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Gene Editing Therapy in Cardiovascular Disease: 2026 ACC Scientific Statement

A Report of the American College of Cardiology

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ABSTRACT

It is increasingly recognized that many cardiovascular diseases have a genetic basis. Advancements in genome sequencing have allowed for dramatically higher rates of genetic testing with improved availability at a reduced cost. Technologic innovations—catalyzed by clustered regularly interspaced short palindromic repeats (CRISPR)–associated protein 9 (Cas9)–related approaches—have enabled the ability to edit an individual patient's genome in a precise and targeted manner. Delivery of these genetic interventions to desired cells specifically, safely, and efficiently has been a challenge, but the development of lipid nanoparticles offers a promising approach in cardiovascular diseases with hepatocyte-expressed treatment targets. Progress in genetic therapies have been exponential such that curative treatments for some cardiovascular diseases are imminent.

Given such rapid advancement and the potential scope of impact, this scientific statement provides an overview of gene editing therapies for the practicing clinician. This includes descriptions of: 1) the basic science that supports gene editing therapy; 2) the cardiovascular diseases that are currently most amenable for initial application of gene editing—diseases that are typically monogenic, that are modifiable by knockdown of protein production, and whose protein synthesis errors occur in the liver (certain variants of hypercholesterolemia and amyloidosis); and 3) the inherent challenges of gene editing including the societal and ethical implications of high-cost, single-treatment cures. As gene editing technology in the treatment of cardiovascular diseases continues to expand and evolve, cardiovascular clinicians are key stakeholders in ensuring that these interventions are applied with the proper clinical indications and with guardrails to promote ethical and equitable treatment.

INTRODUCTION

The American College of Cardiology (ACC) has a long history of developing documents to complement clinical practice guidelines. Among these documents, scientific statements represent a novel approach to inform clinicians about areas where scientific evidence is new and evolving or where sufficient data are more limited. Although gene editing therapy (GET) is a relatively new technology, it is already in wide use outside of medicine, and its clinical applications in human

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diseases are being explored with increasing speed. With the expansion of current and potential applications of GET in cardiovascular diseases (CVDs), this scientific statement was developed to provide the practicing cardiovascular clinician with an overview of GET, including the current state of the science, ongoing clinical trials, and future research directions. While ACC scientific statements typically provide consensus recommendations for clinical practice, the writing committee acknowledges that GET has not yet progressed beyond clinical trials in cardiovascular medicine. As a result, consensus recommendations have been deferred.

To accomplish this work, the ACC convened the "Advancing Gene Editing Therapy for Cardiovascular Disease Heart House Roundtable" on June 4, 2025.[1] This roundtable included a diverse, multidisciplinary group of experts who explored the intersection of science, clinical application, ethics, and policy of GET in CVD. The ACC subsequently convened a writing committee, some members of which were participants in the Heart House Roundtable, in October 2025 via a confidential conference call attended only by writing committee members and ACC staff. A review of seminal publications through December 31, 2025, and outstanding questions was facilitated. Writing assignments were configured according to each committee member's area of expertise. E-mail correspondence was used to provide critical review of contributed content. Differences were resolved by consensus among the writing committee. The committee's work was supported only by the ACC without any commercial input. Writing committee members were all unpaid volunteers. In accordance with the ACC's Policy on Relationships with Industry and Other Entities, relevant disclosures for the writing committee and comprehensive disclosures for external peer reviewers can be found in Appendixes 1 and 2.

DEFINITIONS AND CLASSIFICATIONS

Adeno-associated virus: A nonpathogenic virus widely used in gene therapy as a delivery vehicle for intracellular GET.

Clustered regularly interspaced short palindromic repeats (CRISPR), CRISPR-associated protein 9 (Cas9) system: CRISPR is a family of DNA sequences that serve as a bacterial defense against viral infection. Cas9 is a programmable enzyme used for targeted cleavage of DNA. In combination, this technology allows selective modification of the DNA of living organisms.

Gain-of-function variant: A genetic alteration that results in a new action, enhanced activity, or an abnormal pattern of expression.

GET: A form of gene therapy that uses specific techniques to add, remove, or alter DNA for disease prevention or treatment.

Indel: An insertion or deletion of bases in a genome.

Lipid nanoparticle (LNP): Small, round particles made up of phospholipids, cholesterols, ionizable lipids, and polyethylene glycol-derived lipids; used for drug delivery.

Loss-of-function variant: An alteration that results in the reduction or elimination of a gene's normal activity or product (typically a protein).

Nickase: A nicking enzyme or nicking endonuclease that cleaves a single strand of double-stranded DNA or RNA at a specific site.

Null allele: A specific form in which all gene activity is eliminated.

Off-target effect: An unintended result of medical treatment in which a drug impacts the function of tissues, organs, or systems outside of the targeted organ or system.

