



COMPREHENSIVE **Hemophilia** Management:

A Payer's Guide to the Hemophilia Comprehensive Care Model

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Disease Overview

Etiology and Clinical Manifestations

HEMOPHILIA ETIOLOGY¹

- Hemophilia is an X-linked recessive bleeding disorder caused by a functional or quantitative deficiency of one of the coagulation proteins
 - Factor VIII:** hemophilia A
 - Factor IX:** hemophilia B
- The resulting inability to form a clot leads to spontaneous bleeding or bleeding following trauma or surgery

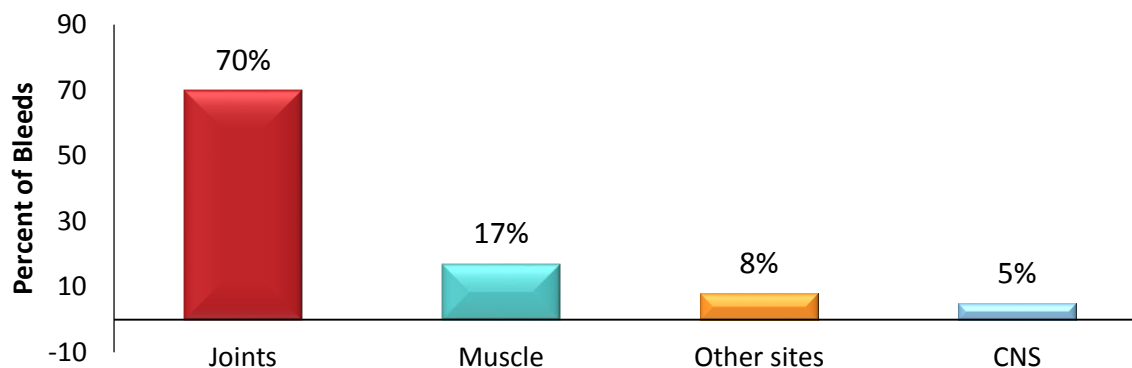
CLINICAL CLASSIFICATION²

Classification (% of patients)	Severe (50%–70%)	Moderate (10%)	Mild (30%–40%)
FVIII or FIX activity	<1%	1%–5%	6%–40%
Pattern of bleeding episode	2-4 per month	4-6 per year	Variable and less common
Causes of bleeding	Spontaneous*	Minor trauma or surgery/procedures**	Major trauma or surgery/procedures

*In addition to any of the causes of bleeding for patients with moderate and mild disease

**In addition to any of the causes of bleeding for patients with mild disease

FREQUENCY OF COMMON BLEEDS³



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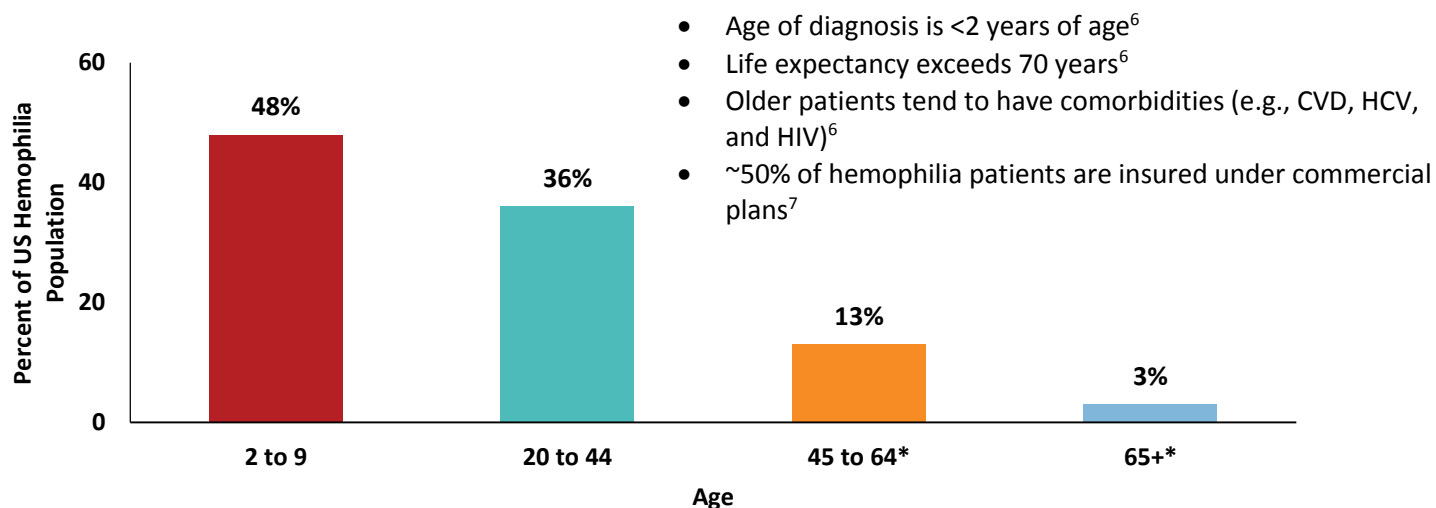
Epidemiology

INCIDENCE AND PREVALENCE⁴

- Current prevalence in the United States: ~20,000 males across all ethnic and racial groups
 - **Hemophilia A:** 1 in 5,000 live (male) births
 - **Hemophilia B:** 1 in 30,000 live (male) births

AGE DISTRIBUTION

Age Distribution of the US Hemophilia Population⁵



*The fraction of patients aged ≥ 45 years is disproportionate to the general population due to death from uncontrolled bleeding episodes, AIDS, hepatitis C, and other hemophilia-related complications. These proportions are shifting due to the development of safer and more effective treatments.

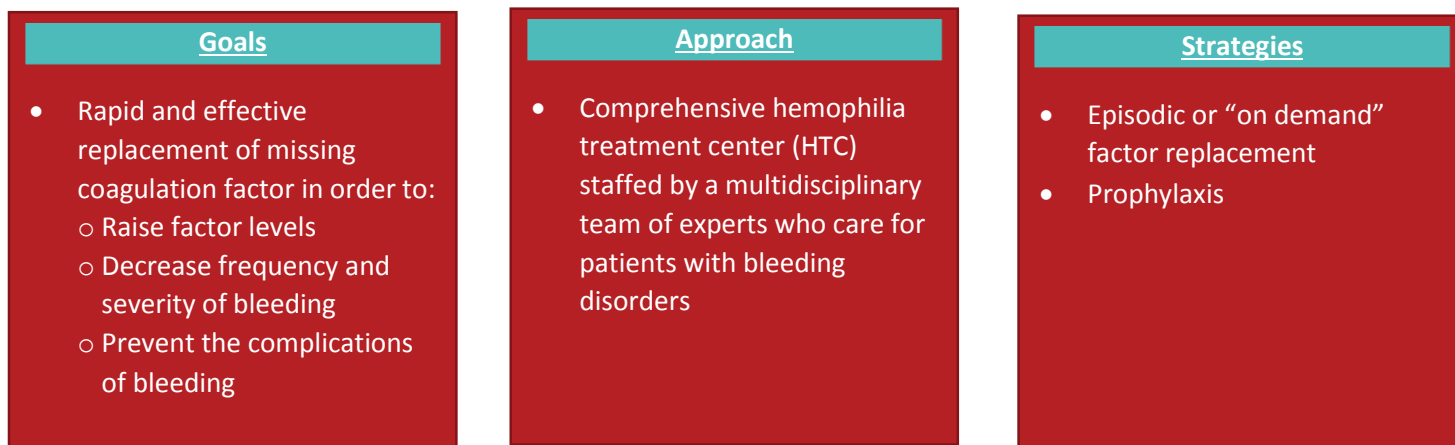
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Management

