

Economic Costs of Hemophilia and the Impact of Prophylactic Treatment on Patient Management

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Hemophilia is a rare X-linked congenital bleeding disorder characterized by bleeding manifestations, including spontaneous bleeding episodes into muscles and joints.^{1,2} Joint bleeding, which commonly affects weight-bearing joints, such as knees or ankles, can lead to the development of painful, disabling hemophilic arthropathy.³ These patients are also at risk for life-threatening bleeding, including intracranial hemorrhage. Clotting-factor concentrates are used for the treatment and prevention of these bleeds.

The major complication of the use of clotting-factor concentrates is the development of inhibitors, alloantibodies that neutralize the infused factor. Consequently, bypassing agents have to be used for the treatment of bleeds in these patients. The bypassing agents are not as effective as the clotting factors VIII (FVIII) and IX concentrates, which further inhibits effective management of bleeding episodes; this places patients with hemophilia at greater risk for target joint development (3 or more bleeds in the same joint in 6 months) and progressive arthropathy that can result in permanent disability.^{4,5} A complication observed in the hemophilia population in the 1980s was the transmission of HIV, along with the hepatitis B virus and hepatitis C virus (HCV), with the use of plasma-derived clotting-factor concentrates. There was a high mortality rate among individuals with hemophilia who developed these viral infections in the 1980s and 1990s. Transmission of these infections, however, has been greatly reduced with the use of recombinant clotting-factor concentrates, the implementation of screening, and effective viral eradication steps in the manufacturing process of the plasma-derived clotting-factor concentrates.

Over the past 20 years, significant improvements have been made in the management of patients with hemophilia, including advances in acute and prophylactic treatment and the availability of safe and effective clotting-factor

Abstract

Hemophilia is a rare congenital bleeding disorder characterized by spontaneous and potentially life-threatening bleeding episodes. In addition to its clinical burden on the patient, the condition also places a significant economic burden on healthcare payers, patients/caregivers, and society. Hemophilia is associated with staggering direct costs from hospitalizations, outpatient visits, and drug treatments, as well as high indirect costs from diminished work productivity and absenteeism from work and school. Additionally, hemophilia incurs tremendous intangible costs, including reduced quality of life, pain and suffering, and the emotional and physical toll on the patient and caregivers.

The evolution of treatment patterns in hemophilia has transformed the once-fatal disease into a chronic but potentially well-managed condition through the use of prophylaxis treatment. However, other complications, such as development of inhibitory antibodies, have added to the complexity of managing the disease and its costs. To ensure optimal treatment outcomes and disease management, there is a critical need to understand the utilization of healthcare resources in the treatment of hemophilia and to educate patients on the importance of treatment adherence and compliance to reduce long-term effects on musculoskeletal health.

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concentrates. These advances have resulted in increases in life expectancy.^{6,7} However, the life expectancy for men with severe disease is still 15 years less than the general population.^{6,8} Sixty percent of individuals with hemophilia have severe disease, with a median age of 1 month at diagnosis.⁹ The debilitating joint disease that results from recurrent bleeding episodes, along with the risk of inhibitor development, has significant negative impacts on the quality of life (QoL) of these individuals.¹⁰⁻¹² The combined factors of ineffective management, pain, potential disability, and reduced QoL translate into a substantial burden to affected individuals, their caregivers, and society.¹³⁻¹⁵

Economic Burden of Hemophilia

Although hemophilia affects only a small portion of the population in the United States, it is associated with high aggregate costs and imposes a high financial burden on individuals, healthcare systems, and society in general. Hemophilia is a chronic condition that requires lifelong treatment, with individual costs varying based on disease severity, complications, and treatment regimen.¹⁴ The majority of these costs are direct costs, which include anti-hemophilic medication, clinician visits, hospitalizations, medical and surgical procedures, and laboratory tests.^{13,16} Indirect costs are those associated with reduced productivity and increased absenteeism caused by hemophilia, its treatment, resulting disability, and death. To maintain perspective, the intangible costs include the impact of the disease on QoL, as well as the emotional and psychological effects of the disease; the pain and suffering resulting from hemophilia are also important to consider.¹³

Indirect Costs

Complications, such as recurrent bleeding, affect the productivity of people with hemophilia and their caregivers in terms of absenteeism from work and/or school. Those patients with inhibitors are at increased risk for bleeding and associated complications. A survey of 90 caregivers and individuals with hemophilia and inhibitors evaluated the relationship between health-related quality of life (HRQoL) and productivity, as measured by absenteeism.¹⁷ Dependent clinical and treatment factors associated with HRQoL included physical, social, and emotional functioning, along with bodily pain, general health, vitality, and mental health.

