A promising model for gene therapy development is outlined that supports a thriving gene therapy community and increases access to therapies, particularly for patients with rare and ultra-rare diseases.

An Open-Access Platform: A NIIMBL Approach to Gene Therapy for Rare Diseases

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Developing gene therapies for rare diseases faces significant challenges, including high costs, lengthy timelines, and the specialized expertise required for technical drug development and manufacturing. Small biotech companies, academic institutions, and philanthropic groups often lack the resources to bridge the gaps

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between diagnosis and therapy development. At the same time, market potential may be questioned by the for-profit pharmaceutical industry. These barriers disproportionately affect the rare disease community, limiting the development pipeline for life-changing therapies.

To attempt to address some of these challenges, the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) has launched an initiative to develop an open-access adeno-associated viral vector manufacturing and analytical platform. This program brings together academic and industry partners to develop scalable solutions derived from their experience developing gene therapies. The platform is designed to be modular and pre-competitive, allowing for adaptation for novel gene therapies while remaining accessible to non-profit and academic research organizations with limited budgets.

Gene therapy represents a groundbreaking approach that has the potential to overcome the limitations of conventional treatments by providing targeted, sustained, and potentially curative interventions.

By leveraging the expertise and infrastructure of the for-profit genetic medicine sector, the Viral Vector Manufacturing and Analytics Program seeks to create a platform that is flexible and scalable for immediate clinical applications and facilitates long-term product development. It is hoped that success in this endeavor will be part of establishing a sustainable economic model to transform philanthropic funding into strategic investments, reduce barriers and accelerate drug development, and ultimately address the unmet needs of patients with rare and ultra-rare diseases.

Introducing Gene Therapy: A Groundbreaking Approach

Genetic medicine has emerged as a groundbreaking approach for delivering lasting and potentially curative benefits for countless debilitating diseases. Conventional therapies—from over-the-counter small molecules to biologics administered at the hospital bedside—often fall short due to issues of imprecise biodistribution, short molecular half-lives, and the need for repeated treatments in the case of lifelong afflictions. In contrast, gene therapies work by providing genetic instructions that enable the body's own cells to continuously produce therapeutic molecules, leveraging the inherent stability of DNA and the cell's native machinery for sustained benefit.

One of the most compelling applications of gene therapy is the potential to treat a vast array of genetic disorders. Currently, there are over 10,000 recognized rare diseases, the majority of which are of genetic origin. Most rare genetic diseases have no effective treatment options, let alone a cure, and many carry devastating prognoses—particularly for children who may not survive into adulthood. Collectively, these conditions affect millions of individuals worldwide. This not only places a significant burden on patients and families but also drives substantial societal costs related to healthcare, special education, and infrastructure to comply with regulatory mandates under the Americans with Disabilities Act (e.g., occupational and/or physical therapy, specialized transportation, in-home nursing care) (Yang et al. 2022).

The precision required to treat genetic diseases presents a significant challenge. Many genetically related disorders exhibit similar clinical presentations, with differential diagnoses achievable only through comprehensive genetic screening to identify the specific mutation in an individual's genome. A gene therapy developed to correct a particular genetic anomaly in one patient cohort will be ineffective against a different anomaly in another. Consequently, there is a critical need to develop a wide array of gene therapies—each tailored to deliver specific genetic corrections to targeted tissues—to address the full spectrum of genetic diseases (Zhao et al. 2021).

A key innovation in advancing gene therapy has been the identification and engineering of novel vectors for targeted cellular delivery of new genetic instructions (DNA). Vectors, in the form of molecules or particles, are themselves non-therapeutic and only serve to transfer a therapeutic payload (gene) to a target cell. When a vector delivers a genetic correction directly to a diseased cell, it is possible to permanently fix a genetic deficiency, thus maximizing therapeutic efficacy while minimizing adverse side effects.

