Five key trends in gene therapy approvals and access

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Big promise — and big challenges — in gene therapy

The November approval of CSL Behring’s HEMGENIX by the U.S. Food and Drug Administration (FDA) brought new hope to patients with Hemophilia B, which affects roughly 15% of the one in 40,000 Americans with Hemophilia. These patients typically required routine IV infusions of Factor IX prophylaxis therapeutics for their blood to be able to clot. HEMGENIX, delivered in a single dose, offered the hope of a long-term fix — a huge improvement in patient quality of life.

The catch? HEMGENIX came with a $3.5-million-per-course price tag — a previously unheard-of sum for a drug or biologic (though calculated to match the five-year cost of traditional treatment). Payers and governments gasped at the number, knowing that while the cost of this particular therapeutic alone might not prove catastrophic, plenty more gene therapies for rare diseases and even more common conditions were waiting in the wings, and at prices like these, the revolution in genetic medicine might prove economically unsustainable.

Half a century after scientists first proposed the idea of modifying defective genes to treat genetic illnesses, the gene therapy revolution is in full swing, with 11 drugs already approved or launched and another 30 in late-stage development, according to Cortellis Competitive Intelligence™ data. These treatments offer the promise of better health outcomes and/or quality of life for patients with rare diseases that were, in many cases, previously untreatable, or for which existing treatments were onerous for patients and produced inadequate results.

However, the gap is enormous between the needs of developers, who must recoup extensive development costs and reward investors, and stretched-thin payers, who are absorbing the costs of a wave of medical innovation elsewhere, along with post-pandemic austerity and economic precarity. Realizing the potential of these miracle treatments will require closing it. Similarly, regulators are wrestling with policies and processes that were not designed with these treatments in mind. We’ll explore these challenges, and ways that biopharmas can begin to address them.
Longevity of gene expression and immune evasion remain challenges for developers

The duration of therapeutic effects — up to eight years, in the case of HEMGENIX — and questions about long-term safety persist as important uncertainties with gene therapies. The risk of immune reactions constrains eligibility for systemically-delivered adeno-associated virus (AAV)-based therapeutics, meaning patients with high levels of AAV-neutralizing antibodies may be ineligible. This brings the risk of significant safety issues and limits re-dosing potential — a relevant concern as durability of gene expression remains in question for most approved and emerging options.

As there may be no one-size-fits-all strategy for circumventing risk of immune reactions, developers of clinical stage gene therapies are exploring several, often through partnerships. For example:

- Hansa Biopharma’s IgC antibody-cleaving Streptococcus-derived enzyme imlifidase, approved in Europe as Idefirix for kidney transplant patients, holds potential as a pre-treatment option to clear neutralizing antibodies prior to system administration of an AAV vector; Sarepta and AskBio have partnered with Hansa to explore this further.

- Selecta Biosciences is advancing strategies to drive immune tolerance to mitigate immune reactions to gene therapy and other modalities; Gingko Bioworks, Genovis, Takeda, and Sarepta are partnering on applications to gene therapy.

- Numerous smaller companies have emerged with novel platforms to produce better AAV capsids to improve safety and tissue targeting, establishing partnerships with key gene therapy players. These include Capsigen (partnered with Biogen), Apertura, Capsida (Preval/Lilly, AbbVie, C RISPR Tx), StrideBio (Takeda, Sarepta, C RISPR Tx), 4D Molecular Tx, Skyline, Lacerta, AAVantgarde Bio, and Taysha Gene Therapies.

- Lentiviruses, with larger capacity are being investigated (e.g., in Stargardt’s disease).

- Liposomes and oligonucleotide delivery systems are also under investigation to reduce immunogenicity; however these delivery modalities may run into issues including payload capacity, transfection efficiency, and delivery to the nucleus.

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Not just "one and done" — developers are betting on the need (and space) for multiple modalities

Next-generation antisense or siRNA strategies (e.g., peptide- or antibody-oligonucleotide conjugates) may provide meaningful competition to single administration AAV-based approaches in therapeutic areas for which the safety of administration, feasibility and durability of expression, and long-term cost-benefit balance of AAV-based options is unclear (e.g., musculoskeletal diseases).

