Hemophilia Managed Care and Specialty Pharmacy SOLUTIONS for Cost Savings in a New Health Care Ecosystem

Jointly provided by

National Hemophilia Foundation
for all bleeding disorders

Impact Education LLC

PIM Postgraduate Institute for Medicine

This activity is supported by independent educational grants from Baxalta US, Inc., Bayer HealthCare Pharmaceuticals Inc., Biogen, Emergent BioSolutions Inc., Grifols, and Novo Nordisk, Inc.

Held in conjunction with AMCP Nexus 2015

AMCP Academy of Managed Care Pharmacy

Agenda

6:15 AM	*The Evolving Managed Care and Specialty Pharmacy Landscape* *Celynda G. Tadlock, PharmD, MBA*
6:40 AM	An Advanced Review of Inhibitors and Prophylaxis Treatment *Jonathan Roberts, MD*
7:10 AM	Measuring Success: Tools and Resources to Document Outcomes of Payer and Specialty Pharmacy Hemophilia Management *Michael Zeglinski, RPh*
7:25 AM	HTC, Managed Care, and Specialty Pharmacy Collaboration *Faculty Panel*
7:40 AM	Moderated Faculty Panel Discussion and Audience Q&A *Faculty Panel*
7:55 AM	Closing Comments, Post-Activity Assessment, and Evaluation

Educational Objectives

After completing this activity, the participant should be better able to:

- Describe current and evolving strategies used by managed care organizations (MCOs) and specialty pharmacy providers to facilitate high quality care for members with hemophilia
- Summarize the most recent clinical recommendations for the treatment of patients with hemophilia, including prophylactic factor replacement
- Explain the severe complication of hemophilia treatment known as inhibitor development, including its significant clinical and economic consequences
- Utilize processes for MCOs and specialty pharmacy providers to improve communications with Hemophilia Treatment Centers (HTCs)
- Apply collaborative methods that enable the benefits of the comprehensive care model provided by HTCs to be realized by multiple hemophilia stakeholders including MCOs and specialty pharmacy providers
- Provide accurate and appropriate counsel as part of the managed care treatment team

Hemophilia Managed Care and Specialty Pharmacy SOLUTIONS for Cost Savings in a New Health Care Ecosystem

Jointly provided by

National Hemophilia Foundation
for all bleeding disorders

Impact Education LLC

PIM Postgraduate Institute for Medicine

This activity is supported by independent educational grants from Baxalta US, Inc., Bayer HealthCare Pharmaceuticals Inc., Biogen, Emergent BioSolutions Inc., Grifols, and Novo Nordisk, Inc.

Held in conjunction with AMCP Nexus 2015

AMCP Academy of Managed Care Pharmacy

The Evolving Managed Care and Specialty Pharmacy Landscape

Celynda G. Tadlock, PharmD, MBA

Vice President, Pharmacy Business Development

Aetna

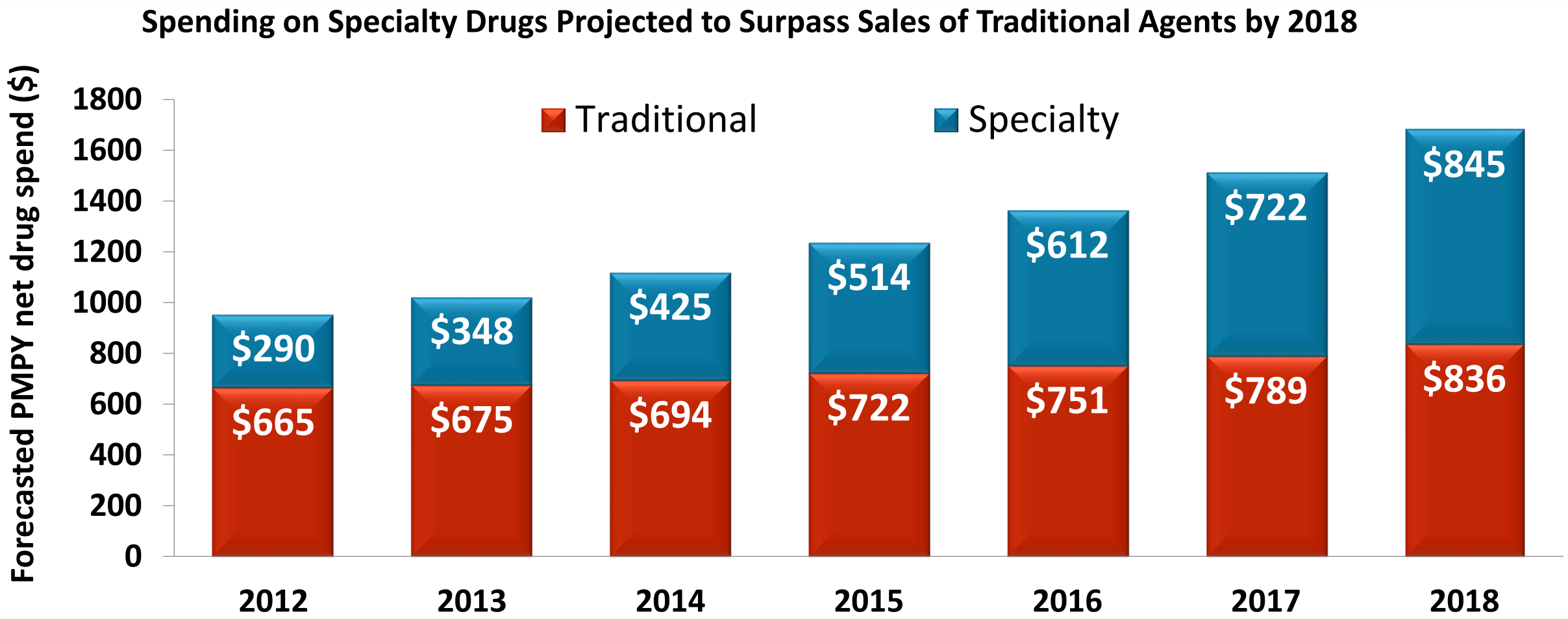
Faculty Disclosure

- The ***faculty*** reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

Celynda G. Tadlock, PharmD, MBA

  - No financial interests/relationships relating to the topic of this activity

Pharmacy Spending on Specialty Drugs Expected to Grow



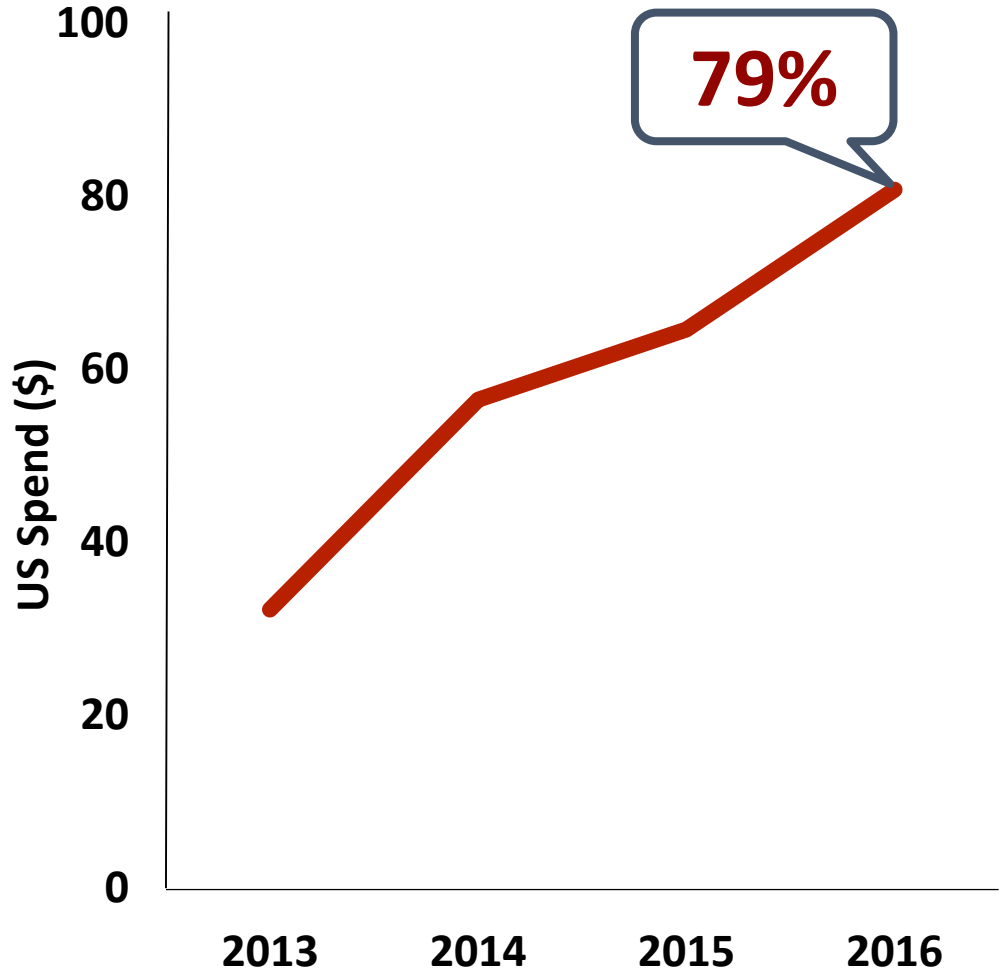
PMPY=per member per year

Artemetrx. Specialty drug trends across the pharmacy and specialty benefit. 2013. Available at: http://www.artemetrx.com/docs/ARTEMETRX_Specialty_Trend_Rpt.pdf. Accessed July 10, 2015.

Key Drivers of Specialty Trend

High Cost Per Patient	Increasing Utilization
Accounts for 25% of pharmaceutical spending in the US	Flourishing pipeline
Annual growth at 15-20%	New indications for existing drugs
Annual drug cost ranges from $15,000-$250,000+ per patient	Earlier use of biologics in treatment regimen for diseases where nonbiologic options are available
Manufacturer price increases for existing drugs	Episodic vs chronic treatment
Limited generics available as products mature: ▪ First wave of nonbiologic specialty drugs losing patent protection ▪ Biosimilars for biologic specialty drugs	

Hemophilia Drug Spending is Projected to Increase



- Drivers of spending trend include:
  - Rising drug acquisition costs and more sophisticated agents entering the market
  - Increased utilization of prophylactic regimens

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

The Hemophilia Trend is Driven Largely By Unit Cost and Body Weight

TOP SPECIALTY THERAPY CLASSES
RANKED BY 2014 PMPY SPEND

			TREND		
RANK	**THERAPY CLASS**	**PMPY SPEND**	**UTILIZATION**	**UNIT COST**	**TOTAL**
I	Inflammatory Conditions	$80.03	8.5%	15.7%	24.3 %
2	Multiple Sclerosis	$52.36	3.2%	9.7%	12 .9%
3	Oncology	$41.64	8.9%	11.7%	20.7 %
4	Hepatitis C	$37.95	76.1 %	666.6%	742.6 %
5	HIV	$27.24	4.5%	10.3%	14.8 %
6	Miscellaneous Specialty Conditions	$11.10	27.3%	8.2%	35.6 %
7	Growth Deficiency	$9.98	-0.9%	7.5%	6.6 %
8	Hemophilia	$5.49	-0.8%	17.6%	16.9 %
9	Pulmonary Arterial Hypertension	$5.41	7.6%	6.2%	13.8 %
10	Transplant	$5.13	0.8%	-3.1%	-2.3 %
	TOTAL SPECIALTY	**$311.11**	**5.8%**	**25.2%**	**30.9%**

