# CELL AND GENE THERAPY

## FROM DISRUPTION TO SUSTAINABLE TRANSFORMATION

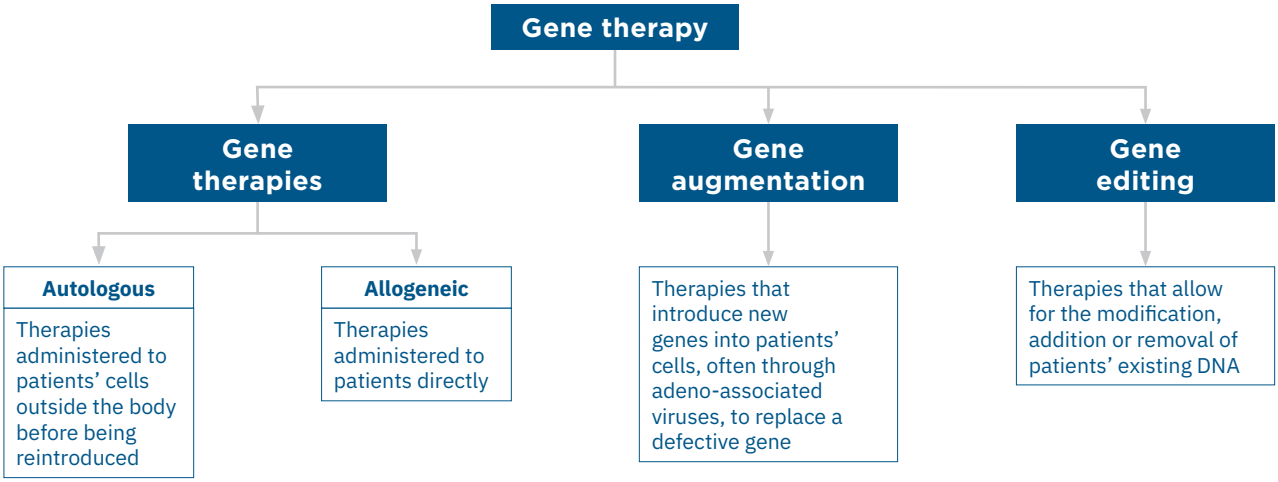
By Andrew Hobbs and Maya Khurana

Cell and gene therapies (CGT) are poised to transform medicine. Analysts estimate up to 550,000 patients in the U.S. alone will undergo CGT treatment by 2031, representing up to $30 billion in reimbursement potential. Through 2024, the budget impact of these treatments could reach as high as $45 billion, according to CVS projections. To date, however, these new therapies have evolved more quickly than the ecosystems that support them.

CGT holds the promise of one-time treatments that can deliver a lifetime's worth of value, disrupting the traditional model of treating patients over extended periods of time. Given the novelty and uncertain risk profile of these new therapies, there are concerns about how drug developers, healthcare providers and payors will evaluate these therapies and make them available to patients in need.

Pharmaceutical organizations will not resolve these challenges alone, but their ability to capitalize on CGT's projected market growth depends on making immediate progress.

### Cell and Gene Therapy (CGT) Classification

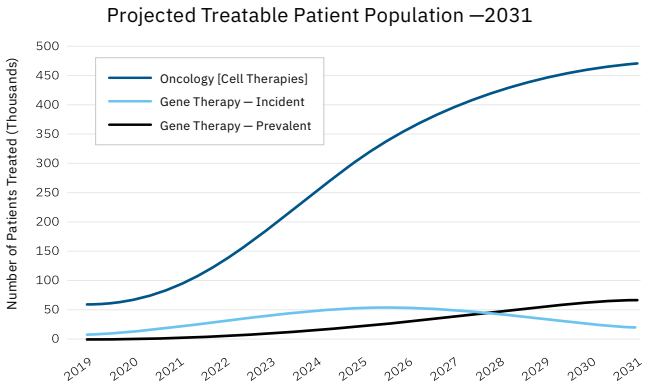



Note: We have used simplified definitions for the purpose of this white paper.

