ECONOMIC BURDEN OF HEMATOLOGICAL DISEASES AND COST-SAVINGS POTENTIAL OF NOVEL GENE THERAPIES

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Executive Summary

Over the last several years, the FDA has approved several innovative and unprecedented cell and gene therapies that treat diseases with high unmet need. The core science behind these therapies is to manipulate, in some manner, an individual’s cells or genes to treat disease. In particular, cell therapy uses genetically modified cells from the patient or a donor and reinserts them into the patient to treat the underlying cause of the disease. With gene therapy, the goal is to add to, silence or alter the gene in the patient that leads to disease. Cell and gene therapies are often discussed together as both involve modifying an individual’s genetic material at the molecular level.

While only a handful of cell and gene therapies have been approved to date, hundreds more are currently in development, several of which may be launched over the next few years, and many of which address hematological diseases. Hematological diseases are comprised of a range of blood disorders, which are often rare and can have a significant impact on patient quality of life and are associated with high healthcare resource utilization. Two of these blood disorders in particular are marked by tremendous burden on patients who require chronic life-long treatment as well as associated economic burden: hemophilia A and beta thalassemia.

The significant burden on patients associated with these two indications is substantial due to the need for invasive and repetitive treatments. Most patients are resigned to chronic treatment to manage their disease with blood transfusions and infusions, factor replacement therapy, and iron chelation therapy. In addition, patients experience significant intangible burdens of disease, including the emotional toll of missed opportunities, inevitability of disease progression, and reliance on caregivers. Hemophilia A and beta thalassemia are also diagnosed in childhood and pose a number of challenges for patients throughout their lifetime.

Commensurate with significant clinical and treatment burden, the economic burden of these diseases is also substantial. The primary cost drivers across indications are treatment and administration costs, and then hospitalizations and ER visits. While direct medical costs represent the greatest portion of costs, indirect costs can also be substantial in adding to total economic burden. These indirect costs are
due to missed days of school and work (“absenteeism”) for patients and their caregivers, respectively, and reduced productivity while at work (“presenteeism”) from pain and fatigue.

Several novel gene therapies are currently in late-stage development for the two hematological indications examined here. Initial data from clinical trials have demonstrated effectiveness in reducing transfusion burden and bleeding rates in hemophilia A and beta thalassemia. A key focus of this research was to estimate how corresponding direct medical and indirect costs can be expected to decline with the introduction of novel gene therapies.

Our analysis found hemophilia A is associated with approximately $441,000 - $1.94 million in total per patient direct and indirect costs over five years, depending on disease severity. Gene therapies have demonstrated in long term clinical trials a 96% reduction in bleeding rates.\textsuperscript{1,2} Based on these findings, we estimate gene therapies could result in $233,000-$1.7 million in per-patient savings over five years, depending on disease severity, due to avoided factor replacement therapy costs. Similarly, reduction in disease burden for hemophilia A patients was also associated with a reduction in per patient indirect costs of $43,000 - $101,000, depending on disease severity, due to avoided missed work for both patients and caregivers over the same period. Collectively, these reductions in direct medical and indirect hemophilia A costs represent a 63%-90% reduction in total per patient costs over five years.

For beta thalassemia patients, our analysis found the disease is associated with $766,000 in total per patient direct and indirect costs over five years. Seventy-five percent of patients in long term clinical trials were able to achieve transfusion independence, while others were able to significantly reduce treatment burden.\textsuperscript{3-5} Based on these findings, we estimate gene therapies could reduce per patient costs by about 41% over five years resulting in a $325,000 in direct and indirect cost savings due to avoided blood transfusion therapy and iron chelation therapy as well as savings from avoided missed work for patients and caregivers. Collectively, these reductions in direct medical and indirect beta thalassemia costs represent a 41% reduction in total per patient costs over five years.

These findings illustrate and underscore the tremendous potential of the cell and gene therapies currently in development to treat a wide range of diseases, by ameliorating significant clinical and
economic burden through reduction in healthcare utilization and avoidances of costs associated with lost productivity for patients and caregivers.