The study found that among employed patients, physical HRQoL deficits contributed to substantial work time missed or compromised. On-demand treatment and the increased number of hemorrhages were negatively asso-

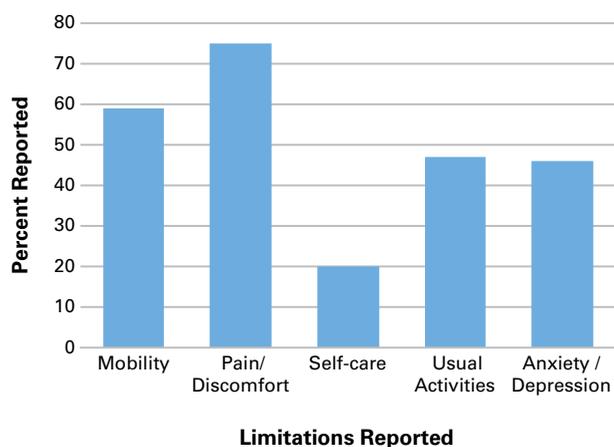
ciated with physical component scores ($P < .05$), which were themselves negatively associated with missed work or school days ($P < .001$). Over a 12-month period before the start of the study, patients with hemophilia reported an average of 20.2 low productive days and 25.7 missed days at work/school. Caregivers reported an average of 19.1 low productive days and 19.1 missed days at work/school. It was concluded that reduction in the number of hemorrhages in patients with hemophilia would likely improve physical functioning and productivity.

The Hemophilia Experiences, Results and Opportunities (HERO) initiative was developed to bring about greater understanding and awareness of the psychosocial issues facing individuals with hemophilia.¹⁸ The study found that 80% ($n = 537$) of patients with hemophilia reported either a very large, moderate, or small negative impact of hemophilia on their employment. Forty percent ($n = 243$) selected their job/training to take into account the needs relating to their hemophilia, and 22% ($n = 132$) believed that they had lost a job in the past because of their hemophilia. Furthermore, 63% ($n = 351$) of parents of children with hemophilia reported that they felt that having a child with hemophilia had a negative impact on their employment. Although 35% felt that their child's current treatment allowed them to work in most situations, 29% said they selected their job/training to take their child's hemophilia and his needs into account. Seventeen percent had voluntarily left their job in order to care for a child with hemophilia.¹⁹ In a more recent study of 474 individuals with hemophilia, 25% of part-time participants and 30% of unemployed participants attributed their employment status to hemophilia. Nineteen percent of parents who had a child with hemophilia were underemployed; underemployment was significantly more likely in adults with severe hemophilia and parents of children with severe hemophilia. Overall, the cost of underemployment due to hemophilia was estimated at almost \$4 million per year.²⁰

HRQoL among individuals with hemophilia is considerably impaired, mainly due to the pain and disability associated with hemophilic arthropathy. However, the HRQoL of untreated patients with inhibitors is even poorer.^{11,12} The HERO study showed that those with hemophilia have poor levels of HRQoL, in terms of mobility, pain/discomfort, self-care, usual activities, and anxiety/depression (Figure 1¹¹). In fact, 89% ($n = 598$) of patients with hemophilia reported that pain had interfered with their daily life in the past 4 weeks, and 301 patients with hemophilia (50%) reported constant pain.¹¹

Psychosocial issues may also prevent individuals with hemophilia from living the life they desire. The HERO

■ **Figure 1.** EuroQol (EQ-SD) Survey on Health-related Quality of Life in Patients With Hemophilia¹¹



study found that psychological or psychiatric conditions were the most common group of comorbidities that were both related and unrelated to hemophilia.¹⁸ Thirty-five percent of patients in the study felt that hemophilia had influenced their son's relationship with them, 46% felt it influenced his relationship with friends at school, and 25% said it made him feel isolated at school.¹¹

Direct Costs

There are several variables that make estimating the cost of care for hemophilia challenging, including the different types of hemophilia, disease severity, frequency of bleeding episodes, presence of inhibitors, type and frequency of treatment, and payer source (private insurance vs Medicare).²¹ Published estimates suggest that mean healthcare costs for patients with hemophilia in the United States reach upward of \$140,000 per year in the absence of inhibitors.^{22,23} Based on 2010 Medicare spending, treatments for hemophilia are the most costly drug average per beneficiary.²⁴