## MIT NEWDIGS has predicted 70-90 new drug approvals by 2031

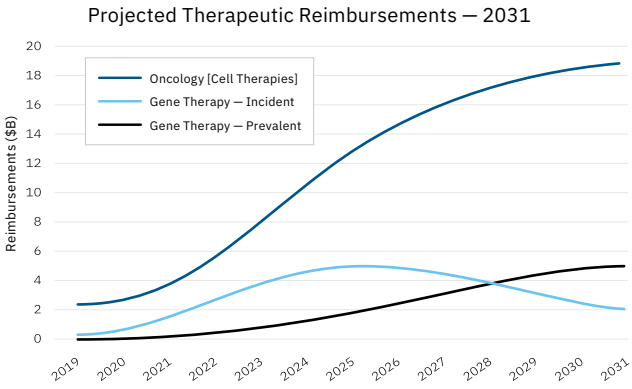
### 410K-550K patients treated by 2031

- 350K-450K in oncology
- 60K-100K in gene therapy




### $20B-$30B total reimbursement by 2031

- $15B-$21B in oncology
- $5B-$9B in gene therapy




# Challenges to Cell and Gene Therapy Success

At a recent Huron roundtable, experts from across the CGT landscape discussed the biggest obstacles surrounding CGT and how to surmount them. Participants, who included treatment developers, healthcare providers, payors and policymakers, shared concerns about demonstrating the durability, pricing, access and value of CGT and creating scalable manufacturing and treatment delivery models.

Some of the primary obstacles to realizing CGT's full potential include:

1. **Clinical development:** Uncertainty and risk in cell and gene therapy development leads to unpredictability. The knowledge of various cell types and treatment modalities is in its early stages and still evolving, therefore the risk-benefit profile for each is not fully established. Long-term safety issues, such as liver toxicity, immunogenicity and off-target effects, need to be addressed and managed. In addition, the durability of adeno-associated virus (AAV)-based therapies is under question, and evidence to support their safety and long-term efficacy will be needed. Although regulators are providing pathways for accelerated clinical trials to encourage innovation and investment in this area, without a clear understanding of translational science, developers are faced with making critical decisions over where to invest their time and resources.

2. **Manufacturing and supply chains:** CGT will also upend pharmaceutical manufacturing models. Currently, both allogenic and autologous therapies rely on centralized manufacturing. This may continue to be viable for allogenic therapies; however, the complex supply chains associated with autologous therapies may require a more decentralized approach. Manufacturing autologous therapies could occur in one of two settings: regional facilities managed by developers or across certified treatment delivery centers (e.g., academic health centers), closer to the patient's bedside (similar to how stem cell transplants are managed currently). The latter option is dependent on establishing closed loop manufacturing that minimizes the infrastructure requirements at treatment facilities and maintains compliance with regulatory quality standards.

3. **Treatment delivery:** Healthcare providers are still refining the infrastructure needed to provide patients with CGT. For instance, although genetic screening will be necessary for selecting candidates for certain types of CGT, this testing is not universally available (nor is it efficient for all developers to invest in it). Rather than create standards and centers of excellence in isolation, the industry needs a consistent and collaborative approach to identifying, treating and monitoring CGT patients. Even the idea of setting up genetic testing infrastructure raises the question of who foots the bill. A "fee for test" model may work initially, but low patient volumes may dissuade providers from investing in the initial infrastructure needed for setup. Noncompetitive industry consortia backed by government investment could be a more efficient option in the future.

   Capacity poses another obstacle, specifically for autologous treatments. Most of these therapies are currently delivered in transplant centers with cell processing and handling capabilities, but this approach will be difficult to scale as patient volumes grow. Even today, providers lack the data collection functionality needed to track patient outcomes over time for both regulatory and reimbursement purposes. Going forward, having robust data infrastructure may become a requirement for treatment delivery centers.

   The question developers must reflect on is twofold: whether to invest in proprietary testing and processing centers or share that risk with providers, and whether they're able to compete with providers who may be further along in standing up cell therapy facilities.

4. **Defining value:** Existing frameworks for defining treatment value were not designed with CGT in mind. Traditional economic evaluation guidelines in many (but not all) markets do not account for the societal effects or mid- to long-term cost of care impacts that CGT can bring, leaving many authorities unable to justify these therapies' high upfront expense. The Institute for Clinical and Economic Review (ICER) published a series of proposals for assessing CGT value in collaboration with the Canadian Agency for Drugs and Technologies in Health (CADTH), the National Institute for Health and Care Excellence (NICE) and other global authorities. Per these developments, ICER plans to seek input on the specific types of uncertainty related to each single and short-term therapy (SST) in order to develop optimistic and conservative estimates of a treatment's benefit. ICER will also outline scenarios to demonstrate how long a therapy's benefit must last in order to achieve cost effectiveness. Lastly, ICER is considering a shared-savings scenario that would spread the cost offsets of a treatment equally with health systems.

