# Optimizing Successful Development of Viral Vector Gene Therapies, Gene Therapy Trials, and Companion Diagnostics

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## Executive Summary

Gene therapy holds great promise and has sparked great interest among researchers, healthcare providers, and patients alike because it offers the possibility of cures, particularly for rare diseases with a genetic basis. However, the field is in its nascent stages, and the ideal methods and solutions for unlocking the full potential of gene therapy are still being developed.

The specifics of gene delivery, from finding a reliable means of introducing genetic material into target cells to reducing the risk of adverse events, can complicate the development process. In addition, it can be difficult to determine the appropriate approach to securing regulatory approval. In this white paper, we explore general principles to optimize the likelihood of preclinical and clinical trial development success, and provide a more specific focus on considerations for adeno-associated virus (AAV) based gene therapies. We describe regulatory guidelines and explain how pharmaceutical sponsors can ensure a scientifically valid gene therapy development plan. Lastly, we outline how Precision for Medicine can assist sponsors in developing gene therapy programs from bench to bedside, including preclinical trial studies, companion diagnostic development, clinical trial execution, regulatory applications, and postmarketing efforts.

# Introduction

Gene therapy is an experimental technique that can effectively deliver nucleic acid into a person's cells through a delivery vehicle known as a vector.[1] Gene therapy can be used to[1]:

- Replace a defective gene due to disease-associated mutation
- Silence a gene that contributes to disease pathogenesis
- Edit a gene to correct a disease-promoting sequence to a disease-preventing sequence
- Genetically modify cells to increase therapeutic potential (ie, chimeric antigen receptor T-cell [CAR T] therapy)

Despite risks associated with gene therapy, the field is growing as a promising treatment for various diseases.[1] Currently, only 5% of all gene therapies are in post-phase 3 status.[2] We will provide a general background of the gene therapy process and discuss hurdles to the development of viral vector gene therapies, with specific considerations for adeno-associated-virus (AAV)–based gene therapies, challenges to initiating a clinical trial with a gene therapy, and how Precision for Medicine can help develop gene therapy programs from bench to bedside.

CAR T, CRISPR, and messenger RNA–based technologies will not be addressed in this paper.

## Gene Therapy vs Small Molecule-Based Therapies

Currently, the most common therapeutic agents are small molecules, but in many cases they only treat the symptoms, not necessarily the cause of a disease. Gene therapy is primarily aimed at the cause of disease by regulating the gene expression. However, it also bears a number of limitations (ie, immunogenicity, delivery, etc).[1,3,4] Potential solutions to these limitations will be discussed later.

## Delivery Mechanisms of Gene Therapy

Gene therapy can be delivered either in vivo or ex vivo, meaning that genes can be delivered directly into the body using viral or nonviral vectors, or by genetically modifying patient-derived cells before their reintroduction into the patient.[4,5] Varying vectors have specific characteristics, benefits, and drawbacks (Table 1)[3]:

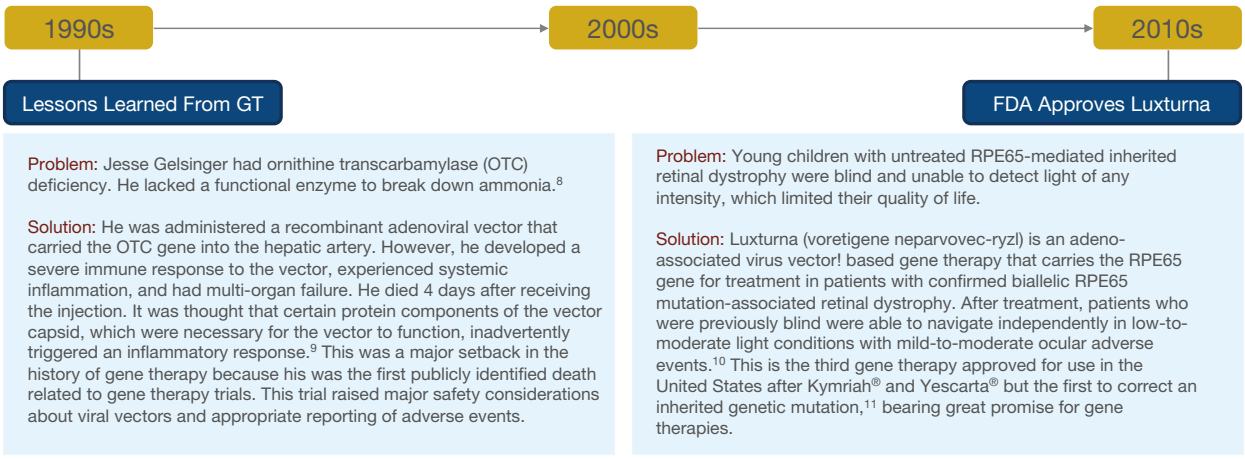
- **Viral vectors:** Transgene delivery by encapsulating transgene in adeno-associated viruses (AAVs), lentiviruses, and adenovirus vectors
- **Nonviral vectors:** Direct injection of transgene[3]