Research Context and Objectives

The primary objective of this project was to inform the dialogue around the economic value of novel cell and gene therapies, with a specific focus on hemophilia A and beta thalassemia. These hematology diseases were selected due to the high treatment and economic burden with which they are associated; additionally, each has several promising cell or gene therapies in the pipeline that may address key unmet needs. This report seeks to characterize the per-patient economic burden and to estimate the cost-savings potential of late-stage investigational novel cell and gene therapies for hemophilia A and beta thalassemia over a 5-year period. We quantified the cost-savings based on a preponderance of clinical data.

Methods

The findings in each chapter were informed by a review of peer-reviewed studies that quantified the economic burden associated with the disease of interest. We also explored the relevant grey literature, such as market research reports and information published by trade associations and patient advocacy groups. In each of the economic burden assessments, direct medical costs were adjusted to 2020 USD based on the medical care component of the consumer price index (CPI). All non-medical or indirect costs were adjusted to 2020 USD based on the standard CPI. Indirect costs were estimated using existing studies, where available, that reported missed days of school and work. Costs attributed to reduced productivity assumed an annual gross income of $63,080 per patient or patient caregiver, based on the US 2020 gross national income (GNI).

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6 Studies were identified through PubMed and Google Scholar search with the following search terms: “hemophilia A”, “beta thalassemia”, “multiple myeloma”, “sickle cell disease”, “cost of illness”, “indirect cost”, “productivity”, and by cross-check against studies considered in review articles.
Hemophilia A

Hemophilia A Overview

Disease Background

Hemophilia is a rare inherited blood disorder presenting in infancy in which blood cannot clot normally at the site of a wound or injury, leading to uncontrollable bleeding episodes, both externally and internally. Hemophilia A is the most common type of hemophilia and is caused by lack of clotting factor VIII. A diagnosis is made from a series of lab tests evaluating hemostasis and factor VIII activity levels, and disease severity is determined based on the level of factor VIII depletion. Of the estimated 20,000 individuals in the US who suffer from hemophilia A, nearly 60% experience severe disease, while 40% experience mild or moderate disease. Long-term, serious complications of hemophilia A include bleeding into the joints, muscles, brain, and other internal organs.7–9

Clinical Management and Unmet Needs

Hemophilia A treatment burden is substantial, often necessitating lifelong factor replacement therapy to substitute the clotting factor that patients lack. Hemophilia A patients range in terms of disease severity and treatment that is required for management of the disease. Patients with mild, moderate, and severe disease each require increasing amounts of factor therapy, which is time-consuming and can result in poor compliance, particularly over time. The majority of severe patients receive prophylactic factor therapy, which is intended to be preventative and is therefore infused at regular intervals independent of bleeding episodes either at home or at an infusion center multiple times a week. Though it is recommended that severe patients receive prophylactic therapy, compliance can be burdensome and challenging which can lead some patients to ultimately rely on episodic therapy as needed. As a result, approximately 70% of severe patients receive prophylactic therapy and approximately 30% forego prophylactic therapy relying on episodic therapy to manage bleeding episodes. Mild and moderate patients typically receive episodic therapy, which is administered only when a patient is triggered by a bleeding episode, though moderate patients who are more frequent bleeders may receive prophylactic therapy (Figure 1).
Over time, continued treatment with factor replacement therapy can cause patients to develop a resistance to the therapy. Approximately 30% of hemophilia A patients develop such a resistance, or inhibitors, to factor replacement therapy, requiring treatment with bypassing agents that are substantially more expensive than factor replacement therapy.\(^8\)