PMPY=per member per year

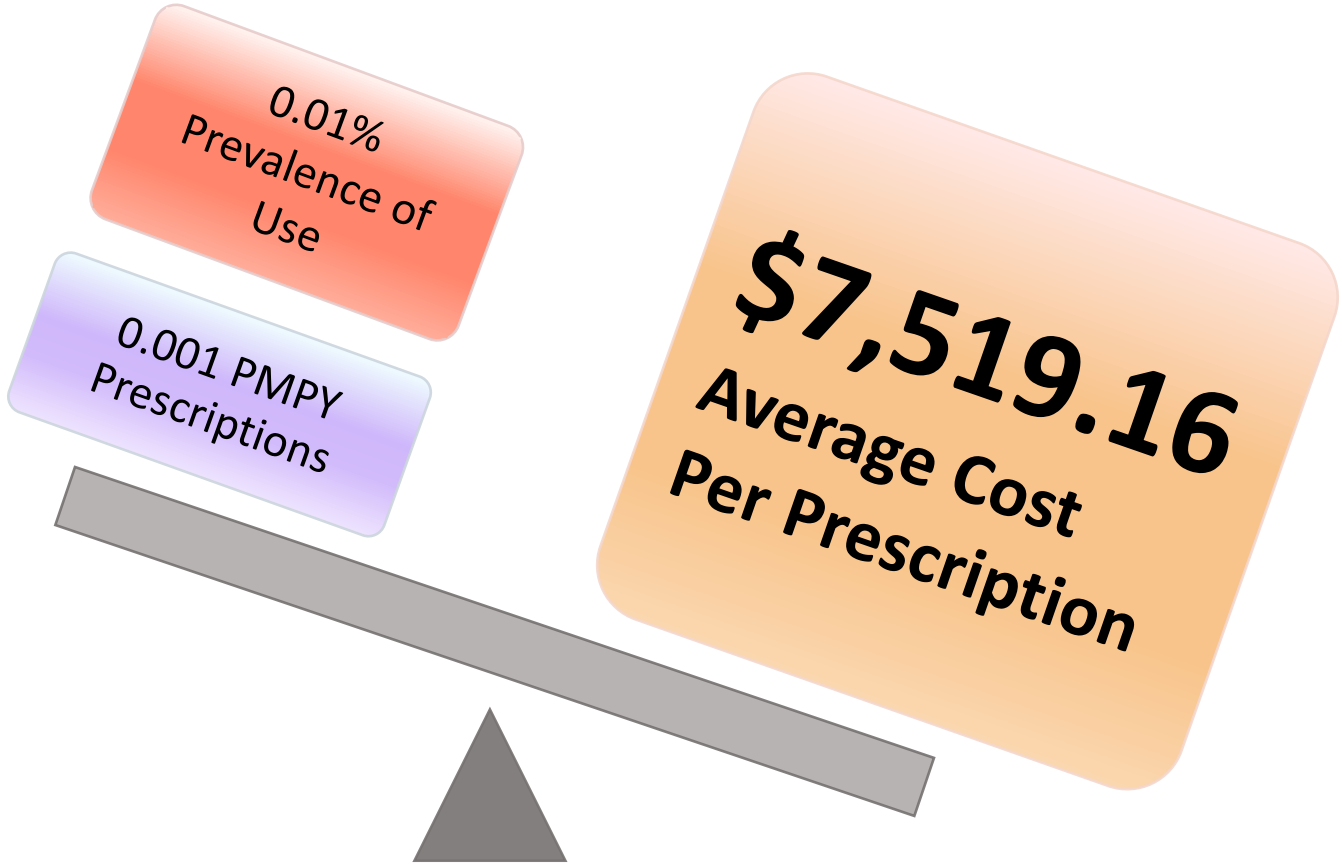
Express Scripts. 2014 Drug Trend Report. http://lab.express-scripts.com/drug-trend-report/. Accessed July 10, 2015.

Hemophilia: A Low Prevalence But High Cost Disease for Members Who Utilize Clotting Factor Replacement

Condition	Estimated Prevalence	Estimated Per Patient Cost of Care ($)
Diabetes[1]	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

1. American Diabetes Association. *Diabetes Care*. 2013;36:1033-46.
2. Dalal AA, et al. *Int J Chron Obstruct Pulmon Dis*. 2010;5:341-9.
3. Gleason PP, et al. *J Manag Care Pharm*. 2013;19:542-8.
4. Rocky Mountain MS Center. https://www.mscenter.org/education/ms-the-basics. Accessed March 31, 2015.
5. Fischer K, et al. *Blood*. 2013;122:1129-36.

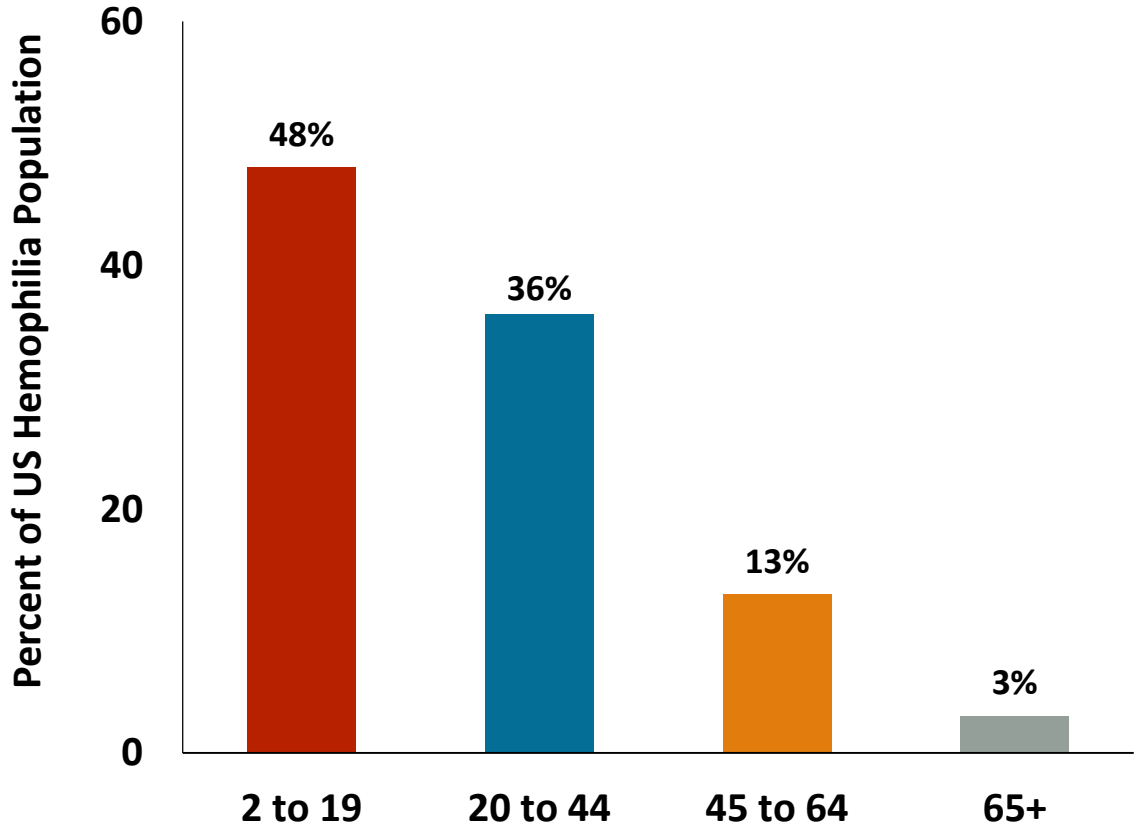
Hemophilia: A Low Prevalence, But High Cost Disease



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

Hemophilia Patients Require Healthcare Across the Lifespan

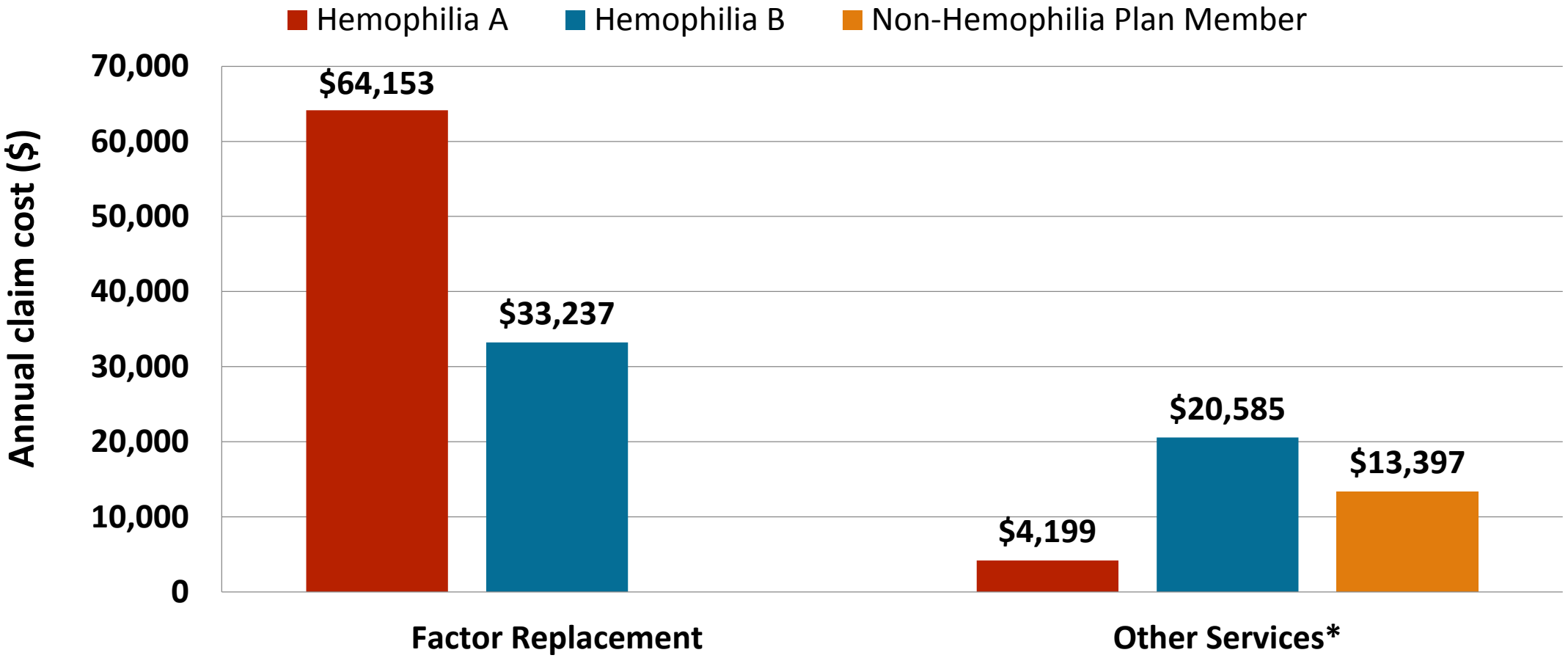
Age Distribution of the US Hemophilia Population[1]



- Age of diagnosis is <2 years of age[2]
- Life expectancy exceeds 70 years[2]
- Older patients tend to have comorbidities (eg, CVD, HCV, and HIV)[2]
- ~50% of hemophilia patients are insured under commercial plans[3]

1. Centers for Disease Control and Prevention. Report on the Universal Data Collection Program, 2005-2009, January 2014:1-26.
2. Centers for Disease Control and Prevention. Hemophilia. http://www.cdc.gov/ncbddd/hemophilia/data.html. Accessed March 12, 2015.
3. Express Scripts. 2014 Drug Trend Report. http://lab.express-scripts.com/drug-trend-report/. Accessed March 12, 2015.

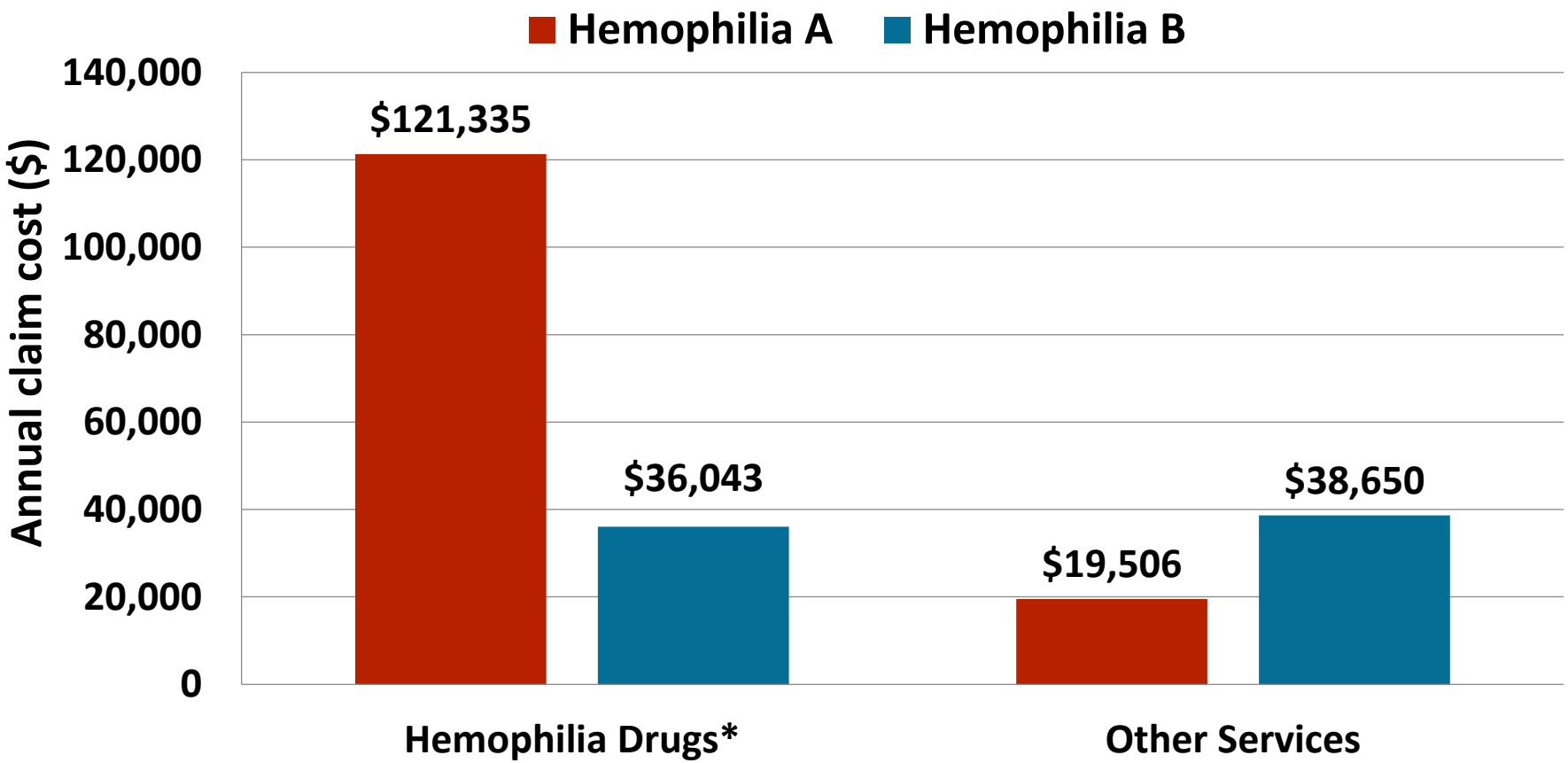
Average Annual Claim Costs for Hemophilia in a Commercial Population



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

Milliman Report. An actuarial study of hemophilia. October 24, 2013.
http://www.milliman.com/uploadedFiles/insight/2014/hemophilia-actuarial-study.pdf. Accessed March 10, 2015.