TREATMENT STRATEGIES

Treatment Goals, Approach, and Strategies⁸



TREATMENT OPTIONS⁹

Replacement of missing clotting protein

- Hemophilia A: concentrated FVIII product
- Hemophilia B: concentrated FIX product

Desmopressin acetate (DDAVP)

- Synthetic vasopressin used in patients with mild hemophilia A for joint, muscle, and oro-nasal bleeding and before and after surgery and dental procedures

Adjunctive therapies

- Antifibrinolytic agents
- Supportive measures including icing, immobilization, and rest

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CLOTTING FACTOR REPLACEMENT

Standard Formulation Factors VIII and IX¹⁰

	FVIII		FIX	
	Plasma-derived	Recombinant	Plasma-derived	Recombinant
Intravenous infusion (either IV push or continuous)	√		√	
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%	
Easy to store	√	√	√	√
May contain immunomodulatory proteins	√/-*		√/-*	
Increase dose up to 1.5 x vs. plasma-derived				√

*Depending on level of purity

Control and Prevention of Bleeding with Factor Replacement¹¹

Bleeding Episode	Factor Level Required (% of normal)	Frequency of Administration*
Minor <ul style="list-style-type: none"> • Early hemarthrosis • Minor muscle or oral bleed 	30-50	Every 12-24 hours ± antifibrinolytic
Moderate <ul style="list-style-type: none"> • Bleeding into muscles or oral cavity • Definite hemarthrosis 	50-80	Every 12-24 hours until resolved
Major <ul style="list-style-type: none"> • GI, intracranial, intra-abdominal, intrathoracic, CNS, or retroperitoneal bleeding 	80-100	Every 12-24 hours until resolved
Special Case Scenarios <ul style="list-style-type: none"> • Patients already on prophylaxis, patients using longer-acting/extended half-life factor products, etc. 	Variable	Variable

Recommended FVIII dosing:

Dosage in FVIII units = (Weight in kilograms) x (Factor percentage desired) x 0.5 (per product indications)

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PROPHYLAXIS¹²

- Prophylactic use of clotting factor concentrates forms the basis of modern treatment of severe hemophilia A and B
- The use of prophylaxis in patients with hemophilia without inhibitors, even in the setting of preexisting joint disease, has become more routine
 - In children, the early start of prophylaxis as primary or secondary prophylaxis has become the “gold standard” of care
 - In adults, prophylaxis is reasonably continued when started as primary or secondary prophylaxis in childhood to maintain healthy joint function
 - Prophylaxis in adult patients who treated episodically throughout childhood and adolescence is likewise becoming more common

Prophylaxis Protocols¹³

Protocol	Definition
Primary prophylaxis	Regular, continuous* treatment initiated in the absence of documented joint disease, determined by physical examination and/or imaging studies, and started before the second clinically evident large joint bleed and age 3 years†
Secondary prophylaxis	Regular, continuous* treatment started after ≥ 2 bleeds into large joints† and before the onset of joint disease documented by physical examination and imaging studies
Tertiary prophylaxis	Regular, continuous* treatment started after the onset of joint disease documented by physical examination and plain radiographs of the affected joints
Intermittent (“periodic”) prophylaxis	Treatment given to prevent bleeding for periods not exceeding 45 weeks in a year

*Continuous is defined as the intent of treating for 52 weeks/year and receiving a minimum of an a priori defined frequency of infusions for at least 45 weeks (85%) of the year under consideration.

†Large joints = ankles, knees, hips, elbows, and shoulders

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Inhibitors

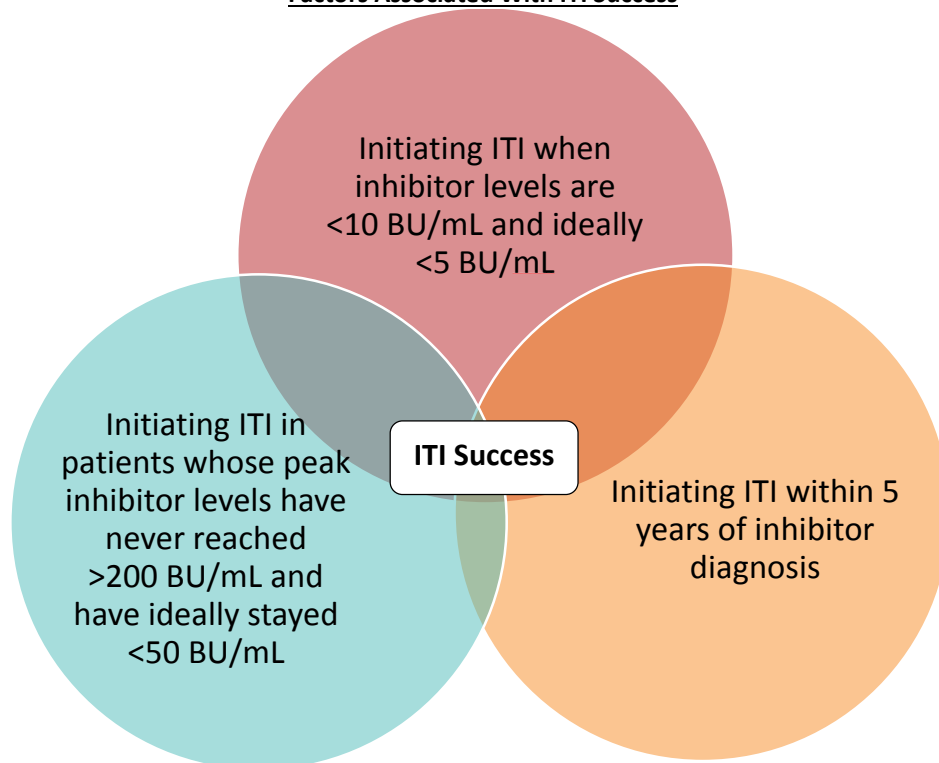
DESCRIPTION AND INCIDENCE

- Inhibitors (antibodies to the infused replacement factor) may develop in ~15-20% of patients¹⁴
 - Prevalence is higher in hemophilia A (~30%) vs. hemophilia B (2-5%)¹⁴
- Inhibitors neutralize the procoagulant effect of the infused factor as well as naturally produced factor protein^{xiv}
- Typically develop early in life (median age 1.7 – 3.3 years)¹⁴
- Greatest risk for inhibitor development occurs within the first 50 exposures to infused product^{14,15}