Several companies have assets in early- and mid-phase clinical development, including:

- Dyne Therapeutics — DM1, FSHD, DMD (differing exons)
- Avidity Biosciences — DM1, FSHD, DMD (differing exons), rare cardiac and skeletal muscle (partnered with Lilly in "immunology and other select indications")
- PepGen (DM1, DMD, other neuromuscular)
- Entrada (several DMD exons, DM1 collaboration with Vertex, Pompe, immune, ocular)
- BioMarin (HAE, PKU, hyperoxaluria, AATD, hypertrophic cardiomyopathy, DMD)
- Wave Life Sciences ALS (Takeda option), Huntington’s (Takeda option), spinocerebellar ataxia 3 (Takeda option), AATD (partnered with GSK), DMD.

Contract manufacturers help startups get up to speed

Contract manufacturers like Catalent, Patheon and WuXi Advanced Therapeutics have moved swiftly to establish integrated solutions that support gene therapy development and manufacturing, filling a near-term gap in experience and expertise that has hobbled smaller companies seeking to build in-house capabilities. Novel incubators such as ElevateBio are seeking to evolve the model offering technology platforms, physical workspace and capabilities to support development as well as manufacturing — for example, by partnering with academia to launch companies.
As drugmakers target broader populations, patients face barriers to access

Most gene therapies continue to target specific subsets of patients, particularly for monogenetic diseases, with the aim of treating the patient as soon as possible in the course of the disease in order to realize sufficient benefit from treatment. In the U.S., for example, ZO LG EN SMA is approved for the treatment of spinal muscular atrophy (SMA) in patients less than 2 years of age with bi-allelic mutations of the SMN1 gene, while LUXTURNA is approved for patients with confirmed bi-allelic RPE65 mutation-associated retinal dystrophy.

These are extremely small subsets of niche patient populations, and accordingly, drugmakers have set extremely high prices for them. These prices reflect, in part, a number of factors potentially limiting adoption, including their complexity and cost, the need for administration by specialists, invasive delivery systems such as intrathecal administration, and limited long term efficacy and safety data in real world settings.

However, gene therapies targeting broader populations are now emerging. These include ZYNTEGLO, for transfusion-dependent beta-thalassemia, and two gene therapies in late-stage development for sickle cell disease. In addition, gene therapies for hemophilia and wet AMD offer the promise of less-frequent administration. Payers are restricting access to these therapeutics — in the case of hemophilia treatments, to patients 18 and up with no presence or history of antibodies against Factor IX (FIX) and AAV factor, and otherwise in good health.

Risk-benefit features prominently in coverage decisions

For companies marketing gene therapies, pricing strategies will, as ever, need to account for unmet need, availability of alternative therapies and their cost. However, payers will be looking closely at other factors, including:

- Risk/benefit profile, which fluctuates by indication based on factors including:
  - Patient age (e.g., wet AMD vs. pediatric populations)
  - Time since onset or disease severity (the average Leber's Hereditary Optic Neuropathy patient progresses to legal blindness within one year, with no hope of recovering vision; for patients approaching the one-year mark or for whom vision is fast deteriorating, the risk-benefit profile of gene therapy might be considered more acceptable by payers)
  - Route of administration vs. standard of care (often intrathecal, but other routes of administration are being considered, e.g. Roche and Ionis' phase 3 RG 6299 for IgA nephropathy)
- Administrator (surgical necessity could limit uptake based on availability of surgeons, operating room capacity, need for training, and practice economics).
Pricey therapeutics demand new metrics and payment models

Primary research revealed that 53% of surveyed pharmacy and medical directors would conduct or consult a cost-effectiveness study when multiple DMD gene therapies are on the market by 2024.

The prospect of paying $2 million or more for a one-time administration of a gene therapy to a member with a rare disease has created an unprecedented financial challenge for health insurers as the pipeline grows for these potentially life-saving cures. Payers are responding by more thoroughly assessing the cost/benefit of therapies in their coverage decisions, contracting with manufacturers to tie reimbursement to real-world outcomes, exploring alternative financing arrangements, and enacting prior authorization and other controls to manage drug utilization.