Average Annual Claim Costs for Hemophilia in a Medicaid Population

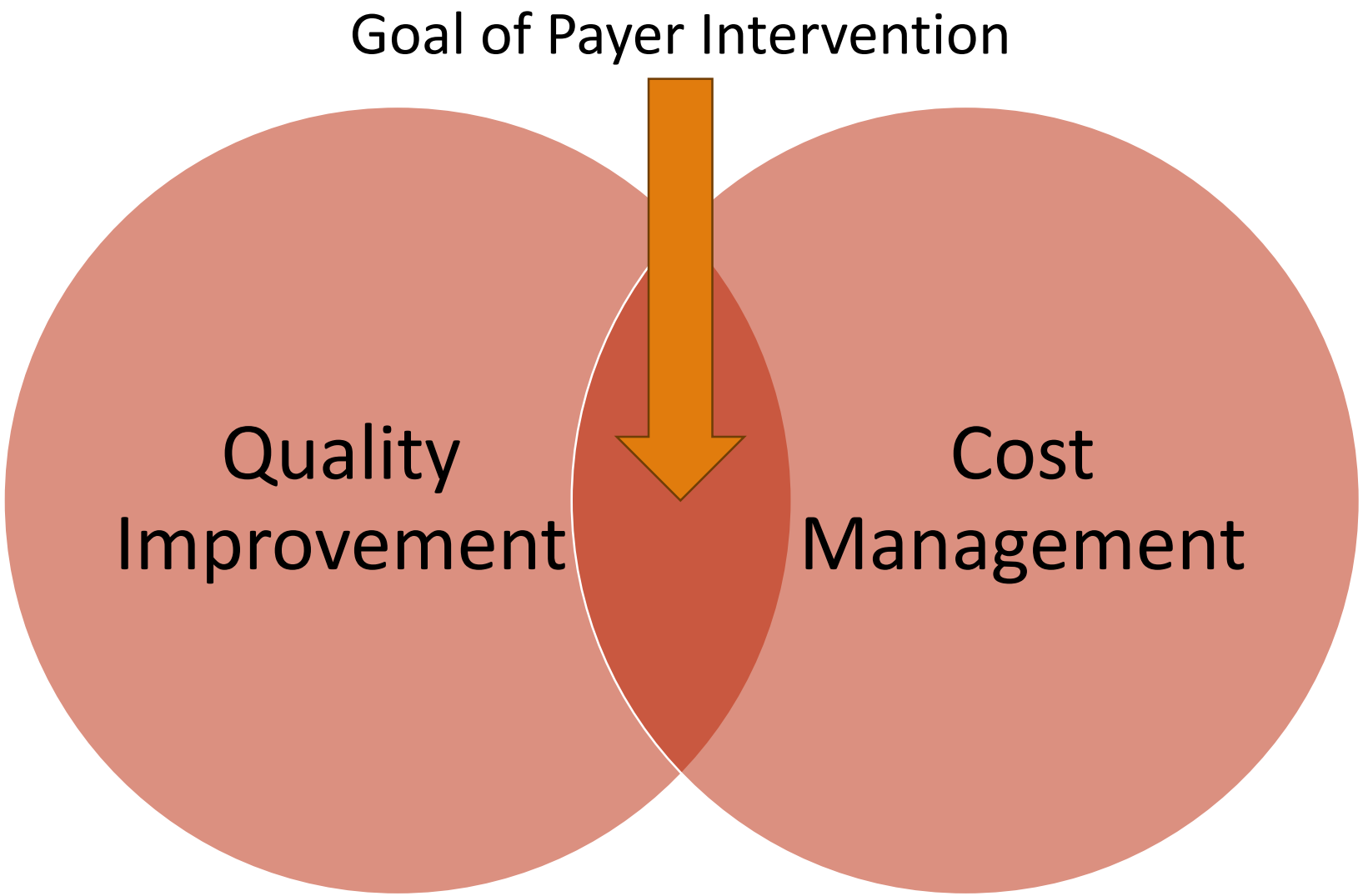


- Medicaid claim costs reflect the increased severity of hemophilia in this population as well as the greater number of comorbidities

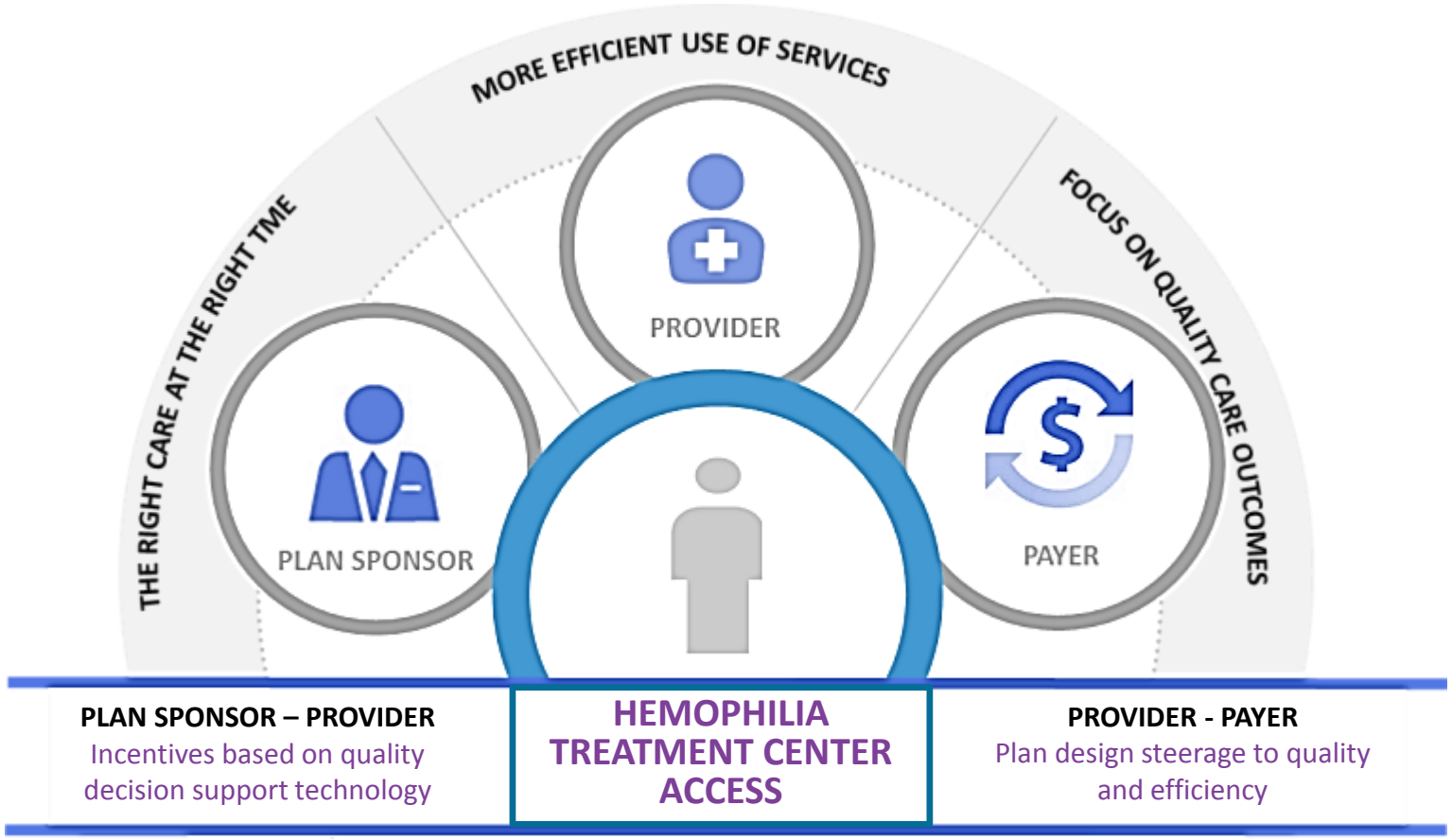
*Includes factor, anti-inhibitor drugs, and other treatment drugs.

Milliman Report. An actuarial study of hemophilia. October 24, 2013.
http://www.milliman.com/uploadedFiles/insight/2014/hemophilia-actuarial-study.pdf. Accessed March 10, 2015.

Payer Management Interventions Seek to Improve Care Quality and Manage Disease Costs



The Right Alignment of Stakeholders Drives the Best Possible Patient Outcomes



Improving the Quality of Hemophilia Care: Payer Perspective

Quality Initiative	Strategy to Achieve
Treatment access and quality	• Integrate hemophilia care in network management and medical management strategies • Establish relationships with HTCs, specialty pharmacy, and specialized medical providers
Care management	• Coordinate multidisciplinary outpatient and home-based services
Cost management	• Utilize cost-effective approaches for administration of factor replacement while keeping in mind the individualized treatment needs of each patient
Pharmacy management	• Evaluate all services required to manage hemophilia • Secure cost-effective and timely factor replacement services for routine and emergency needs
Risk management	• Identify financing solutions (eg, risk adjustment or carve outs) to ensure member access to care
Patient involvement	• Involve patients in all decisions impacting their care • Include support partners and caregivers to increase adherence to recommended care

Balancing Cost and Quality: Payer Cost Management Strategies

Goal: Ensure Lowest Total Costs

- Benefit design
  - Factor drugs covered under Medical or Pharmacy benefit
  - Drug Tier
    - Coinsurance
    - Fixed copayment fee
- Channel management
  - Preferred specialty pharmacy provider(s)
    - Single Source/Multisource
  - Narrow networks
    - Mandatory specialty pharmacy use for purchase/administration of specialty drugs
  - 340B programs

Johnson K. *Formulary Watch*. 2013. http://formularyjournal.modernmedicine.com/formulary-journal/content/tags/specialty-drugs/current-trends-specialty-drug-utilization-and-managem?page=full. Accessed March 12, 2015.
Burns J. *Manag Care*. February 2012. http://www.managedcaremag.com/archives/1202/1202.narrow_networks.html. Accessed March 12, 2015.

Hemophilia Cost Management Best Practices

- Ensure factor dosing is within recommended parameters and generates appropriate clinical response (assay management)
- Ensure that pharmacy benefits managers (PBMs) or specialty pharmacy providers (SPPs) deliver required services including patient education, home care services, and factor management
- Minimize waste by developing protocols for the number of doses kept in patient homes
- Prevent expensive complications by coordinating with hospitals and other providers to plan for elective surgery and preparing for emergencies
- Monitor and evaluate total cost of care, including inpatient and emergency services, to assess use of avoidable acute care

Balancing Cost and Quality: Utilization Management Strategies

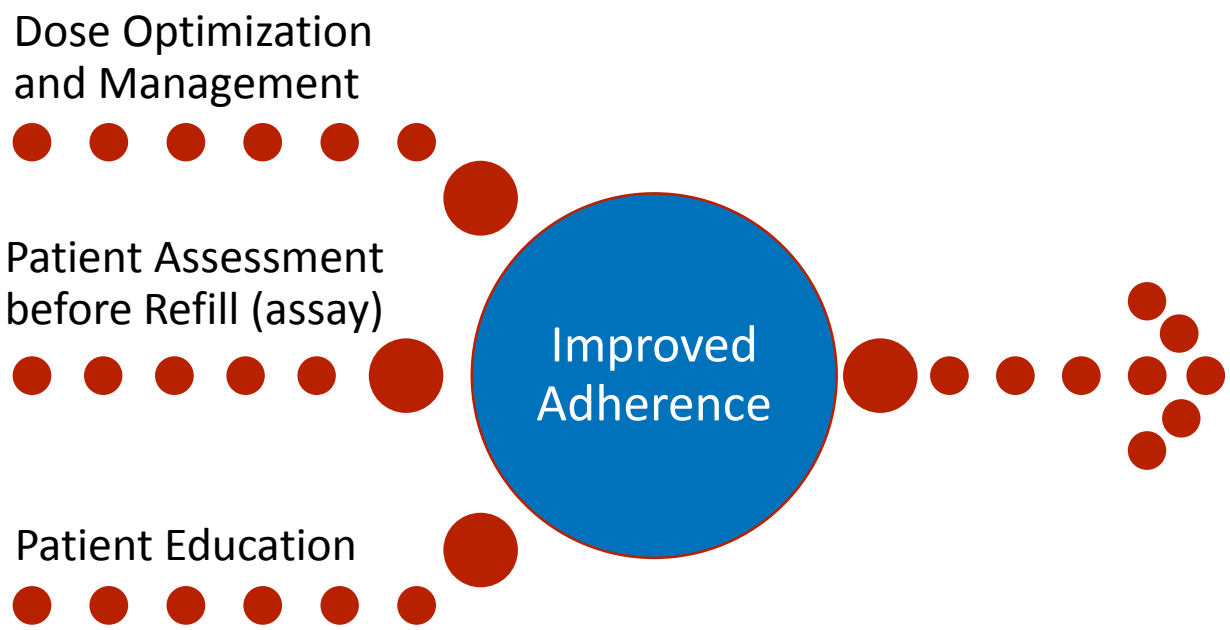
Goal: Ensure Appropriate Use

- Formulary management
- Clinical management including personalized regimens
- Prior authorization, quantity limits
- Maximize operational efficiency by reducing waste, mitigating billing errors, minimizing inappropriate use
- Managed care often contracts with specialty pharmacy providers for utilization management services including prior authorization, formulary management, clinical management, reporting, access, etc.

