Potential Gene Therapies Hold Promise for Transforming the Trajectory of Many Blood Disorders and in Reducing Significant Treatment Burden and Costs

Patients with blood disorders face tremendous treatment burden, and the management of these conditions is associated with significant costs. Blood disorders often require lifelong treatment, involving routine drug infusions or blood transfusions to manage the condition and help prevent serious complications, which may involve emergency room visits, hospitalizations and other costly medical care. They can also be associated with frequent visits to physician offices or infusion centers, and patients with these disorders often experience debilitating pain, disability, reduced life expectancy and quality of life.

Because many blood disorders are caused by genetic abnormalities, gene therapies in development hold tremendous promise in offering long-term benefits or in some cases a cure for patients with these conditions. As a result, they offer to dramatically reduce existing treatment burden and costs. The blood disorders described here illustrate the role that gene therapies may play in transforming the trajectory of these burdensome diseases and in producing significant savings by potentially eliminating the costs associated with the current standard of care.

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HEMOPHILIA A

Hemophilia A is a rare genetic bleeding disorder characterized by insufficient levels of a blood protein called factor VIII, which the body needs for blood clotting. The disease is caused by a mutation in the F8 gene located on the X chromosome. About 400 babies are born with hemophilia A each year.[1,2]

With insufficient clotting factor, individuals with hemophilia A are at risk for painful and in severe cases life-threatening bleeding events, arising from minor injuries or even spontaneously without an obvious cause. Severe hemophilia A, especially, is associated with recurrent spontaneous bleeding and progressive joint damage, which can lead to functional impairment, disability, poor quality of life and loss of productivity and employment.[3,4] Individuals with the severe form account for approximately half of the hemophilia A population.[5]

The standard of care for many hemophilia A patients, particularly those with more severe disease, includes lifelong treatment with factor (FVIII) replacement therapy administered up to 2-3 times a week, or 100-150 times a year, to prevent dangerous bleeding events and preserve joint function.[6,7] More recently, a new type of prophylactic therapy has also become available, which may be self-administered less frequently.[8] Though many patients are well managed on available therapies, some continue to experience breakthrough bleeds, resulting in progressive, painful and irreversible joint damage which can have a negative impact on quality of life.[9,10]

As a result of the tremendous treatment burden and the costs associated with the current standard of care, the role of potential gene therapies in reducing this burden is substantial:

Average health care costs range between $650,065 - $759,661 annually for patients with hemophilia A treated prophylactically, with 96% of such costs attributed to factor replacement therapy.[11,12,13]

Gene therapies in the late stages of development for severe hemophilia A have demonstrated significant and sustained reductions in bleeding rates as well as an **almost complete reduction in factor replacement therapy utilization in the years following a one-time administration of therapy**.[14,15,16,17]

Gene therapies, therefore, have the potential to dramatically reduce or even eliminate the costs associated with routine factor replacement therapy, **leading to as much as $730,000 in savings the year following a single administration of gene therapy**.[18]

Likewise, the cost savings potential to the health care system of completely transforming the treatment paradigm for hemophilia A, with continued savings offered potentially over the course of a lifetime, is truly remarkable.

Beyond the impact to the health care system, as gene therapies can provide quality of life that had previously been lacking and reduce the need for missed work, patients may **earn as much as $9,500 more in income each year**, on average, primarily due to avoiding hemophilia-related underemployment and early retirement.[19,20]

HEMOPHILIA B

Hemophilia B, like hemophilia A, is a rare genetic bleeding disorder characterized by similar symptoms. However, hemophilia B is caused by insufficient levels of a blood protein called factor IX. The disease is caused by mutations in the F9 gene on the X chromosome and is less prevalent than Hemophilia A. About 100 babies are born each year with hemophilia B.[21] [22]

Like hemophilia A, hemophilia B patients often require life-long prophylactic infusions of factor replacement therapy to replace or supplement low levels of IX blood-clotting factor. The goal of regular factor replacement infusions is to prevent life-threatening bleeding events and to reduce joint bleeding events and preserve joint function. Infusions are generally administered 2-3 times a week, or 100-150 times a year,[23] though some newer factor replacement therapy products offer to extend the frequency of infusion to once every 1-2 weeks.[24]

As a result of the tremendous burden of the disease and the costs associated with the current standard of care, the role of potential gene therapies in reducing this burden is substantial:

Average annual health care costs are $614,886 for patients with severe hemophilia B treated prophylactically, with more than 99% of those costs driven by blood replacement therapy.[25] [26]

Gene therapies in the late stages of development for severe and moderately severe hemophilia B have demonstrated significant and sustained reductions in bleeding rates as well as an **almost complete reduction in factor replacement therapy utilization in the years following a one-time administration of therapy**.[27] [28]

Gene therapies, therefore, have the potential to dramatically reduce or even eliminate the costs associated with routine factor replacement therapy, **leading to as much as $600,000 in savings the year following a single administration of gene therapy**.[29]

Likewise, the cost savings potential to the health care system of completely transforming the treatment paradigm for hemophilia B, with savings offered potentially over the course of a lifetime, is truly remarkable.