Treatment with factor replacement therapy is a lifelong burden which requires frequent visits to infusion centers or regular home-based infusion therapy, significantly impacting patients’ daily lives.\(^{10}\) School and workplace absenteeism is among the greatest hardship: patients reported missing 5-15 days of school and 4-19 days of work annually due to hemophilia-related treatments or events.\(^{11}\) Despite the burden of factor replacement therapy, there are currently no other treatment options and no cure. Less burdensome and more efficacious treatments are therefore in high demand. Several gene therapies in late-stage development aim to address these needs. One gene therapy, currently in pre-registration with the FDA, has shown promise of reducing annual bleeding rates in its Phase II and III studies.\(^1\) Additionally, two other candidates have demonstrated in Phase II an ability to halt the decline of factor VIII levels; both of these candidates are now in Phase III.\(^{12,13}\)
Findings

Hemophilia A Total Economic Burden

On a per-patient basis, the economic burden of Hemophilia A is substantial. Severe patient costs were calculated using a weighted average of the patient populations receiving prophylactic vs. episodic treatment (70% and 30%, respectively). Severe Hemophilia A patients incur total annual direct medical and indirect costs of $349,000, largely driven by the costs of receiving factor replacement therapy (Figure 2).

Mild and moderate patient costs were calculated using a weighted average of the patient population with mild vs. moderate disease (25% and 15%, respectively). Costs account for the small portion of moderate patients who may be receiving prophylactic therapy today, though largely these patients only receive episodic therapy. Compared to severe patients, those with mild/moderate disease incur more limited total annual costs due to less use of factor replacement therapy, amounting to $88,000 per patient (Figure 2).

Because there are at present no investigative cell or gene therapies in the pipeline that address the 30% of patients who develop inhibitors to factor replacement therapy, these patients were excluded from this analysis.

Direct Medical Costs
Direct medical costs comprise the majority of costs incurred by hemophilia A patients, driven by the need for frequent factor replacement therapy. However, given cost of factor replacement therapy accounts for 91% of direct medical costs for severe patients and 62% of direct costs for mild/moderate patients, assumptions about the frequency of treatment lead to important variation in reported costs.

From a 2015 study of US administrative claims, Zhou et al. report annual direct medical costs of $293,000 for severe patients who receive frequent prophylactic administration of factor VIII, amounting to $377,000 when extrapolated to 2020 dollars. In contrast, severe patients who rely on episodic therapy administer comparatively less factor VIII due to poor compliance and incur direct medical costs of $185,000, or $238,000 PPPY in 2020 dollars, though this population is a significantly smaller proportion of severe patients (~30% of severe patients receive episodic treatment only, see Figure 1). However, more recent studies estimate much higher direct medical costs for prophylactically-treated patients. For example, Cook et al. estimated direct medical costs of $725,000 PPPY based on a Markov model that assumed factor treatment three times per week at $4,500 per dose. The discrepancy in these direct medical costs may be due to variation in real-world use of prophylactic treatment. While three doses per week is considered the standard of care for prophylactically treated patients, in practice, patients receive fewer infusions per week due to the burden and factor costs. Apart from factor replacement therapy, 10% of direct medical costs for severe patients are due to non-treatment-related care such as outpatient and inpatient visits as well as other pharmaceutical agents used to treat disease complications.

Mild/moderate patients rely on episodic treatment with factor replacement therapy to manage bleeding episodes and to a lesser extent moderate patients receive prophylactic therapy. Direct medical costs for patients with mild and moderate hemophilia A are far lower due to less utilization of factor VII replacement therapy, estimated at $79,000 PPPY. Differing from severe patients, 40% of direct medical costs for mild and moderate patients are due to non-treatment-related care, as factor replacement therapy makes up less of the overall cost. Zhou et al. found that mild and moderate patients experience 4-9 bleeding episodes per year and require minimal factor VIII.

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Dosing dependent on patient weight. Dosing estimate here is based on an average patient weight of 70kg.
Indirect Costs

Hemophilia A patients and caregivers also incur indirect costs from missed school and work days that are required to receive transfusions. Indirect costs range from $9,000-$14,000 annually for patients.\textsuperscript{11} These costs are higher for patients with more severe disease and for those who receive episodic treatment, since spontaneous bleeding events lead to unplanned transfusion and even more school and workplace absenteeism.