Adeno-associated viral vectors (AAVs) have proven particularly effective for targeted gene delivery. Naturally

occurring AAVs are quite diverse, prevalent, and, most importantly, benign (Kruzik et al. 2019). Their non-pathogenic nature and established tissue tropism, the ability to preferentially infect and establish persistent gene expression for years in non-dividing, specific tissue or cell types as illustrated in figure 1a, make them ideal candidates for gene delivery (Mendell et al. 2021; Wang et al. 2024). Still, clinical applications of AAV are not entirely without risk, as in some cases significant adverse events have been documented when using high systemic doses of AAV. Today, sophisticated molecular libraries and artificial intelligence are being employed to develop synthetic AAV serotypes with enhanced targeting capabilities or suppressed immunogenicity, which is expected to improve the precision and safety of AAV for gene therapy applications (Pupo et al. 2022).

A key advantage of AAV vectors is their modular architecture. A single AAV vector platform can be adapted with different genetic payloads, as illustrated in figure 1b, to address various disorders affecting a specific cell type and/or organ. Although exchanging the genetic payload in an AAV vector may lead to markedly different therapeutic outcomes in patients, it generally has only a marginal impact on the vector manufacturing process or overall product quality. Thus, a single AAV manufacturing platform is expected to be broadly applicable to manufacture gene therapies for a wide spectrum of genetic diseases.

In summary, gene therapy represents a groundbreaking approach that has the potential to overcome the limitations of conventional treatments by providing targeted, sustained, and potentially curative interventions. This technology is poised to significantly impact the treatment of rare genetic disorders, offering hope to patients and reducing the broader societal and economic burdens associated with these conditions. Moreover, an AAV vector platform has the potential to not only accelerate the development of new treatments but also holds promise for efficiently addressing a wide spectrum of genetic disorders.

A Need to Work Together

The molecular complexity that makes AAV vectors effective platforms for gene therapy also presents significant challenges in achieving consistent, high-yield, and high-quality production. Typically, AAV vectors are produced in genetically modified cell cultures, followed by purification using a series of engineered separation techniques. The development and manufacturing of AAV vectors

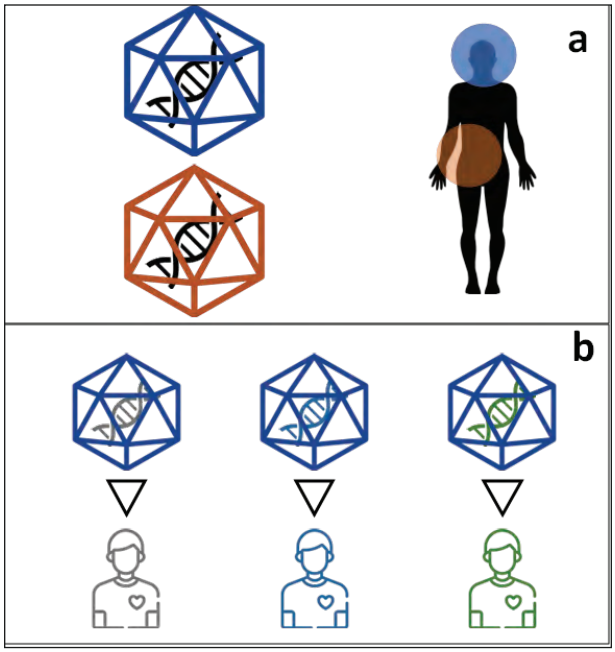

FIGURE 1 a) Diverse serotypes of AAV vectors exhibit unique tropisms, inherent from the properties of their capsids. This enables the targeted delivery of a genetic payload to specific affected parts of the body. b) By exchanging the therapeutic DNA through the selection of starting materials in a manufacturing process, different patient groups can leverage identical capsid and manufacturing technologies.

are constrained by the need for sophisticated equipment, specialized raw materials, and highly trained scientists with a prerequisite for extensive process development. Overcoming these limitations necessitates a substantial investment of both time and capital for each novel gene therapy.

Smaller biotech companies, academic research laboratories, and philanthropic organizations are frequently at the forefront of research in gene therapies for rare diseases. However, these entities often lack the robust financial and infrastructural resources necessary to transition from early-stage research to clinical application. Their contributions are critical in identifying novel targets and establishing proof-of-concept studies; yet, the "valley of death" between diagnostic breakthroughs and clinical application remains a hurdle. Limited access to advanced manufacturing facilities, regulatory expertise, and the capital required to fund extensive clinical trials often hampers the progression of even promising drug candidates into proven treatments.