Hemophilia Utilization Management Best Practices

- Contract with an experienced hemophilia pharmacy provider
- Ensure pharmacy providers meet patient needs for consistent, timely services, products, and infusion supplies
- Ensure any vendor manages factor cost through appropriate assay testing and product inventory management
- Develop policies to ensure correct dosing and stock for at-home use
- Monitor quality and accountability of pharmacy providers

Specialty Pharmacy Interventions May Improve Quality and Manage Total Costs



Increased Appropriate Factor Utilization

Fewer Bleeding Events/ Hospitalizations

Improve Quality of Care

Decrease Cost of Care

Balancing Cost and Quality: Care Model Delivery Strategies

Goal: Ensure the Delivery of Quality Care at the Best Price

- Utilize health care delivery strategies that may provide lower costs without sacrificing quality, including:
  - Centers of Excellence
  - Accountable Care Organizations (ACOs)
  - Patient-centered Medical Homes (PCMH)
- Utilize networks of pharmacy providers that can reduce drug costs through appropriate utilization

Hemophilia Care Delivery Best Practices

- Comprehensive Hemophilia Treatment Centers (HTCs) emphasize prevention services to reduce or eliminate complications
- Includes the use of preventive medicine, education, and psycho-social support
- Provides access to multidisciplinary health care professionals:
  - Hematologists
  - Orthopedists
  - Physical therapists
  - Nurses
  - Social workers
  - Other specialists (eg, pharmacist, dentist, nutritionist, genetic counselor)

Summary

- While the traditional pharmaceutical trend has remained relatively flat, specialty drug spending has increased consistently over the past several years
  - Unit cost increases among specialty agents have contributed significantly to this trend
- Hemophilia is a low prevalence, but high cost disease and patients require treatment across their lifespan with specialty therapeutics such as clotting factor concentrate and bypassing agents
- Access to care is necessary to optimize treatment outcomes; however, there is a need to strike a balance between cost and quality of care
- Several strategies have been devised to effectively manage cost and utilization while delivering high quality care from the payer and specialty pharmacy perspective

Hemophilia Managed Care and Specialty Pharmacy SOLUTIONS for Cost Savings in a New Health Care Ecosystem

Jointly provided by

National Hemophilia Foundation
for all bleeding disorders

Impact Education LLC

PIM Postgraduate Institute for Medicine

This activity is supported by independent educational grants from Baxalta US, Inc., Bayer HealthCare Pharmaceuticals Inc., Biogen, Emergent BioSolutions Inc., Grifols, and Novo Nordisk, Inc.

Held in conjunction with AMCP Nexus 2015

AMCP Academy of Managed Care Pharmacy

An Advanced Review of Inhibitors and Prophylaxis Treatment

Jonathan Roberts, MD
Hematologist
Assistant Research Director
Bleeding & Clotting Disorders Institute

Faculty Disclosure

- The ***faculty*** reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

Jonathan Roberts, MD

- *Consulting Fees:* Baxalta US, Inc., CSL Behring

Hemophilia Etiology and Epidemiology

- 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
- Inability to form a clot leads to spontaneous bleeding or bleeding following trauma or surgery
- 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

Srivastava A, et al. *Haemophilia.* 2013;19:e1.
Centers for Disease Control. Hemophilia facts. http://www.cdc.gov/ncbddd/hemophilia/facts.html. Accessed March 9, 2015.

Clinical Classification

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	uncommon
Cause of bleeding	Spontaneous	Following minor trauma	Following major trauma or surgery

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

Hemophilia Care Management: Treatment Goals, Approach, and Strategies

Goals	Approach	Strategies
•Rapid and effective replacement of missing coagulation factor: • Bleed prevention: decrease frequency and severity of bleeding • Raise factor levels • Prevent the complications of bleeding	•Comprehensive hemophilia treatment center (HTC) staffed by a multidisciplinary team of experts who care for patients with bleeding disorders	•Episodic or "on-demand" factor replacement •Prophylaxis

Centers for Disease Control. Hemophilia. http://www.cdc.gov/ncbddd/hemophilia/facts.html. Accessed March 10, 2015.

Treatment Options

- Replacement of missing clotting protein
  - Hemophilia A: concentrated FVIII product
  - Hemophilia B: concentrated FIX product
- Desmopressin acetate (DDAVP)/Stimate
  - Synthetic vasopressin analog used in many patients with **mild** hemophilia A for joint, muscle, and oro-nasal bleeding and before and after surgery
- Adjunctive therapies
  - Antifibrinolytic agents
  - Supportive measures including immobilization and rest

National Hemophilia Foundation. http://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders. Accessed March 10, 2015.

Control and Prevention of Bleeding with Factor Replacement

Bleeding Episode	Factor Level Required (% of normal)	Frequency of Administration*
Minor • Early hemarthrosis • Minor muscle or oral bleed	30-50	Every 12-24 hours ± antifibrinolytic
Moderate • Bleeding into muscles or oral cavity • Definite hemarthrosis	50-80	Every 12-24 hours until resolved
Major • GI, intracranial, intra-abdominal, intrathoracic, CNS, or retroperitoneal bleeding	80-100	Every 12-24 hours until resolved
Special Case Scenarios • Patients already on prophylaxis, patients using long-acting 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)

World Federation of Hemophilia. http://www1.wfh.org/publications/files/pdf-1494.pdf. Accessed March 10, 2015.
National Hemophilia Foundation. http://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders. Accessed March 10, 2015.

Factors VIII and IX

	FVIII	FIX
Intravenous infusion (either IV push or continuous)	√	√
Dose	20 - 50+ units / kg body weight	40 - 100+ units / kg body weight
Half-life	8 - 12 hours	18 - 24 hours
Average change in plasma factor activity with each unit/kg infused	+2%	+1%

National Hemophilia Foundation. http://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders. Accessed March 10, 2015.

Hemophilia Management Challenges

- Prophylaxis[1-6]
  - Identification of optimal trough level
  - Cost-benefit of targeting higher trough levels
  - Use of prophylaxis beyond pediatric patients
  - Perisurgical considerations
  - Impact of prophylaxis on CVD risk
- Formation of inhibitory antibodies[7,8]
  - Genetic predisposition
  - Factor exposure during heightened immune response
    - Infections, immunizations, surgery
    - More frequent (or continuous) factor infusions in mild or moderate cases
  - Eradication of the inhibitor in severe cases

1. Fischer K, et al. *Blood*. 2013;122:1129-1136. 2. Manco-Johnson MJ, et al. *Haemophilia*. 2013;19:727-735. 3. Gringeri A, et al. *Haemophilia*. 2012;18:722-728. 4. Simpson ML, Valentino LA. *Expert Rev Hematol*. 2012;5:459-468. 5. Sørensen B, et al. *Haemophilia*. 2012;18:598-606. 6. Konkle BA. *Am J Hematol*. 2012;87(Suppl 1):S27-32. 7. National Institutes of Health. http://www.nhlbi.nih.gov/health/health-topics/topics/hemophilia/signs. Accessed July 15, 2015. 8. Shapiro A. *Hematology Am Soc Hematol Educ Program*. 2013;2013:37-43.

Prophylaxis

- 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

Oldenburg J. *Blood*. 2015; Feb 23. pii: blood-2015-01-528414. [Epub ahead of print]
Kempton CL, Meeks SL. *Blood*. 2014;124(23);3365-3372.

Prophylaxis Protocols

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

World Federation of Hemophilia. http://www1.wfh.org/publications/files/pdf-1494.pdf. Accessed March 10, 2015.

New Therapeutics Have the Potential to Revolutionize Prophylaxis

- Extended half-life (EHL) or long-acting factor products
  - FVIII and FIX
  - EHL agents have been recently approved with several more expected in the next few years

What the Data Says…	What We Hope…	The Unknowns…
• Longer half-life • Less frequent dosing	• More effective prophylaxis • Improved adherence • Greater individualization of treatment	• Will long-acting factors work as well as expected? • What impact will they have on cost, adherence, and quality-of-life?

EHL Hemophilia Replacement Factor Research and Development

- Extending the half-life of FVIII and FIX has been a major focus of current efforts to improve therapy
- Current therapies must be administered multiple times per week to maintain circulating FVIII and FIX >1% of normal
- Strategies have been applied to extend the plasma half-life of these coagulation factors and two long-acting products have been FDA-approved
  - March 2014: Alprolix™ approved as the first long-acting recombinant Factor IX concentrate1
  - June 2014: Eloctate™ approved as the first long-acting recombinant Factor VIII concentrate2

1. Alprolix™ [Coagulation Factor IX (Recombinant), Fc Fusion Protein] prescribing information. Cambridge, MA: Biogen Idec, Inc.; March 2014.
2. Eloctate™ [Antihemophilic Factor (Recombinant), Fc Fusion Protein] prescribing information. Cambridge, MA: Biogen Idec, Inc.; June 2014.

Recently Approved and Emerging Treatments

FVIII Agent	Description	Status
NOVOEIGHT (turoctocog alfa)	rFactor VIII	Approved October 2013
ELOCTATE (rFVIIIFc)	rFactor VIII, long-acting	Approved June 2014
Nuwiq	rFactor VIII	Pending regulatory review
Bax855	rFactor VIII, long-acting	Pending regulatory review
Simoctocog alfa	rFactor VIII	Phase 3
N8-GP	rFactor VIII, long-acting	Phase 3
BAY94-9027	rFactor VIII, long-acting	Phase 3

FIX Agent	Description	Status
RIXUBIS	rFactor IX	Approved June 2013
ALPROLIX (rFIXFc)	rFactor IX, long-acting	Approved March 2014
IXinity	rFactor IX	Approved June 2015
C255238539	rFactor IX	Phase 3
rIX-FP	rFactor IX, long-acting	Phase 3
NN79 (N9-GP)	rFactor IX, long-acting	Phase 3

Recently Approved and Emerging Treatments (cont'd)

Inhibitor Agent	Description	Status
OBIZUR	rFactor VIII (porcine seq)	Approved October 2014
BAY 86-6150	rFactor VIIa	Phase 3
LR769	rFactor VIIa	Phase 2/3
ACE910	Factor VIIIa-mimetic bispecific antibody	Phase 2/3; Breakthrough Therapy Designation

Inhibitors

- Inhibitors (antibodies to the infused replacement factor) may develop in ~15-20% of patients[1]
  - Prevalence is higher in hemophilia A (~30%) vs hemophilia B (2-5%)
- Inhibitors neutralize the procoagulant effect of the infused factor as well as naturally produced factor protein[1]
- Typically develop early in life (median age 1.7 – 3.3 years)[1]
- Greatest risk for inhibitor development occurs within the first 50 exposures to infused product[1,2]

1. DiMichele D. World Hemophilia Federation. Inhibitors in Hemophilia: A Primer. Available at: http://www1.wfh.org/publication/files/pdf-1122.pdf. Accessed July 15, 2015.
2. Bray GL, et al. *Blood*.1994;83:2428-2435.

Inhibitors

What Are Inhibitors?