Data from 2002 to 2008 were collected through the Market-Scan Commercial and Medicare Research Databases to estimate mean and median medical expenditures during 2008 of 1164 males with hemophilia enrolled in employer-sponsored insurance plans. Thirty-three percent of the patients had at least 1 emergency department (ED) visit during the 11-month enrollment period, with an average of 2.8 admissions. Fourteen percent of patients had at least 1 hospital admission during the enrollment period, with an average of 1.4 admissions (Table 1²³).²² The overall annual average cost per patient for males with hemophilia was \$155,136 (median \$73,548), with higher

costs for those with hemophilia A (\$162,054 [median \$78,598]) than those with hemophilia B (\$127,194 [median \$55,220]; $P = .06$) (Figure 2^{22,23}).^{22,23} Eighty percent of the patients included in the final analysis had hemophilia A.²²

Using the same database, the cases of 435 males with hemophilia who were enrolled in Medicaid for at least 11 months between 2004 and 2008 were identified.²³ About one-third of all patients with hemophilia in the United States are covered through their state's Medicaid program,²¹ and most with hemophilia qualify based on disability. In the Medicaid population, the average expenditure in 2008 was \$142,987 (median \$46,737) per patient, similar to patients in the employer-sponsored insurance group. The incidence of admissions to a hospital and visits to the ED were significantly higher for patients in the Medicaid group than for patients covered by an employer-sponsored insurance program (Table 1²³).²³

Lifelong treatment with factor-replacement therapy, either as prophylaxis or as acute or on-demand therapy, is the mainstay of hemophilia management. In fact, spending on factor replacement therapy makes up over 80% of the total direct expenditures for patients with hemophilia A and B.²¹⁻²³ Similar results were seen in a broader cost analysis, where data were collected from the PharMetrics Patient-Centric database, which was derived from at least 73 US health plans, covering more than 43 million beneficiaries.¹⁴ The annualized costs, in 2004 dollars, was similar to other studies discussed,^{22,23} with anti-hemophilic medication accounting for more than 80% of the annual cost of treatment, even in patients without inhibitors (Figure 3¹⁴).¹⁴

Treatment-related costs are often the focus of attention because of their significant burden. However, inpatient hospitalization for hemophilia care can also have a significant financial impact. Average inpatient costs for patients with hemophilia A are more than 9 times greater than for the average insured member without hemophilia (Table 2²⁵). Average annual non-drug claims for non-hemophilia patients were \$1065 for inpatient services and \$2394 for outpatient services. Comparatively, claims for patients with hemophilia A were \$9661 and \$7433, respectively. Similar results were seen for patients covered by Medicaid.²⁵

The Hemophilia Utilization Group Study, an analysis examining the annual utilization and cost of hemophilia-related healthcare services, found that patient clinical characteristics and clinician practices predominantly drove the costs of care in hemophilia and that patients with severe arthropathy had greater healthcare

costs.²⁶ Treatment-related costs vary substantially based on disease-related complications, such as the presence of inhibitors or HIV or HCV.^{22,23} Costs also differ when treatment is given on an on-demand basis versus as prophylaxis.¹⁴