In contrast, larger for-profit institutions and pharmaceutical companies possess the requisite funding, expan-

sive research infrastructure, and deep technical expertise needed to navigate the multifaceted process of drug development. Due to market forces, these organizations typically operate under business models that prioritize therapies with commercial potential. Rare diseases, by definition, affect a limited patient population, which can result in little or no commercial return on investment. This economic calculus often results in hesitance to allocate significant resources toward developing gene therapies for conditions that may not promise financial returns, despite their potentially profound impact on affected individuals. Consequently, many patients suffering from rare diseases are left without therapeutic options, and the development pipeline for potentially life-changing treatments remains critically underfunded and underdeveloped.

By aligning scientific innovation with supportive regulatory policies and sustainable business strategies, it is possible to foster an environment where gene therapies for rare diseases can thrive.

Addressing these challenges will require a concerted effort from multiple stakeholders. Innovative funding models, such as public-private partnerships, government incentives, and dedicated rare disease research funds, may bridge the financial gap between therapeutic discovery and patient dosing. Collaborative frameworks that bring together academic institutions, philanthropic organizations, and small biotech and larger pharmaceutical companies can also create synergies that leverage the strengths of each partner. By aligning scientific innovation with supportive regulatory policies and sustainable business strategies, it is possible to foster an environment where gene therapies for rare diseases can thrive.

NIIMBL

NIIMBL is a leader in advancing US biomanufacturing. Since launching in 2017, NIIMBL has catalyzed collaborations between industry and academia, driving technology advancements and innovative products. In 2023, NIIMBL launched its Viral Vector Program (VVP) to address challenges in translating genetic medicine into commercial therapies.[1]

The VVP exemplifies NIIMBL's commitment to fostering public–private partnerships. By uniting stakeholders from pharmaceuticals, academia, and biotech manufacturing, the VVP promotes pre-competitive collaboration. Its goal is to extend industry-standard technologies to academic, non-profit, and philanthropically funded research, democratizing access to high-quality manufacturing capabilities.[2]

To overcome technical barriers in AAV gene therapy production, the program is developing a standardized manufacturing platform that uses proven technologies aligned with regulatory expectations for use in patients. This platform is being designed to ensure scalable and reliable production, enabling robust manufacturing of AAV gene therapies.

NIIMBL also recognizes the need for accessible analytical methods to ensure the quality, efficacy, and safety of manufactured gene therapies. The VVP is pursuing development of an analytical method toolbox and establishment of analytical reference materials aligned with regulatory requirements to facilitate rapid translation of pre-clinical candidates into early-phase clinical trials. Using these resources maintains short-term affordability and compliance while also enabling longer-term product and process understanding that can serve to guide and de-risk use of AAV for further indications.

Gene therapy for rare diseases presents unique challenges that we believe can be overcome through collaborative development of pre-competitive processes and analytical technologies. Unlike high-volume commercial biologics, rare disease therapies require low-volume manufacturing and flexible platforms that accommodate diverse therapeutic genes. Low production volumes often preclude the necessity to generate the extensive manufacturing history that most biologics leverage for regulatory approvals. At the same time, researchers in rare disease therapeutics prioritize simplicity and modularity, ensuring that the system delivers maximum value from limited available input. Reproducing core functionality, defined by product-independent platform development and demonstrated across diverse small-volume productions, can

[1] See https://www.niimbl.org/

[2] See https://www.niimbl.org/projects-programs/viral-vectors/

be used to establish real-world production history for conserved platform modules while lowering the burden on each individual program.

NIIMBL's VVP is designing a platform to support a decentralized user base, potentially accommodating hundreds or even thousands of user applications. Platform services will prioritize growth and maturity in digital resources, data aggregation, and critical starting material availability. The platform is intended to be compatible with existing industrial infrastructure and thus will remain agnostic as to competing product lines of noncritical equipment and materials. This approach fosters sustainable and scalable development, reducing the financial and logistical burdens of large capital projects and extensive administrative overhead.