Intangible Costs

The intangible costs associated with hemophilia A are equally substantial but are not easily captured in traditional approaches to estimate disease burden. In general, patients and caregivers experience significant social and emotional instability from not knowing when the next bleeding event will occur. School-age children must forego certain activities including sports that could make them susceptible to a bleeding event. This, in turn, can make them feel ostracized or isolated. Children with hemophilia A are then required to miss days of school for their routine factor replacement treatments or because of a spontaneous bleeding event. Into adulthood, recurrent bleeding episodes can lead to joint disease and other painful complications, ultimately impacting activities of daily living and general well-being.\textsuperscript{11,18} If the full psychosocial impact on caregivers and patients were fully quantified, the hemophilia A cost burden and the associated value of new therapies would be even higher than what can be estimated today.

Moreover, the patients who require prophylactic treatment have the additional burden of needing to receive infusions either at home or at an infusion center multiple times a week. Likewise, the time-consuming and burdensome aspects of this reality means real world adherence to these guidelines often fall short, underscoring the daily challenges that chronic infusion therapy poses for these patients.\textsuperscript{11,18}

Potential Cost-Savings of a Gene Therapy for Hemophilia A

New gene therapies are expected to offer a 96% reduction in annualized bleeding rates (ABR).\textsuperscript{1,2} Given the large costs associated with the disease, the total cost-savings potential for the latest stage gene therapy in the hemophilia A pipeline is significant. Reduced expenses due to avoiding factor VIII
replacement therapy are the primary driver for decreased direct medical costs. Three-year follow-up data for a Phase II study of this gene therapy showed a 96% reduction in annualized bleeding rates (ABR) in patients with severe hemophilia.\textsuperscript{1,2} Since bleeding rates are directly proportional with factor VIII infusions, reductions in ABR can serve as a proxy for reduced factor therapy.

In order to estimate the potential per-patient reduction in cost over five years with gene therapy, we summed the total direct and indirect costs from Figure 2 for mild/moderate patients and severe patients over this period, respectively. Today, hemophilia A is associated with approximately $441,000 to $1.94MM in total costs per patient over five years, depending on disease severity. Severe patients treated prophylactically represent the most costly population to treat, averaging \textasciitilde $1.94MM in direct medical and indirect costs over a five year period. Episodically-treated severe patients amount to \textasciitilde $1.3MM in direct and indirect costs over the same period. The 5-year average direct medical and indirect costs for severe patients weighted relative to the proportion of patients treated prophylactically versus episodically is $1.75MM. The weighted average for mild/moderate patients primarily receiving episodic therapy is $441,000.

Based on the Phase II study noted above, we estimate that gene therapy can reduce factor replacement and commensurate costs over a five-year timeframe by as much as 96% across patients with various disease severities and treatment regimens. This reduction represents direct medical cost savings of $1.7MM for prophylactically treated severe patients, $960,000 in episodically-treated severe patients, and $233,000 for a mild/moderate patient over a five-year timeframe.\textsuperscript{a} (Figure 3).

\textsuperscript{a} While this trial studied the effects in a severe population only, we assume commensurate reductions in factor replacement therapy for mild and moderate populations as well.
Similarly, patients who receive the gene therapy are projected to miss fewer school and work days due to reduced administration of factor replacement therapy, with some patients no longer needing factor replacement therapy at all. We therefore estimate that indirect costs due to loss of productivity for these patients will decrease correspondingly by the same percentage, representing $43,000, $101,000, and $53,000 of indirect cost savings over five years for mild/moderate patients, episodically-treated severe patients, and prophylactically-treated severe patients, respectively.

Collectively, these direct medical and indirect reductions in costs represent about a 63%-90% reduction in total hemophilia A patient costs, depending on disease severity, over five years.