- Polyclonal allo-antibodies of the IgG isotype, predominantly of the IgG4 subclass that is directed to clotting factor
- Highly heterogeneous and display changes in epitope specificity over time
- Neutralize the procoagulant activity of clotting factor, increase factor clearance, and render infusion of clotting factor concentrate ineffective

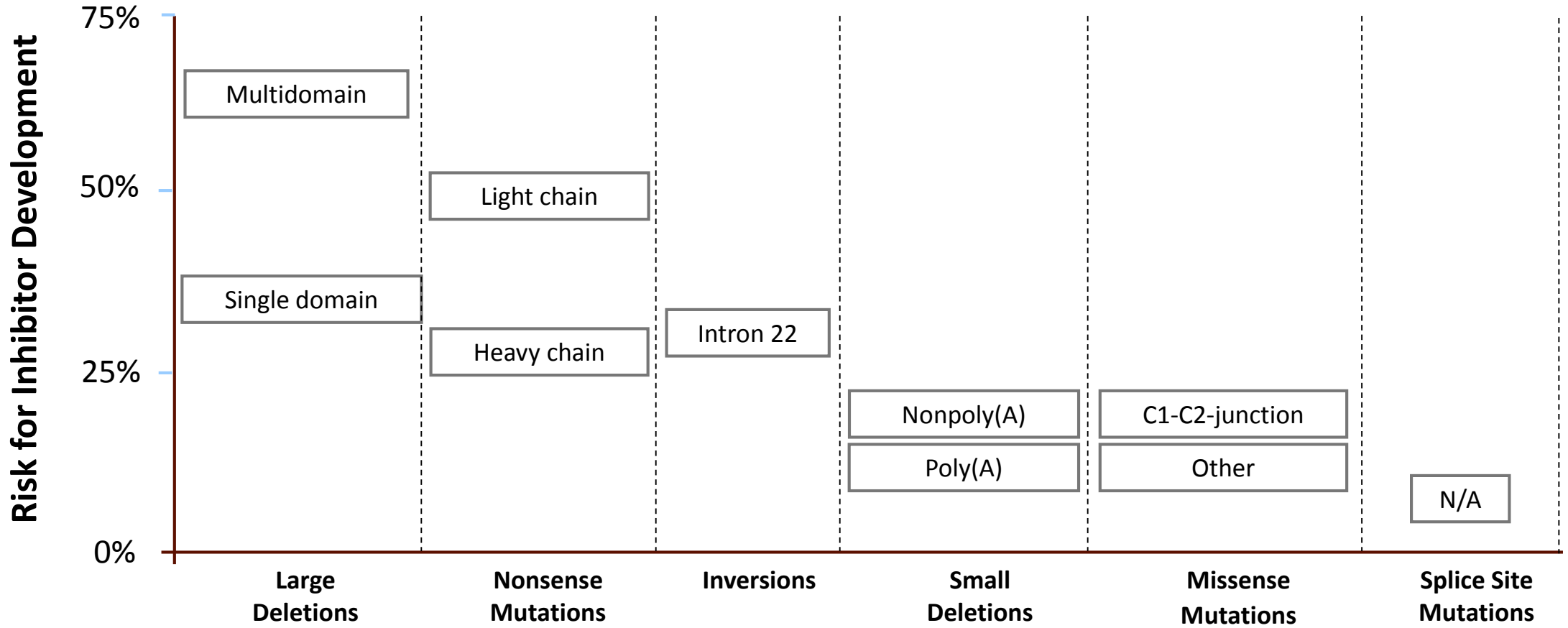
How Do They Develop?

- Clotting factor is a soluble glycoprotein; administration to an immune competent individual may result in immune response
- Genotype of deficient clotting factor protein may influence for the development of inhibitors

Ragni MV, et al. *Haemophilia*. 2009;15:1074–1082.

Inhibitor Development

Risk for Inhibitor Development, by Mutation Type



N/A = not applicable (ie, risk unknown).

Adapted from Oldenburg J, et al. *Haemophilia.* 2002;8(suppl 2):23-29.

Development of Inhibitors

Who Will Develop An Inhibitor?

- Risk Factors
- Ethnicity
  - People of African or Hispanic ancestry have a 2x greater risk
- Family history of antibodies to factor
- Inherited predisposition
  - Siblings with hemophilia >> Extended relatives with hemophilia
- Severe hemophilia

When Will An Inhibitor Develop?

- Development occurs most often between the age of 1 and 2 years, after an average of 9 to 12 treatments with rFVIII
- Risk is greatest during the first 50 exposures to rFVIII

DiMichele D. World Hemophilia Federation. Inhibitors in Hemophilia: A Primer. Available at: http://www1.wfh.org/publication/files/pdf-1122.pdf. Accessed July 15, 2015.

What Prevents Inhibitors from Developing More Frequently?

There are several possible mechanisms:

1. Anti-factor antibodies are neutralized in the periphery
2. B cells (and T cells) can be rendered anergic by an intrinsic mechanism (also referred to as “tolerance”)
3. Any antibodies produced are primarily directed towards sites of the factor molecule that are not involved in its function (also referred to as “non neutralizing antibodies”)

Ragni MV, et al. *Haemophilia*. 2009;15:1074–1082.

Managing Inhibitors

- Treating bleeds: Use of high-dose factor or bypassing agents
  - FVIII impractical and ineffective if BU > 5
  - Activated prothrombin complex concentrates (aPCC)
  - Recombinant FVIIa
    - Factor VIII Inhibitor-Bypassing Activity
    - Coagulation Factor VIIa (Recombinant)
  - 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
  - Limitations include variable efficacy (70%-85% for FVIII and ~30% for FIX)
  - Time consuming and expensive

World Federation of Hemophilia. http://www1.wfh.org/publication/files/pdf-1122.pdf. Accessed March 10, 2015.

Preventing Bleeding in Persons with Hemophilia and an Inhibitor: Rationale for Prophylaxis

- Goals for prevention of bleeding should be the same for persons with or without inhibitors
- FVIII prophylaxis can prevent joint hemorrhage and subsequent arthropathy, target joints, and disability[1-3]
  - Recommended by MASAC, WFH, and WHO as optimal therapy for persons with severe hemophilia without inhibitors[4-6]
- Patients with inhibitors are at increased risk for difficult-to-control bleeding and complications; therefore, bleed prevention or reduction is of critical importance[7,8]
  - Prophylactic treatment may also improve Health-Related Quality-of-Life (HRQoL)[9-11]

1. Manco-Johnson MJ, et al. *N Engl J Med*. 2007;357(6):535-544. 2. Gringeri A, et al. *J Thromb Haemost*. 2011;9(4):700-710. 3. Manco-Johnson MJ, et al. *J Thromb Haemost.* 2013;109(4):625-632.4. US National Haemophilia Foundation. MASAC [Medical and Scientific Advisory Council] Recommendation 179. Available at: http://www.hemophilia.org/NHFWeb/MainPgs/MainNHF.aspx?menuid=57&contentid=1007; Accessed October 12, 2015. 5. Srivastava A, et al. *Haemophilia.* 2013;19(1):e1-47. 6. Berntorp E, et al. Bull World Health Organ. 1995;73:691-701. 7. Kasper CK. World Federation of Hemophilia: 2004, No. 34. 8. Leissinger CA. *Haemophilia*.1999;5(suppl 3):25-32. 9. Leissinger C, et al. *N Engl J Med.* 2011;365:1684-1692. 10. Gringeri A, et al. *Haemophilia.* Published online April 14, 2013; DOI:10.1111/hae.12178. 11. Antunes S, et al. *Haemophilia*. Published online August 1, 2013; DOI:10.1111/hae.12246.

Pro-AICC–Study Results

When compared with Anti-Inhibitor Coagulant Complex (AICC; FEIBA®) on-demand treatment, AICC prophylaxis 85 U/kg ± 15% given on 3 nonconsecutive days weekly:

Reduced all bleeding by **62%** (*P*<0.001)

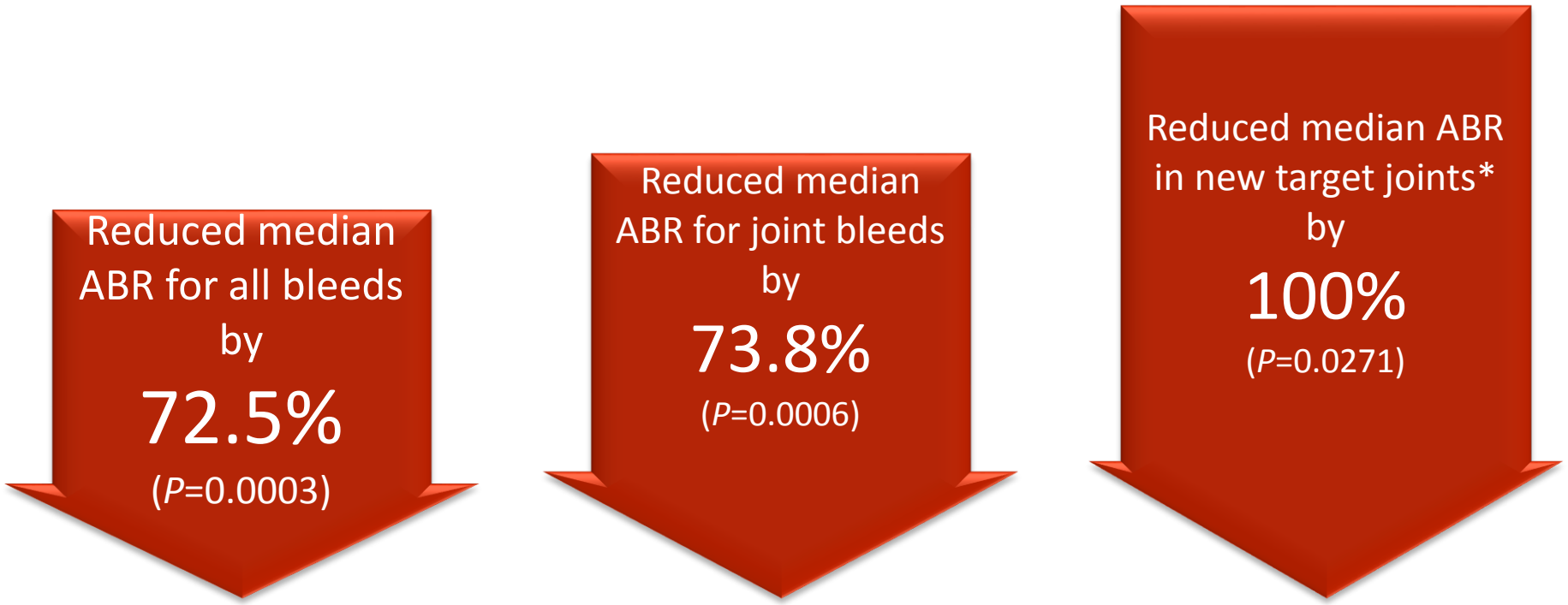
Reduced joint bleeding by **61%** (*P*<0.001)

Reduced target joint bleeding by **72%** (*P*<0.001)

Leissinger C, et al. *N Engl J Med*. 2011;365:1684-92.

PROOF–Study Results

When compared with AICC on-demand treatment, AICC prophylaxis 85 ± 15 U/kg given every other day:

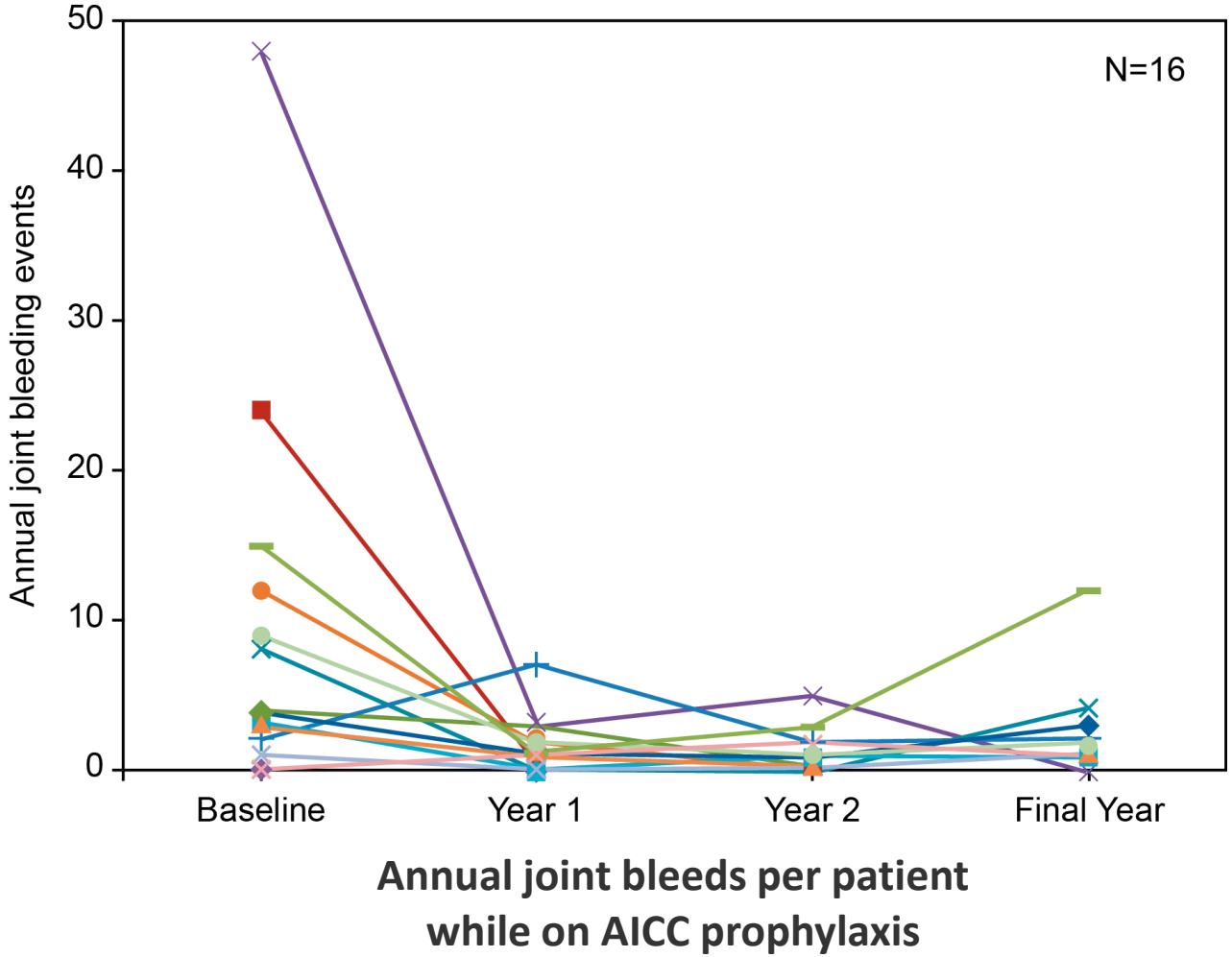


ABR=Annualized bleeding rate; AICC=Anti-Inhibitor Coagulant Complex (FEIBA®)
*Not significant

Antunes S, et al. *Haemophilia* 2014;20:65-72.