To maximize impact, NIIMBL is committed to making their vector platform open access. The program will publicly share its standardized production and analytical methods and supporting data packages, providing a low-cost, user-friendly entry point for new research initiatives. Transferring, applying, and demonstrating process performance at multiple manufacturing sites can further streamline the maturation of new projects, accelerating the transition from research to clinical development.

The NIIMBL Viral Vector Platform

NIIMBL's VVP is developing a detailed suite of process and analytical methods for manufacturing pharmaceutical-grade AAV vectors for gene therapies. The production process, depicted in figure 2 as a process flow diagram, initially uses an industry-standard HEK293 triple-transfection cell culture system (Durocher et al. 2007) with chromatography and filtration purification (Lorek et al. 2025). The analytical tests were chosen to reliably measure prospective critical quality attributes (CQAs) to ensure the safety and efficacy of the vector, as listed in table 1.

A foundational philosophy for the platform is a balance of rigor and flexibility. Fixed, high-quality starting materials—such as the HEK293 cell line, cell culture media, and helper plasmids —ensure consistency across investigational drugs and development phases. Other platform components like chromatography media and RepCap plasmid may need to be tailored for each specific serotype.

Flexibility in a subset of a platform's critical process parameters, within a well-characterized, allowable range, provides the ease in adaptability needed to accommodate variations in a vector's genetic cargo. Factors like transfection ratios and elution gradients require the end user to adapt to variations in transgene sequence and size, with careful risk assessment guiding acceptable product-specific optimizations from the NIIMBL reference process. With these few tasks fully functional, manufacturing capability is defined.

For small-volume, ultra-rare indications and early clinical trials, process robustness is prioritized over peak productivity. In these cases, a mid-scale production bioreactor typically meets patient needs, while employing scalable technology allows for rapid expansion when commercial demand is viable.

An open-access platform lowers financial, technical, and regulatory barriers, creating an environment where more investigational drugs reach early-phase trials.

To achieve broad application in rare indications, the platform is being designed to offer simplified methods and scaled-down models that match the capabilities of small research institutions; risks associated with transferring processes into regulated environments are reduced. By providing clear manufacturing targets and normal operating ranges for key parameters, early development can proceed within a defined and reliable operating space.

NIIMBL's analytical suite will enable consistent measurement of the minimal essential CQAs listed in table 1. As with all parenteral pharmaceuticals, gene therapies must be thoroughly tested by several compendial USP methods to ensure batch quality and safety. Other key product purity controls include monitoring the percentage of empty capsids, aggregation levels, and residual impurities. These methods are generally applicable across products, independent of the transgene sequence, though some may be tailored to specific capsids (Gimpel et al. 2021).

The modularity of gene therapies necessitates adapting some measurements for the specific identity and length of each therapeutic vector genome. For assessing transgene quantity and quality, promoting standardized PCR methods (ddPCR or qPCR) and sequencing techniques can be a stepping stone toward product-specific methods.