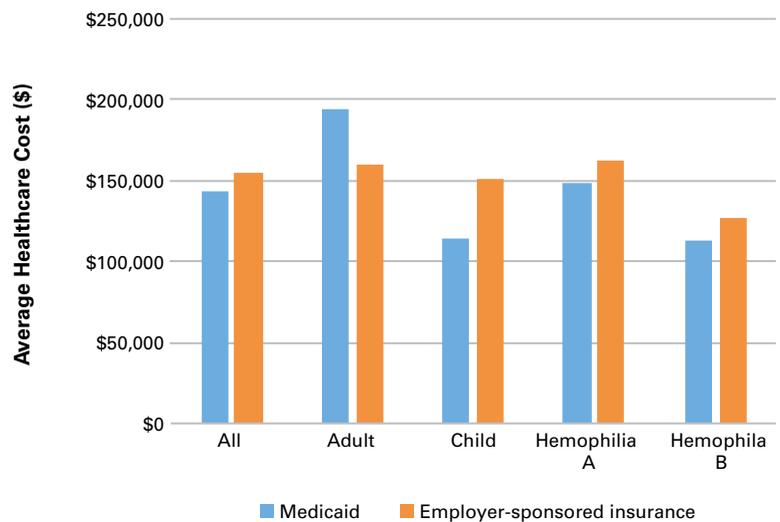
Cost of Complications

Costs rise substantially for patients with complications, such as HIV seropositivity, arthropathy, and/or development of inhibitors.^{21,23} Some estimates claim treatment costs as high as \$1 million per year for these patients.²¹ The majority of these treatment costs are attributed to the cost of clotting-factor concentrates.¹⁴ Coinfection with HIV and HCV is associated with significantly greater component costs for clotting-factor concentrates, prescription drugs, and inpatient and outpatient services. Coinfection results in a 59% increase in total annual medical costs (95% CI, 34.8%-82.9%).¹⁴ Within the employer-sponsored insurance population in the study, about one-third were infected with HIV or HCV, resulting in 1.5-times higher mean expenditures than with adults with hemophilia without blood-borne viral infections.²² The treatment costs for patients with blood-borne viral infections in the Medicaid population were the same as in the general hemophilia population, but the median was 1.6 times higher.²³

Costs increase even more when patients develop inhibitors, which affect 25% to 30% of patients with severe hemophilia A and 1% to 5% with hemophilia B.²⁷ Although treatments (high-dose clotting-factor concentrates, bypassing agents, immune-tolerance induction therapy) do exist for patients with inhibitors, the economic burden associated with the care can be staggering. Patients with hemophilia who develop inhibitors are twice as likely to be hospitalized for a bleeding complication, and treatment costs associated with inhibitors can be 5 times greater than for those without inhibitors.^{22,23,28}

Among patients with employer-sponsored insurance in the study, adults with an inhibitor were more likely to use clotting-factor concentrates (100% vs 74%; $P < .01$), more likely to visit the ED (63% vs 28%, $P < .01$), and more likely to require inpatient services (31% vs 12%, $P < .05$) than those without an inhibitor. Overall, the costs were 5 times higher for adults with an inhibitor than for those without (mean cost: \$697,000 vs \$144,000, respectively; median costs: \$330,835 vs \$73,321, respectively).²² Within

■ **Figure 2. Average Annual Healthcare Cost of Males With Hemophilia, 2008^{22,23}**



the Medicaid population, the average costs for males with hemophilia A and an inhibitor were 3.6 times higher than those for individuals without an inhibitor. The majority of expenditures were attributable to clotting-factor concentrates, with or without bypassing agents. Clotting-factor concentrates accounted for 64% of total mean costs for patients with an inhibitor (\$287,245) compared with 86% for those without an inhibitor (\$106,807).²³

Optimizing Outcomes

Treatment of hemophilia accounts for 80% to more than 85% of the overall cost of treatment. Study results have shown that clotting-factor concentrates make up 86% to 92% of total direct costs in patients without inhibitors.^{23,29} The high cost of hemophilia poses a definite barrier to patient access. A 2011 survey administered to patients/caregivers and healthcare professionals (HCPs) found that 54% of patients/caregivers and 81% of HCPs felt the economic downturn negatively impacted hemophilia care.³⁰ Most patients made treatment decisions, including modifying treatment and skipping doses and clinical visits, based on their financial situation. HCPs also made decisions based on financial restraints, including delaying elective surgeries, delaying initiation of prophylaxis, and switching to lower-priced treatment options.

Fortunately, healthcare reforms have helped change this trend. Twenty-two percent of patients and 58% of HCPs indicated that they expect to initiate treatment decisions they had previously delayed because of the greater affordability resulting from the elimination of

Table 1. Healthcare Utilization by Type of Payer, 2008²³

	Medicaid	Employer-sponsored Insurance	P
Total male patients	435	1164	
No. of patients with admission (%)	95 (22%)	164 (14%)	<.01
No. of patients with an emergency department visit (%)	224 (51%)	379 (33%)	<.01

lifetime caps. This turn in healthcare reform is perceived as positive for the treatment of hemophilia and may lead to more optimal treatment behaviors.³⁰ Looking at long-term goals for hemophilia is also critical to ensuring long-term cost-effectiveness over short-term cost savings.