Value assessments informing coverage decisions

The proliferation of high-cost biologics — cell and gene therapies in particular — has ramped up the use of health economic outcomes research to bring the value equation to coverage decisions, which have historically revolved around clinical assessments and budget impact analyses. Comparative effectiveness research and cost-effectiveness studies are becoming more common, driven in large part by the Institute for Clinical and Economic Review (ICER), a nonprofit organization whose nonbinding health technology assessments have influenced various stakeholders, including MCOs, in assessing the value of high-cost therapies and, in some cases, served as fodder for payers’ price negotiations with pharmaceutical companies.

Primary research by Clarivate™ on rare disease therapies for Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA) conducted in March 2022 revealed that 53% of surveyed pharmacy and medical directors from 30 MCOs said their entities would conduct or consult a cost-effectiveness study when multiple DMD gene therapies are on the market by 2024.
ICER’s December 2022 assessment of gene therapies for hemophilia A and B, expected to the $3 million mark, raised a key issue that is confronting payers—how to determine the cost/benefit of a high-impact one-time therapy in the context of standards of care administered chronically over time. The group advised payers to not rush to judgment on the comparative cost offsets of the single therapy versus chronic therapies, in part because of the uncertainty around durability of gene therapies. Only 37% of the MCO directors surveyed by Clarivate noted they would be more inclined to cover a hypothetical single-gene therapy at $5 million than a chronic therapy that costs $1 million a year, if each therapy offset direct medical costs by $500,000 a year, but another 37% were unsure, illustrating the uncertainty around such assessments. Collecting real-world evidence will be an important component of value assessments.

Figure 1 displays the survey results. Respondents replied to the question: Assume a hypothetical chronic ASO therapy (requiring multiple re-administrations) has a net cost to a commercial plan of $1 million a year but a hypothetical onetime GT is $5 million. If each therapy offsets direct medical costs by $500,000 per year, which would you be more likely to cover, assuming that each therapy has an otherwise identical clinical profile and delivery/administration logistics? Select one.

**Figure 1: MCO directors show willingness to cover single-gene therapies that show value equaling chronic treatments.**

- 10% (D) I’m not sure
- 37% (A) No preference between the two therapies
- 37% (B) Single-administration gene therapy
- 17% (C) Chronic antisense therapy

Source: Clarivate, Access & Reimbursement study: Gene therapies for rare diseases (Duchenne muscular dystrophy and spinal muscular atrophy).

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*Illustration: (Graph showing survey results with options A, B, C, and D representing preferences and percentages noted.)*
The trend toward outcomes-based contracts takes on new urgency

The inordinately high upfront costs of gene therapy have rendered the traditional reimbursement models (e.g., buy-and-bill) unfeasible for many insurers, prompting payers to explore alternative payment models. Outcomes-based contracts (OBCs) between payers and manufacturers have gained the most traction from years of experience managing the costs of the increasing number of high-cost biological therapies in the commercial market. In fact, ICER has recommended that payers pursue OBCs for gene therapies treating hemophilia. An OBC holds the manufacturer responsible for some level of financial risk if the therapy does not deliver expected results in a real-world setting. The consequences range from higher rebates on an under-performing drug to outright refunds in the event of a therapy failure. For instance, Bluebird Bio has offered to pair the upfront payment for its $2.8 million gene therapy Zynteglo with an OBC that reimburses contracted payers up to 80% of the cost of the therapy if the patient fails to achieve and maintain transfusion independence up to two years following infusion.

The federal government is accelerating the use of value-based reimbursement in the Medicaid program by developing a Cell and Gene Therapy Access Model that could be in place by 2026. This model — which could become a major funding source for gene therapies used to treat sickle cell disease — will allow state Medicaid agencies to delegate authority to the Centers for Medicare & Medicaid Services to pursue outcomes-based payment arrangements with cell and gene manufacturers, using the federal government’s collective bargaining power.

