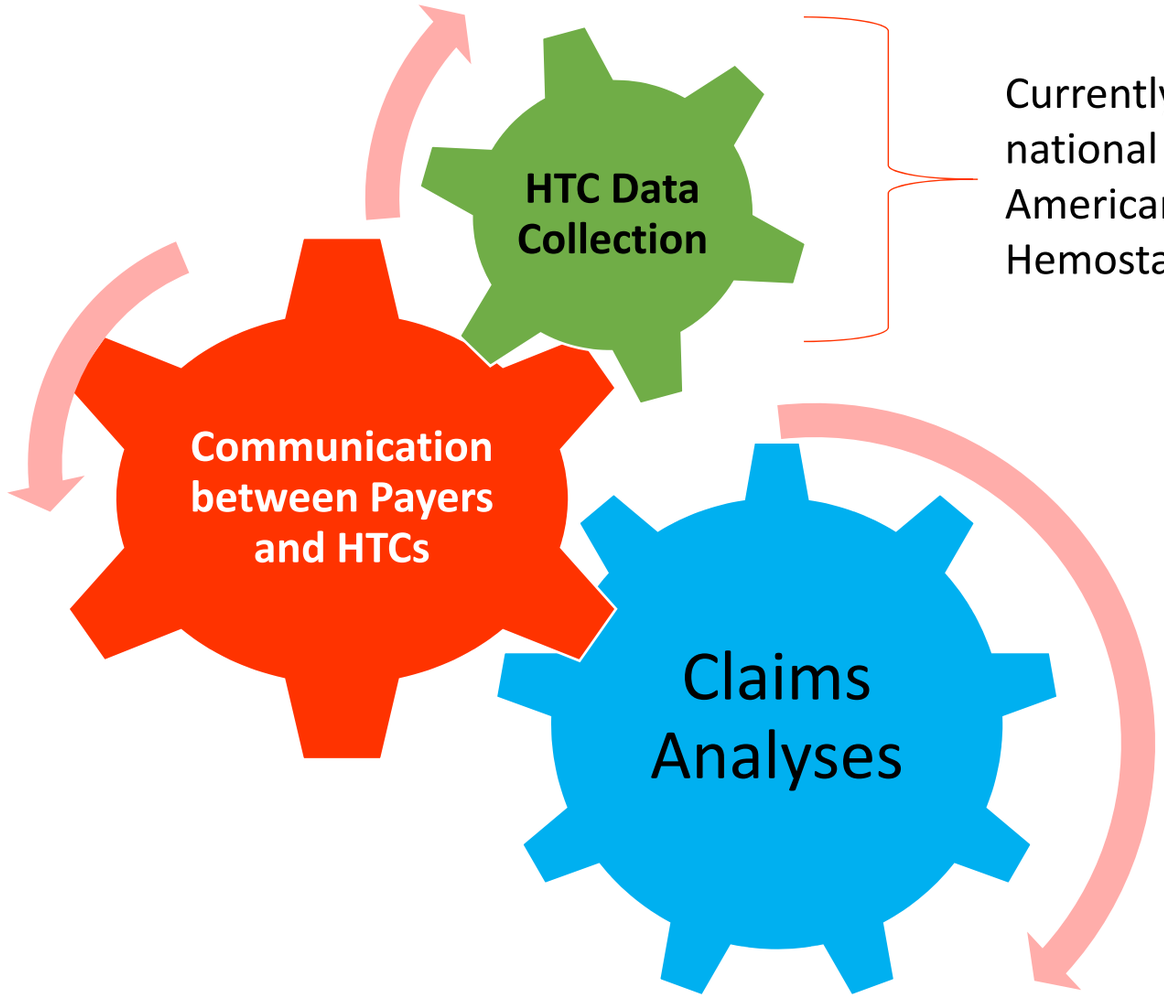
- Designated point of contact between the providers (HTCs/SPPs) and payers
- Proactive implementation of steps to avoid ER visits
- Proactive monthly calls to monitor bleed activity and inventory on hand
  - No shipments when patient has adequate supply of factor and supplies on hand
- Gathering and share information via bleed/infusion logs
- Communicate expected changes in costs to payer
  - Planned surgeries and procedures
  - Significant changes in utilization (i.e., weight gain, injury)
  - Identify barriers to optimal patient outcomes
  - Establish communication with case managers

Key Components of Data Collection and Analysis for Hemophilia Quality Improvement

Data and Information Sharing is Imperative

Providers

Payers



Currently reporting on a national level through the American Thrombosis and Hemostasis Network (ATHN)

The Role of Patient-Reported Outcomes Measures (PROMs) in Improving Care Quality and Demonstrating Value

- PROMs represent one way by which HTCs and SPPs can demonstrate value-based care to payers
- Use of PROMs in rare disease research and clinical practice offers the potential to improve patient care and clinical outcomes
- Given the large number of rare diseases, small numbers of patients living with each condition and the cost of instrument development, creative and pragmatic solutions to PROM development and use may be necessary
- Solutions include qualitative interviews, modern psychometrics and resources such as item banking and computer adaptive testing
    - Many HTCs currently employ such measures in the form of bleed logs, telephonic outreach/follow-up, and patient surveys

Slade A, Isa F, Kyte D, et al. *Orphanet J Rare Dis*. 2018;13(1):61.

Key Payer Concerns Pertaining to Hemophilia Management

- The concept of coordination is key, but cost transparency is also crucial, as financial risk falls to the payer
- Payers desire more documentation and risk-sharing as it pertains to the value of HTC clinical services
- Preferred products and contracting are becoming the norm across many disease classes, and management efforts may likewise become more intensive for hemophilia

Summary

- In addition to improved clinical outcomes, many HTCs feature an integrated 340B pharmacy model that allows for the provision of ancillary services
- Promotion of therapeutic adherence, assay management, and potentially lower per unit factor costs further contribute to the value of HTCs in the provision of care for bleeding disorders
- Communication and data sharing with payers is necessary to promote the value of integrated specialty pharmacy management, ensure adequate coverage and reimbursement, and leverage the delivery of care in contracting discussions
- Cost transparency and clinical data collected by HTCs and SPPs can help improve the quality of care and demonstrate the value of the care delivered

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HEMOPHILIA

Clinical Updates and Cost Management Solutions

Jointly provided by

National Hemophilia Foundation
for all bleeding disorders

Impact Education

Medical Education Resources

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