Table 1: Characteristics, Benefits, and Limitations of Viral and Nonviral Vectors[6]

| Gene Delivery Systems | Characteristics | Benefits | Limitations |
|---|---|---|---|
| Adeno-associated viral (AAV) vectors | ▪ Derived from replication-defective parvovirus<br>▪ Episomal vector DNA in cells | ▪ Nonpathogenic, nonintegrating vectors<br>▪ Long-term transgene expression achievable | ▪ Size limitation<br>▪ Long-term expression limited to post-mitotic cells<br>▪ Preexisting immunity in humans |
| Lentivirus vectors | ▪ Vector DNA integrates into genome | ▪ Accommodates large transgenes<br>▪ Sustained transgene expression in dividing cells<br>▪ Low immunogenicity | ▪ Low production yields<br>▪ Increased risk for insertional mutations |
| Adenoviral vectors | ▪ Episomal DNA in cells<br>▪ >50 human serotypes identified | ▪ Accommodates large transgenes<br>▪ High transduction efficiency | ▪ Able to elicit strong antiviral immune response<br>▪ Long-term expression limited to post-mitotic cells |
| Nonviral | ▪ Various approaches can be used to deliver gene | ▪ Low risk of immunogenicity and insertional mutagenesis | ▪ Lower transfection efficiency<br>▪ Transient gene expression |

To date, one of the safest strategies for gene therapies is the use of recombinant AAV (rAAV) particles lacking any viral genes. They can be cell-type specific, efficient, and lack pathogenicity because they need a helper virus to replicate.[7] Figure 1 highlights an advance and a setback for the field of AAV gene therapy.[8-11]

Figure 1: **Two case studies highlight a death that occurred in the late 1990s and the first FDA-approved gene therapy for a genetic disease nearly 2 decades later. Abbreviations: FDA, Food and Drug Administration; GT, gene therapy.**




## Development of a Gene Therapy Vector

The first step to developing gene therapy is to understand disease pathogenesis and the underlying genetic defect that needs to be modified. The genetic defect can help identify a target product profile, which is the anticipated product label that demonstrates safety and efficacy. Afterward, a transgene construct can be created for in vitro gene transfer, used in larger animal studies, and implemented in clinical trials (Figure 2).

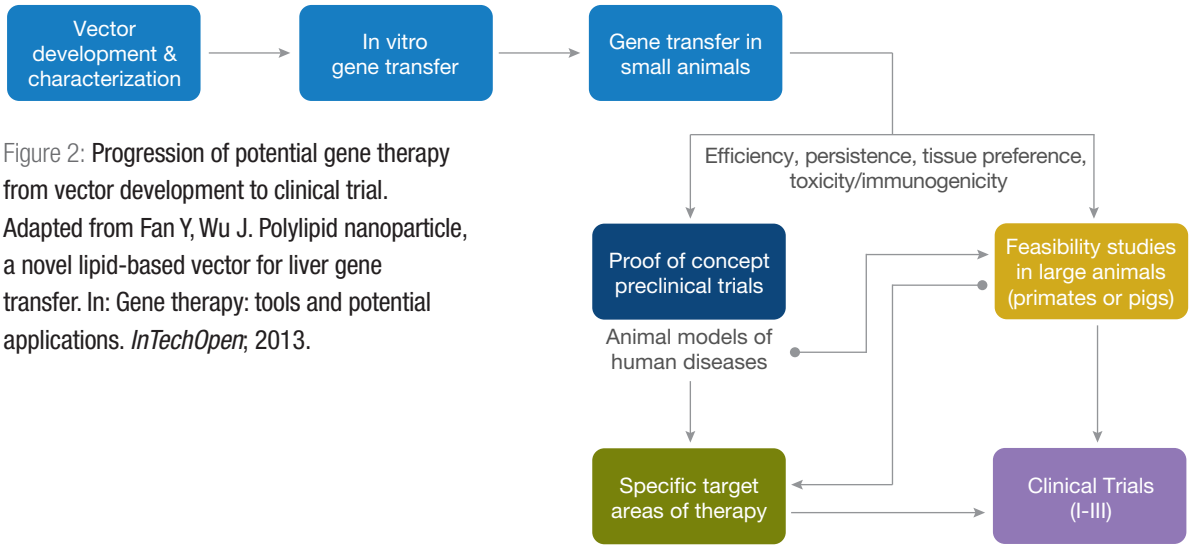



Figure 2: **Progression of potential gene therapy from vector development to clinical trial. Adapted from Fan Y, Wu J. Polylipid nanoparticle, a novel lipid-based vector for liver gene transfer. In: Gene therapy: tools and potential applications. *InTechOpen*; 2013.**

