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Molecular Therapy

# Gene Therapy for Hemophilia: Addressing the Coming Challenges of Affordability and Accessibility

Treatment and care for those living with hemophilia are undergoing the biggest transformation since that brought on by the discovery of cryoprecipitate in the mid-1960s. Over the next few years, we will see treatment-product advances on all fronts, including biosimilars ("generic" versions) of current therapies, products with substantially longer-lasting efficacy, and the increasingly real prospect that through gene therapy[1,2] a "cure" may become a reality. Indeed, the ability to convert a patient permanently from a severe to a moderate or mild disease state, coupled with a dramatic reduction in treatment burden, would be nothing short of revolutionary. However, these advances will bring new challenges in terms of accessibility and affordability of the treatment in both advanced and developing nations.

The current standard of care for a child born with hemophilia in the United States is a prophylactic (preventative) regimen of clotting factor infusions to reduce the risk of long-term joint damage, related morbidities, and early mortality. A single gene transfer intravenous treatment could replace a lifelong regimen of prophylactic infusions two or three times per week. Even with prophylaxis, significant lifestyle and quality-of-life limitations remain as a result of the half-life limitations of existing therapies resulting in peaks and troughs of circulating clotting factor–replacement coverage. Normal blood clotting levels are not consistently restored. Care is still required in planning daily activities that would be taken for granted by most people living without hemophilia.

Enthusiasm for the arrival of gene therapy is tempered by concerns over whether it will be affordable or accessible for all. The annualized cost of prophylactic treatment is high—estimated to be $300,000 or higher per year.[3] The cost is magnitudes higher for those who develop inhibitory antibodies to the current therapies. The cost for gene therapy is not yet known. The vision of the World Federation of Hemophilia and its national member organizations, such as the US National Hemophilia Foundation, is to achieve treatment for all regardless of where they live. For those living in the United States, payment for treatment is a complex and often confusing labyrinth with no single system to ensure access for all. For those living outside of developed health economies, the ability to access care is less certain. Of the individuals living with hemophilia in the world today, 75% receive inadequate care, if any, and suffer significantly reduced life expectancies.

The Patient Protection and Affordable Care Act (ACA), passed by Congress and signed into law in March 2010, contains numerous provisions promising patients access to affordable care. The most notable provisions for those living with a high-cost chronic genetic disease such as hemophilia are the repeal of lifetime or annual dollar limits (i.e., caps) on payments for covered benefits and the prohibition of an insurer from refusing coverage or renewal of coverage because of an individual's preexisting medical conditions. These key provisions will not be fully implemented until 2014 (ref. 4). The outcomes of the 2012 US elections put to rest the prospects for repeal of the ACA and ensure that the major provisions of the new law will become effective. The core provisions of the ACA have also been upheld by the US Supreme Court.[5]

However, many uncertainties remain as to how the law will be implemented and the range of benefits that will be covered. Provisions of the ACA related to definition of "essential benefits," comparative-effectiveness research, and implementation of affordable-care organizations, as well as the possibility of closed drug formularies, all pose risks to accessing the full range of existing and advanced therapies. Within affordable-care organizations providers will be compensated, in part, for reducing the overall cost of care for each patient. Each of these considerations brings challenges for high-cost diseases such as hemophilia. Will the treatment options be limited or restricted to one medication class to achieve a

favorable economic outcome for payers? The willingness of governments and payers to provide funding or insurance coverage for gene transfer is not well established. Recent experience with health technology assessments in Sweden and advancement of health technology assessments and similar tools such as comparative-effectiveness research in other countries underscore the importance of research to support the high cost of present-day (and future) treatment practices for hemophilia.[6,7] The challenges of answering government and payer demands for evidence-based medicine and cost justification for the introduction and further enhancement of treatment, are ever-present and growing.

The pathway for commercialization of gene therapy may play a big role in its ultimate affordability and accessibility. In a commercial setting, one might expect gene therapy to command a premium price, at least in the early years to recover the development costs. If the companies that bring gene therapy to market already have traditional hemophilia therapies within their product portfolio, their incentive to offer gene therapy for a low price may be lacking because the new technology would disrupt their existing market. More affordable options may well come from new competitor ("innovator") companies outside the traditional hemophilia sector. Additionally, significant efficiencies have been achieved in vector production and therapy administration over the years.

Current treatment paradigms around the world are often dictated by scarcity of treatment products, rationing of care, or limitations on reimbursement based on cost per quality-adjusted-life-year analysis. Thus, treatment levels have been minimized in many environments. This shortsighted approach is a significant shortcoming of existing health-care financing models. Typical health economic analyses fail to take a whole-of-life view, omitting the cost of avoidable comorbidities (e.g., joint disease, viral infection), lifelong management of complications (e.g., inhibitors), and economic impact over a lifetime for individual patients and their families due to loss of social, educational, and career opportunities. The cumulative lifetime savings for one individual who undergoes successful gene transfer would yield significant savings for the payer and would appear to be an efficient investment for governments. If payers can be persuaded to think of an unconstrained health environment in which true demand is not distorted by scarcity, we could foresee a rise in global demand for gene therapy, thus creating a higher volume demand and lower margins required for gene therapy commercialization.

In fact, one could also easily argue that gene transfer may be the key for patients living in developing countries to also finally achieve access to care on a wide scale. It is not unreasonable to predict that developing countries could skip steps in development—that is, from limited or no specialized hemophilia treatment to a situation in which, following a single high-tech intervention, people with hemophilia could experience a reasonable quality of life without the need for access to frequent and sophisticated medical interventions.[8]

It is important to mention that emerging therapeutic advances should not be justified or brought to market based only on the notion that they will be more affordable—although that might be the case—but also, and more importantly, that they will be therapeutically more advantageous. Improvements in treatment adherence, reductions in bleeding frequency (including microhemorrhages), better management of trough levels, and improved health outcomes (including quality of life) should be the foremost considerations.

The research challenges of the past decade may soon be replaced by advocacy challenges in the next decade. The challenges to achieve access to advanced therapy will extend beyond the laboratory and clinical research setting. To achieve a future in which gene transfer is widely accessible and affordable to all, we should actively focus today on building the policy arguments, economic justifications, outcomes scenarios, and global strategies to achieve it.

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