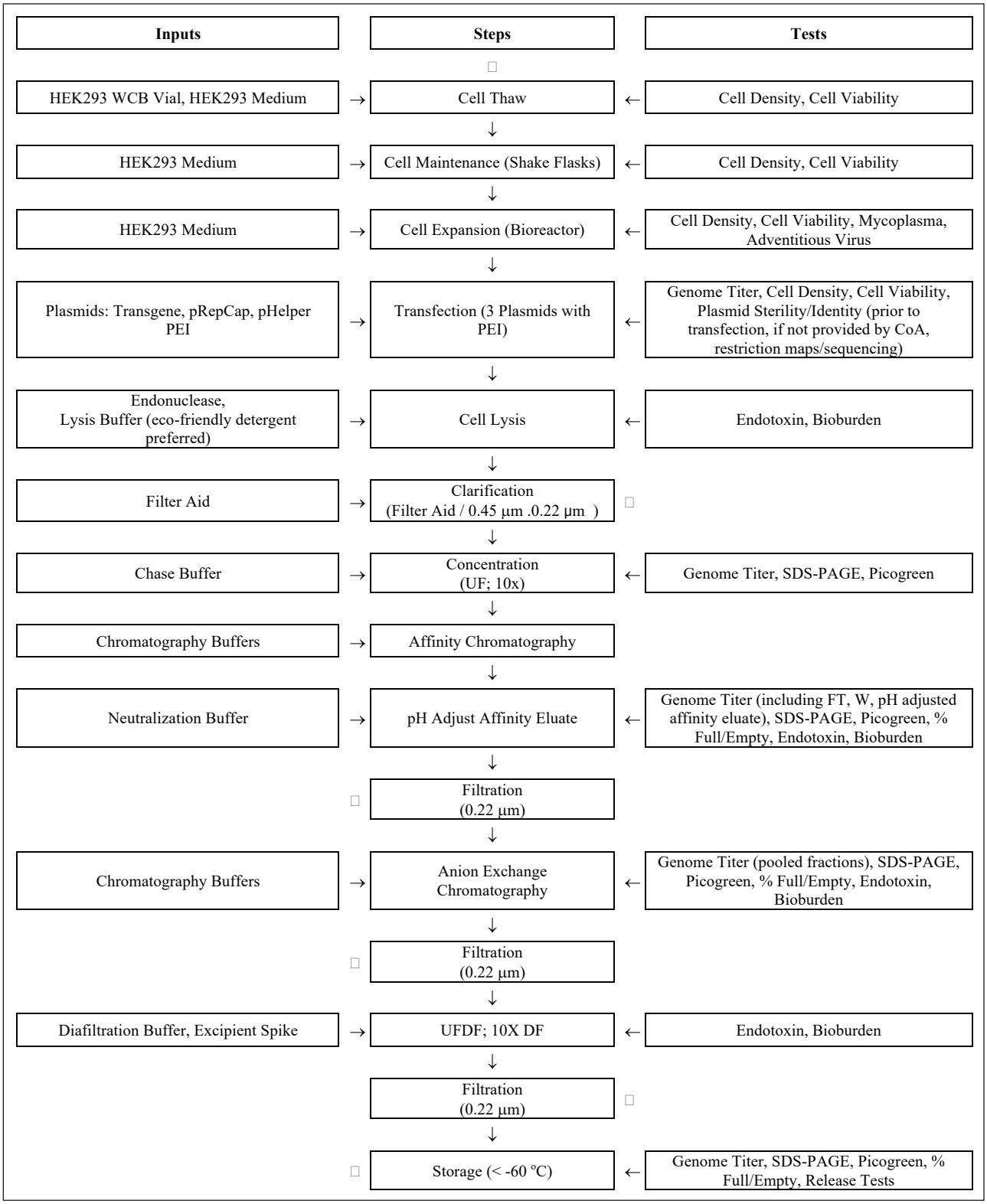

FIGURE 2 A process flow diagram illustrating the critical material inputs, production steps, and control tests describes the most conserved elements of the NIIMBL production platform.

For example, while many PCR method steps are broadly applicable, primer selection and amplicon design often require customization for each new product.

Potency assays, which measure the specific activity of a gene therapy, are inherently product specific and less amenable to standardization. In early development, semi-quantitative potency measurements relative to a reference material may be sufficient. Although the NIIMBL platform does not cover potency assay development, its robust methods for other quality attributes provide critical support for overall product evaluation.

The platform process approach allows for the sharing of development data across multiple disease indications, sponsor organizations, and genes of interest, reducing redundant process optimization efforts and streamlining development timelines.

By leveraging a common data framework, stakeholders can:

- Guide the establishment of prospective CQAs and critical process parameters
- Reduce the number of preclinical development studies needed per individual gene therapy candidate, ultimately accelerating the transition from research to clinical trials
- Lower overall development costs by minimizing duplicative work and optimizing process development investments
- Provide a shared risk assessment framework that enhances transparency and de-risks process scalability and regulatory compliance for emerging gene therapy developers

This collaborative and pre-competitive approach ensures that companies and institutions working on AAV-based gene therapies can benefit from collective process and analytical knowledge—enabling more rapid, cost-effective, and well-characterized translation of gene therapy candidates from the laboratory to the clinic.

TABLE 1 Prospective Critical Quality Attributes of AAV-vectored gene therapies are necessary for ensuring patient safety and fulfilling phase appropriate regulatory expectations.