Clarivate research indicates that among several trending payment models, MCOs consider OBC the most feasible approach to reimbursing gene therapies, followed by the use of stop-loss insurance. MCO pharmacy and medical directors surveyed in March 2022 rated the various payment models as moderately feasible (3.07-3.53 on a 5-point scale, with 5 being most feasible), including subscription-based payment models, payments spread over time, and case-by-case reimbursement contracts with providers. When asked about specific gene therapies for DMD and SMA, approximately 60% of directors said their MCOs either had a signed OBC in place or were working on one.

Figure 2 displays the survey results. Respondents replied to the question: What is the feasibility of your MCO adopting the following approaches to cover the costs of emerging gene therapies? Rate each row on a scale of 1-5, with 1 being not feasible and 5 being most feasible.
As an example of a subscription-based model, the pharmacy benefit manager, Optum, has instituted an Optum Gene Therapy Risk Protection product for plan sponsors, which will pay a flat per-member, per-month fee to Optum for guaranteed access for members to receive gene therapies LUXTURNA and ZOLGENSMA when clinically appropriate, which will be determined through utilization management strategies such as prior authorization. As added protection, the PBM is negotiating OBCs with manufacturers.

Utilization management

With MCOs under intense pressure to cover life-saving therapies, one of their most effective strategies to control costs is to closely manage drug utilization among their membership. The most common of these tools is prior authorization, mostly to confirm the patient is eligible for treatment as per the FDA label but also, in some cases, to align with professional associations’ clinical guidelines and clinical pathways. Additionally, physicians will likely have to document eligibility through any diagnostic tests that are available. Indeed, 2022 Clarivate primary research on DMD and SMA therapies indicates that most MCOs would demand of genetic tests to reimburse two of three emerging gene therapies for DMD. Other likely payer utilization controls include limiting therapy to patients who fit the clinical trial criteria, requiring first use and failure on another therapy, patient precertification (ahead of prior authorization), and requiring outpatient instead of inpatient procedures when possible. Additionally, PBMs have also set up care management programs to closely monitor and assist patients. Payers will have to balance utilization management against the potential to overly constrain access to life saving treatment, or risk backlash from patients and their families, physicians and policymakers.
In the U.S., regulators wrestle with accelerated approvals model

Gene therapy developers are making use of accelerated approvals to market their products in the United States. Accelerated approval is a pathway for the U.S. Food and Drug Administration (FDA) to approve drugs that treat serious or life-threatening conditions based on a surrogate endpoint that is reasonably likely to predict clinical benefit, rather than requiring a traditional clinical trial that shows a statistically significant improvement in survival or irreversible morbidity or mortality.

To be eligible for accelerated approval, a drug must meet the following criteria:

• It must be intended to treat a serious or life-threatening condition

• There must be no adequate or approved treatment for the condition

• The drug must have demonstrated a favorable benefit-risk profile based on a surrogate endpoint that is reasonably likely to predict clinical benefit

• The sponsor must agree to conduct a post-market study to verify and describe the clinical benefit of the drug.

Drugs approved through accelerated approval are still required to undergo confirmatory studies to verify and describe the clinical benefit. These studies are designed to provide robust evidence of the drug’s safety and effectiveness.

According to the FDA, as of January 2023, there have been 111 drugs approved through the accelerated approval pathway. Of these, 65 have been approved for cancer, 22 for rare diseases, 14 for cardiovascular diseases, and 10 for other conditions.

The trend for accelerated approvals has been increasing in recent years. In the first 10 years of the program (1992-2001), only 13 drugs were approved through accelerated approval. In the next 10 years (2002-2011), 36 drugs were approved. And in the last 10 years (2012-2021), 62 drugs have been approved.

The increase in accelerated approvals is likely due to a number of factors, including:

• The increasing number of serious and life-threatening conditions that have no effective treatments

• The development of new technologies that allow for earlier detection of disease and more precise measurement of treatment response

• The growing awareness of the importance of patient-centred outcomes.

The catch with accelerated approvals is, of course, that these products have not been vetted for safety and efficacy to traditional standards. The FDA therefore requires companies to conduct confirmatory studies to verify the clinical benefit of these drugs, and some drugs have been withdrawn from the market after it was found that they were not effective.
Reasons for these withdrawals vary, but they typically involve a lack of efficacy or safety concerns — for example, Avastin was withdrawn from the market for metastatic breast cancer after it was found that it did not provide a significant benefit over standard chemotherapy. Erbitux was withdrawn from the market for recurrent glioblastoma after it was found that it did not provide a significant benefit over standard chemotherapy.