5. **Access and pricing:** Although value-based agreements for CGT hold promise in theory, bringing them to bear will require a robust system for tracking outcomes as patient populations grow. Payors currently cite the administrative burden of manually monitoring patients and collecting data as a key barrier to alternative financing, according to a Massachusetts Institute of Technology New Drug Development Paradigms (MIT NEWDIGS) survey. Different payor types will also require different financing solutions: Currently, commercial payors use the strictest utilization management strategies to accommodate CGT, with larger states having less restrictive policies than smaller ones. Self-insured employers rely more heavily on pharmacy benefit managers and medical carriers to address challenges associated with managing financial burden with CGTs.

   Effective contracting solutions need to account for not only the type of payor involved but also uncertainty related to the efficacy of the product. For example, if long-term durability is an issue, then repeat dosing might be covered by the manufacturer (rather than the manufacturer losing reimbursement because efficacy at a certain time was not

demonstrated). For therapies where provider networks are a key stakeholder (such as autologous therapies), contracts between managed care organizations and manufacturers must account for the risk of treatment administration error on the provider side that manufacturers don't directly control.

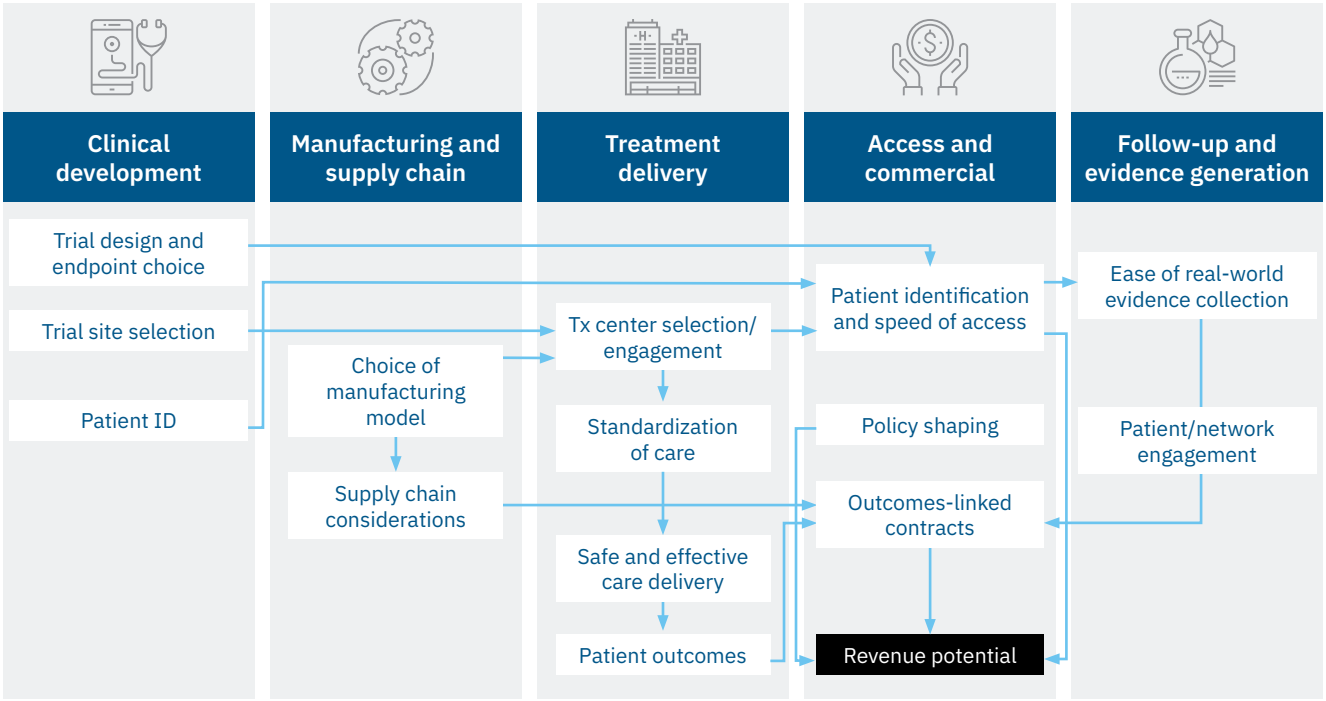
Beyond these core challenges, additional barriers remain. Medicaid "best price" reporting requirements in the U.S. can limit developers' ability to offer innovative pay-over-time or outcomes-based rebates without triggering a lower price among commercial payors for subsequent product sales.