Prophylaxis with AICC in Pediatric Patients with Hemophilia A and Inhibitors

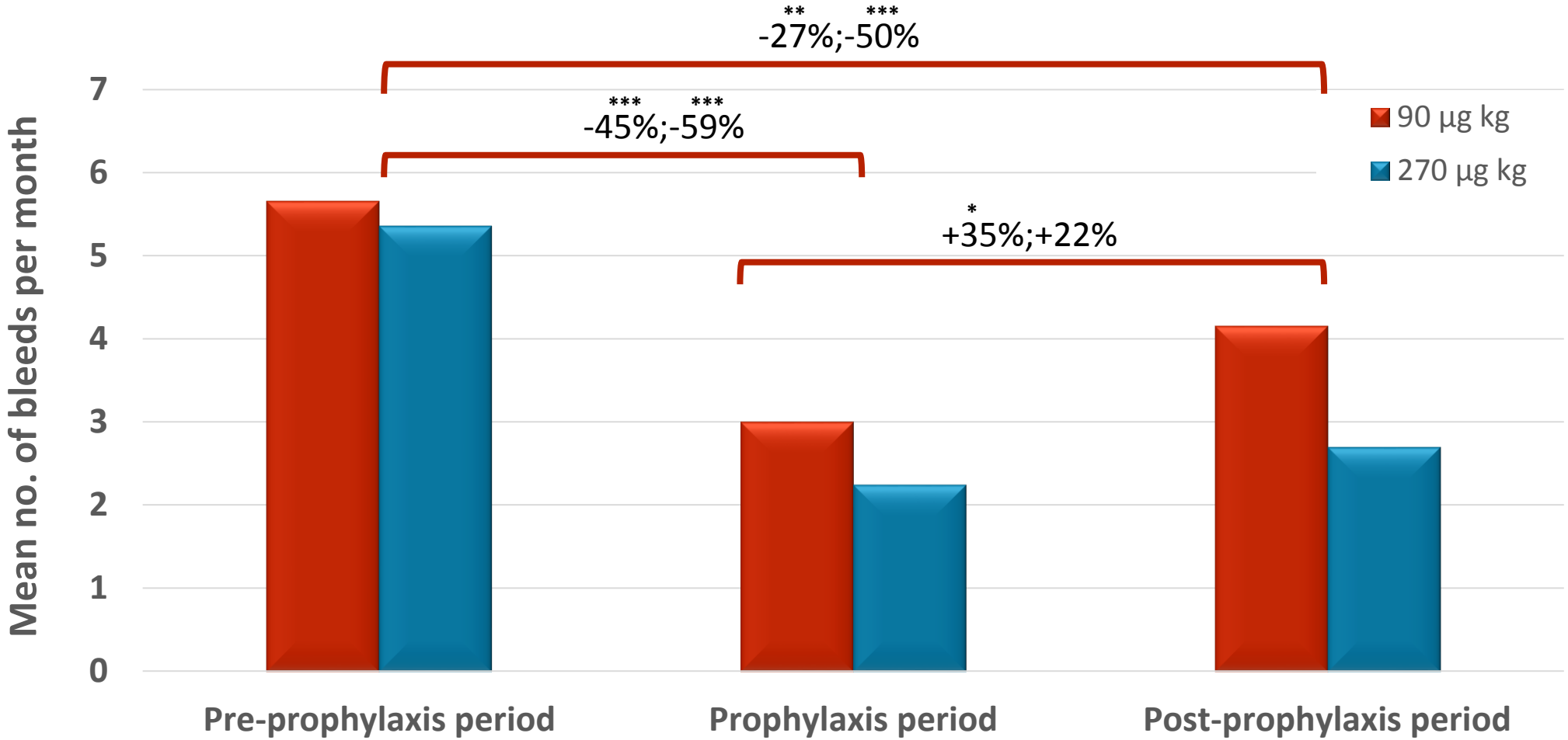
- AICC prophylaxis in pediatric patients decreased the annual number of joint bleeds by a mean of 85.4% the first year (*P*=0.0179) and improved joint status



AICC = Anti-Inhibitor Coagulant Complex (FEIBA®)

Ewing N, et al. *Haemophilia*. 2015;21:1-7.

Randomized, Prospective Clinical Trial of Recombinant Factor VIIa for Secondary Prophylaxis in Haemophilia with Inhibitors



*$P \leq 0.05$; **$P \leq 0.01$; ***$P \leq 0.001$

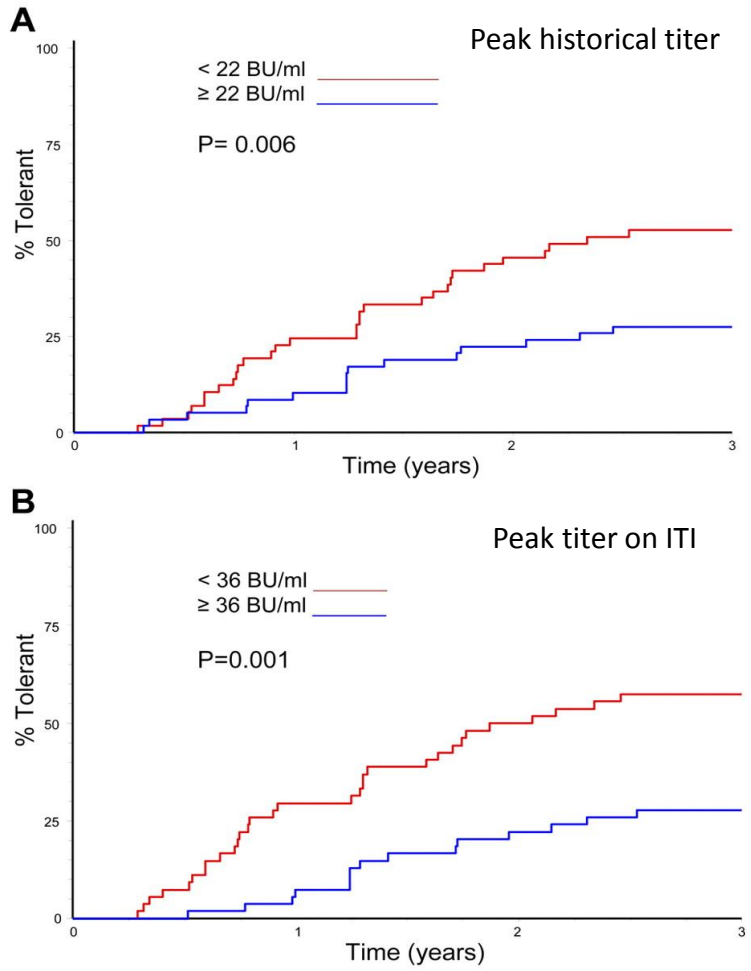
Konkle et al. *J Thromb Haemost.* 2007;5:1904-13.

Dilemmas in Treating Hemophilia with Inhibitors Present

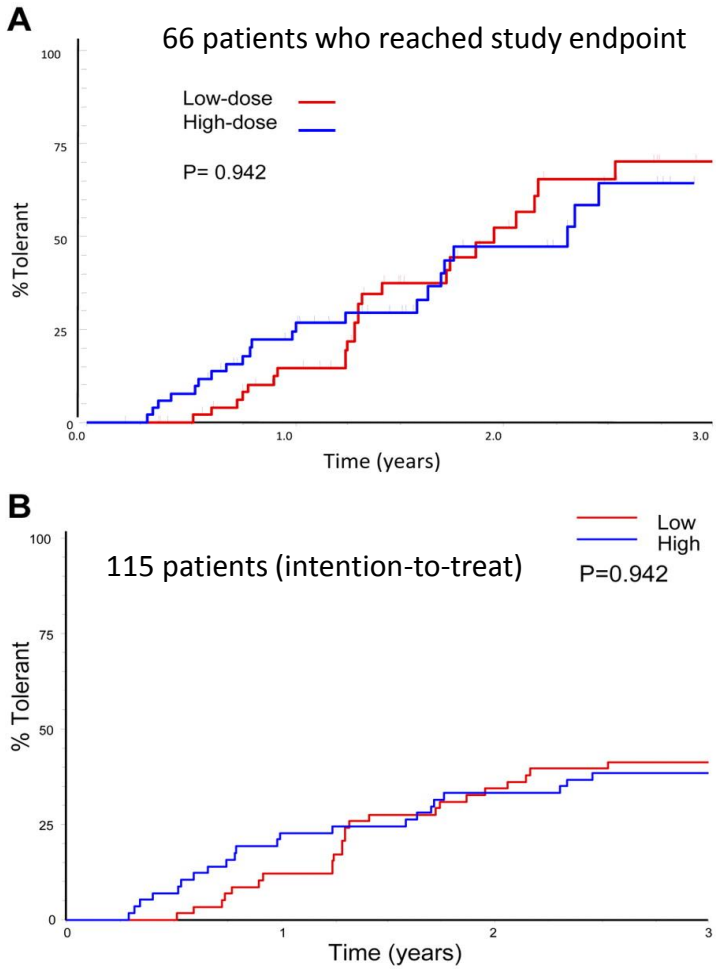
- Treating and preventing bleeds
  - No universally effective agent
    - aPCC work in some, for some, not all
    - rFVIIa works in some, for some, not all
  - No laboratory test that accurately predicts or confirms hemostasis
  - rFVIIa has short half-life, needs frequent infusions
- Inducing Immune Tolerance
  - Not effective in 1/4 to 1/3 of patients
  - The role of or need for von Willebrand factor in preventing and clearing inhibitors is uncertain
  - Immune suppression/modulation (ie, anti-CD20 agents) variably effective that may be temporary

The Principal Results of the International Immune Tolerance Study

Time to tolerance by median peak inhibitor titres



Time to success by treatment arm



Hay CRM, DiMichele DM. *Blood.* 2012;119:1335-1344.

von Willebrand Factor-containing pdFVIII in Hemophilia A Immune Tolerance Induction

OBJECTIVES:

- To report retrospective collection of data on the use of a single vWF/pd-FVIII concentrate in primary and rescue immune tolerance induction (ITI)

METHODS:

- Retrospective chart review of hemophilia A inhibitor patients at 11 US institutions who received vWF/pd-FVIII concentrate in primary or rescue ITI

RESULTS:

- Primary ITI complete or partial success in 75% (6 of 8)
- Secondary ITI complete or partial success in 52% (13 of 25)

Kurth M, et al. *J Thromb Haemost.* 2011;9:2229-34.

Primary and Rescue Immune Tolerance Induction in Children and Adults: a Multicentre International Study with a vWF-containing Plasma-derived FVIII

Immune tolerance induction (ITI) outcome in primary and rescue ITI patients (children: <18 years old; adults: ≥18 years old). Results are shown as number of patients and percentage.

		ITI regimen		
	Outcome	Primary	Rescue	All regiments
Children	Complete success	21 (65.6)	6 (35.3)	27 (55.1)
	Partial success	7 (21.9)	6 (35.3)	13 (26.5)
	Failure	4 (12.5)	5 (29.4)	9 (18.4)
	Total	32	17	49
Adults	Complete success	5 (55.6)	1 (50)	6 (54.5)
	Partial success	3 (33.3)	1 (50)	4 (36.4)
	Failure	1 (11.1)	0 (0)	1 (9.1)
	Total	9	2	11
All patients	Complete success	26 (63.4)	7 (36.8)	33 (55)
	Partial success	10 (24.4)	7 (36.8)	17 (28.3)
	Failure	5 (12.2)	5 (26.3)	10 (16.7)
	Total	41	19	60

Values within parenthesis are expressed in percentage.

Oldenburg J, et al. *Haemophilia.* 2014;20:83-91.