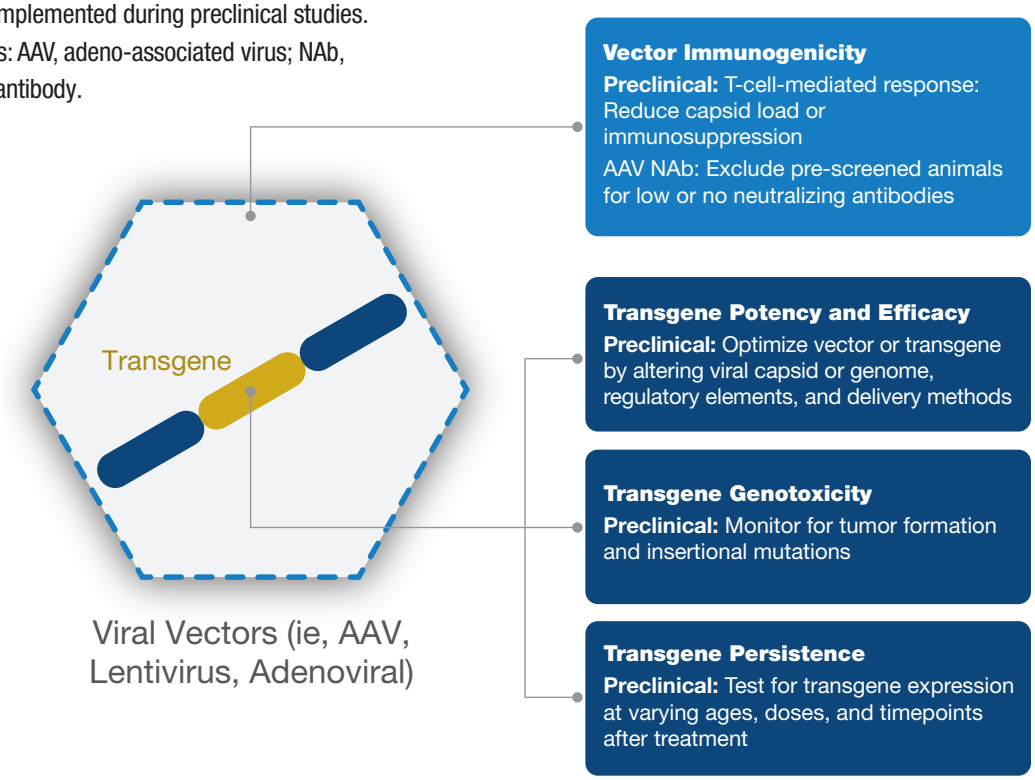
## Challenges in Vector Development

The road from vector development to clinical trials bears many challenges, including (1) vector immunogenicity, (2) potency and efficacy, (3) genotoxicity, and (4) persistence, but solutions can be implemented in preclinical studies (Figure 3).[12]

- **Vector immunogenicity:** Viral vectors can lead to innate and adaptive immune responses, which lead to reduced efficiency of gene transfer. When using AAV as a vector, there are specific considerations related to immunogenicity. Both humans and animals have ongoing exposure to AAV and may have developed humoral and cell-mediated immunity directed toward the AAV capsid. This immunity may result in neutralizing antibodies (NAbs) and/or cytotoxic T-cells directed against the AAV-transduced cells and thus compromise both safety and efficacy of AAV vectors. Although NAbs neutralize the activity of AAV, the impact of NAb levels associated with neutralization of AAV activity is not well understood[12]
- **Potency and efficacy:** Transgene expression levels required to achieve therapeutic efficacy can differ based on the inherent pathophysiology of the targeted disease and the transgene product
- **Genotoxicity**: Viral vectors may be subject to random insertional mutations that can disrupt gene expression (ie, tumor suppressor or oncogenes), leading to cancer.[3] While AAV vectors typically do not integrate into the host DNA, rare instances of random integration into the host genome have been reported in neonatal mice, which has led to tumor formation.[12] To date, no insertional events in humans after gene transfer resulted in tumors[13,14]
- **Persistence:** Long-term transgene expression may be difficult to achieve in dividing cells[12]

Because there are many challenges to developing a vector, a consensus recommendation from a group of gene therapy experts is that a gene therapy product should be optimized early in development before starting investigational new drug (IND) activities.[15]

Figure 3: Challenges in vector development with solutions that can be implemented during preclinical studies. Abbreviations: AAV, adeno-associated virus; NAb, neutralizing antibody.