Beyond the impact to the health care system, as gene therapies can provide quality of life that had previously been lacking, and reduce the need for missed work, patients may **earn as much as $7,000 more in income each year**, on average, by avoiding hemophilia-related unemployment and early retirement.[30] [31]

SICKLE CELL DISEASE

Sickle cell disease (SCD) is a rare blood disorder characterized by malformed red blood cells. These sickle- or crescent-shaped blood cells clog blood vessels preventing normal flow of nutrition and oxygen throughout the body. SCD is caused by a mutation in the β-globin gene. The disease typically manifests in children before 1 year of age, and life expectancy averages 54 years.[32]

Pain is the most common manifestation of the disorder bearing a heavy burden on SCD patients, with 50% reporting pain half of their days and 30% reporting pain most of the time.[33] Though SCD is a rare disease affecting 100,000 Americans, it is far more common among Black and African Americas, who are disproportionately affected by the disease. SCD affects 1 out of every 365 Black or African American births.[34]

When sickle red blood cells become stuck in blood vessels, they can lead to pain crisis, known as vaso-occlusive crisis, and if they prevent the flow of oxygen to the chest, they can cause a serious and deadly complication known as acute chest syndrome. Blocked flow of oxygen to the brain can also lead to stroke. Though chronic red blood cell transfusions and medications may help to prevent these serious and life-threatening complications, patients with sickle cell disease experience frequent hospitalizations. For example, SCD patients on average are hospitalized more than once a year for significant pain, with an average length of stay of 5 days.[35] Additionally, on average patients visit the emergency room 2 to 3 times a year, most commonly due to pain crisis.[36]

As a result of the significant pain and limitations caused by SCD as well as frequent hospitalizations, SCD patients experience significant barriers to employment. In fact, 50%-60% of patients reported the disease negatively impacted their employment status, having to stop working completely or take a leave of absence, or having to take unpaid time off or reduce work hours.[37] As a result, SCD patients are estimated to earn $750,000 less over a lifetime than patients without SCD, representing a significant burden particularly on the Black and African American communities disproportionately impacted by this devastatingly painful and burdensome condition.[38]

As a result of the tremendous burden of the disease as well as its negative impact on employment, the role of potential gene therapies in reducing this burden is substantial:

Gene therapies in the late stages of development have demonstrated an **almost complete reduction in pain crisis as well as acute chest syndrome in the years following a one-time administration of therapy**.[39]

Reduction of these serious complications can help reduce the burden of this painful disease, restore quality of life in SCD patients and the Black and African American communities disproportionately impacted by the disease, thereby enabling patients to maintain more consistent and reliable employment.

Considering the wide discrepancies in income and life expectancy of SCD patients, this could lead to **as much as $21,000 more in average income in the year following gene therapy administration alone, with even greater potential over the course of a lifetime for these patients**.[40] [41]

BETA THALASSEMIA

Beta thalassemia (BT) is a rare and inherited blood disorder that affects about 2,000 U.S. patients. This condition impacts red blood cells by reducing the production of oxygen-carrying hemoglobin, resulting in a lack of oxygen carried to 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. About half of patients experience severe disease and lack appropriate levels of functional hemoglobin, leading to severe anemia.[42] [43] [44]

Patients with severe beta thalassemia and debilitating anemia may be eligible to receive a curative stem cell transplant, but suitable donors are identified for less than 30% of patients, and even fewer patients may actually receive a transplant due to the high costs and often significant clinical risks.[45] It is estimated that fewer than 10% of beta thalassemia patients ultimately receive a stem cell transplant.[46] Instead, most severe patients are treated through a regimen of lifelong blood transfusions to maintain levels of functional hemoglobin. On average, patients in the United States will require 17 transfusions a year, which are typically performed at outpatient or hospital transfusion centers and last multiple hours per procedure.[47]

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 excess iron. 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.[48] Patients with severe beta thalassemia often die from cardiac complications of iron overload by 30 years of age.[49]

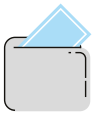
As a result of the tremendous burden of the disease and the costs associated with the current standard of care, the role of potential gene therapies in reducing this burden is substantial:

Average health care costs are estimated at $122,622 annually for patients with severe, transfusion-dependent disease.[50] These costs are primarily attributed to regular transfusions and therapy to manage the iron overload side effects of treatment.

Gene therapies in the late stages of development for transfusion-dependent adults and children with beta thalassemia have demonstrated **the potential to eliminate dependence on regular blood transfusions and medicines to manage side effects of treatment in the years following a one-time administration of therapy**.[51] [52] [53]

Gene therapy, therefore, has the potential to dramatically reduce or even eliminate the costs of regular blood transfusions and associated treatments in beta thalassemia patients, leading to **as much as $125,000 in savings in the year following a single administration of therapy**.

Likewise, the potential avoided costs over the course of a lifetime are substantial.



Beyond the impact to the health care system, by avoiding the burden of regular blood transfusions on average 17 times each year, beta thalassemia patients and caregivers would be able to avoid substantial amounts of missed workdays and associated income–potentially leading to **more than $4,000 in additional income annually**.[54]

Gene therapies and many other innovative approaches explored across the biopharmaceutical pipeline today offer the potential to completely transform the trajectory of many burdensome and costly diseases–yielding tremendous value not only to patients and caregivers but also to the health care system. While many gene therapies are administered just one time with long-lasting or even potentially curative effects, the full value they provide to patients, caregivers and the entire health care system may only be realized over the lifetime of the patient. Addressing the unique challenges presented by groundbreaking therapies that offer the potential to transform health care requires a rethinking of the current reimbursement system to adapt and evolve to account for the long-term value these therapies provide.

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