Predictors of “Good Response” to ITI

- Consistently recognized predictors of ITI success
  - Peak historical inhibitor titre ≤200 BU mL^{-1}
  - Inhibitor titre <10 BU mL^{-1} before ITI initiation
  - Peak inhibitor titre during ITI ≤200 BU mL^{-1}
- Other predictors of better outcomes
  - Age <8 years at start of ITI
  - ITI initiated <5 years after inhibitor diagnosis
  - Interruptions in ITI <2 weeks in duration

Valentino L. et al. *Haemophilia.* 2015;21:559-567.

Prompt IT Induction at Inhibitor Diagnosis Regardless of Titer May Increase Overall Success in Hemophilia A: Data From Two US HTCs

- DEFINITIONS
  - SUCCESS: negative inhibitor titer and ability to use FVIII concentrate for treatment/bleed prevention;
  - PARTIAL SUCCESS: inhibitor titer 1 to <5 BU with ability to use FVIII concentrate for treatment of bleeding;
  - FAILURE: ITI ongoing >3 years without achieving success/partial success, or ITI discontinuation.
- 58 SUBJECTS: 32 of 39 (82%) with high-responding inhibitor (HRI) achieved success, 7 failed.
- HRI subjects were subdivided based on ITI start time:
  - 23/39 subjects started within 1 month of detection and 22/23 **(96%)** achieved success.
  - Of these 23, 13 started ITI with an inhibitor titre ≥10 BU; 13/13 **(100%)** achieved success.
  - 11 of 39 HRI subjects had an interval >6 months until ITI start; 7 **(64%)** achieved success.
- A titer ≥10 BU at ITI start did not influence outcome in subjects when ITI was initiated within 1 month of detection.

Nakar C, et al. *Haemophilia.* 2015;21:365-73.

Summary

- Inhibitors and prophylaxis considerations represent two of the greatest clinical challenges in the treatment of hemophilia
  - Aggressive and vigilant therapeutic intervention is crucial to success and the minimization of morbidity/mortality
  - Emerging therapeutics in the form of recombinant and EHL agents present promising options for the elimination of inhibitors and the advancement of prophylaxis, respectively

Hemophilia Managed Care and Specialty Pharmacy SOLUTIONS for Cost Savings in a New Health Care Ecosystem

Jointly provided by

National Hemophilia Foundation
for all bleeding disorders

Impact Education LLC

PIM Postgraduate Institute for Medicine

This activity is supported by independent educational grants from Baxalta US, Inc., Bayer HealthCare Pharmaceuticals Inc., Biogen, Emergent BioSolutions Inc., Grifols, and Novo Nordisk, Inc.

Held in conjunction with AMCP Nexus 2015

AMCP Academy of Managed Care Pharmacy

Measuring Success: Tools and Resources to Document Outcomes of Payer and Specialty Pharmacy Hemophilia Management

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

Faculty Disclosure

- The ***faculty*** reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

Michael Zeglinski, RPh

- *Consulting Fees:* Sanofi

The Evolving Role of Specialty Pharmacy

Manage Patient

- Access to service
- Holistic care model

Manage Outcomes

- High quality care focus
- Adherence & persistency

Manage Payer

- Control spend
- Demonstrate quality care services
- Network requirements

Issue Brief: Specialty Drugs—Issues and Challenges. July 2015. http://www.ahip.org/IssueBrief/Specialty-Drugs-Challenges-Issues/. Accessed July 30, 2015.

Managing the Complexities of Specialty Pharmacy is Multi-Faceted

Improving Member Well-Being

Providing Proactive Service

Balancing Cost & Care

Connecting Communities

Driving Outcomes through Clinical Excellence

Key Components of Specialty Pharmacy Care in the Management of Hemophilia

Strategies for Improving Outcomes While Managing Spend

Appropriate Access

Ensuring appropriate use by navigating the right patients, to the right drugs, administered at the right site-of-care

Benefit Design

Optimize pharmacy spend through a comprehensive approach to benefit architecture

Care Optimization

Maximize the impact of specialty drug utilization through high touch specialty pharmacy care

Enabling Technology

Leverage technology leadership to enable better decisions across the continuum of care

Issue Brief: Specialty Drugs—Issues and Challenges. July 2015. http://www.ahip.org/IssueBrief/Specialty-Drugs-Challenges-Issues/. Accessed July 30, 2015.

Patient Engagement Improves Outcomes While Managing Cost

Innovative Tools & Resources

- Video consultation
- Educational videos
- Mobile app
- Individualized plan of treatment

Promoting Quality Outcomes

- Dedicated clinical management team
- Intervention-based monthly assessment and monitoring

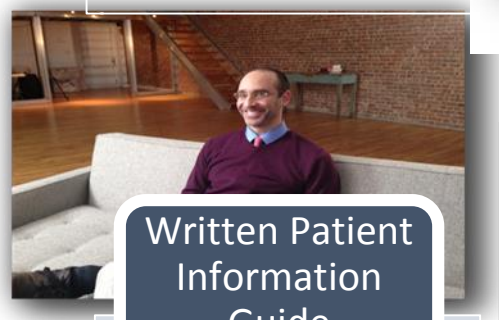
Managing Payer Cost

- Manage appropriateness of treatment
- Monitoring of in-home inventory
- Minimal assay variance

Innovative Tools and Resources Promote Engagement and Adherence

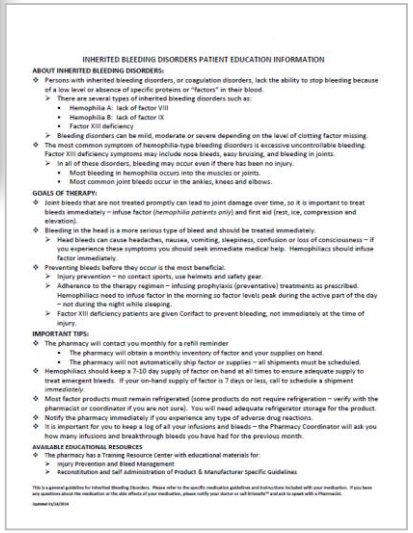
Live Multimedia

Live video education and counseling sessions with pharmacist



Written Patient Information Guide

Written resources to promote understanding of condition and treatment



INHERITED BLEEDING DISORDERS PATIENT EDUCATION INFORMATION

ABOUT INHERITED BLEEDING DISORDERS:

- Persons with inherited bleeding disorders, or coagulation disorders, lack the ability to stop bleeding because of a low level or absence of specific proteins or "factors" in their blood.
  - There are several types of inherited bleeding disorders such as:
    - Hemophilia A: lack of factor VIII
    - Hemophilia B: lack of factor IX
    - Factor XIII deficiency
  - Bleeding disorders can be mild, moderate or severe depending on the level of clotting factor missing.
- The most common symptom of hemophilia-type bleeding disorders is excessive uncontrollable bleeding. Factor XIII deficiency symptoms may include nose bleeds, easy bruising, and bleeding in joints.
  - In all of these disorders, bleeding may occur even if there has been no injury.
    - Most bleeding in hemophilia occurs into the muscles or joints.
    - Most common joint bleeds occur in the ankles, knees and elbows.

GOALS OF THERAPY:

- Joint bleeds that are not treated promptly can lead to joint damage over time, so it is important to treat bleeds immediately – infuse factor (*hemophilia patients only*) and first aid (rest, ice, compression and elevation).
- Bleeding in the head is a more serious type of bleed and should be treated immediately.
  - Head bleeds can cause headaches, nausea, vomiting, sleepiness, confusion or loss of consciousness – if you experience these symptoms you should seek immediate medical help. Hemophiliacs should infuse factor immediately.
- Preventing bleeds before they occur is the most beneficial.
  - Injury prevention – no contact sports, use helmets and safety gear.
  - Adherence to the therapy regimen – infusing prophylaxis (preventative) treatments as prescribed. Hemophiliacs need to infuse factor in the morning so factor levels peak during the active part of the day – not during the night while sleeping.
  - Factor XIII deficiency patients are given Corifact to prevent bleeding, not immediately at the time of injury.

IMPORTANT TIPS:

- The pharmacy will contact you monthly for a refill reminder.
  - The pharmacy will obtain a monthly inventory of factor and your supplies on hand.
  - The pharmacy will not automatically ship factor or supplies – all shipments must be scheduled.
- Hemophiliacs should keep a 7-10 day supply of factor on hand at all times to ensure adequate supply to treat emergent bleeds. If your on-hand supply of factor is 7 days or less, call to schedule a shipment immediately.
- Most factor products must remain refrigerated (some products do not require refrigeration – verify with the pharmacist or coordinator if you are not sure). You will need adequate refrigerator storage for the product.
- Notify the pharmacy immediately if you experience any type of adverse drug reactions.
- It is important for you to keep a log of all your infusions and bleeds – the Pharmacy Coordinator will ask you how many infusions and breakthrough bleeds you have had for the previous month.

AVAILABLE EDUCATIONAL RESOURCES

- The pharmacy has a Training Resource Center with educational materials for:
  - Injury Prevention and Bleed Management
  - Reconstitution and Self Administration of Product & Manufacturer Specific Guidelines

This is a general guideline for Inherited Bleeding Disorders. Please refer to the specific medication guidelines and instructions included with your medication. If you have any questions about the medication or the side effects of your medication, please notify your doctor or call Eloctate™ and ask to speak with a Pharmacist.

Web-based Tools & Mobile App

Easily accessible information to connect patients with education tools and community

Community Resources

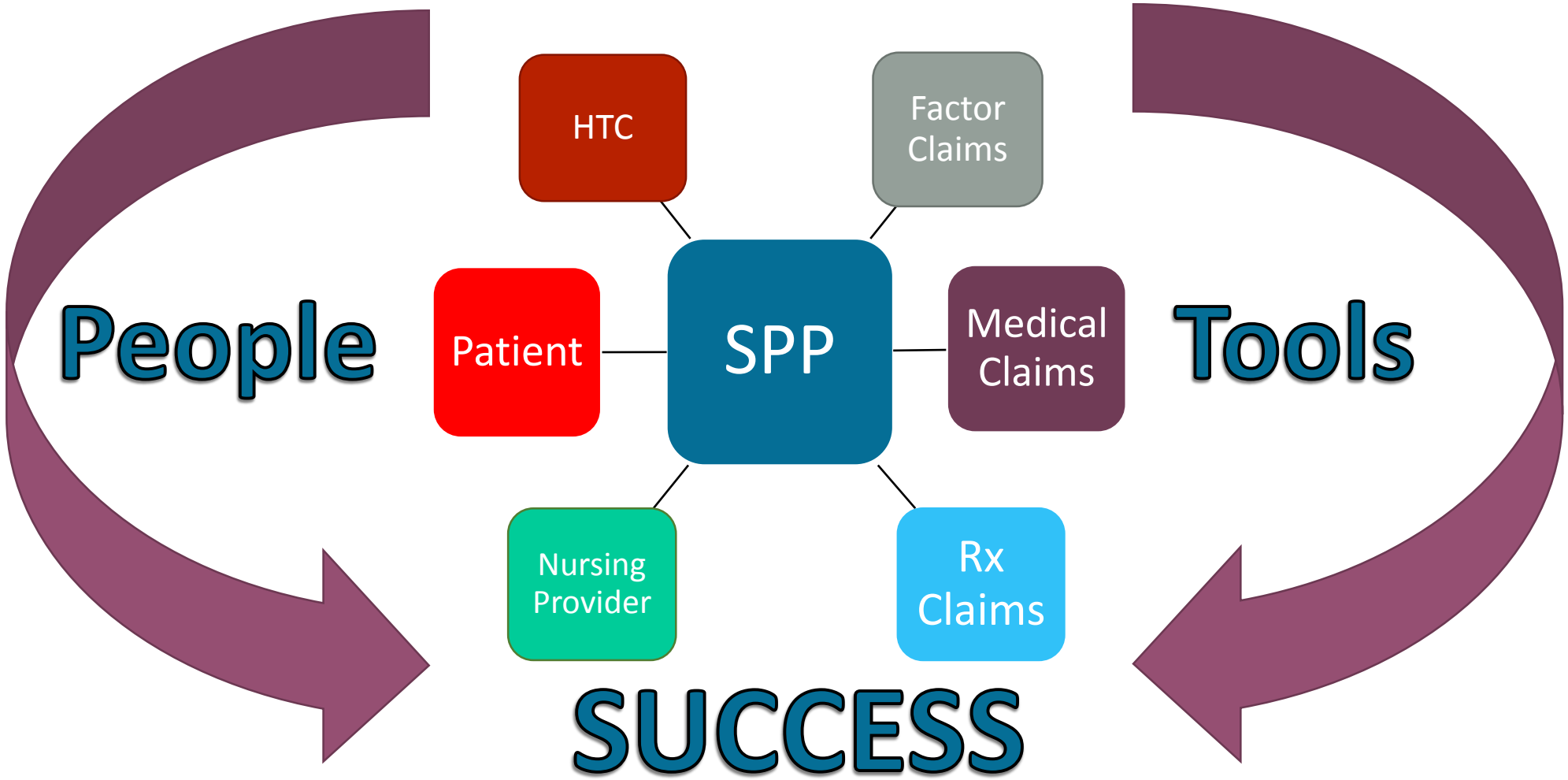
Educational and instructional videos designed to engage patients in disease management & treatment