MANAGEMENT¹⁶

- Treating bleeds: Use of high-dose factor or bypassing agents
 - High-dose factor
 - FVIII impractical and ineffective if titer is >5 BU
 - Bypassing agents
 - Activated prothrombin complex concentrate (aPCC)
 - Recombinant FVIIa
 - Limitations include their unpredictable efficacy and lack of lab monitoring
- Eradicating the Inhibitor: Immune Tolerance Therapy (ITT)
 - Regular infusions of factor VIII or IX administered for a period of weeks to years in an effort to increase the tolerance of the immune system
 - Immunomodulating agents may also be used in certain cases
 - Limitations include variable efficacy (70%-85% for FVIII and ~30% for FIX), length of time and duration of treatment necessary, and cost

Factors Associated With ITI Success



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Economic Burden and Associated Costs

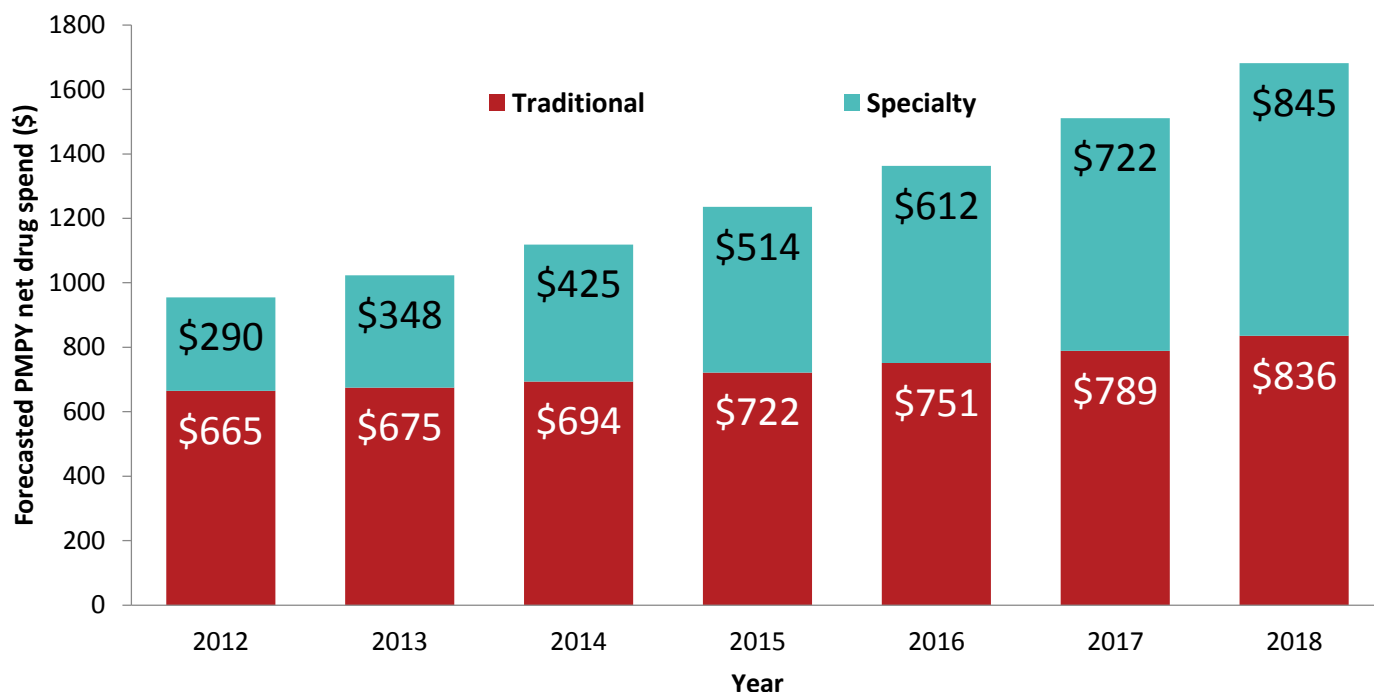
Specialty Drug Cost Considerations

RISING SPECIALTY DRUG TREND

Condition	Estimated Prevalence	Estimated Per Patient Cost of Care (\$)
Diabetes ¹⁷	25,800,000	7,900 – 14,000
COPD ²	15,000,000	2,000 – 43,000
Multiple Sclerosis ^{3,4}	300,000	28,000 – 58,000
Hemophilia ⁵	20,000	180,000 – 300,000

Overall Pharmacy Spending on Specialty Drugs is Expected to Grow¹⁸

Spending on Specialty Drugs Projected to Surpass Sales of Traditional Agents by 2018