# FDA Guidance on Gene Therapy

Table 2: FDA Guidance Documents for Industry That Provide Recommendations for Vector Testing, Preclinical Development, Clinical Trial Design, and FDA Approval of Gene Therapies

| Guidance Document | Published Date |
|---|---|
| Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products | 1/2011 |
| Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products | 9/2013 |
| Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products | 6/2015 |
| Draft Guidance for Industry: Human Gene Therapy for Retinal Disorders | 7/2018 |
| Draft Guidance for Industry: Human Gene Therapy for Rare Diseases | 7/2018 |
| Draft Guidance for Industry: Human Gene Therapy for Hemophilia | 7/2018 |
| Draft Guidance for Industry: Long-term Follow-up After Administration of Human Gene Therapy Products | 7/2018 |
| Draft Guidance for Industry: Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications | 7/2018 |
| Draft Guidance for Industry: Testing of Retroviral Vector–Based Human Gene Therapy Products for Replication-Competent Retrovirus During Product Manufacture and Patient Follow-up | 7/2018 |
| Guidance for Industry: Expedited Programs for Regenerative Medicine Therapies for Serious Conditions | 2/2019 |

In light of the many hurdles to successful gene therapy production and increasing efforts to create therapeutic products using gene therapy, the US Food and Drug Administration (FDA) has provided some guidance for industry regarding cellular and gene therapy. Table 2 highlights some of the guidance documents related to the development and application of gene therapies, and which the FDA is considering finalizing or updating in 2019.

## Regulatory Guidance in Gene Therapy Development

Because safety is a major consideration for vector development, it is important to evaluate safety thoroughly in preclinical studies. The FDA has outlined some recommendations related to preclinical study design in "Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products."[16] Understanding the design and conduct of preclinical studies can refine regulatory decisions that will help define safe administration of an investigational gene therapy product to humans.[15] The recommendations are nonbinding and are related to (1) use of the investigational gene therapy product, (2) proper selection of animal species that enable permissiveness or susceptibility of animal species to infection and model disease, and (3) proof-of-concept studies. Specifically, for the proof-of-concept studies, the following recommendations were included[15,16]:

- **Vector-specific considerations:** Perform long-term preclinical studies to identify any delayed adverse events or potential immune responses
- **Transgene-specific safety considerations:** Conduct long-term preclinical studies and test for quantitative transgene expression or monitor for potential immune responses
- **Biodistribution:** Evaluate biodistribution data, preclinical safety endpoint, and tissue and biological fluid analysis at the molecular level

These considerations are important for preclinical studies because they establish feasibility and rationale for clinical use and characterization of the gene therapy's safety profile.

# Considerations in Initiating Clinical Trial Using a Gene Therapy Product

Given that human clinical trials with gene therapy are time consuming and require much planning, ensuring a scientifically valid and sound trial design is essential.[15] Some of the key issues to consider when initiating a gene therapy trial include:
(1) expedited review of gene therapy products, (2) low recruitment and biostatistical challenges associated with small sample sizes, (3) inclusion/exclusion criteria for patients, (4) biomarker data and antiviral antibody status, and (5) interactions with the FDA.

## Accelerated Approvals for Gene Therapies

With the new guidance from the FDA, therapies for serious or life-threatening conditions with significant, unmet needs are eligible for accelerated approval through regenerative medicine advanced therapy designation, breakthrough therapy designation, fast track designation, accelerated approval, and priority review.[17,18] However, gene therapy for symptomatic therapy undergoes the traditional approach, which is not expedited.[19]

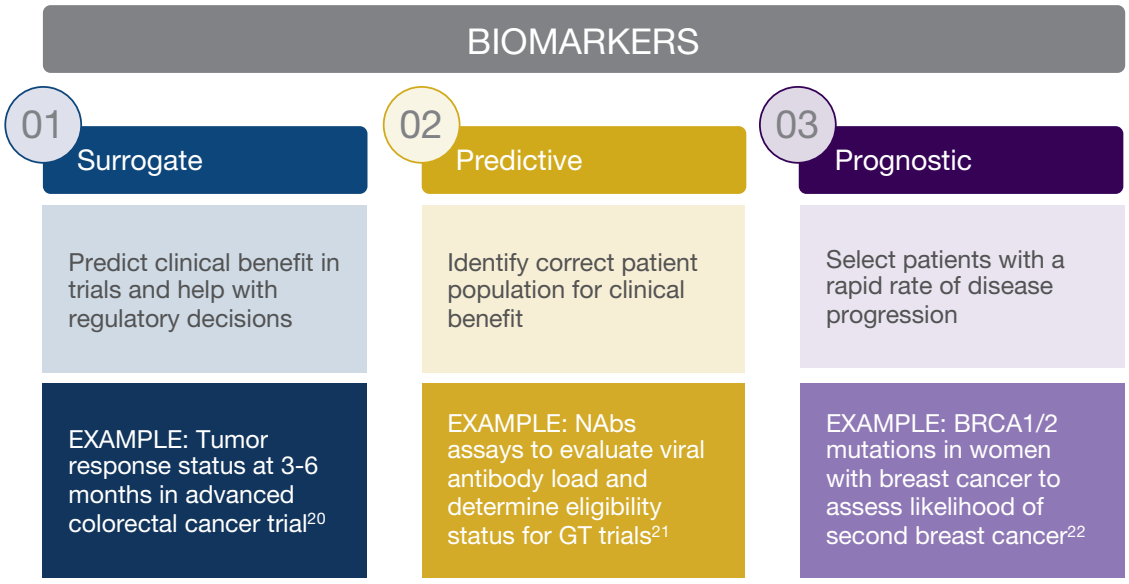
## Biomarker Data and Viral Antibody Status