Quality Category	Quality Attribute	Method Type
Identity	Vector Genome Identity	Sequencing
	Capsid Identity	Various
Purity	Capsid Protein Purity	CE-SDS
	AAV Vector Aggregation	SEC / DLS
	Residual Plasmid DNA	PCR
	Residual Host Cell DNA	PCR
	Residual Host Cell Protein	ELISA
	Residual Transfection Reagent	Various
	Residual Endonuclease	Various
	Residual Affinity Ligand	Various
Strength	Vector Genome Quantity	PCR
	Capsid Quantity	ELISA
	Full/Partial/Empty %	Various
	Cell-Based Potency[1]	*In vitro*
Safety	Adventitious Agents	*In vitro*
	rcAAV	*In vitro*
	Bioburden	USP <61>
	Endotoxin	USP <85>
	Sterility	USP <71>
	Osmolality	Freezing Point Depression
	pH	Potentiometric
Quality	Appearance	USP <631>, USP <790>
	Extractable Volume	USP <1>
	Particulate Matter (Visible and Sub-Visible Particles)	USP <787>, <790>

[1] Cell-Based Potency is a recommended standard but will not be developed as part of a product agnostic platform due to the uniqueness of each investigational therapeutic.

Building a Healthier Community

An open-access platform offers a practical solution for reducing cost, time, and risk for gene therapy development that has historically been slow, costly, and fraught with technical and regulatory hurdles. By eliminating proprietary restrictions and fostering collaboration, this approach benefits a broad range of stakeholders, as illustrated in figure 3. From researchers and manufacturers to