Prophylaxis is recognized as the standard of care for the treatment of patients with severe hemophilia. The World Federation of Hemophilia recommends starting primary prophylaxis before the second clinically evident large joint bleed, and before 3 years of age, to prevent future bleeding episodes and the resulting complications.¹ Recommendations such as these, along with vast clinical trial data demonstrating the long-term effectiveness and superiority of prophylaxis over on-demand use, have shifted the debate from whether to use prophylaxis to optimize strategies for cost-effective use.³¹⁻³³ Although this may result in increased costs in the short term, a vast body of clinical trial data has demonstrated the long-term effectiveness of prophylaxis over on-demand treatment in patients with hemophilia—preventing conditions leading to severe or permanent impairment, improving clinical outcomes (preventing bleeding episodes, minimizing articular damage), and reducing long-term total costs compared with on-demand treatment.¹⁶

Cost-Effectiveness of Prophylaxis

Data from short-term analyses of 1 year of healthcare utilization and 2 years of clotting-factor concentrates dispensing records of patients with hemophilia A in the United States showed that the use of prophylaxis in patients with severe hemophilia significantly reduced the numbers of ED visits and bleeding episodes compared with on-demand treatment.²⁹ The cost of treatment, as expected, was higher for prophylaxis use. The mean direct medical costs for patients with severe hemophilia were \$184,518 for those receiving on-demand treatment and \$292,525 for those receiving prophylactic treatment (*P* = .009). Clotting factor accounted for 92% of these costs (\$170,037 and \$289,172, respectively). However, other direct costs were lower for patients receiving prophylaxis (\$3353) than

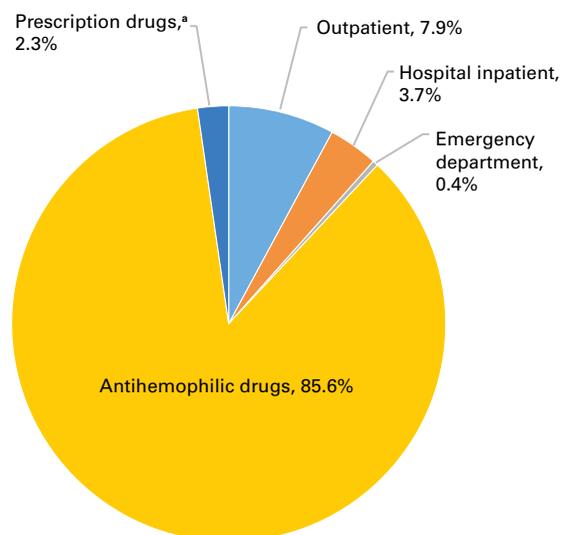
for on-demand treatment (\$14,481), as were indirect costs (\$8867 vs \$16,952, respectively). Compared with on-demand treatment, patients receiving prophylaxis had fewer ED visits (1.0 vs 0.4), fewer hospitalizations (0.4 vs 0.2), shorter length of hospital stay (7.8 vs 3.9), and fewer bleeding episodes (19.6 vs 9.4, *P* <.05).²⁹ The reduction in bleeding episodes is especially important because it indicates

the potential reduction in long-term repercussions of the disease, namely, hemophilic arthropathy.¹⁶ These results are only from a short-term perspective (1 to 2 years).²⁹

Prophylaxis has also been shown to be beneficial in decreasing potential long-term disability and adverse outcomes. In a 6-year longitudinal uncontrolled study, the bleeding episodes, X-ray exams, and treatment regimens of patients younger than 21 years with severe hemophilia A were analyzed.³⁴ The results showed that high doses of FVIII did not necessarily result in improved orthopedic outcomes. However, full-time prophylaxis significantly reduced the rate at which joints deteriorated, both on physical (*P* = .02) and X-ray examination (*P* ≤.001). Patients on prophylaxis also had significantly fewer days lost from work or school, as well as fewer days spent in a hospital (*P* ≤.01).

Cost-effectiveness of prophylaxis is also an important issue in managed care practice. The use of primary prophylaxis

Figure 3. Annualized Healthcare Cost per Patient With Hemophilia (January 1997-April 2004)¹⁴



Outpatient, inpatient, and emergency department costs were classified based on place of service codes.
^aPrescription drugs, excluding hemophilia drugs.

Table 2. Average Annual Healthcare Costs²⁵

	Commercially Insured			Medicaid		
	Non-hemophilia Patient ^a	Hemophilia A	Hemophilia B	Non-hemophilia Patient ^a	Hemophilia A	Hemophilia B
Inpatient costs	\$1065	\$9661	\$5384	\$1488	\$13,900	\$24,009
Outpatient costs	\$2394	\$7433	\$7062	\$1217	\$3905	\$11,033

^aCosts for non-hemophilia patients may include drug costs.