In clinical trials, biomarkers are integral as measurable substances whose presence can influence the characteristics of the trial (ie, recruitment, efficacy, safety). Biomarkers should be considered in preclinical models because investigators can leverage this information to identify and validate biomarkers that are important for the disease of interest. Depending on the disease, some of these biomarkers are closely linked to the underlying pathophysiology of disease; restoration of the disease pathway can yield clinical benefit.[18] Biomarker choices and examples of these are described in Figure 4.[20-22] In rare diseases, biomarkers can be used to guide dose selection and monitor drug efficacy.[21]

## Recruitment and Statistical Challenge

Most rare diseases have genetic origin (~80%),[23] making them amenable to gene therapy. Although rare diseases can result from aberrations in a single

Figure 4: **Descriptions of biomarker choices with examples. Abbreviations: BRCA, breast cancer gene; GT, gene therapy.**



gene, the types of mutations within that gene can vary; some of these include missense, nonsense, and frameshift mutations, in addition to insertions, deletions, and translocations.[24] Noting the specific type of mutation may be important because safety and effectiveness of gene therapy may be linked to genotype in unpredictable ways. Thus, the specific type of mutation should be considered and tested for during the recruitment process.[18] Additionally, the inheritance patterns for genetic diseases (ie, dominant or recessive, X-linked recessive) could be important to consider for patient recruitment.[24,25] For example, for X-linked disorders, random X-linked inactivation can result in high phenotypic variability among female carriers of X-linked genes. As a result, disease heterogeneity due to gender can occur and should be considered during the study design.[18,25]

Similar to other rare disease trials, gene therapy trials may face challenges in recruitment and adherence. From a statistical standpoint, small sample sizes along with high intersubject variability can diminish study power to detect treatment-related effects.[18] Intersubject variability refers to how a measured endpoint varies across subjects. For some rare diseases, rare pathogenic variants have been linked to some severe Mendelian early-onset disorders that are highly penetrant with little phenotypic variability, making them somewhat predictable. Thus, the intersubject variability may be smaller in these well-defined populations because the nature of the disease is deterministic.[26] For example, patients with the same mutation can have a predictable phenotype, considering no environmental factors, which can result in a study that is well powered with small sample sizes.[27] One method to reduce intersubject variability for patients with rare diseases is to conduct natural history studies to help define patient populations based on the specific type of mutation and select proper endpoints to ensure sufficient power to detect efficacy.[28] For example, a treatment outcome that never occurs in the natural course of the disease can be a good endpoint, resulting in a well-designed, small study.[18]

Given potential recruitment difficulties for gene therapy trials, the FDA recommends collecting pertinent data (ie, adverse events, efficacy outcomes, biomarkers) to inform patient selection, randomization in early stages of development, stratified randomization based on disease stage/severity (if relevant), intrasubject control (if possible), and single-arm trials using historical controls. The FDA also recommends conducting first-in-human studies as a randomized, controlled trial to provide efficacy and safety results to support registration, but realizes there may be feasibility limitations. In that case, historical controls may be considered, but knowledge of the natural history of the disease is still essential.[18] As a result, conducting natural history studies early is necessary to obtain robust data and endpoints in small studies.[15]

## Eligibility Criteria for Gene Therapy

Eligibility criteria for patients undergoing gene therapy can be evaluated based on expected risks and potential benefits determined from preclinical studies. The study population can also affect the ability to detect the product's efficacy. As a result, inclusion of patients with varying severities of disease should be considered carefully. Healthy volunteers should be excluded in most gene therapy trials. Early-phase gene therapy trials may sometimes only enroll patients who do not have any other acceptable treatment options. Lastly, patients who may have characteristics that influence the safety or efficacy of the therapy may also be excluded from trials, as these can affect results.[29]

## Importance of Interactions With the FDA

The complexity of trial design in most gene therapy trials, whether preclinical or clinical, reinforces the need for early correspondence with the FDA to ensure a development program that can support a marketing application. The FDA recommends meeting with the Office of Cellular, Tissue and Gene Therapies early (ie, before IND submission) for sponsors who are developing gene therapy for rare diseases or those who are unfamiliar with the IND process.[18,29] Gene therapy experts agree on the importance of discussing plans early with the FDA.[15]

# Development of Companion Diagnostics

When used with gene therapy, companion diagnostics (CDx) can help inform treatment decisions. Thus, the identification of appropriate CDx has been proposed in multiple guidelines relevant to gene therapy.[18,30,31] CDx are often in vitro diagnostic devices that provide information essential for safe and/or effective use of a corresponding drug or biological product. CDx can help identify patients who are likely to benefit from therapy or those likely to experience treatment-related adverse events. These tools may facilitate the monitoring of treatment response, enabling healthcare providers to adjust therapy and achieve improved safety or effectiveness.[32] A few examples of approved CDx include polymerase chain reaction kits to detect mutations in patients and immunohistochemistry or enzyme-linked immunosorbent assays (ELISA) to detect protein expression related to disease or treatment. Current regulatory guidance recommends the development of CDx assays for gene therapy.