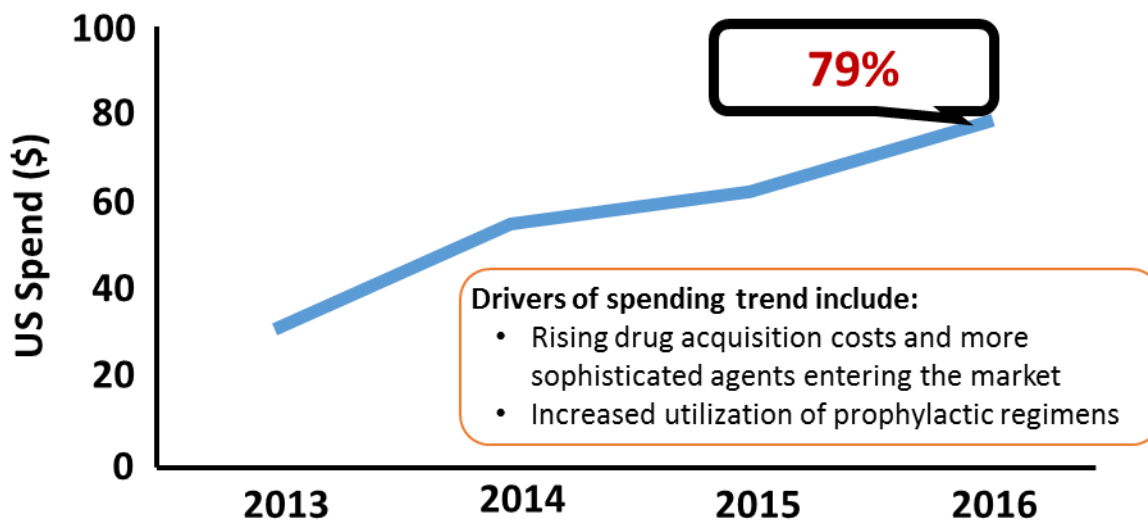
PMPY=per member per year

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HEMOPHILIA DRUG TREND¹⁹

Hemophilia Drug Spending is Likewise Projected to Increase

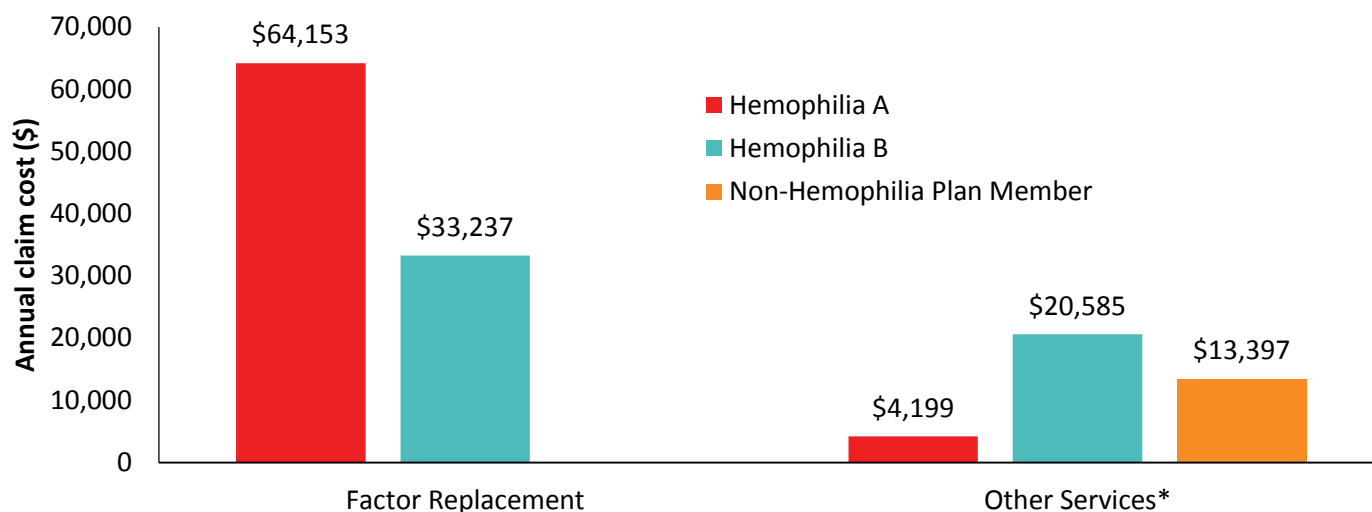


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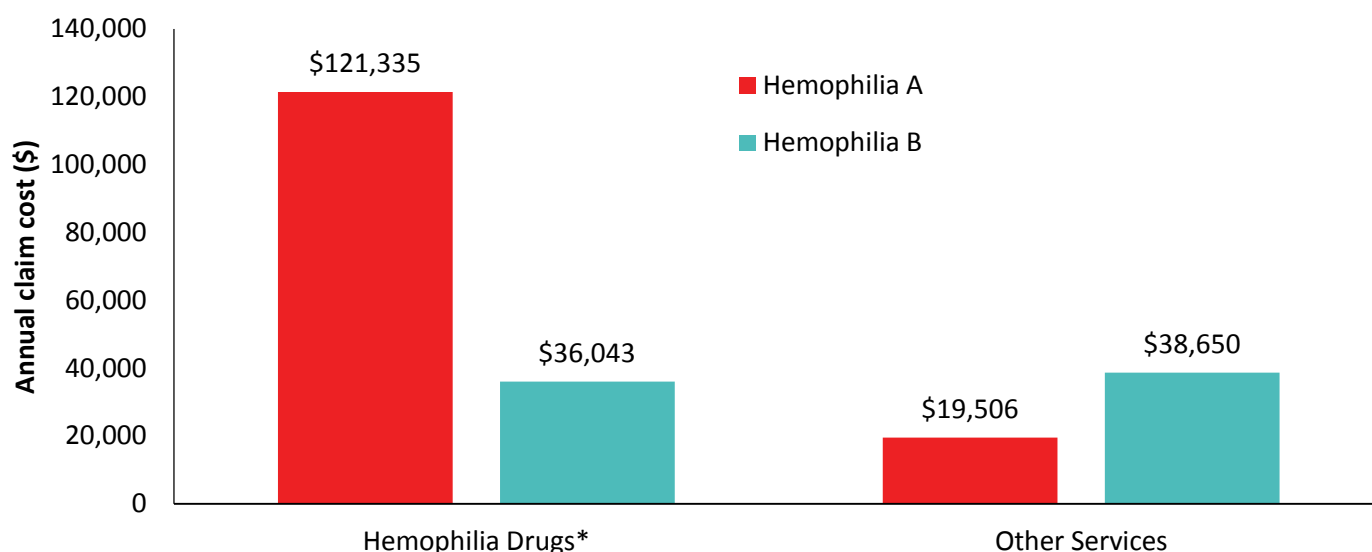
Claims Costs

AVERAGE ANNUAL CLAIM COSTS FOR HEMOPHILIA IN A COMMERCIAL POPULATION²⁰



*In- and outpatient facility fees, professional costs, and other non-pharmacologic direct healthcare costs.

AVERAGE ANNUAL CLAIM COSTS FOR HEMOPHILIA IN A MEDICARE POPULATION²⁰



*Includes factor, anti-inhibitor drugs, and other treatment drugs.