ABBREVIATIONS

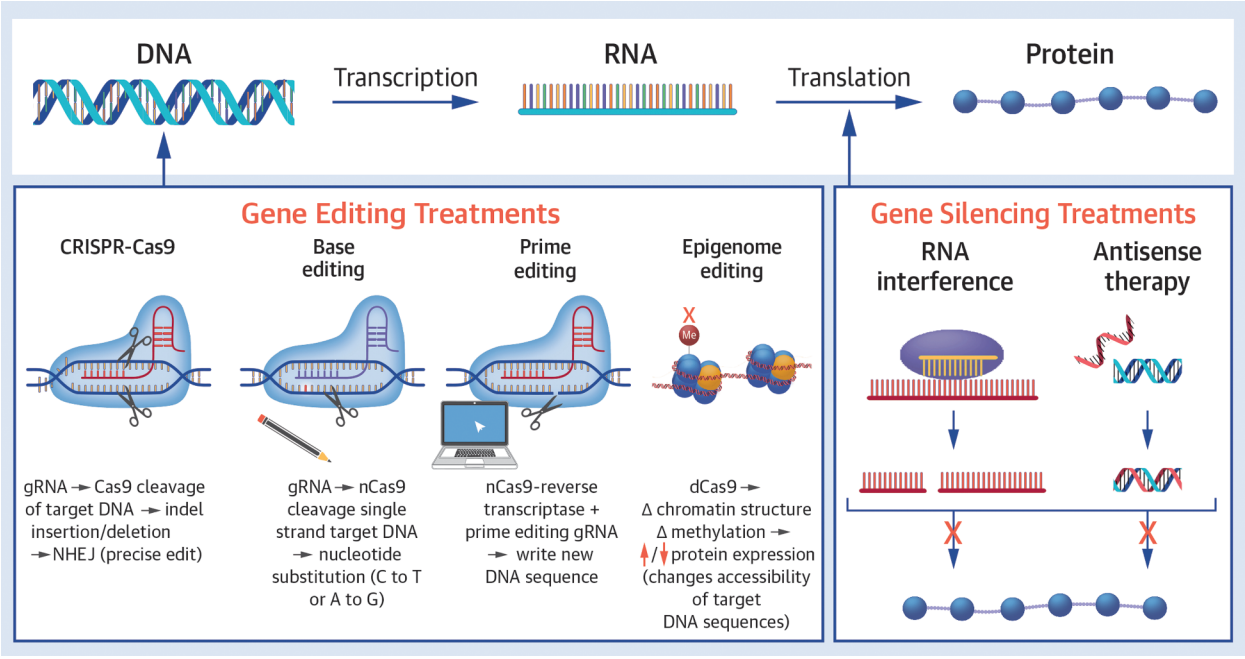
Abbreviation	Meaning/Phrase
AAV	adeno-associated virus
ATTR-CM	transthyretin amyloid cardiomyopathy
Cas9	CRISPR-associated protein 9
CRISPR	clustered regularly interspaced short palindromic repeats
CVD	cardiovascular disease
FH	familial hyperlipidemia
GET	gene editing therapy
gRNA	guide RNA
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LNP	lipid nanoparticle
nCas9	nickase Cas9

BACKGROUND

Scientific basis of gene editing therapy tools

Advancements in cell biology led to the development of therapies that target the genetic basis of disease. Gene silencing treatments such as RNA interference and antisense therapy prevent the translation of RNA into protein but require repeated dosing as they do not permanently change the genome. Gene therapy treats diseases by adding, removing, or altering faulty genetic material. Gene editing is a more precise and advanced type of gene therapy that involves the insertion, deletion, or replacement of DNA at precise locations to permanently alter the

FIGURE 1 **Targeting the Molecular Biology of Disease With Gene Editing and Gene Silencing**

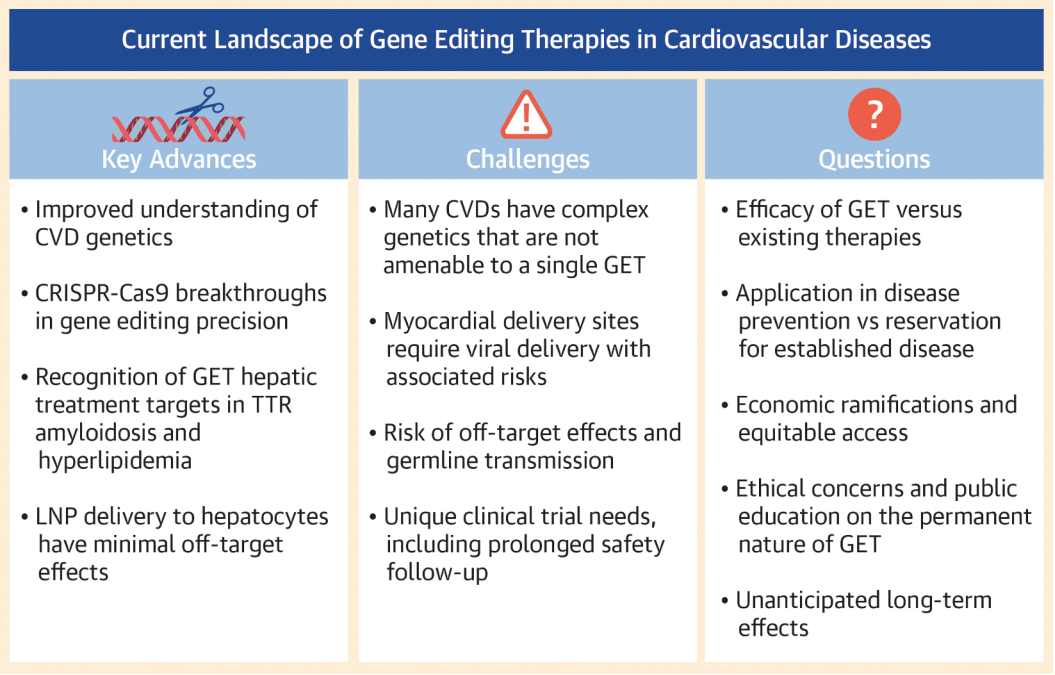


Genetic information in cells flows from DNA to RNA to protein. Gene silencing treatments (ie, RNA interference and antisense therapy) prevent the translation of RNA into protein; however, they require repeated dosing to prevent protein production because they do not permanently change the genome. In contrast, GET uses various methods to permanently alter the genome, offering the potential of a 1-time curative treatment. CRISPR-Cas9 acts like molecular scissors, where the Cas9 enzyme uses the CRISPR nucleic acid sequences as a guide to recognize and cleave specific strands of DNA complementary to the CRISPR sequences allowing the removal and insertion of new genetic sequences. The Cas9 protein also contains a gRNA that acts like a global positioning system or GPS to deliver the molecular scissors to the correct genomic address. In base editing, 1 DNA base is substituted for another at any given position and is likened to a pencil and eraser, offering more precision, particularly for inactivating genes. Prime editing offers the precision of base editing with the additional advantage of making any possible base change (eg, small indel variants, large deletions, and even large gene insertions) and is likened to a word processor. Epigenome editing differs from other forms of editing in that it does not modify DNA sequences but rather changes the accessibility of the DNA sequence to expression, thereby increasing or decreasing protein expression. Cas9 = CRISPR-associated protein 9; CRISPR = clustered regularly interspaced short palindromic repeats; dCas9 = dead Cas9; GET = gene editing therapy; gRNA = guide RNA; NHEJ = nonhomologous end-joining.

genome. The first methods developed for gene editing used programmable proteins that create so-called double-strand breaks in both strands of the DNA at specific target sites in the genome. Accordingly, these proteins (ie, nucleases) are often described as molecular scissors (**Figure 1**). The most common response of cells to broken DNA is to repair it through a process called nonhomologous end-joining (NHEJ).[2] During NHEJ, the free ends of the DNA created when a break occurs are reconnected in an error-prone process that can result in the semirandom insertion or deletion (indel) of incorrect DNA base pairs. These indel variants most often result in a nonfunctional protein. NHEJ is most useful for disruption of regulatory sequences or genes that influence gene expression or the amount of protein made, respectively.