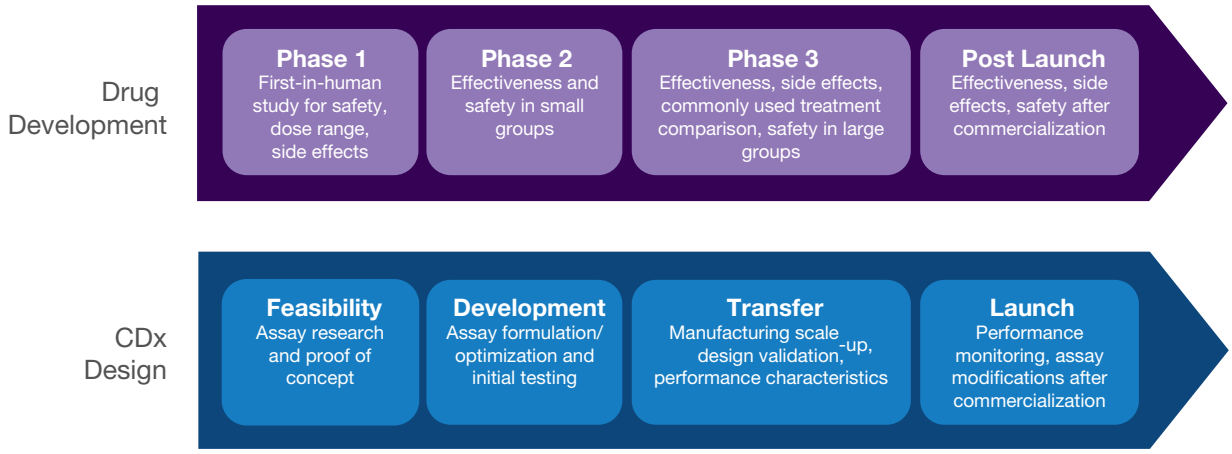
- **Tests used to confirm genetic disorders:** For diseases caused by a genetic defect, genetic testing should be performed. In the absence of a readily available, reliable means of obtaining the necessary genetic diagnosis, a CDx may be needed and should be considered early in development of the gene therapy[18]
- **Tests to evaluate preexisting antibodies:** To ensure the therapeutic potential of a gene therapy product, sponsors should consider developing a CDx to detect total antibodies (TAbs) and NAbs in patient serum. If the CDx is needed to appropriately select patients for clinical trials and, ultimately, for treatment, then submission of the marketing application for the CDx and the biologics license application for the gene therapy should be coordinated to support contemporaneous marketing authorizations[18]

## Key Considerations for Development of a CDx for a Gene Therapy

Ideally, CDx development should occur in parallel with drug development (Figure 5).[33] As with development of a CDx for any other type of drug, development of a CDx for a gene therapy should begin with a clear definition of the assay's use and what it measures, as well as the risks and benefits associated with it. In addition, it is important to define which patient population(s) would benefit from use of the assay in conjunction with therapy.[33]

The investigational device exemption (IDE) for the CDx to be used in clinical studies will be based on the level of risk, because the IDE regulation distinguishes between nonsignificant and significant device risks[34]:

Figure 5: Example of drug and IVD/CDx development processes occurring in parallel, aligning CDx development with clinical trials. Abbreviations: IVD, in vitro diagnostic.



- **Exempt:** CDx has no direct effect on treatment
- **Nonsignificant-risk IDE:** A wrong result with CDx does not constitute a safety risk
- **Significant-risk IDE:** A wrong result with CDx constitutes a safety risk

Sponsors are advised to carefully consider the type of IDE sought, because the type of CDx and how it is used in phase 2 studies can have either a positive or negative impact on phase 3 study design.