Everything in the CGT landscape is interconnected. One decision or change to manufacturing models, clinical development or commercialization can have cascading effects throughout the entire value chain. Pharmaceutical developers, healthcare providers and payors face a dual imperative: to create holistic processes and technologies that effectively bring CGT to patients who need it, and to adapt the current industry paradigm around these emerging solutions.

# Spurring Cell and Gene Therapy Growth: Collaborative Solutions for Sustainable Transformation

Despite these complexities, roundtable participants identified several possible solutions that could accelerate CGT adoption and growth, each focused on collectively adapting the broader treatment paradigm. These solutions are twofold: systemic changes that must occur across the life sciences and healthcare environment, and technology innovations that will be required to support and scale CGT.

## Developing impactful solutions across the value chain is complicated — one decision can have a cascading effect across several others




This is meant to be an illustrative, not an exhaustive, example.

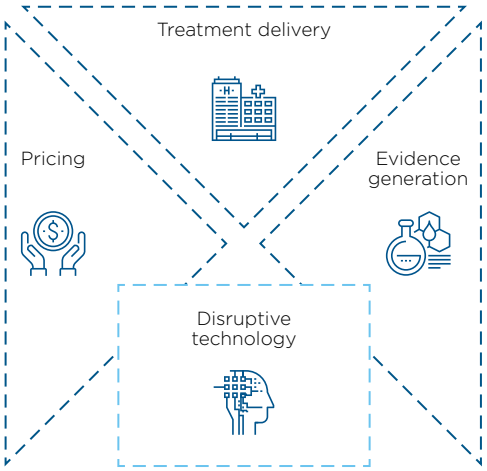
From a system perspective, developers, payors, providers and regulators must collaborate to transform the current landscape to accommodate CGT, advocating for:

- **Treatment delivery standardization:** Shared governance for manufacturing and delivering CGT is essential for ensuring consistency and safety across care settings, particularly for autologous cell therapies where provider facilities can have a major impact on outcomes. Delivery standards will help accelerate pharmaceutical partnerships with hospitals, academic health centers and other facilities, setting a foundation for risk sharing and efficiency. Organizations such as Be the Match BioTherapies and Sarah Cannon, the Cancer Institute of HCA Healthcare, are making an effort toward standardization, managing Blood Cancer Network programs across the U.S. and U.K. that offer CAR-T cell clinical trials and therapies.
- **Payment mechanisms that link uncertain outcomes to financial risk, underpinned by risk sharing:** Payors agree that short-term, milestone-based contracts are the most feasible immediate solution for managing the financial burden and risk associated with CGT. But demystifying reimbursement will depend on multiple components falling into place, including a framework for risk-benefit assessments. Risk-benefit assessment frameworks should be designed with payors and regulators in mind, so that no one stakeholder shoulders the risk alone. In an example of what can happen when these frameworks are misaligned, Novartis' gene therapy Zolgensma was labeled for patients 2 years old and under; however, clinical trials only included patients under 6 months, putting pressure on payors to cover populations for whom evidence was lacking.

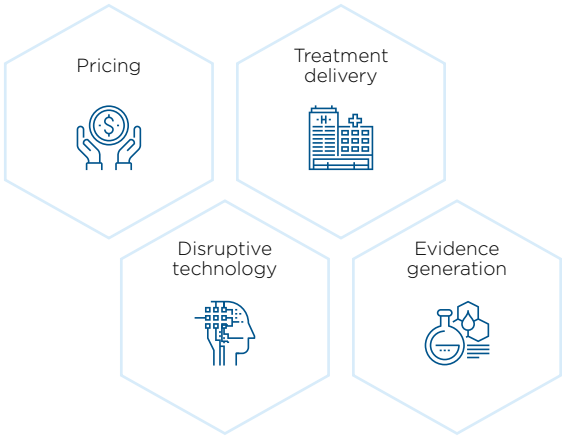
  A scalable framework would guide short- and long-term clinical trial endpoint selection based on the outcomes criteria regulators and payors need. This framework should be flexible enough to account for variation between different treatment modalities and their risk-benefit profiles, guiding stakeholders to determine a new therapy's uncertainty — which could be around safety, outcomes or delivery of the claimed value to the health system — identify when risk sharing is required and select a risk-sharing solution relevant to the specific treatment being considered.
- **A healthcare system that enables outcomes-based contracts:** The effectiveness of new payment mechanisms depends on having a