A number of parties have expressed concerns about accelerated approvals, including patient advocacy groups, which worry about safety and efficacy, public interest groups concerned with drug price inflation, and academic researchers fearful of drugs being approved on weak evidence.

Potential legislative actions could impact this pathway — The Modernizing Accelerated Approval Act of 2022, introduced in the U.S. Senate in December 2022, would require confirmatory studies to verify clinical benefit, improve communication of risks and benefits to patients, and implement new tools to assess safety and efficacy.

Table 1: A dozen accelerated approval drugs have been subsequently pulled by FDA.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
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<tbody>
<tr>
<td>Avastin (bevacizumab)</td>
<td>metastatic breast cancer</td>
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<tr>
<td>Avastin (bevacizumab)</td>
<td>recurrent glioblastoma</td>
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<tr>
<td>Erbitux (cetuximab)</td>
<td>metastatic colorectal cancer</td>
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<tr>
<td>Tarceva (erlotinib)</td>
<td>metastatic non-small cell lung cancer</td>
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<tr>
<td>Xalkori (crizotinib)</td>
<td>metastatic non-small cell lung cancer</td>
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<tr>
<td>Zelboraf (vemurafenib)</td>
<td>metastatic melanoma</td>
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<td>Tafinlar (dabrafenib)</td>
<td>metastatic melanoma</td>
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<td>Mekinist (trametinib)</td>
<td>metastatic melanoma</td>
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<td>Brigatinib (osimertinib)</td>
<td>metastatic non-small cell lung cancer</td>
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<td>Entrectinib (entrectinib)</td>
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<td>Larotrectinib (larotrectinib)</td>
<td>metastatic solid tumors with NTRK gene fusions</td>
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<tr>
<td>Vitrakvi (larotrectinib)</td>
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</tbody>
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As of January 2023, 12 drugs that were approved through the accelerated approval pathway have been withdrawn from the market:

- Avastin (bevacizumab) for metastatic breast cancer
- Avastin (bevacizumab) for recurrent glioblastoma
- Erbitux (cetuximab) for metastatic colorectal cancer
- Tarceva (erlotinib) for metastatic non-small cell lung cancer
- Xalkori (crizotinib) for metastatic non-small cell lung cancer
- Zelboraf (vemurafenib) for metastatic melanoma
- Tafinlar (dabrafenib) for metastatic melanoma
- Mekinist (trametinib) for metastatic melanoma
- Brigatinib (osimertinib) for metastatic non-small cell lung cancer
- Entrectinib (entrectinib) for metastatic solid tumors with neurotrophic tyrosine receptor kinase (NTRK) gene fusions
- Larotrectinib (larotrectinib) for metastatic solid tumors with NTRK gene fusions
- Vitrakvi (larotrectinib) for metastatic solid tumors with NTRK gene fusions

Source: FDA.
Key takeaways

Companies developing gene therapies will want to consider several factors in order to be successful:

Even as the number of therapies in pipelines and on the market begins to accelerate, the picture on market access and commercial launch for these products remains fuzzy. In order to be successful, companies developing gene therapies will want to consider:

- **The patient journey.** When are patients diagnosed with a condition, and by which medical professionals/in which practice settings? At what point might patients be prescribed a gene therapy, and following which earlier lines of therapy?

- **Market and competitive landscape.** What is the clinical and commercial outlook for gene therapies on the market and/or in pipelines for a condition? What might a marketplace with multiple gene and conventional therapies look like? How might the market evolve over the next ten years?

- **Regulatory landscape.** What is the optimal pathway for multi-market launches, considering treatable population sizes, pricing, prioritization, and sequencing? How can companies utilize real world data and real-world evidence to shorten time to market through the use of accelerated approval and similar pathways?

- **Payer landscape.** Which physicians are issuing genetic tests, and how are payers reimbursing them? How do payers perceive genetic tests and treatments and/or single dose versus chronic treatments? How are payers reimbursing gene therapies?
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