Important Components of Hemophilia Patient Education Messaging

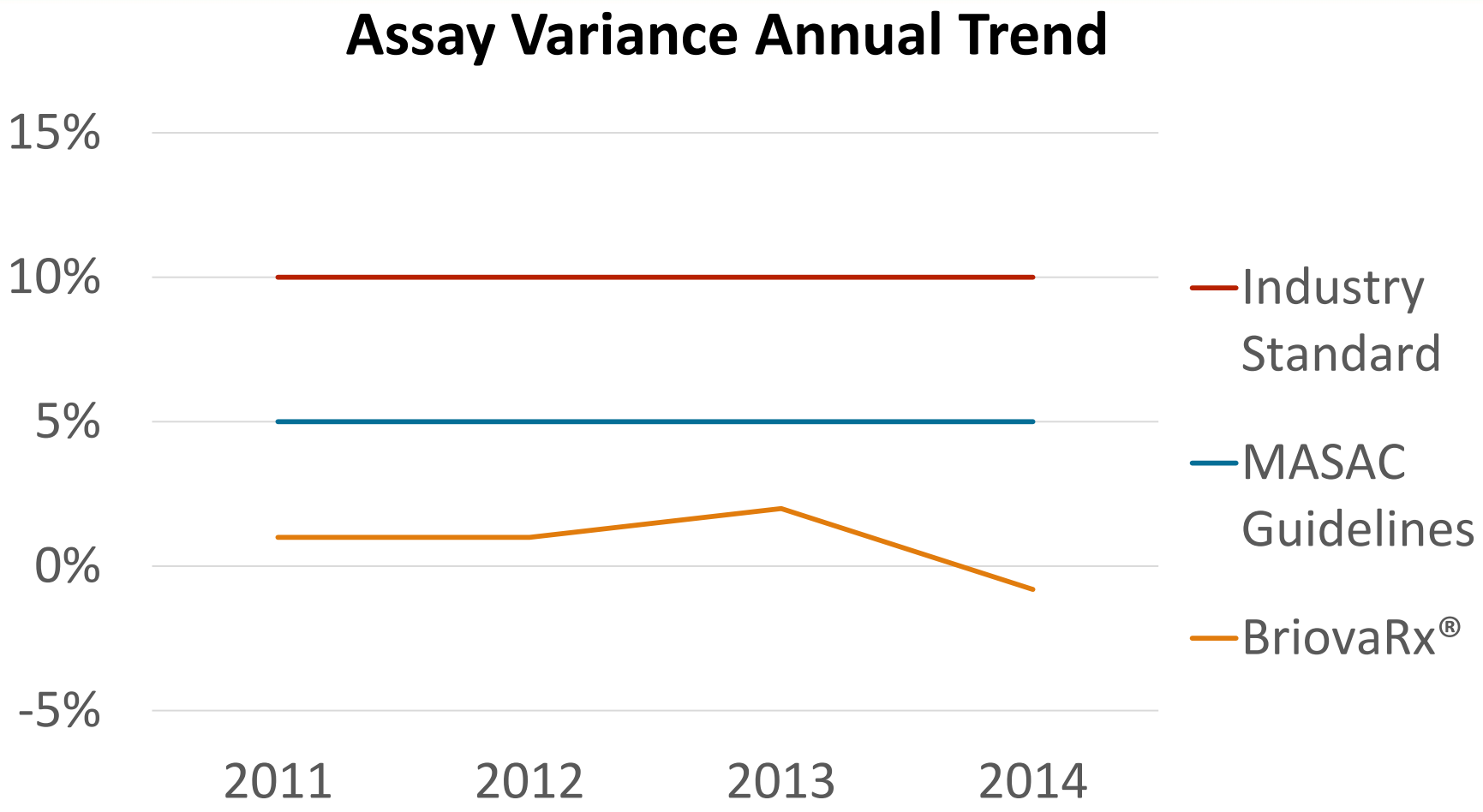
- Highlighting the importance of adherence
- Self-administration technique and training
- Preparing for and coping with adverse events
- Clotting factor concentrate storage
- Immediate treatment for breakthrough bleeding

Bauer KA. *Am J Manag Care.* 2015;21:S112-S122.

The Formula for Successful Hemophilia Management and Quality Care



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 July 30, 2015.

Assay Prescription Management Results: Payer Savings

Sample Savings Model*			
Variance	**Dose (IU)**	**Cost PMPM****	**Cost PMPY**
10%	1650	$19,800	$237,600
5%	1575	$18,900	$226,800
2%	1530	$18,390	$220,680

Lower variance drives cost down for payers

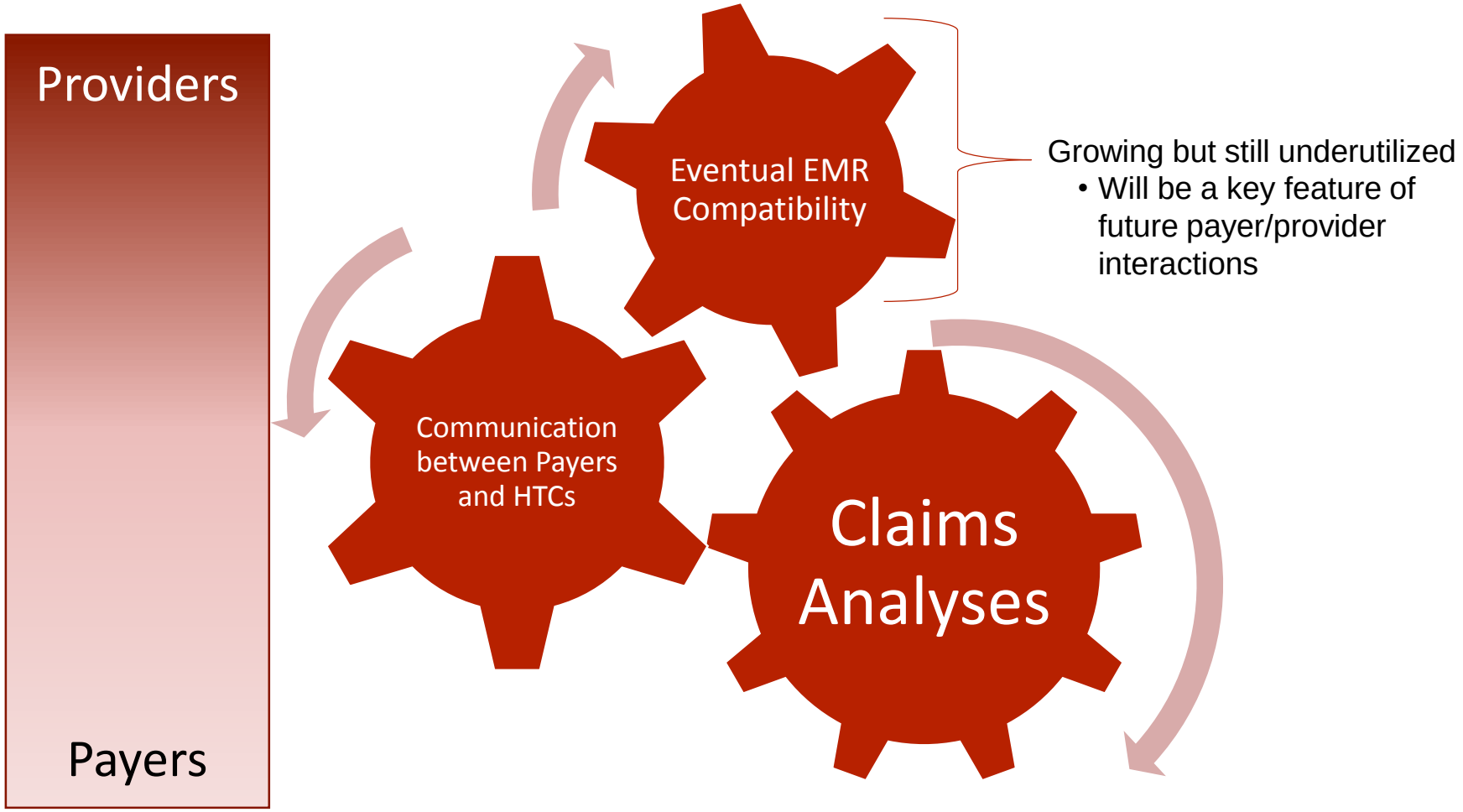
$16,920 annual savings at 2% variance compared to 10%

*Based on 40% desired factor rise for 75kg FVIII severe deficiency patient
**Calculated at cost of $1.00 per IU for 12 doses per month

PMPM=per member per month; PMPY=per member per year

Key Components of Data Collection and Analysis for Hemophilia Quality Improvement

Collaboration Between Payers and Providers is Imperative



The CCSC Initiative Strives to Facilitate Payer-Provider Collaboration

Comprehensive Care Sustainability Collaborative

CCSCHemo.com

- Ongoing quality improvement (QI) 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

Goal: facilitate cost-effective hemophilia management integrating the HTC comprehensive care model

Summary

- Specialty pharmacies are increasingly called upon to provide quality care in the management of patients with costly chronic diseases such as hemophilia
- In certain scenarios, SPPs may be called to coordinate care and data management for these patients
  - Coordination with prescribing physicians, HTCs, and home health care
  - Appropriate dosing based on weight and/or assay values
  - Patient education and follow-up for adherence and appropriate administration
- Quality improvement initiatives must likewise be driven through the specialty pharmacy, which is relied upon for data collection and reporting

Hemophilia Managed Care and Specialty Pharmacy SOLUTIONS for Cost Savings in a New Health Care Ecosystem

Jointly provided by

National Hemophilia Foundation
for all bleeding disorders

Impact Education LLC

PIM Postgraduate Institute for Medicine

This activity is supported by independent educational grants from Baxalta US, Inc., Bayer HealthCare Pharmaceuticals Inc., Biogen, Emergent BioSolutions Inc., Grifols, and Novo Nordisk, Inc.

Held in conjunction with AMCP Nexus 2015

AMCP Academy of Managed Care Pharmacy

HTC, Managed Care, and Specialty Pharmacy Collaboration

Donald: A 49-year-old Male with Moderate Hemophilia B

Donald: A 49-year-old Male with Moderate Hemophilia B

- Primary diagnosis: moderate hemophilia B (3% circulating factor)
- Secondary diagnoses: hypertension, sleep apnea, hemarthrosis, nasal polyps, and deviated septum
- Donald primarily uses factor for surgical procedures or major bleeding events
- He lives in an area where there are very few home infusion nurses and on-call home nursing support is unavailable

Social/Family Background

- Donald prefers to remain very active, working out daily in a gym and running 5 miles per day
- Works as a bookkeeper for a locally owned business
- He lives with his wife and his adult son, who has disabilities

Chief Complaints

- When Donald develops a major bleed, he typically must visit the local emergency department (ED) for infusions of factor
- Frequently the local ED has insufficient supply of factor on hand, and he must then drive to a hospital >1 hour from his home for an infusion
- Donald's hemarthrosis has progressed and he recently has stopped his workouts to reduce the inconvenience of having to travel to receive his infusion when he develops a bleed
- He also recently changed insurance plans and now has a $500 copay for each ED visit

Intervention

- The specialty pharmacy coordinated with the HTC to obtain a prescription and insurance coverage authorization for Donald to have 2 doses of factor on hand at home
  - Patient could then ensure that he would have doses of factor on hand to take into the local ED for infusion, should he have a bleed
  - Using this option patient still incurs an ED visit and a $500 copay
- The specialty pharmacy next worked with the HTC to coordinate in-home nursing to teach the patient to self-infuse

Outcome

- Donald has gained confidence and independence in his treatment
- He has returned to the gym 3-4 days per week and is able to run 3 miles again
- He has product on hand to treat his bleeds early, and now that he is learning to self-infuse, he happily anticipates not needing to visit the ED

Faculty Discussion

Clinical

- What considerations weigh into decisions regarding in-home factor infusion and product selection for patients such as Donald?
- Under what circumstances would other clinical interventions, such as physical therapy and/or prophylaxis, play a role in the management of these patients?

Payer/SPP Management

- Can you describe the different ways in which SPPs support HTCs and community hematologists in the management of patients with hemophilia?
- What tools and interventions do SPPs have at their disposal for addressing hemophilia-specific challenges such as in-home infusion and therapeutic adherence?

Hemophilia Managed Care and Specialty Pharmacy SOLUTIONS for Cost Savings in a New Health Care Ecosystem

Jointly provided by

National Hemophilia Foundation
for all bleeding disorders

Impact Education LLC

PIM Postgraduate Institute for Medicine

This activity is supported by independent educational grants from Baxalta US, Inc., Bayer HealthCare Pharmaceuticals Inc., Biogen, Emergent BioSolutions Inc., Grifols, and Novo Nordisk, Inc.

Held in conjunction with AMCP Nexus 2015

AMCP Academy of Managed Care Pharmacy