The discovery and application of the CRISPR-Cas9 system represented a significant breakthrough in the development of gene editing technology (**Central Illustration**). CRISPR is a family of DNA sequences found in bacteria that serves as a detection and defense mechanism against viral infections. Cas9 is an enzyme that uses the CRISPR nucleic acid sequences as a guide to recognize and cleave specific strands of DNA complementary to CRISPR sequences. The combination of CRISPR and Cas9 allows for the removal and insertion of new genetic sequences and is the most widely used programmable nuclease to introduce double-strand breaks at target genomic sites because of its high editing efficiencies and relatively user-friendly nature.[3] It has 2 separate components that have distinct, separable activities, allowing for applications beyond nuclease editing. Although the Cas9 protein is a nuclease that cuts the 2 DNA strands with 2 distinct enzymatic components, it also contains a single guide RNA (gRNA) approximately 100 bases in length. The gRNA acts as a global positioning system or GPS that directs the Cas9 scissors to a target

CENTRAL ILLUSTRATION **Current Landscape of GET in CVD**



Ambardekar AV, et al. JACC. 2026;■(■):■–■.

Cas9 = CRISPR-associated protein 9; CRISPR = clustered regularly interspaced short palindromic repeats; CVD = cardiovascular disease; GET = gene editing therapy; LNP = lipid nanoparticle; TTR = transthyretin.

genomic site with the correct address (ie, a matching sequence) (Figure 1). Altering 1 or both enzymatic components of Cas9 yields a nickase Cas9 (nCas9) that can cut only 1 DNA strand[4] rather than both strands, or dead Cas9 (dCas9) that cannot cut DNA at all.[5] In either case, the gRNA will still act as a GPS to direct the altered Cas9 to the intended target genomic site. This makes the Cas9/gRNA combination a useful platform for attaching additional enzymes that can modify DNA in targeted ways, resulting in other forms of gene editing.

Another form of gene editing is base editing, where 1 DNA base is substituted for another at any given position, often likened to a pencil and eraser (Figure 1). In this instance, nCas9 is attached either to a cytidine deaminase enzyme to make a cytosine base editor[6] (converting cytosine [C] bases to thymidine [T]) or with an adenosine deaminase enzyme to make an adenine base editor[7] (converting adenine [A] bases to guanine [G]). As implied by this analogy, base editors offer much more precision than nucleases. Base editing is most effective for inactivating genes (eg, disruption of the start codon, introduction of a nonsense variant, or altering a splice site sequence) or for correcting the specific base that causes disease.

Another approach is prime editing, offering the precision of base editing with the additional advantage of making any possible base change (eg, small indel variants, large deletions, and even large gene insertions). As such, it is often compared with a word processor (Figure 1).[8] To accomplish prime editing, alterations are made to both the Cas9 protein and gRNA components: nCas9 is attached to a reverse transcriptase enzyme, and the gRNA is extended to serve as a template carrying a desired edit(s). The reverse transcriptase can then write a new DNA sequence, replacing the original sequence.

Finally, epigenome editing (Figure 1) differs from other forms of editing in that it does not involve any cutting of DNA strands or modification of DNA sequences. Rather, it changes the accessibility of the DNA sequence to influence the expression of a target gene and, thus, the amount of protein made from the gene. In 1 form of epigenome editing, dCas9 is attached to an enzyme that modifies the local chromatin structure around the target genomic site, alters the amount of methylation of cytosine bases near the site, or both,[9] increasing or decreasing protein expression.

All of the aforementioned editing technologies have been deployed in at least 1 clinical trial, either ex vivo (ie,

in cells collected and edited outside the body and transplanted into the body) or in vivo (ie, within tissues and organs inside the body). To date, 1 CRISPR-based therapy has received approval from the U.S. Food and Drug Administration (FDA): exagamglogene autotemcel (exacel) is for the treatment of sickle cell disease with recurrent vaso-occlusive crises or transfusion-dependent beta thalassemia. In this ex vivo therapy, the Cas9 nuclease from *Streptococcus pyogenes* (SpCas9) acts on hematopoietic stem cells harvested from a patient to disrupt an enhancer sequence in the *BCL11A* gene by NHEJ (resulting in increased fetal hemoglobin expression) with subsequent autologous transplantation of the edited cells into the patient.[10,11] Editing technologies are also being used in several nontherapeutic areas, including viral diagnostic testing, cellular and animal model development for biomedical research, and agricultural applications.

APPLICATION OF GET IN CVD

Selection of patients with CVDs who are candidates for GET

GETs offer the prospect of durable and potentially curative treatments for some CVDs currently managed with lifelong pharmacologic therapies. For many conditions, regularly taken medications to manage CVDs are often limited by access, polypharmacy, adverse effects, and adherence challenges. For some CVDs, RNA-based therapies are beginning to address some of these challenges by permitting longer interval dosing (ie, 1 dose every 3-12 months). However, the potential for a 1-time treatment with GET, which results in a cure and avoids the need for ongoing pharmacologic therapy and monitoring, has significant promise.

The suitability of a CVD for GET is closely tied to its genetic architecture. Monogenic diseases, each caused by a large-effect variant in a single gene, naturally lend themselves to disease interruption via the implicated gene for curative therapy. However, polygenic diseases, caused by typically weaker variants in numerous genes, would require significant multiplexing, increasing risks for off-target effects, variable efficiency, and unpredictability. Nevertheless, polygenic disease trajectories may be significantly altered by targeting single genes. For example, although atherosclerotic CVD is a polygenic disease, individuals with loss-of-function variants in *PCSK9* (proprotein convertase subtilisin/kexin type 9), whose gene product degrades low-density lipoprotein (LDL) receptors in hepatocytes, have lower low-density lipoprotein cholesterol (LDL-C) concentrations and lower risk of atherosclerotic CVD events.[12] Pathogenic variants can result in dominant-negative effects (ie, sufficient amounts of protein production are observed, but the protein has deleterious function) or haploinsufficiency (ie, insufficient amounts of production of an essential protein are observed). CVDs that result from dominant-negative pathogenic variants are better candidates for GET, because inhibition of protein production is easier than restoring or repairing an insufficient or defective protein.