Common Hemophilia Claims Characteristics

- Hemophilia A carries higher annual claims costs than hemophilia B
- The majority of claims costs are allocated to specialty drugs/therapeutics
- Claims costs associated with other services are often similar to non-hemophilia commercial plan members

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Costs Associated with Inhibitors^{21,22}

Inhibitors Negate the Clinical Effect of Already Costly Factor Replacement Therapy

- Patients with undiagnosed inhibitors are vulnerable to potentially severe bleeding episodes
 - This has the potential to increase health care expenditures through emergency department utilization and prolonged inpatient stays
- Individuals who develop an inhibitor are twice as likely to be hospitalized for a bleeding complication as those without an inhibitor

Management of Bleeding and Eradication of Inhibitors Likewise Results in Further Costs

- In terms of product utilization, inhibitors result in greater direct medical expenditures
 - The cost and amount of clotting factor concentrate required to stop bleeding
 - ITI used to neutralize inhibitors carries a substantial cost at a duration of up to 18 months, in addition to polypharmacy interventions incorporating bypassing agents and additional recombinant factor products
- These factors culminate in the development of inhibitors having the highest reported cost burden among the potential complications of all chronic diseases

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Hemophilia Treatment Centers (HTCs) and the Comprehensive Care Model

The Comprehensive Care Model

The comprehensive care model seeks to:

- Deliver family-centered comprehensive care to individuals with hemophilia
- Utilize the skills of multidisciplinary team members in order to provide optimal care to individuals with hemophilia and their families
- Incorporate the role of the family in planning and providing care for individuals with hemophilia

History of HTCs as Centers of Excellence

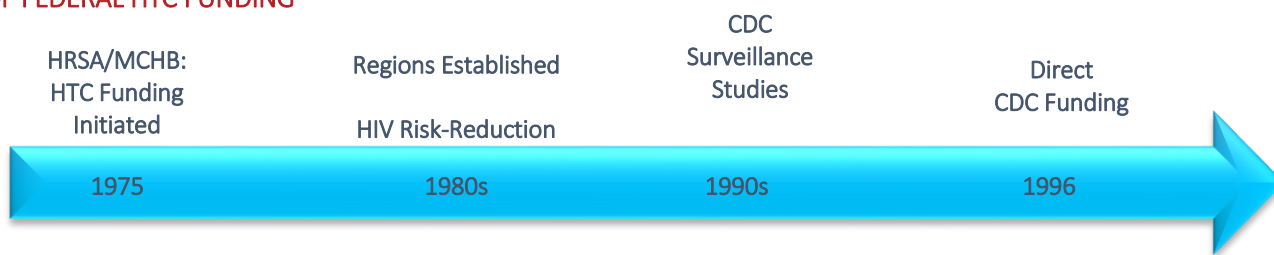
WHAT IS AN HTC?²³

An HTC is a federally recognized comprehensive **hemophilia treatment center** that has a multidisciplinary team expert in the care of patients with bleeding disorders and whose staff spend a **majority** of their time caring for these patients

ORGANIZATION OF HTCS

- Multidisciplinary team
 - Core team: physician, nurse coordinator, physical therapist, social worker
- Federal grant funding per HTC averages \$35,000/year
 - Funding is either granted directly from the CDC or allocated by Regional Core Centers
 - State and federal funding is inadequate to support full services of center
- Centers may include a thrombophilia population

TIMELINE OF FEDERAL HTC FUNDING



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ACCOUNTABILITY OF HTCS

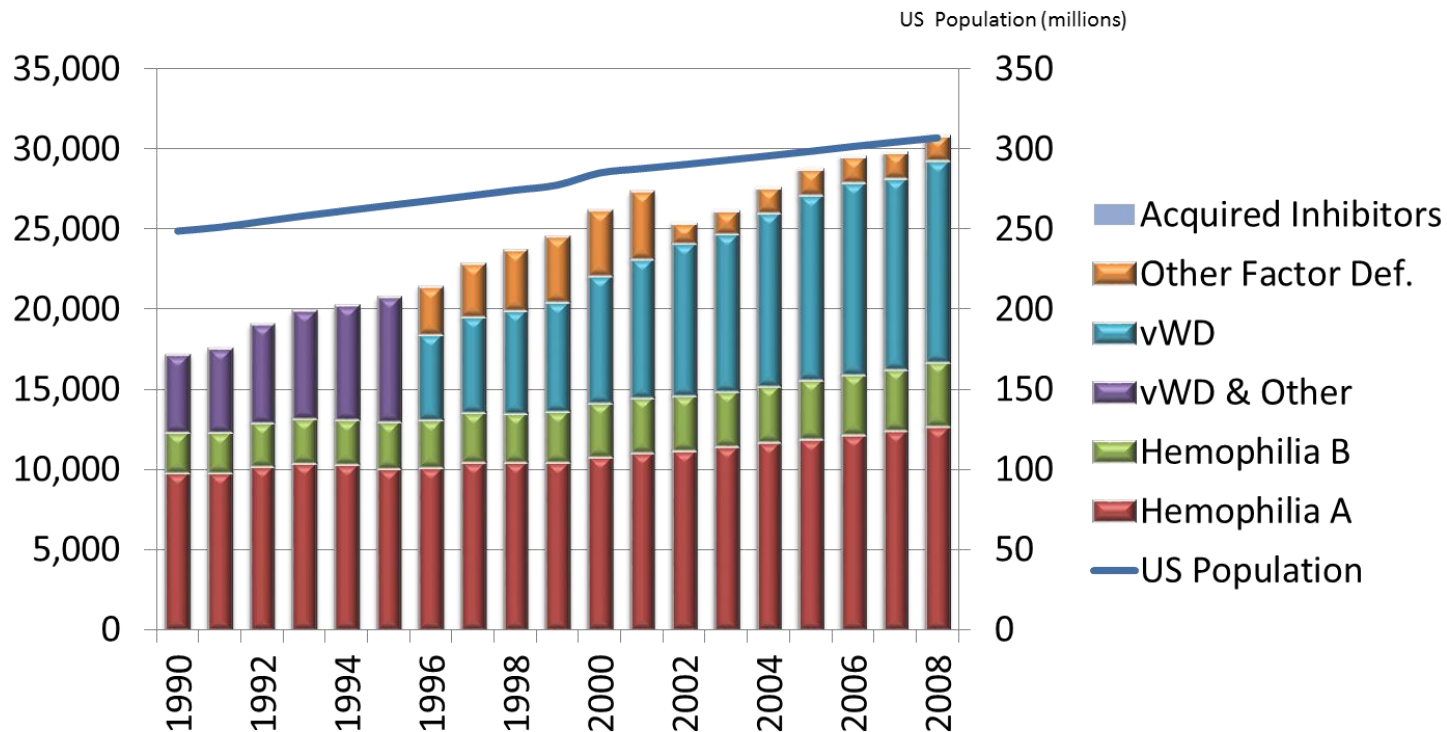
- Organized according to the American Thrombosis and Hemostasis Network (ATHN) and Regional Core Centers
- Health Resources and Services Administration (HRSA)
 - Maternal and Child Health Bureau (MCHB)
 - Genetic Services Program
- Centers for Disease Control and Prevention (CDC)
 - National Center on Birth Defects and Developmental Disabilities
 - Division of Blood Disorders
- Requirements for National Data Collection
 - Reporting requirements are detailed in handouts and do not include progress reports and activities
 - National statistics are important to demonstrate the following:
 - Population served
 - Need
 - Impact of initiatives, e.g., women with bleeding disorders
- Reporting justifies continued allocation of funds
- Federal data reporting requirements often differ from data typically desired by payers