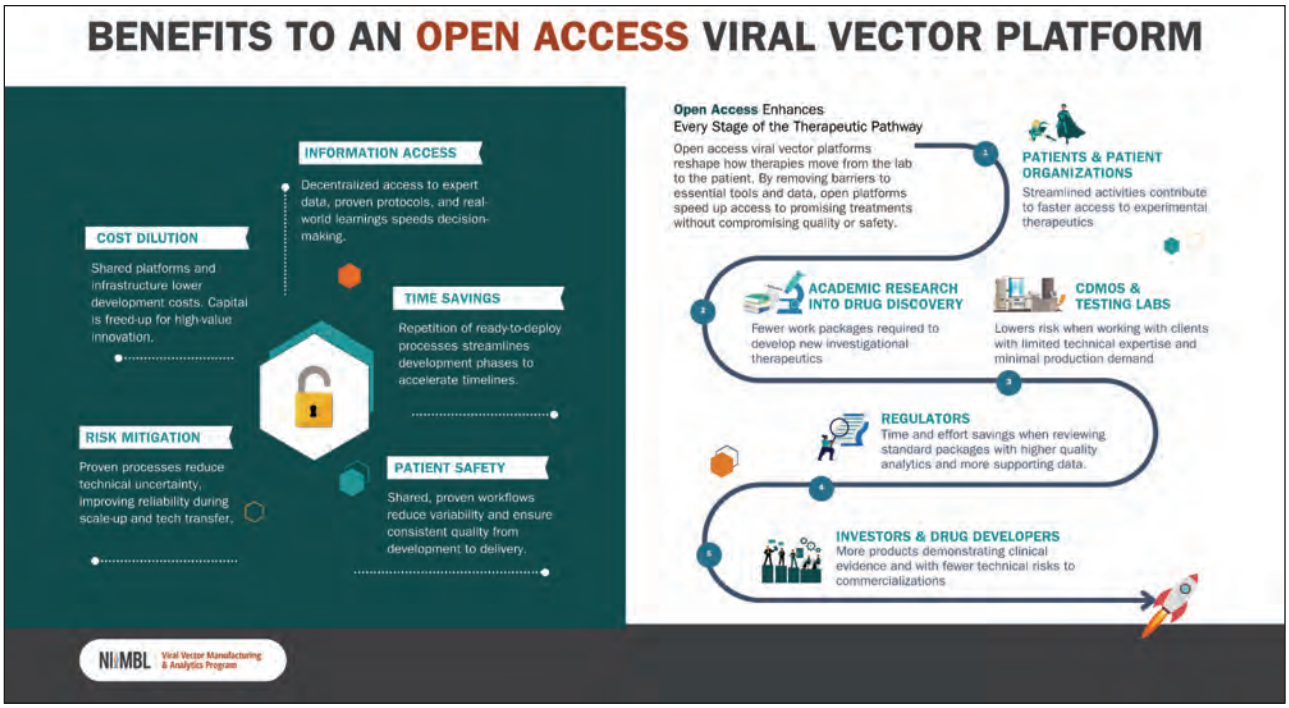

FIGURE 3 The manifold benefits of an open-access technology platform are shared by numerous stakeholders throughout the development lifecycle of an investigational gene therapy.

regulators, investors, and, most importantly, the patients who stand to gain the most, NIIMBL aims to support a thriving gene therapy community.

For ultra-rare diseases, high manufacturing and analytical complexities often prevent promising therapies from progressing beyond preclinical stages. NIIMBL's open-access AAV vector platform attempts to address this bottleneck by providing a standardized, well-characterized process that streamlines early development. By eliminating the need for each organization to build custom production and analytical frameworks, researchers can concentrate on advancing therapies rather than optimizing manufacturability. Accelerating the transition from lab-scale production to clinical-grade AAV vectors, thereby reducing time and cost, also benefits universities and startups looking to ensure their innovations reach the bedside of patients.

Contract development and manufacturing organizations can leverage the open-access production platform to distribute tech transfer costs across multiple users. This model makes small-batch manufacturing for ultra-rare indications, where trial sizes are inherently small and economically viable. Manufacturers may be able to shrink production gaps or fill excess capacity. The flexibility of the platform also provides commercial pharmaceutical developers with options to work with a contract development and manufacturing organization or transition production in-house as their needs evolve. Moreover, analytical testing laboratories can adopt standardized methods to enhance product characterization, compliance, and data standardization, resulting in faster, more reliable batch-release testing.

The biotech industry's rapid growth has also created a pressing need for workforce development in gene therapy manufacturing and analytics. Training programs can incorporate open-access platforms into their curricula, equipping workers with the technical skills needed for careers in viral vector production and regulatory compliance. Initiatives supported by the National Institute for Bioprocessing Research and Training, NIIMBL, and state-level workforce programs can use this approach to build a talent pipeline that supports the expanding gene therapy sector.

A standardized, transparent production model benefits regulatory agencies by simplifying the regulatory review process. Familiarity with a well-characterized platform allows regulators to efficiently assess new submissions, while high-quality analytics bolster confidence through robust data on safety, potency, and purity. Furthermore, the open-access system may help gene therapy

manufacturing sites with the creation of regulatory-relevant drug master files and obtaining platform-based designations, further accelerating the product approval timeline.

An open-access platform lowers financial, technical, and regulatory barriers, creating an environment where more investigational drugs reach early-phase trials. This expanded pipeline of potential treatments makes the gene therapy field more attractive to investors. By reducing uncertainty and leveraging shared data and peer review, the model improves risk-adjusted returns and positions the sector for sustainable growth, thereby drawing further investment into therapies for rare and ultra-rare diseases. Transparency in collaborative learning may also benefit sponsors of novel AAV therapeutics for more prevalent indications where manufacturing costs and relative safety concerns also permeate.

Health insurers and reimbursement agencies may also stand to benefit from the predictability afforded by standardized manufacturing and process validation. Potentially reduced batch variability leads to more predictable pricing and simplifies reimbursement decisions. Moreover, robust real-world data on safety and efficacy may provide the evidence needed to assess long-term cost-effectiveness, potentially enhancing access to life-changing treatments for patients.

An open-access AAV vector platform represents more than just a technical solution; it is a catalyst for broader change in the gene therapy landscape. By clearing away financial and technical thickets of manufacturing, this model creates an environment where more therapies can potentially reach patients, particularly those with rare and ultra-rare diseases. The ability to move investigational drugs more efficiently into early-phase trials expands the pipeline of potential therapies—seeding innovation, nurturing unmet medical need, and shining a light on collaborative science for the benefit of society.

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