Rectifying the single gene defects that cause inherited CVDs remains challenging for several reasons. Allelic heterogeneity, where different variants within the same gene can cause disease, is often implicated, potentially requiring targeted customization for each patient for both efficacy and safety. Disease pathology often occurs early in life, necessitating earlier identification and administration, potentially even during development. Relative to hepatocytes, the therapeutic threshold is higher for nondividing cells such as cardiomyocytes, and off-target edits may have greater consequences. Finally, allele-specific targeting of the pathogenic copy in heterozygous genotypes poses additional complexity. Nevertheless, preliminary investigations of base editing of human cardiomyocytes carrying the recurrently observed hypertrophic cardiomyopathy variant *MYH7* p.R430Q in vitro and knock-in mice with ortholog *MYH6* p.R403Q in vivo to wild-type have been promising.[13,14] In short, the current cardiovascular GETs in development focus on monogenic conditions that could be treated by genetic disruption of an overexpressed or critical pathogenic gene target as opposed to rectifying the disease-causing variant (Table 1). Nevertheless, novel GETs such as prime editing-mediated readthrough of premature termination codons have been shown to engineer suppressor transfer RNAs to readthrough prematurely introduced termination codons (ie, nonsense variants) in a generalized manner.[15]

In vivo delivery of GET in CVDs

A major challenge in applying GET to treat disease is how to safely deliver the genetic modifying machinery in vivo solely to the intended target organ(s). The ideal pharmacokinetic profile would include rapid delivery to the target organ, minimal delivery to off target organs, rapid blood clearance, and sustained target organ therapeutic effects. Currently, 2 classes of GET delivery vehicles can be used: viral vectors and nonviral delivery systems (Figure 2), with the most common being LNPs. Although advantages and disadvantages to each delivery system are seen, the choice of which to use is largely based on the organ that needs to be targeted. Viral vectors are used if the GET needs to be delivered to the heart and nonviral systems are used if the GET can be delivered to the liver alone.

In viral vector delivery, GET tools are placed inside a nonpathogenic viral envelope with packaging machinery and capsids to prevent immune degradation. Adeno-associated virus (AAV) vectors are most commonly used for several reasons. AAVs span multiple serotypes with tissue-specific tropism, rarely integrate into the genome

TABLE 1 In-Human Clinical Trials of GET in CVD

Genetic Target	Trial Name	Mechanism	Development	Trial Identifier
Trials for hypercholesterolemia, including homozygous FH and heterozygous FH, and refractory hyperlipidemia				
PCSK9	Heart-2[16]	mRNA-encoded adenine base editor and gRNA packaged in a GalNAc LNP	Phase 1	NCT06164730
	Clinical Exploration Trial of YOLT-101 in the Treatment of Familial Hypercholesterolemia[17]	LNP-delivered base editing	Phase 1	NCT06461702
	Multicenter, Open-Label, Single-Arm, Investigator-initiated Trial of ART002[18]	LNP-based gene editing	Phase 1	
ANGPTL3	A Safety and Tolerability Study Evaluating CTX310 in Subjects With Refractory Dyslipidemias[18]	LNP-encapsulated CRISPR-Cas9 editor	Phase 1	ACTRN12623000809639
	Phase 1b Study of VERVE-201 in Patients With Refractory Hyperlipidemia[19]	mRNA-encoded adenine base editor and gRNA packaged in a GalNAc LNP	Phase 1	NCT06451770
LDLR	AAV8-mediated LDL Receptor Gene Replacement in Subjects With HoFH[20]	AAV-mediated gene replacement	Phase 1 (Terminated)	NCT02651675
Trials for ATTR-CM				
TTR	MAGNITUDE[21]	Nonviral LNP delivery	Phase 3	NCT06128629
	Efficacy and Safety of Intravenous YOLT-201 for Transthyretin Amyloidosis Cardiomyopathy[22]	LNP-delivered base editing	Phase 1	NCT06082050

ATTR-CM = transthyretin amyloid cardiomyopathy; Cas9 = CRISPR-associated protein 9; CRISPR = clustered regularly interspaced short palindromic repeats; FH = familial hyperlipidemia; GalNAc = N-acetylgalactosamine; gRNA = guide RNA; Heart-2 = Open-label, Phase 1b, Single Ascending Dose Study to Evaluate the Safety of VERVE-102 Administered to Patients With Heterozygous Familial Hypercholesterolemia or Premature Coronary Artery Disease Who Require Additional Lowering of Low-density Lipoprotein Cholesterol; LNP = lipid nanoparticle; MAGNITUDE = A Phase 3 Study of NTLA-2001 in Participants with ATTR-CM; *PCSK9* = proprotein convertase subtilisin/kexin type 9; TTR = transthyretin.