**Key Assumptions and Limitations**

Our cost-savings and burden of illness estimates consider some key assumptions and are also subject to broader limitations in the available data. First, our results are derived principally from a 2015 claims analysis study by Zhou et al. We elected not to include the more recent data from Cook et al., since those estimates are modeled and assume a hypothetical patient population of prophylactically-treated severe patients that receives factory therapy three times per week, per the guidelines. In light of the literature about the burden of factor infusions, we reasoned it would be more appropriate to consider more conservative estimates, recognizing we could be underestimating the full impact of these therapies. We assume perfect patient compliance with three times weekly therapy, however, the cost-savings potential for prophylactically-treated severe hemophilia A patients could be twice as great, reaching $3.5MM over a five-year period.

Second, few studies report costs by patient severity and type of treatment, but rather group all hemophilia A patients together. The generalizations in these studies do not accurately depict disease burden by patient population and may mischaracterize the level of burden experienced by some patient segments. Third, most available publications based on empirical data are older and do not reflect the evolution in treatments and costs associated with the disease. More recent real-world
studies are needed to better estimate the medical resource use and costs associated with hemophilia A. Finally, few studies have been published that estimate the indirect costs for hemophilia A patients, such as productivity losses, or intangible burdens of disease. Dedicated research is warranted to fully quantify and characterize the pain, suffering, and reduced quality of life that hemophilia A patients and their caregivers experience.
Beta Thalassemia

**Beta Thalassemia Overview**

**Disease Background**

Beta thalassemia is a rare and inherited form of sickle cell disease that affects red blood cells by reducing the production of hemoglobin, resulting in a lack of oxygen in many parts of the body. The genetic component of beta thalassemia is caused by mutations in one or both genes coding the beta chains in hemoglobin. Severe patients who lack appropriate levels of functional hemoglobin experience anemia, but mild patients remain mostly asymptomatic.\(^{19}\)

While beta thalassemia is a fairly common blood disorder worldwide, with highest prevalence in patients from Mediterranean countries, North Africa, the Middle East, and Asia, there are only an estimated 2,000 thalassemia patients living in the United States.\(^{20}\) Patients are either diagnosed at birth via newborn screening or within the first year of life after onset of symptoms. Diagnosed patients are then referred to hematologists for continued disease management.\(^{21}\)

**Clinical Management and Unmet Needs**

Around 40-50% of patients suffer from mild forms of the disease and may only require minimal treatment to control the disease. On the other hand, patients with more severe anemia will often require extensive medical intervention (*Figure 4*).
Severe patients with debilitating anemia may be eligible to receive a curative stem cell transplant, but less than 30% of patients have suitable donors, and even fewer actually receive a transplant due to high costs or clinical risks. It is estimated that fewer than 10% of beta thalassemia patients ultimately receive a stem cell transplant. Instead, most severe patients will be treated through a regimen of lifelong blood transfusions to maintain levels of functional hemoglobin. On average, patients in the US will require 17 transfusions a year, which are typically performed at outpatient or hospital transfusion centers and last multiple hours per procedure.

Unfortunately, these regular transfusions can also lead to various side effects, the most notable of which is iron overload. Each unit of transfused blood contains approximately 200 to 250 mg of excess iron, for which the body has no physiologic process of removal. Accumulation of this excess iron can be toxic to many organs in the body. To counter iron overload, transfusion-dependent beta thalassemia patients will often need to take iron chelator therapies on a chronic basis. These therapies are either infused overnight, approximately 5 times a week, or taken orally.

In November 2019, the FDA approved a first-in-class erythroid (red blood cell) maturation agent providing a new therapy option for the treatment of anemia in transfusion-dependent thalassemia patients. This therapy has been shown to reduce transfusion burden by approximately half and...
reduce ferritin levels (a measure of iron in the blood) by approximately 350 ng/mL in responders. Uptake of this therapy is currently estimated to be minimal given the recent approval date, although use may reach approximately 25% of transfusion-dependent patients within five years, according to financial analyst forecasts. Given relatively low anticipated uptake and a lack of published data on the economic burden it may impose, the impact of this new therapy was omitted from this analysis.