## Companion Diagnostics Regulatory Strategy

If the CDx is eligible, the Breakthrough Devices Program could facilitate FDA approval. The Breakthrough Devices Program replaced the FDA's Expedited Access Pathway and Priority Review Program for 510(k), de novo device or PMA submissions. To be eligible for the Breakthrough Devices Program, the sponsor must demonstrate evidence suggesting that the CDx would provide for more effective treatment or diagnosis of a life-threatening or irreversibly debilitating disease or condition. The FDA released final guidance on the Breakthrough Devices Program in December 2018.[35] The program offers 3 options for interactions with the FDA, or the option for the sponsor to propose alternative methods of interaction[35]:

1. **Breakthrough device sprint discussions,** in which the sponsor can provide the FDA with additional information or revisions on a single topic with specific goals within a set period. The number, format, and duration of interactions within a sprint discussion may vary based on program needs and should be defined in advance.
2. **Data development plan,** which allows the sponsor to coordinate with the FDA regarding a high-level document that outlines the clinical and nonclinical test designs and data collection strategy for the entire product life cycle.
3. **Clinical protocol agreement,** in which the FDA and the sponsor work interactively to agree in writing on a protocol and any previously agreed-upon changes.

Another regulatory approach that serves as an alternative to de novo or Premarket Approval (PMA) pathways is the Humanitarian Device Exemption, which is similar to a PMA but exempt from requirements for clinical trial effectiveness. A Humanitarian Use Device is defined as a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4000 individuals in the United States per year.[36]

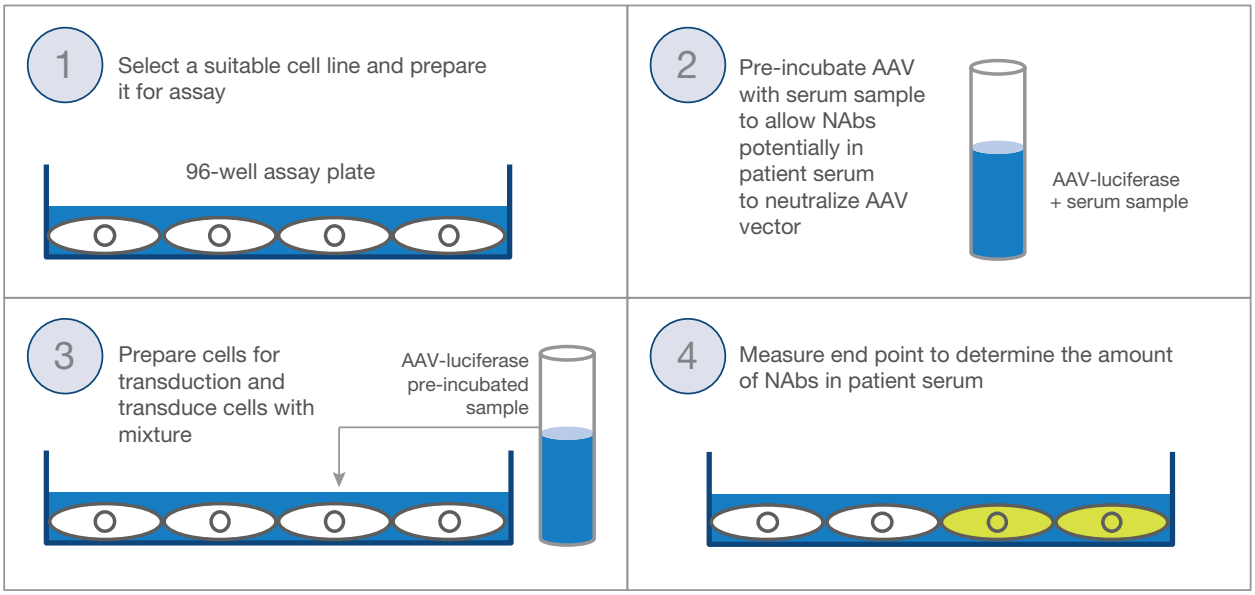
## Antiviral NAb Assay Development

In vitro cell-based assays provide a functional physiological system for NAb detection. Such assays are used primarily for development of AAV-based gene therapies, although some of the principles apply to other viral vectors such as adenovirus, herpes simplex virus, and lentivirus. However, these assays are complex to develop and use in a regulatory setting because they must reflect the mechanism of action of the gene therapy product. Key steps in assay development include (1) selecting a suitable cell line, (2) choosing the proper cellular response or endpoint, (3) identifying proper controls, (4) optimizing assay parameters, and (5) validating the assay for its intended purpose. Figure 6 provides an example of how a NAb assay may be performed.

Bear in mind that NAb assay development can be difficult for several reasons. Two essential considerations are: (1) the skill required to effectively validate a cell-based therapy, and (2) critical reagents for these assays include cell lines, which require the creation of master cell banks.

Sponsors who are developing an AAV NAb assay should also note that these assays are generic measurements of the delivery vehicle and are not necessarily specific to the gene therapy. Thus, communications with the FDA should focus on the ultimate intended use of the NAb assay.