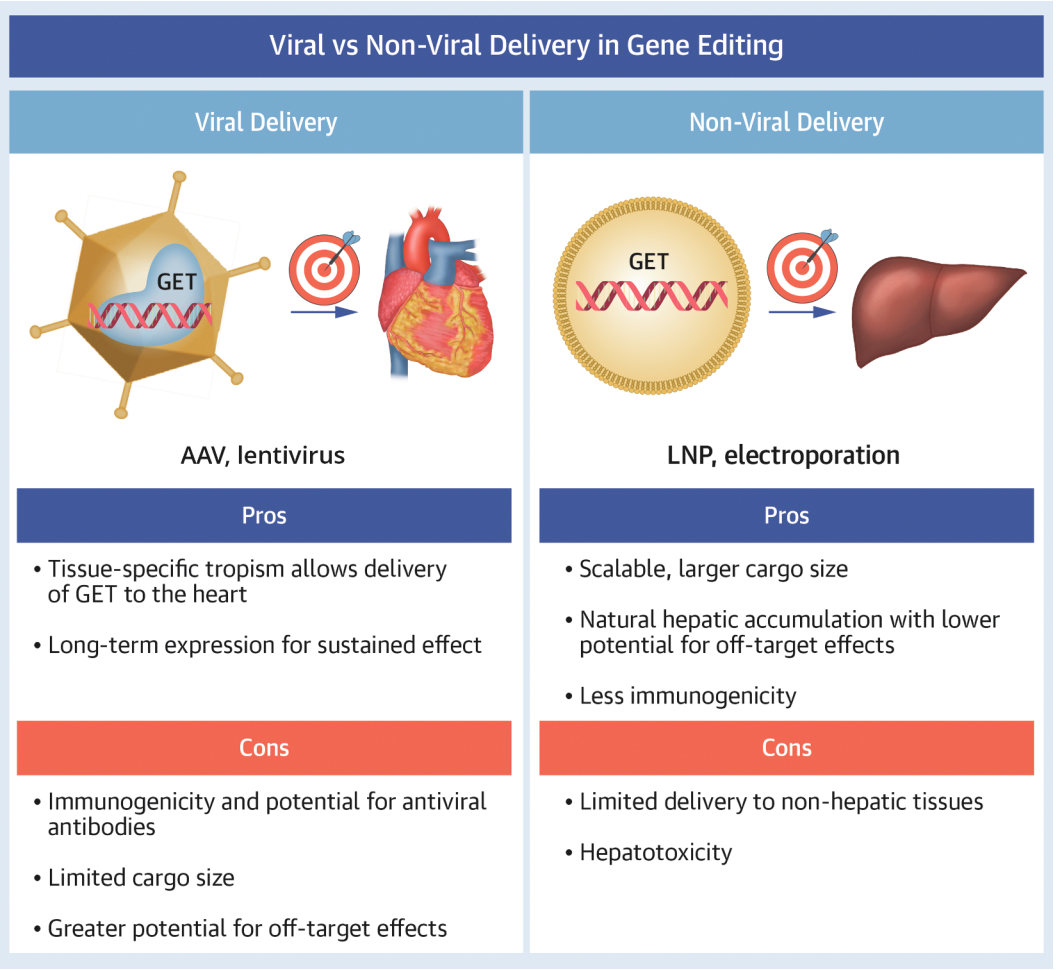
of the cell, and persist in organs for prolonged periods of time without adverse effects. Thus, an AAV with myocardial tropism could be used if a GET needed to be delivered to the heart.

However, AAV vectors have key disadvantages. First, immune-mediated adverse effects can be significant. Viral vector treatment often requires concomitant immunosuppression with the added potential for infusion-related hypersensitivity reactions. Existing neutralizing antibodies against AAV may limit efficacy of initial GET delivery, or the development of new anti-AAV antibodies after a first GET may limit the ability to administer repeat treatments. Although AAV vectors are typically used to achieve prolonged and ideally lifelong expression of a replacement gene, prolonged expression of a GET can be counterproductive if it is recognized as a foreign antigen by the body. In addition, AAV vectors have limited cargo sizes that diminish the ability to deliver GET in a single vector, especially base editors and prime editors. Therefore, the GET typically should be split among multiple AAV vectors, dictating the use of a much higher overall treatment dose with a corresponding increase in risk of toxicity. Finally, a greater accumulation of undesired off-target editing over time may be observed. Interaction with tumor suppressor genes and oncogenes may theoretically increase the long-term cancer risk. Moreover, because AAV vectors have a strong predilection for integration at the sites of double-strand breaks, the use of nucleases can potentially introduce foreign and potentially genotoxic DNA sequences into the genome at high rates.

Nonviral delivery systems using LNPs were developed to overcome the limitations of AAV vector GET delivery, particularly as the CRISPR-associated machinery requires precise delivery to the target tissue to minimize unintended edits in other tissues (**Central Illustration**). LNPs are microscopic lipid spheres that form a protective bubble to encapsulate the GET payload. LNPs have many advantages versus AAV vectors, including ease of large-scale manufacturing, lower immune response (enabling redosing as needed), natural accumulation in the liver with intravenous administration, and previous clinical experience (notable examples include the delivery of transthyretin silencer treatments and COVID-19 mRNA vaccines). Furthermore, N-acetylgalactosamine (GalNAc) conjugation guarantees hepatic specificity attributable to high binding affinity for asialoglycoprotein receptors on the surface of hepatocytes. Thus, although the potential for hepatotoxicity exists for any intravenous LNP-based GET, the risk of off-target effects in other organs can be significantly minimized.

Practically, the current limitation of LNP-based GET delivery is that only disorders with a hepatic protein production pathogenic basis are candidates for treatment—this is the rationale for why most GET trials in CVD have focused on the treatment of lipid disorders and transthyretin amyloid cardiomyopathy (ATTR-CM). Looking to the future, LNP modifications are being

FIGURE 2 **Viral and Nonviral Delivery Methods for GETs**



In viral vector delivery, GET tools are placed inside a nonpathogenic viral envelope with tissue-specific tropism (most commonly AAV). In nonviral delivery systems (most commonly LNPs), GET tools are placed inside small, round particles made up of phospholipids, cholesterols, ionizable lipids, and polyethylene glycol-derived lipids that naturally accumulate in the liver. Both delivery vehicles bind to cell surface receptors of the target organ. Through endocytosis and endosomal escape, the GET is released to the nucleus with subsequent gene editing. AAV = adeno-associated virus; GET = gene editing therapy; LNP = lipid nanoparticle.