Beta thalassemia patients continue to face many challenges in managing their disease. Given that the vast majority of patients are unable to receive curative stem cell transplants due to lack of a suitable donor, curative therapies remain the aspirational treatment for all patients. In addition, the need for lifelong transfusions and iron chelation is cumbersome, costly, and can lead to complications. Therapies that alleviate the need for transfusions and iron chelation could thereby improve quality of life for beta thalassemia patients and significantly reduce costs.

In an effort to meet these needs, several pipeline assets are in late-stage development, with seven assets currently in Phase II, one in Phase III, and one in pre-registration. The most advanced asset has recently launched in the EU and is in pre-registration with the FDA.

Findings

Beta Thalassemia Total Economic Burden

Beta thalassemia results in a substantial economic burden to the healthcare system and society as a whole. Total direct medical and indirect costs are $139,000 per year for a typical transfusion-dependent patient (Figure 5). The vast majority of this economic burden is due to direct medical costs arising from transfusions, iron chelation, medical visits, and lab tests, which together contribute about $135,000 in costs per year (97% of total costs). Indirect costs due to missed time from work for transfusion therapy are comparatively lower at $4,000 PPPY (3% of total costs).
Direct Medical Costs

Beta thalassemia is a costly disease to manage. For our ‘base case’ typical transfusion-dependent beta thalassemia patient, direct medical costs amount to about 97% of total costs, or $135,000 per year.\(^{24}\) The primary driver is iron chelation therapy and administration, which costs $68,000 PPPY or just over half of total costs. Blood transfusions also contribute highly to the total cost burden, responsible for $44,000 PPPY or roughly a third of direct medical costs. Additional expenses are relatively minor in comparison to iron chelation and transfusion costs. MRI screenings (to examine liver iron concentrations) and bone mineral density tests (to monitor bone health) together cost approximately $3,000 PPPY. Additional lab and medical fees – such as those for comorbid conditions, specialty visits, or surgeries – contribute $17,000 PPPY in costs. Finally, additional supportive medications cost $4,000 PPPY.

Indirect Costs

Indirect costs of beta thalassemia are comprised primarily of missed time from work due to transfusions. Assuming on average 17 missed days of work for a patient in the base case scenario, the indirect cost is estimated to be $4,000 per year.\(^{a}\) These costs are attributed to missed time for a

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\(^a\) Cost assumes daily productivity of $250 based on US GNI per capita ($63,080) according to World Bank and number of working days in a year (250).
caregiver caring for a pediatric patient or direct hours missed for an adult patient. Given that beta thalassemia patients achieve roughly equal levels of employment status to the general population, indirect costs from foregone or lost employment are assumed to be minimal.\textsuperscript{30} In addition, decreased productivity while at work due to disease burden (presenteeism) is also assumed to be minimal based on findings from a study in Italy that examined this dynamic.\textsuperscript{31}

**Intangible Costs**

Beta thalassemia can result in additional intangible costs for patients in the form of practical, emotional, and educational challenges. First, the need for regular transfusions can hinder the ability of patients to undertake long-term travel, which affects their quality of life.\textsuperscript{32} Second, some children have reported feeling ostracized by peers due to their condition, which affects their emotional well-being.\textsuperscript{33} Finally, transfusion-dependent children will often need to miss many days from school in order to receive transfusions or attend medical visits, which can pose learning difficulties.\textsuperscript{33}

*Potential Cost-Savings of a Gene Therapy in Beta Thalassemia*

In order to estimate potential reduction in cost over five years with gene therapy, we first summed the total direct and indirect costs from Figure 5 for a typical patient over this period to determine the current cost of standard of care. Accounting for healthcare-related inflation in the direct medical costs and standard rates of inflation for indirect costs, the typical beta thalassemia patient treated with standard of care will amount to $766,000 in total costs over five years.