Figure 6: **Major principles of NAb assay development and execution are described, with selection of cell line and end points being important steps outlined here.**

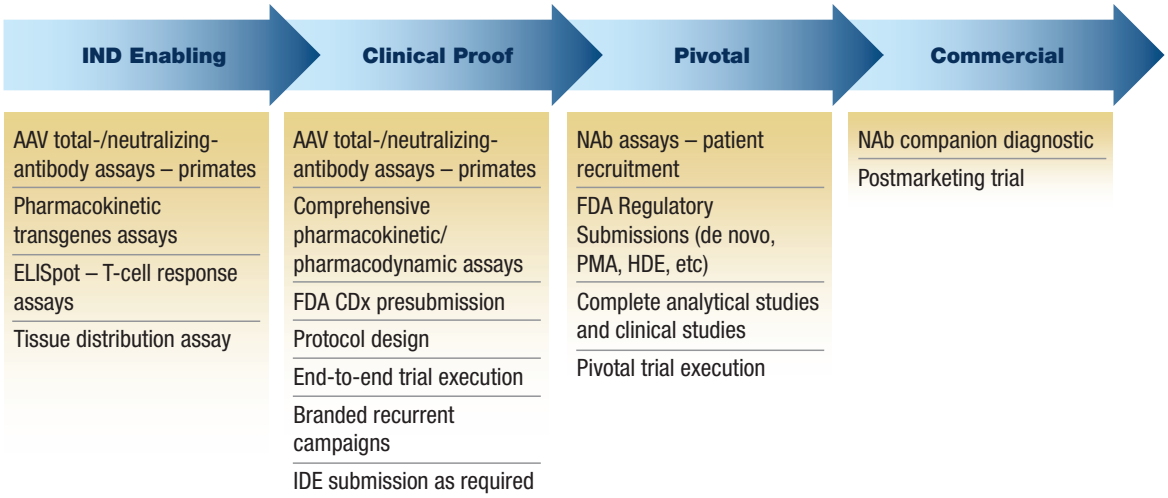


# Precision for Medicine Capabilities: From Bench to Bedside

Because of the inherent complexity of developing gene therapy trials from a clinical and regulatory perspective, it is important to have a good partner throughout development. Precision for Medicine has the infrastructure to support gene therapy programs from conception to commercialization, including the ability to develop assays to evaluate safety and efficacy of gene therapy, to correspond with the FDA for diagnostics presubmission and premarket approval submissions, and to conduct the pivotal and postmarketing gene therapy trials (Figure 7).[37] Precision for Medicine has supported the development of gene therapies in multiple vector types, and has experience in more than 50 rare disease trials and more than 100 orphan disease projects.

Precision for Medicine has developed assays that evaluate T- and B-cell–dependent immunogenicity of gene therapy vectors. For T-cells, Precision for Medicine has an assay that characterizes T-cell responses via ELISpot and intracellular cytokine staining. Precision for Medicine also has a NAb CDx designed to characterize binding and neutralizing antibodies to AAV serotypes, which can be used as a cell-based NAb screening method for study enrollment for either human trials or nonhuman primate trials.

Figure 7: Precision for Medicine capabilities to evaluate safety and efficacy for gene therapy trials. Here, specific capabilities with respect to AAV gene therapies are listed. Abbreviations: CDx, companion diagnostics; FDA, Food and Drug Administration; HDE, humanitarian device exemption; IDE, investigational device exception; PMA, premarket approval.




## Case Study: NAb CDx for Gene Therapy

**Problem:**
Because preexisting antibodies may hamper transduction efficiency and reduce efficacy of an AAV8 vector-based therapy, the sponsor wanted an AAV8 NAb CDx to be developed and validated to test human plasma samples for AAV8 antibodies to determine inclusion in a clinical trial.

**Solution:**
Precision for Medicine was able to develop and optimize a cell-based assay for detection and measurement of anti-AAV8 capsid antibodies capable of neutralizing the HEK 293 cell transduction using the luciferase reporting system. This included maintenance of the cell bank, running the assay, and testing clinical samples to help select patients for the clinical trial.[37] Precision for Medicine is also developing a single-site CDx under the control of their ISO 13485-certified and FDA 21 CFR 820-compliant laboratory facilities. As of early 2019, Precision for Medicine is also providing full regulatory, biostatistical, and commercial services for the CDx, including both strategic and tactical support for all activities throughout the product life cycle.

## Conclusion

Development of a gene therapy is a complicated undertaking, fraught with technical challenges and regulatory complexities. However, as gene therapy development advances with better technology and increased FDA regulatory guidance, there is great promise for this therapeutic area to yield clinical benefit. As the field advances, it is important to be able to successfully navigate the complexities of gene therapy development programs. Certain considerations should be made before starting a gene therapy trial, including evaluating the need for an accelerated FDA-approval process, assessing biomarker data and viral antibody status, reconciling challenges with low recruitment and small sample sizes, clearly defining eligibility criteria for patients, and having interactions with the FDA. Companion diagnostics should be created prior to gene therapy to alleviate some of these challenges. With careful planning and conduct of preclinical and clinical studies, validated CDx, clear FDA communications, and well-informed regulatory strategy, sponsors of investigative viral vector gene therapies can increase their likelihood of development success.

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