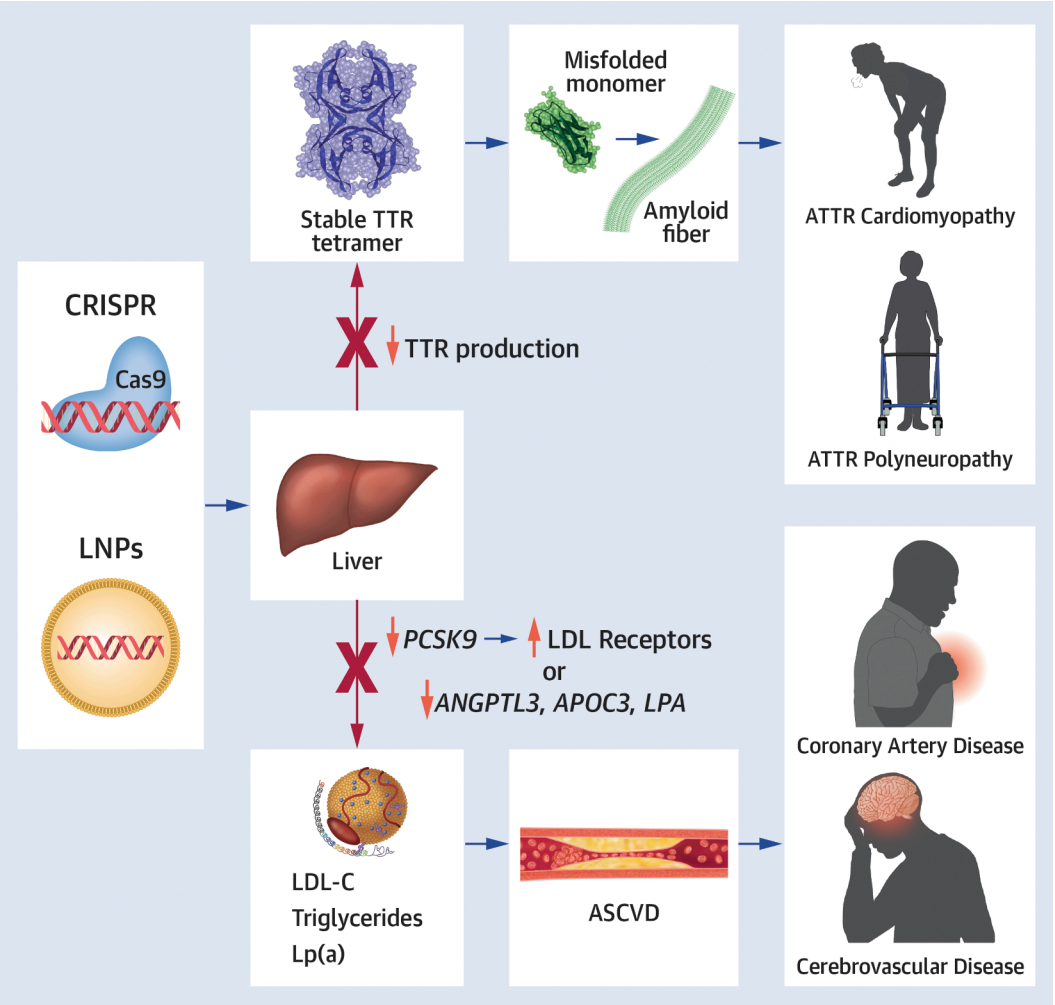
investigate to enhance delivery efficiency and target nonliver sites.[23]

CURRENT STATE OF GET IN CVD

GET in ATTR-CM

ATTR-CM has historically been considered a rare disease but is now an increasingly recognized and treatable cause of heart failure. Outcomes in patients with ATTR-CM have significantly improved because of advances in noninvasive diagnosis, increased use of heart failure therapies such as mineralocorticoid receptor antagonists and sodium glucose-cotransporter 2 inhibitors, and most importantly, disease-modifying therapies with transthyretin stabilizers and silencers.[24] The pathogenesis of ATTR-CM (Figure 3) centers on the liver's production of the transthyretin protein. The transthyretin protein has a role in both retinoid and thyroid hormone physiology, but destabilization of this protein can occur either through inherited pathogenic genetic changes in variant transthyretin amyloid cardiomyopathy (ATTRv-CM) or because of the aging process in wild-type transthyretin amyloid cardiomyopathy (ATTRwt-CM). Destabilized transthyretin proteins become monomers that misfold and form amyloid fibrils that aggregate in the heart, ligaments, and nerves, with resultant clinical

FIGURE 3 Liver Protein Production Is an Ideal Target for GET in CVD



In ATTR, circulating TTR tetramers destabilize into monomers and subsequent fibrils that deposit in tissues, causing cardiomyopathy and neuropathy. Established pharmacotherapy with TTR gene silencers decrease circulating TTR levels; permanent knockdown of the *TTR* gene could be a permanent treatment for this condition. In hyperlipidemia, elevated plasma levels of LDL-C, triglycerides, and lipoprotein(a) are established risk factors for atherosclerotic cardiovascular disease. Multiple protein production pathways are potential targets of gene editing for this disease process. The gene product of *PCSK9* results in the degradation of LDL receptors. Inhibition of *PCSK9* increases LDL receptors, dramatically reducing circulating LDL-C. *ANGPTL3* increases LDL-C levels by stimulating very LDL secretion. *ANGPTL3* and *APOC3* increase triglyceride levels by blocking the ability of triglyceride-rich lipoproteins such as very LDL to eliminate their triglyceride content via lipolysis. *LPA* expression modulates plasma levels of the highly atherogenic lipoprotein species lipoprotein(a). Permanent knockdown of any of these hepatically expressed genes could be an effective treatment for hyperlipidemia. ASCVD = atherosclerotic cardiovascular disease; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloid cardiomyopathy; Cas9 = CRISPR-associated protein 9; CRISPR = clustered regularly interspaced short palindromic repeats; CVD = cardiovascular disease; GET = gene editing therapy; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; LNP = lipid nanoparticle; LPA = lysophosphatidic acid; PCSK9 = proprotein convertase subtilisin/kexin type 9; TTR = transthyretin.

manifestations that can include heart failure, arrhythmias, polyneuropathy, autonomic dysfunction, and orthopedic manifestations.

The pathophysiology and evolution of disease-modifying therapies in ATTR-CM make it a disease that is uniquely positioned to be at the forefront of cardiovascular GET. First, the pathogenesis of ATTR-CM (both ATTRv-CM and ATTRwt-CM) starts with the liver's production of the transthyretin protein. Because this is a monogenic disorder and the transthyretin protein is almost exclusively expressed by the liver, a GET delivered with a nonviral LNP vehicle to knockdown hepatic

transthyretin production could be an effective treatment for this condition. Inhibition of transthyretin protein production does not appear to have negative consequences. Disruption of the *TTR* gene in transgenic mice resulted in phenotypically normal animals without impairment in retinol-dependent responses and function.[25,26] Also, the nearly decade-long experience of hepatic silencing of transthyretin production in variant amyloid polyneuropathy supports the opportunity of GET in ATTR-CM. In 2018, the FDA approved 2 treatments—patisiran (a small interfering RNA) and inotersen (an antisense oligonucleotide)—that effectively stop the liver's production of the transthyretin protein.[27,28] Subsequent agents with more favorable administration schedules (ie, vutrisiran and eplontersen) were approved for the treatment of variant amyloid polyneuropathy, and the use of vutrisiran was shown to be effective and safe for both ATTRv-CM and ATTRwt-CM with resultant FDA approval in 2025.[29] Consequently, intermediate-term follow-up data suggest that no significant adverse effects arise from systemic transthyretin knockdown if these agents are administered with daily-recommended doses of vitamin A supplementation. Finally, the older age of disease onset of ATTR-CM is also a factor that can positively influence the choice to potentially apply GET in this specific CVD. Other than a few particularly aggressive ATTRv-CM variants, most patients with ATTR-CM who would benefit from transthyretin knockdown treatments are adults past reproductive age, thereby limiting the potential of future germline effects.