## Success depends not only on the effectiveness of the technology, but on how the system can adapt

From healthcare system and technology misfit …




… to a fertile system that encourages innovation and provides access to patients



healthcare system that aligns with it. Many health systems today operate with short-term, siloed budgets; cost savings in one area are not always felt across the organization nor are they realized over an extended timeline. To execute outcomes-based contracts, providers and payors must shift toward calculating the total cost of care, as CGT can yield benefits across an organization over multiple years.

Digital infrastructure and legislation to support sophisticated data capture and data sharing will be key to enabling this shift and strengthening transparency across the CGT value chain. These systems need to be capable of consistently tracking relevant data from development (including clinical trial results) to post-treatment delivery (such as real-world evidence to inform outcomes-based payment models). Digital smart contracts that use blockchain to verify and secure transactions could serve as a decentralized tool to track and collect data along the patient journey, creating firewalls to ensure integrity across data collection and reporting.

- **Consensus on a fair starting price:** Another vital element of a successful payment mechanism is having an agreed-upon baseline. Critics argue that the move toward value-based care encourages pharmaceutical developers to impose high prices, which cannot be sustained as patient volumes rise. Instead, stakeholders need to align around a starting price point, or at least an equation for deciding a fair starting price based on a treatment's value criteria and intended population. Future value frameworks adapted to the nuances of these therapies could serve as a tool for starting price agreements.

  There's also an opportunity to consider more dynamic pricing. CGT provides test cases for differential pricing for specific patient populations based on treatment efficacy. And rather than only halting reimbursement when treatments do not yield baseline outcomes, payors and regulators could also introduce incentives when outcomes exceed expectations.

## Bluebird Bio's Installment-Based Payments Proposal

In June 2019, Massachusetts-based gene therapy developer Bluebird Bio won European Medicines Agency (EMA) approval for Zynteglo, a one-time treatment for patients with transfusion-dependent beta-thalassemia, a rare blood disease.

Bluebird Bio priced Zynteglo at $1.8 million, with the cost spread over five-year installments if the treatment is effective in preventing patients' need for chronic blood transfusions. If the treatment is unsuccessful, the company will reduce or halt payments altogether.

Zynteglo's unconventional pricing framework assumes that the treatment provides patient benefits totaling $2.1 million due to improved quality of life and longer life spans. Unlike traditional pricing methodologies (including ICER's), Zynteglo's intrinsic value is not defined by its projected reductions in the cost of care, which the developer estimates at an additional $2 million.

Bluebird Bio intentionally chose to root Zynteglo's value in patients' terms — if quality of life doesn't increase, is the treatment truly worthwhile? Quality-of-life improvements will be more complex for payors to quantify than cost reductions, but many are willing to entertain and refine the concept. If successful, Zynteglo could set an influential precedent for future CGT pricing and access strategies.

- **Third-party intervention to hedge financial risk:** Pharmaceutical developers, providers, payors and regulators will not be the only stakeholders defining the future of the CGT landscape. New partners will be integral at every step in the CGT supply chain. Dedicated reinsurers, for example, could emerge to handle CGT patient management and risk pooling. Advisory and technology providers will also play an important role in helping implement the processes and technology required to standardize treatment delivery. Technology

partners specifically have the potential to provide the objective data and price validation necessary to support and arbitrate outcomes-based agreements.

# Next Steps for Pharmaceutical Developers

In parallel to broader, systemic transformation, pharmaceutical developers have an imperative to transform internally. To position their organizations for long-term success, CGT leaders will need to invest in:

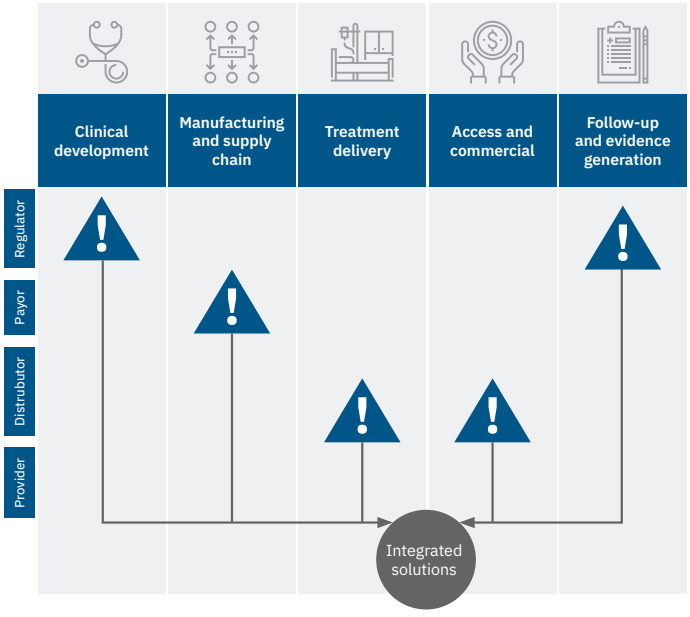
- **Elevated treatment safety and efficacy profiles:** As the science behind CGT advances and developers hone their expertise, organizations will collect more data to reinforce the effectiveness of these therapies. A more thorough understanding of the translational science in CGT will help mitigate the risk currently associated with these therapies and better inform developers' decisions around which products to invest in going forward.
- **Scalable manufacturing:** To accommodate and scale all types of CGT, modular systems and standardized manufacturing processes will be essential. Improvements in manufacturing processes and technology will be necessary to lower the cost of goods involved in development. Greater investment in solutions that ensure the quality assurance and control of assays will also help accelerate partnerships with academic and healthcare facilities, expanding the pharmaceutical industry's manufacturing and delivery network.

## A holistic view and cross-functional alignment is required in order to co-develop solutions with external stakeholders

Developing integrated solutions

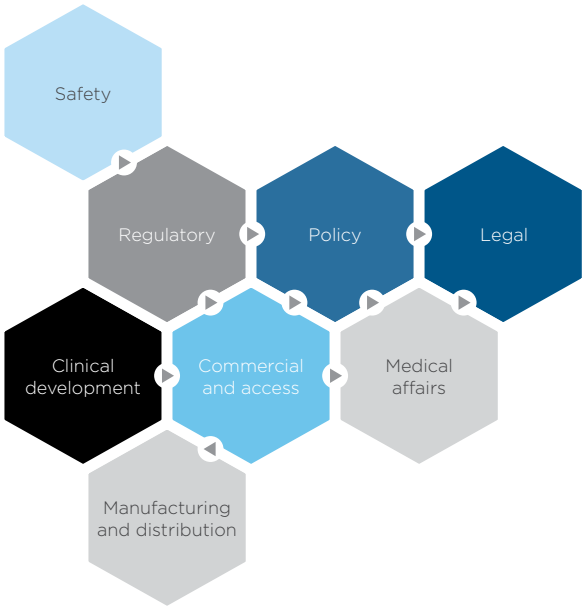
### External component

Mapping all the challenges by stakeholder across the product value chain and developing integrated solutions




### Internal component

Rapid action team bringing together all relevant functions with a mandate to make joint and timely decisioins



- **Evolving their organizational structures:** To position cell and gene therapies for mainstream success, pharmaceutical organization structures should mirror the integrated nature of the CGT landscape. Leaders have a responsibility to form cross-functional teams — with experts from regulatory and legal, commercial and access, manufacturing, and clinical development functions — and empower them to make joint, timely decisions to seize CGT opportunities. Leaders must promote a culture that perceives external stakeholders as vital partners, positioning their firms to be more active participants in creating resources that illustrate the impact their treatments can bring to different populations.

CGT has the potential to transform the way treatment is delivered and save lives. The window of opportunity for creating scalable development, manufacturing, delivery and payment models to support CGT, however, is fleeting. Organizations must play a leading role in shaping CGT industry standards, rather than being subject to them. The long-term success of CGT will not be defined by one organization or regulatory authority, but by the level of collaboration and flexibility between all stakeholders that touch the value chain.

Thank you to the following Huron roundtable participants whose expertise was integral to shaping these perspectives:

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- **Jane Barlow**, Senior Advisor, MIT Center for Biomedical Innovation/NEWDIGS
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- **Emily Minkow**, Chief Business Officer, Prevail Therapeutics
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- **Surya Singh**, President, Singh Healthcare Advisors
- **Lucas de Breed**, Founder and Managing Director, August
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