"Preventative" Gene Therapies:

Perspectives on Payer Access Challenges and Solutions

PRECISIONadvisors
a precision value & health team

Introduction

Gene therapies are bringing transformational, long-term benefits to patients with severe genetic diseases for which there are few, if any, disease-modifying therapies available. While gene therapies have been shown to be useful in stopping the progression of disease, they have been much less effective in reversing damage already caused. Thus, there has been a push to move the use of gene therapies upstream, namely screening and then treating patients earlier in the disease pathway before they reach a symptomatic stage. Although this so-called “preventative” approach has the potential to bring greater long-term benefits for patients and society, it is also associated with a greater time lag between treating patients in the pre-symptomatic stage and seeing either improvements in patient outcomes or reductions in healthcare-related costs.

The enigma of gene therapies from a payer perspective

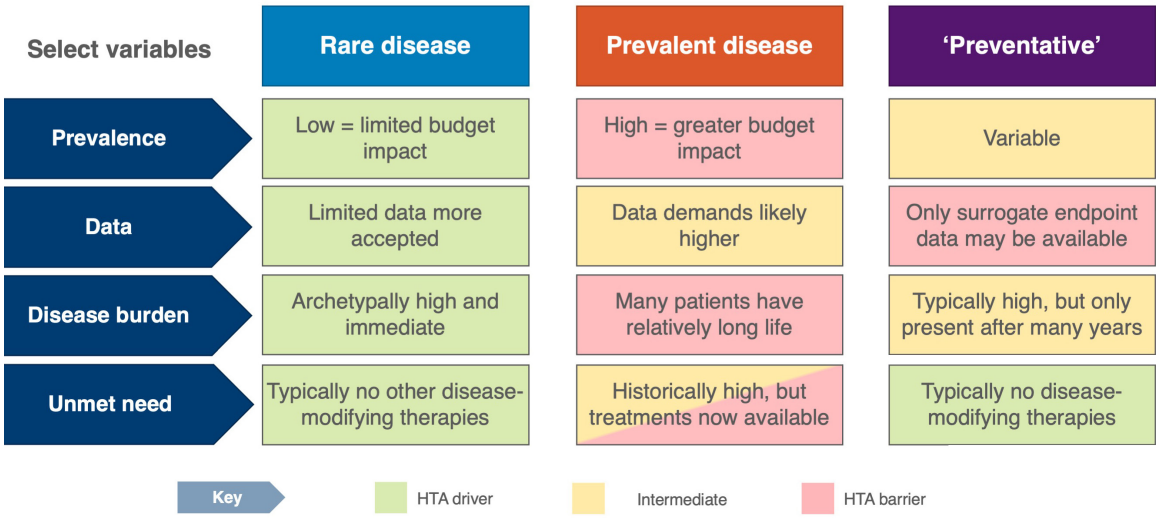
Gene therapies offer the promise of long-term—and even curative—benefit from a single intervention for patients with severe genetic diseases. Given their potential to address areas of high unmet need, gene therapies often receive regulatory approval early in their development based on small, single-arm trials with short periods of follow-up. For payers, evaluating the long-term benefit of these therapies—and, thus, the true patient value and appropriate price—is a challenge when evidence of treatment durability is lacking.

Evolution of the gene therapy landscape

Most of the gene therapies approved to date have focused on rare diseases such as spinal muscular atrophy and metachromatic leukodystrophy. With rare diseases, low prevalence mitigates payer concerns about potential budget impact. Payers may adopt a more pragmatic approach to evidence requirements, given the rarity of the disease. In addition, the high disease burden and unmet needs associated with rare diseases reinforce payer willingness to pay for these therapies.

As the focus of research and development shifts to more prevalent diseases—such as thalassemia, hemophilia, cystic fibrosis, diabetes, and heart failure—payer and access challenges will increase. Greater prevalence translates into greater payer concern over potential budget impact. Payers will demand more robust, rigorous data packages to support expenditures. Relatively lower disease burden and unmet needs will also be barriers to health technology assessments (HTAs) for gene therapies targeting more common conditions.

Figure 1. **Comparing payer and access challenges for gene therapies across disease types.**



The payer and access challenges associated with therapies targeted at earlier stages of the disease pathway will vary depending on the disease. One key differentiator in the preventative space is the time that elapses between treatment and benefit realization. This lag can vary widely between different diseases depending on their natural history and mortality rates. For example, patients with neuronal Gaucher disease are born with significant impairment and have an extremely curtailed lifespan. At the opposite end of the spectrum, patients with inherited retinal diseases may experience gradual loss of vision in the second or third decade of life, but not premature mortality.

Another confounding factor for preventative gene therapies is disease heterogeneity. Adrenoleukodystrophy, for instance, is caused by a mutation in the ABCD1 gene and can present with childhood or adult onset or may be asymptomatic. Treating all patients who have the ABCD1 mutation with a preventative gene therapy would result in treating individuals who might not actually require treatment. On the other hand, waiting until symptom onset before initiating therapy could lead to irreversible damage.

Access considerations for preventative gene therapies

Gene therapies in the preventative space further amplify the existing enigma for payers. Access for such therapies will be driven by 4 major questions:

1. **When to treat?** Earlier treatment may lead to greater potential benefit but will also increase the time between treatment and benefit realization in the real world.