This background has provided the impetus for preliminary clinical studies on the application of GET in ATTR-CM. In a phase 1 open-label trial, a single intravenous infusion of nexiguran ziclumeran (also known as NTLA-2001 [Intellia Therapeutics, Boston, MA]), a CRISPR-Cas9 GET targeting *TTR* was administered to 36 patients with ATTR-CM, 31% of which had ATTRv-CM.[30] Of the 36 patients treated, 5 had transient infusion-related reactions and 2 had transient liver enzyme elevations, but serum transthyretin levels were lowered by an average of 90% at 12 months among the cohort. The potential for therapeutic efficacy based on the sustained reduction in serum transthyretin levels in this phase 1 trial led to the initiation of the MAGNITUDE study[21] (A Phase 3 Study of NTLA-2001 in Participants with ATTR-CM, NCT06128629). This large, multicenter, placebo-controlled, randomized trial of patients with ATTR-CM aims to assess whether nexiguran ziclumeran versus placebo reduces cardiovascular events and death. Although the trial is ongoing, in October 2025, new screening and infusion treatments were paused because of concerns about the risk of severe hepatotoxicity in a very small percentage of participants including a death from liver failure.

GET in lipid disorders

Hypercholesterolemia, characterized by elevated plasma levels of LDL-C,[31] and to a lesser extent hypertriglyceridemia,[32] are established risk factors for the development of atherosclerotic CVD. Although the LDL-C receptor is essential for the clearance of LDL-C particles from circulation[33] in the blood, gene therapy has not yet been applied in the clinical setting to directly influence LDL receptor function. However, potential is increasing in the application of gain-of-function variants or the correction of loss-of-function variants. It has been established that individuals with loss-of-function variants in *PCSK9* whose gene product degrades LDL receptor in hepatocytes have lower LDL-C concentrations and lower risk of atherosclerotic CVD events. Furthermore, individuals with and without familial hypercholesterolemia who were administered pharmacologic PCSK9 inhibitors similarly have lower LDL-C concentrations and experience fewer atherosclerotic CVD events.[34,35] As such, *PCSK9* is a spotlighted target in ongoing gene therapy trials for high-risk patients with atherosclerotic CVD. However, several other lipid metabolism-related genes also have been identified as potential targets for GET, including angiopoietin-like 3 (*ANGPTL3*) and apolipoprotein C3 (*APOC3*). The rationale in targeting these genes is evident: 1) they are primarily expressed in hepatocytes; and 2) naturally occurring genetic variants are associated with a significantly lower hyperlipidemia and atherosclerotic CVD risk. In the schematic overview of **Figure 3**, *PCSK9* impairs recycling of the LDL receptor to the plasma membrane and thereby diminishes hepatic LDL-C particle uptake, while *ANGPTL3* increases plasma LDL-C levels by stimulating very LDL secretion. *ANGPTL3* and *APOC3* induce the development of hypertriglyceridemia by blocking the ability of triglyceride-rich lipoproteins to eliminate their triglyceride content via lipolysis.

Proof-of-concept for the efficacy of lipid metabolism-directed gene editing has been acquired by modulating *PCSK9* functionality in a number of early phase trials. Treatment of patients with heterozygous familial hypercholesterolemia, premature coronary artery disease, or both on maximum oral therapies and insufficiently controlled LDL-C levels with a GalNAc-coupled LNP carrying a base editor targeting the *PCSK9* gene developed by Verve Therapeutics (VERVE-102, Boston, MA; NCT06164730) was associated with a mean reduction in LDL-C levels of 53% and a maximum reduction of 69% in an interim analysis of the Heart-2 phase 1b trial.[16] In addition, *PCSK9* gene silencing by the LNP-based gene therapy products YOLT-1 (Yoltech Therapeutics, Shanghai, China; NCT06461702) and ART002 (Accuredit Therapeutics, Acton, MA) has been shown to induce

reductions of ≥50% in LDL-C levels in 2 small cohorts of patients with hypercholesterolemia.[36]

Similarly, loss-of-function variants in *ANGPTL3* have been shown to cause reduced levels of LDL-C and triglycerides and lower coronary artery disease event rates,[37-39] also prompting GET development and early phase 1 testing. *ANGPTL3* is hepatically expressed, and its influence on LDL-C levels is (unlike *PCSK9*) independent of the LDL receptor that is genetically defective in patients with familial hyperlipidemia (FH). A phase 1 trial in 15 patients with severe hyperlipidemias executed by CRISPR Therapeutics showed that a GET targeting *ANGPTL3* (CTX310) was associated with few adverse events, resulted in reductions from baseline in ANGPTL3 levels, and, in the highest dose administered cohort, resulted in a mean reduction of 49% in LDL-C and 55% in triglyceride levels.[40] Also, Pulse-1 is an ongoing phase 1b trial evaluating a base editing GET targeting *ANGPTL3* (VERVE-201) for patients with homozygous FH and refractory hypercholesterolemia.[41]

Notably, apolipoprotein(a) constitutes an additional lipid metabolism-related target for gene therapy. Variation in the apolipoprotein(a) gene is the primary determinant of plasma levels of lipoprotein(a) [Lp(a)][42]—a highly atherogenic lipoprotein species (a LDL particle covalently bound by apolipoprotein[a]) that is poorly recognized by hepatic LDL receptors. The Lp(a) macromolecule is uniquely differentiated from other lipoproteins with the hepatically expressed apolipoprotein(a), encoded by *LPA*. Several early trials are investigating this mechanism. For example, a phase 1 dose-ranging program for treatment of elevated Lp(a) using primary human hepatocytes in vitro (CTX320) is ongoing and has noted dose-dependent editing of primary human hepatocytes in vitro up to >80% with mean 94% reduction in Lp(a) in nonhuman primates in vivo at 7 months.[18] Separately, a GET targeting *LPA* (VERVE-301) was recently advanced to clinical development.[43] CRISPR Therapeutics is also initiating a phase 1 clinical trial into the safety and Lp(a)-lowering efficacy of apolipoprotein(a) gene editing in patients with elevated Lp(a) levels and CVD.[44] Although no clinical data are publicly available yet, another trial has recently been initiated by CorrectSequence Therapeutics that evaluates whether *APOC3*-directed base editing can improve hypertriglyceridemia in patients with familial chylomicronemia syndrome.[45]