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Clinical Characteristics of HTC Patients²⁴

TYPES OF BLEEDING DISORDERS²⁵



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SEVERITY AND COMORBIDITIES

- HTC's often take on the most difficult cases and complicated demographics of patients

Distribution of Clinical Characteristics by Source of Care Among 2950 Males with Hemophilia in 6 States ²⁶			
Characteristics	HTC (%)	Non-HTC (%)	P
Severity			
Mild	21.8	52.8	<.001
Moderate	24.2	26.7	
Severe	54.0	20.5	
Inhibitors	6.0	2.3	<.001
Liver disease	2.3	0.7	.002
HIV infection	31.1	17.1	<.001
AIDS	8.2	5.9	.02

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Benefits of HTC Care Provision

ENROLLMENT AND RESULTING OUTCOMES

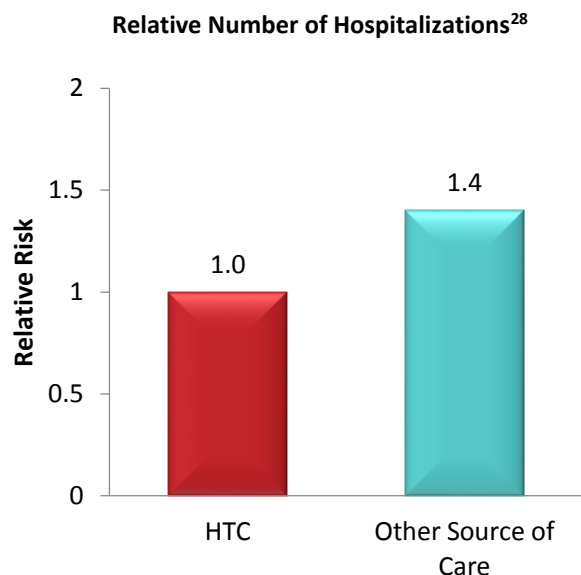
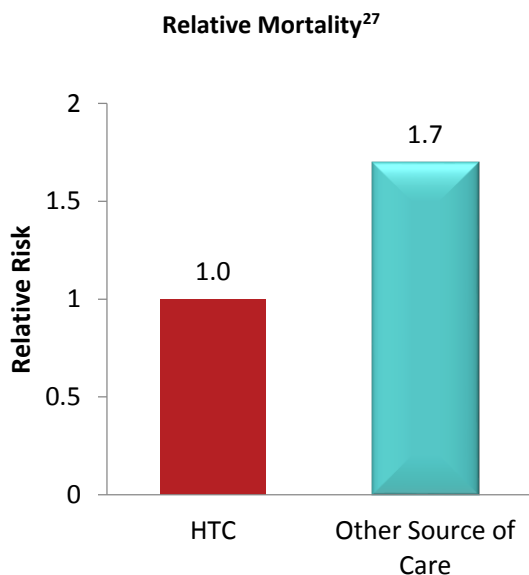
- As the Proportion of Patients Seen in HTCs has Increased, Outcomes Have Improved

Enrollment and Outcomes Data From 31 HTCs Over 10 Years			
Measure	Year Before Program (1975)	10 th Year of Program (1985)	% Increased (+) % Decreased (-)
Number patients receiving regular comprehensive care	1,333	5,683	+ 326%
Number patients on homecare	514	2,517	+ 390%
Average days/year lost from work/school	14.5	3.9	- 73%

MORTALITY AND HOSPITALIZATIONS

- Benefits of Care Delivered Through an HTC

HTC Care Reduces the Mortality Rate by 70% and the Hospitalization Rate by 40% Compared with Care Received Outside of an HTC