laxis with FVIII concentrate versus secondary prophylaxis, treatment on demand, and a “hybrid” form of therapy (primary prophylaxis followed by on-demand treatment) was evaluated in patients with severe hemophilia A in a study by Colombo and colleagues.³⁵ Performed with a Markov model using different sources of clinical and cost-utility data, the results demonstrated that the incremental costs per quality-adjusted life years (QALY) gained for patients receiving primary and secondary prophylaxis were substantial (€40,229 to €40,236) versus on-demand treatment. Another study assessing cost-effectiveness of primary prophylaxis in the United Kingdom found that patients on prophylactic treatment could expect 55.9 QALYs, compared with 41.1 QALYs for patients with on-demand treatment. However, the associated costs were sensitive to the type of hemophilia, amount of factor used, and the price per unit of the factor.³⁶

Optimizing Prophylaxis—Individualized Care

The rationale for prophylaxis is based on studies demonstrating that patients with moderate hemophilia (clotting-factor activity level >1 IU/dL) rarely experienced episodes of spontaneous bleeding. These patients also had better preservation of joint function.¹ This observation led to the theory that artificial elevation of plasma levels of specific factors could change the phenotype of a severe patient to that of a moderate patient. However, a variety of aspects influence bleeding patterns. These include the pharmacokinetic profile of the patient, musculoskeletal status of the underlying joint at the time prophylaxis is initiated, potency of the dose and the factor product, and the relationships of these aspects to each other.^{16,37} As such, it is important that treatment be individualized for each patient. Higher doses of factor-replacement product may not harm the patient, but when lower doses are optimal, excess doses will result in unnecessary costs.

The presence of treatment-induced inhibitors are significant variables in cost-utility models, and ensuring optimal pharmacokinetic dosing is the most valuable tool for cost-effective therapy.³⁸ Assay management by way of tighter

pharmacy standards is one tool that can enable cost-effective factor prescribing. Utilization management programs that encourage frequent HCP–patient interaction can also help. These programs ensure that prophylactic treatments are reassessed and adjusted based on each patient’s individual needs and circumstances. The frequent interaction also enables greater patient education regarding the need for and importance of treatment adherence.¹⁶

Optimizing Care

Ensuring optimal cost-effective care in hemophilia has never been more important. The number of patients with hemophilia who are covered under Medicaid health plans is expected to rise.²¹ This results from reforms in the healthcare system, including expansion of benefits, and the eligibility of current Medicaid members with hemophilia who qualify under disability eligibility rules. A larger number of states also are utilizing the services of health plans to cover their disabled and dual-eligible populations. Medicaid health plans have better care-coordination programs and quality-reporting systems than fee-for-service Medicaid. However, the high costs of treating hemophilia may present a challenge to health plans.

Key drivers in ensuring quality and cost-effective care include optimizing pharmacy management and ensuring patient involvement. Optimizing pharmacy management is crucial to cost management in hemophilia care. Pharmacies need to ensure treatment access, in a timely manner, of safe and effective products and supplies so that patients can adhere to their treatment regimen. Patient involvement entails education on recognizing the signs and symptoms of a bleed, home infusion, care management, and treatment adherence, which can ensure that patients and their caregivers are active participants in their care and take responsibility for management decisions.²¹

Conclusions

Although a rare condition, congenital hemophilia places a significant economic burden on healthcare payers, patients/caregivers, and society. It results in not only

direct costs from hospitalizations, outpatient visits, and drug treatments, but also indirect costs from diminished work productivity and absenteeism. Hemophilia also has intangible costs, including reduced QoL, pain and suffering of the individual and family, and the emotional and physical toll on the patient and caregivers.

The significant evolution of treatment patterns in hemophilia have transformed it from a fatal disease into a chronic, well-managed condition. This can be seen in the advances in therapeutic agents and the increased use of prophylaxis treatment in persons with hemophilia. However, complications, such as inhibitors, have added to the complexity and cost of its management, as well as the complexity of individualized treatment, especially for patients with inhibitors. This has resulted in a critical need to understand the utilization of health resources in the treatment of hemophilia. Patient education and factor management are key to minimizing waste, ensuring optimal therapy and management, and improving outcomes.

As both the clinical and economic complexities surrounding hemophilia prophylaxis can be significant, it is imperative that managed care pharmacists, clinicians, and providers be aware of the complications of hemophilia, the role of prophylaxis, and the health-care implications and costs surrounding the disease and its prophylactic management. Cooperation among the key stakeholders—healthcare professionals, patients and their caregivers, and managed care professionals—will help provide individualized treatment strategies for patients with hemophilia, strategies designed to prevent complications and optimize clinical and economic outcomes while enhancing patient QoL.

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