There is significant cost-savings potential for the most advanced gene therapy in the beta thalassemia pipeline. Two long-term trials were considered in estimating the potential decrease in transfusion and iron chelation therapy costs. In these Phase I/II trials, 75% of patients were able to achieve transfusion independence while others were able to achieve partial independence with \textasciitilde53% reduction in transfusion burden.\textsuperscript{3–5} In addition, the vast majority of study participants were able to discontinue iron chelation for a portion of time before returning to regular iron chelation therapy. Other patients were able to discontinue iron chelation altogether and transition to much less costly therapeutic
phlebotomy in order to control iron levels.\textsuperscript{3,5,34,35a} Based on these studies, we collectively assume an average 81% reduction in transfusion burden and an average 32% decrease in need for iron chelation therapy for all patients treated with this gene therapy.

Proportionally applying the reductions in medical burden found in clinical trials with a gene therapy, a total of $325,000 could be alleviated after five years for a transfusion-dependent patient largely due to reduced transfusion burden. Of these savings, $196,000 would be due to a 81% reduction in blood transfusion therapy costs, $111,000 due to a 32% reduction in iron chelation therapy costs. Finally, patients on gene therapy are able to take less time off work for blood transfusions, with some patients no longer needing transfusions at all, significantly improving quality of life. Similar to the estimated 81% decrease in transfusion burden due to gene therapy, indirect costs for this patient population are expected to also decrease by the same percentage, representing $18,000 in productivity savings over five years (\textit{Figure 6}). Collectively, these direct medical and indirect reductions in costs represent about a 41% reduction in total beta thalassemia patient costs over five years.

\textit{Figure 6: Per-Patient Cost-Savings Potential of the Most Advanced Gene Therapy in Beta Thalassemia Pipeline Over Five Years.}

\textit{Note: The cost-savings analysis does not include the cost of gene therapy because these products are still investigational, and prices have not yet been determined. Standard of care assumes base case scenario without luspatercept.}

\textbf{Key Assumptions and Limitations}

\textsuperscript{a} Percentage decrease in iron chelation usage was calculated using a weighted average of patients who discontinued iron chelation (100% reduction, \textit{n}=3) and those who discontinued but restarted iron chelation (22% reduction, \textit{n}=19). Costs of therapeutic phlebotomy ($4,000) were bundled together with iron chelation costs.
Our cost estimates should be placed in the context of some key assumptions and broader limitations in the available data. First, our direct medical costs are derived from a single, recent US study. Second, our cost-savings analysis was only performed for the base case scenario of a transfusion-dependent patient not on red blood cell maturation therapy. This is because: 1) adoption of this new medicine is not expected to be high; 2) the data from the clinical trials for the most advanced gene therapy in the pipeline are only applicable to patients who were not previously on red blood cell maturation therapy, and; 3) this therapy was only recently launched and therefore lacks published data about the economic burden it may impose. Our cost estimates for these patients were therefore only a best effort, using various assumptions.

Third, we assumed that all study participants who resumed iron chelation therapy after use of gene therapy would incur the same iron chelation costs as prior to gene therapy. However, since use of gene therapy likely leads to decreased iron levels in many patients, actual usage of iron chelation post-treatment could be lower. This would imply even higher potential cost savings than estimated here. We also assumed a direct 1:1 relationship between reduction in transfusion burden and reduction in transfusion costs. However, since transfusion costs may be mostly due to administrative costs rather than the actual costs of transfused blood, our estimated cost savings in this category may be an overestimate. Finally, there is a dearth of data on the indirect costs of beta thalassemia in the US, with no studies from the last five years identified that calculate this cost. As such, additional research into both the direct and indirect costs of beta thalassemia would help to corroborate our findings.

**Conclusion**

For patients with hematologic conditions such as hemophilia A and beta thalassemia who must endure chronic treatment regimens that interfere with their daily life, a novel cell or gene therapy can offer significant promise. These therapies also offer the potential to reduce significant economic costs, including those that impact patients, the healthcare system, and society. The ability for these therapies to catalyze a seismic shift in both clinical and economic burden for patients with a wide range of costly and burdensome diseases cannot not be understated.
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