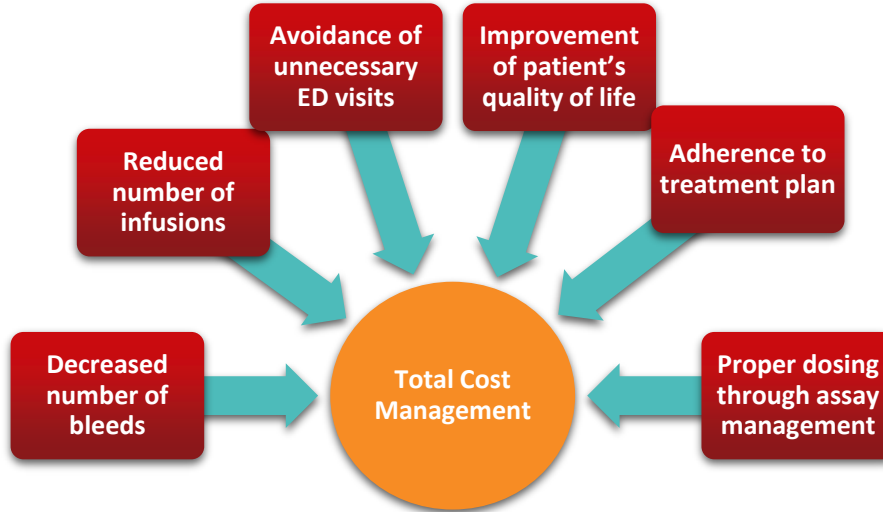


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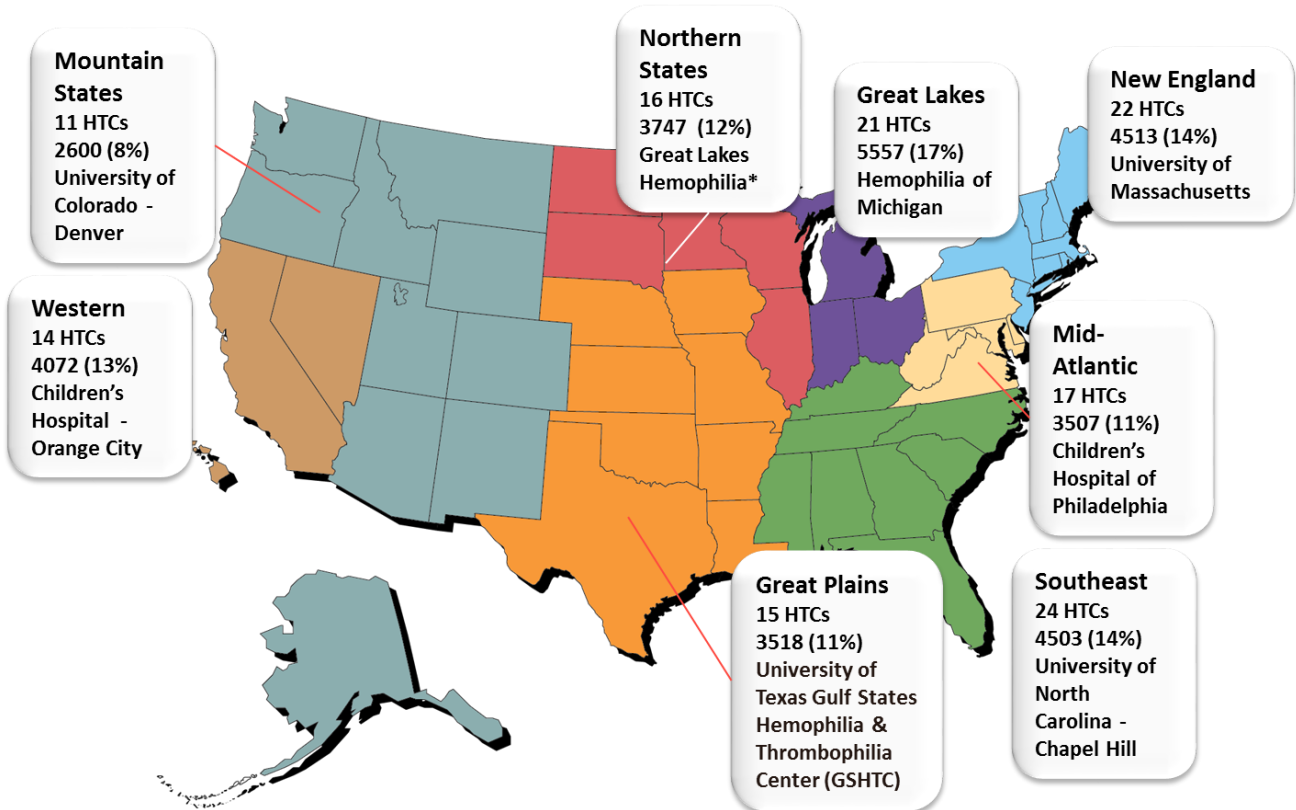
ECONOMIC IMPLICATIONS

The Cumulative Benefits of HTC-delivered Care Have Apparent Economic Implications



THE REGIONAL HTC NETWORK

The US is Divided into 8 Regions of HTC Under the MCHB Grant



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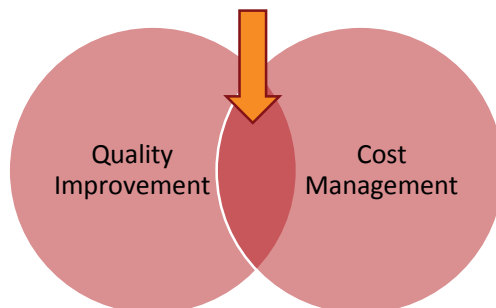


Payer and HTC Collaboration

Payer Hemophilia Management Interventions

GOAL

- Payer Management Interventions Seek to Improve Care Quality and Manage Disease Costs
Goal of Payer Intervention



EXAMPLES OF QUALITY INITIATIVES

- Payer Initiatives for Improving the Quality of Hemophilia Care

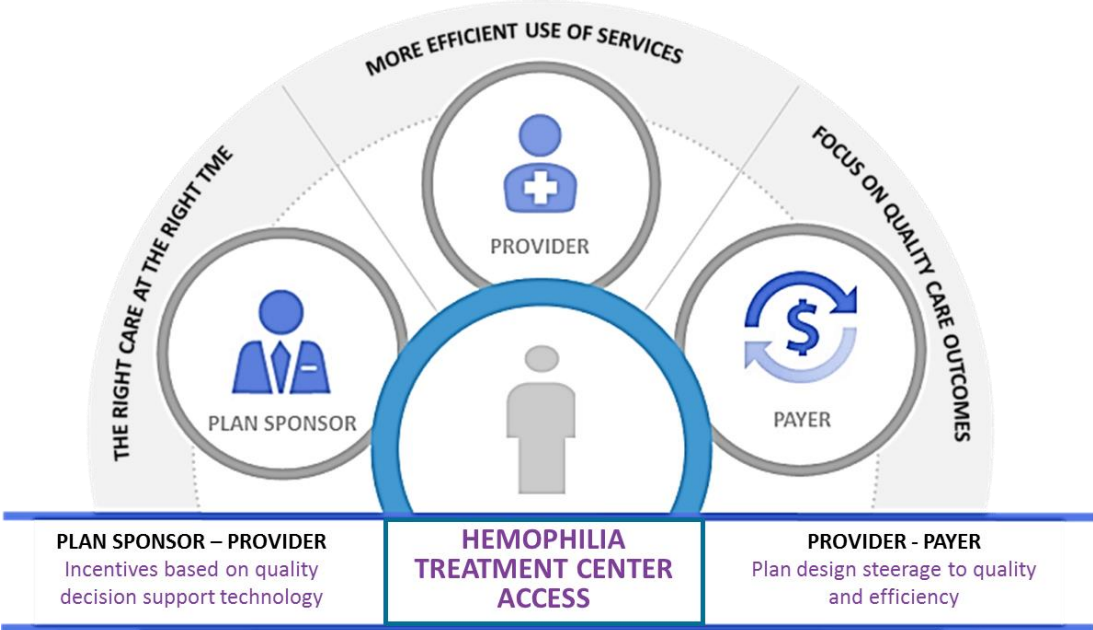
Quality Initiative	Strategy to Achieve
Treatment access and quality	<ul style="list-style-type: none"> • Integrate hemophilia care in network management and medical management strategies • Establish relationships with HTCs, specialty pharmacy, and specialized medical providers
Care management	<ul style="list-style-type: none"> • Coordinate multidisciplinary outpatient and home-based services
Cost management	<ul style="list-style-type: none"> • Utilize cost-effective approaches for administration of factor replacement while keeping in mind the individualized treatment needs of each patient
Pharmacy management	<ul style="list-style-type: none"> • Evaluate all services required to manage hemophilia • Secure cost-effective and timely factor replacement services for routine and emergency needs
Risk management	<ul style="list-style-type: none"> • Identify financing solutions (e.g., risk adjustment or carve outs) to ensure member access to care
Patient involvement	<ul style="list-style-type: none"> • Involve patients in all decisions impacting their care • Include support partners and caregivers to increase adherence to recommended care

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THE IMPORTANCE OF COLLABORATION

- Collaboration and Alignment Among Stakeholders Drives the Best Possible Patient Outcomes



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The Comprehensive Care Sustainability Collaborative (CCSC)