2. **Who to treat?** It is difficult to predict or measure who will benefit most, especially for diseases with heterogeneous presentations and disease courses.

3. **What data are needed?** It can be challenging to produce comparative data in disease settings that are amenable to preventative gene therapy. Even when such data can be developed, there may be a very long lag between starting a trial and generating any patient- or payer-relevant endpoints.

4. **How will these therapies be financed?** To date, many gene therapies have leveraged alternative reimbursement models where payment is made in installments, linked to performance, or reassessed as more mature data emerge. Will these be sufficient to support access for preventative gene therapies, or will novel models be needed?

Further, to the feasibility of financing, these models are typically contingent on availability of payer-relevant data within a 5- to 7-year timeframe. For therapies where there may be a 10- to 20-year lag, or more, between initiation of treatment and realization of payer-relevant endpoints, new pricing and reimbursement models will be needed. As gene therapies become available for more prevalent diseases, more sophisticated price-volume agreements will need to emerge to support the sustainability of these treatments in any healthcare market.

Industry and payer perspectives

In September 2022, Precision Value & Health hosted a panel discussion with industry and payer representatives from Germany and the UK who have experience with gene therapies. Highlights of key discussion points and the panel's input generated additional important perspectives on the topic and are summarized below.

Reimbursement for approved gene therapies to date

The consensus of the payer representatives on the panel was that, thus far, reimbursement and access to many approved gene therapies has been good, with Libmeldy®, Luxturna®, and Zolgensma® being publicly reimbursed in both Germany and the UK. Some of these agreements were tied to innovative reimbursement schemes. For example, in Germany, Libmeldy and Luxturna were both subject to time-limited benefit resolutions, meaning that they must undergo another benefit assessment—and reimbursement price negotiation—later, after additional data have been generated. In contrast, in the UK, these 2 therapies were both recommended by the National Institute for Health and Care Excellence (NICE) contingent on simple confidential discount access schemes.

Other gene therapies have not fared as well in terms of access. A notable example is Zynteglo®, which is indicated for treating transfusion-dependent beta-thalassemia and may be considered the first gene therapy to address a disease with higher prevalence. Zynteglo® was withdrawn from Europe after failure to reach an agreement on the price of the drug in Germany and after initial negative draft guidance from NICE.

Views on the concept of prevention

Prevention can fall outside the traditional remit of many payers. However, this typically is in reference to primary prevention, which is distinct to the intention of preventative gene therapies:

- **Primary prevention** aims to prevent disease or injury before it occurs
- **Secondary prevention** focuses on detecting diseases early to facilitate early intervention
- **Tertiary prevention** seeks to manage established diseases and avoid further complications

The intent of preventative gene therapies is to treat asymptomatic or pre-symptomatic patients who have a known genetic mutation. For manufacturers and payers, the relevant questions regarding the real-world feasibility and value of these therapies include:

- How will patients be identified?
- Are diagnostic tools or screening programs available to facilitate patient identification?
- What is the likelihood that those identified will develop the disease?
- What is known about the benefits provided to patients if they are treated in an asymptomatic or pre-symptomatic disease state?

Ultimately, the manufacturer is tasked with specifically defining the target patient population, demonstrating that the right patient receives the right treatment at the right time, and quantifying the benefits in a payer-relevant manner.

Access challenges for preventative gene therapies

From a payer perspective, affordability and availability of hard endpoint data or comparative data may be the biggest access challenges for gene therapies targeting earlier stages of the disease journey. Regarding pricing, payers may take different approaches to adjusting for the significant uncertainty created by lack of "hard" endpoint data. Payers in the UK may accept surrogate endpoints, especially if clinicians think those endpoints are sufficiently robust. Payers in Germany, however, are likely to expect a patient-relevant endpoint that reflects mortality, morbidity, or quality of life; or established, validated links between the intervention, the surrogate endpoint, and such a patient-relevant endpoint.

Gene therapies are fundamentally changing value assessments as they are associated with a single upfront payment and potentially provide benefits that extend many years into the future and spread to societal areas beyond healthcare systems. These challenges are amplified when bringing such therapies into the preventative setting. New financial models and innovative approaches to pricing, contracting, and reimbursement that reflect shared recognition of potential risks and benefits will be needed to reimburse these therapies. Early engagement with all stakeholders—including regulators and payers—may help manufacturers better understand what trial design and evidence are needed to support approval, access, reimbursement, and adoption.

Early engagement with all stakeholders **—including regulators and payers—** may help manufacturers

Conclusion

The field of gene therapies is moving towards more prevalent diseases and even preventative treatment. In this evolving environment, proactive collaboration among manufacturers and payers to co-create evidence requirements and reimbursement models may help to optimize launch success and sustainability.

At PRECISIONadvisors, we have developed approaches to integrate stakeholder insights and build data infrastructures that are both robust enough to generate actionable information and flexible enough to evolve as new data emerge or priorities change. By combining market data, evidence, and engagement strategies with commercial expertise to optimize product value and maximize patient access to life-changing therapies, PRECISIONadvisors is uniquely positioned to help navigate payer strategies for gene therapies. To learn more about our expertise, **visit us here**.

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PRECISIONadvisors
a precision value & health team

2 Bethesda Metro Center, Suite 850
Bethesda, MD 20814
precisionformedicine.com