DESCRIPTION

The CCSC Initiative Strives to Facilitate Payer-Provider Collaboration

- Ongoing quality improvement and cost management initiative
- Driven by the insights of a prominent group of stakeholders:
 - Hemophilia treatment center (HTC) directors, clinicians, and administrators
 - Payer/managed care medical and pharmacy directors from a mix of large national and regional health plans
- Developing a framework for metric-driven pilot programs incorporating data reporting between payers and HTCs to be replicated across the United States
- Ultimately seeking to facilitate cost-effective hemophilia management integrating the HTC comprehensive care model



FURTHER INFORMATION AND OPPORTUNITIES FOR PAYERS

CCSC White Paper

- Initial findings and recommendations from the CCSC are reported in a white paper available at: www.CCSCHemo.com
- *Highlights Include:*
 - Analysis of the current state of hemophilia care and the benefits of the comprehensive care model
 - Expert feedback and consensus recommendations to facilitate cost-effective hemophilia management integrating the HTC comprehensive care model
 - Information regarding competitive factor pricing and a thorough explanation of the role of 340B pricing in funding ancillary services provided at HTCs
 - Recommended HTC- and payer-reported metrics to facilitate information sharing across multiple health care stakeholders

CCSC Pilot Program Participation Offers a Unique Opportunity for Payers in the Management of Hemophilia

- Benefits of CCSC Pilot Program Participation for Health Plans
 - Access to extensive hemophilia-related outcomes data from network HTCs
 - Increased connectivity with HTC directors and other plan managers seeking more rigorous standards in the care quality and cost containment for hemophilia
 - National recognition for a commitment to quality improvement in hemophilia management

For further information on a possible pilot program contact: CCSC@ImpactEdu.net

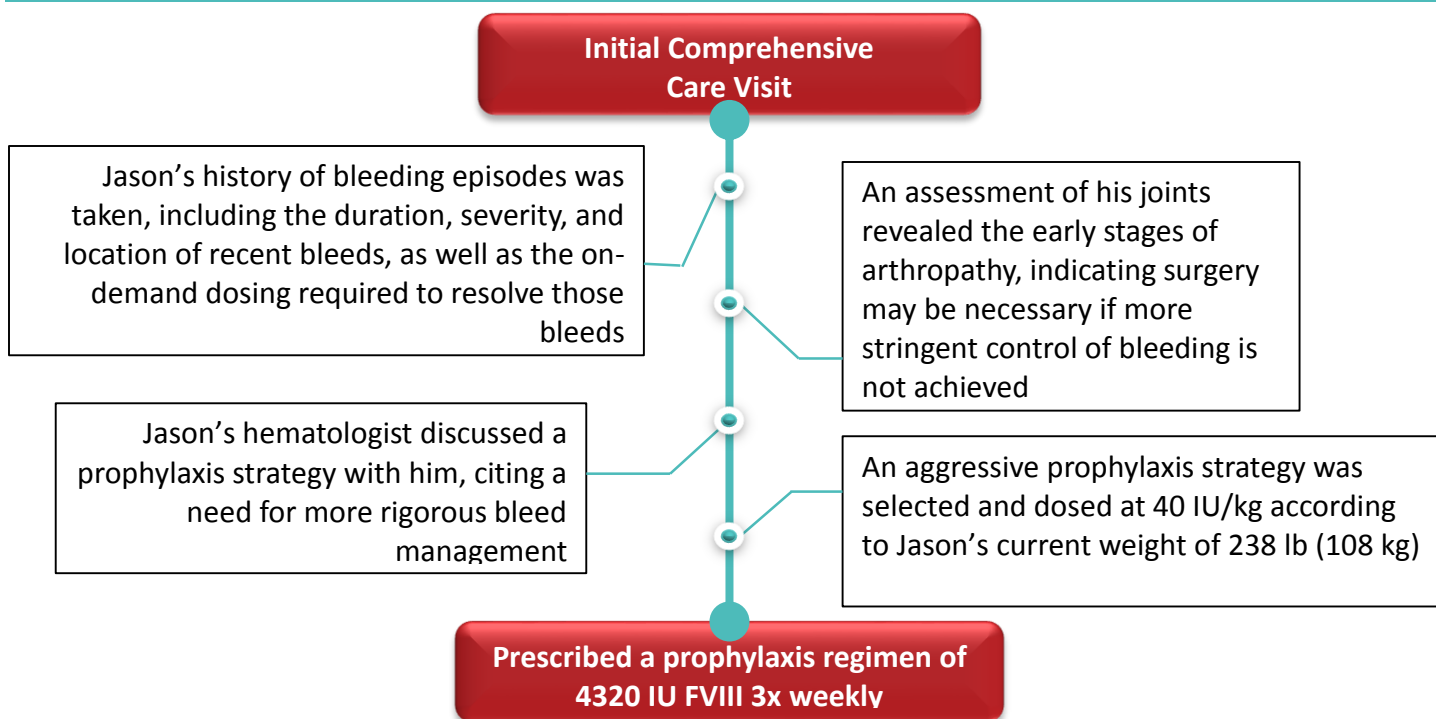
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Prophylaxis Case Study

- Jason is a 27-year-old male with severe hemophilia A
- He was previously managed by a community hematologist with on-demand self-infusion of factor VIII
- Recurrent bleeding episodes and worsening range of motion in Jason's knees led to a decline in physical activity and subsequent weight gain
- Desiring more intensive management of his disease, Jason sought out care from a local HTC

Comprehensive Care Visit and Prophylaxis Dosing



Claims Denial, Appeal, and Follow-Up

- Upon submission to his insurer, the claim for Jason's prophylaxis regimen is initially denied
- The hematologist followed up with the medical director of his health plan to appeal the claim denial, outlining several key points of Jason's case:
 - His lack of adequate bleed control via on-demand therapy
 - Worsening range of motion in both knees and subsequent weight gain resulting from inactivity
 - The potential necessity of synovectomy in the future if adequate bleed control is not achieved
 - Aggressive dosing according to the Malmö protocol²⁹ (25-40 IU/kg, 3x week) and his current weight of 238 lb (108 kg)
- The claim for Jason's prophylaxis regimen was approved as a result of this follow-up and his disease is being managed accordingly

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² Adapted from Henry's Clinical Diagnosis and Management by Laboratory Method. 21st edition; Table 38-4; Copyright Elsevier.

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¹⁹ Express Scripts. 2014 Drug Trend Report. <http://lab.express-scripts.com/drug-trend-report/>. Accessed July 10, 2015.

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Tu TC, et al. *Yonsei Med J*. 2013;54(2):358-365.

²³ Soucie JM, et al. *Blood* 2000;96(2):437-42.

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²⁶ Soucie JM et al. *Blood* 2000;96(2):437-42.

²⁷ Soucie JM, et al. *Blood*. 2000; 96:437-442.

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