Preliminary application of GET in other CVDs

Preliminary studies have investigated the application of GET in various other CVDs. Hypertension is a common risk factor for atherosclerotic CVD, and GET may have a future role in refractory hypertension. Angiotensinogen is a hepatically expressed protein encoded by *AGT* and acts as a master regulator of the renin-angiotensin-aldosterone system; a GET targeting *AGT* (CTX340) was recently advanced to clinical development.[46]

In addition, proof-of-concept studies in animal models have demonstrated the potential for GET to treat or prevent diseases affecting the myocardium such as Duchenne muscular dystrophy,[47] hypertrophic cardiomyopathy,[14] and dilated cardiomyopathy,[48] as well as vascular conditions such as syndromic aortopathies.[49] However, all of these proof-of-concept studies have suffered from the limitation of using AAV vectors as the delivery vehicle to introduce the editing tools into the target tissues and were accompanied by the associated limitations of AAV vectors (**Central Illustration**). More specifically, the hazards associated with the use of AAV vectors have been confirmed in some of these preliminary studies. One study examined CRISPR-Cas9-mediated gene editing in dogs with Duchenne muscular dystrophy.[50] Although initial rescue of muscle dystrophin expression was observed after treatment, Cas9-specific humoral and cytotoxic T-lymphocyte responses resulted in muscle inflammation and elimination of dystrophin-expressing cells, compromising the efficacy of the treatment. These immune responses were evident even in healthy dogs. Similarly in a clinical setting, administration of an AAV-based CRISPR epigenome editing therapy to a 27-year-old patient with Duchenne muscular dystrophy resulted in the death of the patient 8 days after treatment because of an innate immune response to the AAV vector that aggravated the patient's baseline poor state of health from advanced disease.[51] Moreover, the first 2 boys with Duchenne muscular dystrophy who were provided with an AAV-based CRISPR-Cas12 therapy in a clinical trial displayed minimal evidence of long-term rescue of dystrophin expression.[52] In summary, these results highlight the challenges of clinical translation of AAV-based GETs for the treatment of myocardial and vascular diseases and suggest that ongoing efforts to develop nonviral methods to transiently deliver gene editing tools into these tissues will be more fruitful over time.

The issues raised by AAV-based GETs also underscore the unique considerations for clinical trial design in this field (**Table 2**). Therapeutic efficacy is more likely to be evident in younger patients (ie, prevention of disease or early intervention halting the progression of disease) rather than in older patients (ie, reversal of advanced disease). Furthermore, younger and healthier patients with a less advanced pathology are more likely to avoid serious adverse effects. The potential long-term adverse effect of GETs that is of greatest concern—cancer caused by off-target editing—may take many years to emerge.

TABLE 2 Special Considerations in Clinical Trials Using GET

Optimal patient population for trial enrollment
Which group(s) should clinical trials prioritize for enrollment? ■ Patients with minimal symptoms where treatment of pre-clinical disease has the potential for greatest impact **OR** patients with advanced symptoms with no alternative treatments? ■ Younger patients who may have more time to benefit from treatment and higher tolerance for acute treatment-related adverse events **OR** older patients with less longitudinal exposure for the development of malignancy and other possible off-target effects? ■ Individuals with child-bearing potential **OR** only those individuals past reproductive age to avoid risk for germline transmission? ■ In conditions with existing treatments, will there be equipoise to randomize patients to placebo to demonstrate therapeutic efficacy of GET?
Assessment of therapeutic efficacy
■ What endpoints and threshold of efficacy are required to demonstrate the efficacy of primary prevention GET? ■ What is the optimal length of follow-up required to demonstrate the durability of the therapeutic effect? ■ In conditions with existing therapy, is a noninferiority trial design sufficient to lead to approval? If so, what level of efficacy is required to demonstrate greater benefit of a 1-time GET treatment versus existing pharmacologic treatment?
Safety monitoring
■ What is the optimal length of follow-up required before approval of GET? ■ In clinical trials, when will a patient be considered to have completed the trial for purposes of reporting adverse events? Are unique considerations needed for data and safety monitoring boards, site investigators, and study monitors if GET is a lifelong treatment? ■ What is the minimum postapproval surveillance required to ensure safety after approval of GET? ■ Who is responsible for long-term safety monitoring if the sponsor of a GET clinical trial becomes financially insolvent? ■ Is there a responsibility to follow children of patients treated with GET as well as their potential offspring? ■ What duration of follow-up is needed to demonstrate that a single administration of a GET with drug clearance is safer than existing therapies that require repetitive dosing and persistent drug exposure?

GET = gene editing therapy.

Although to our knowledge, no reports of this occurring in human beings have been published. Moreover, demonstrating causation may be challenging in consideration of the population's background rates of cancer. Similarly, the potential of germline transmission of edits because of unintended effects in the gonads might not manifest for many years, if not decades, arguing for preferential enrollment of patients past their reproductive age when feasible. Current guidance from the FDA requires clinical trial subjects receiving gene therapies to undergo a minimum of 15 years of long-term follow-up[53]; indeed, some degree of lifetime monitoring may be warranted (**Central Illustration**).

Finally, CRISPR-Cas9 gene editing may have future potential in the treatment of a broad array of CVDs in application of xenotransplantation for end-stage heart failure. Much attention has been brought to the case report of the first genetically modified porcine-to-human cardiac xenotransplant.[54] Scientists used CRISPR-Cas9 technology to edit 10 porcine genes to increase immune compatibility for transplantation into a human being. Specifically, 4 pig genes were knocked down (3 genes associated with the porcine vasculature to prevent hyperacute rejection and 1 growth hormone receptor gene to prevent accelerated growth of the xenograft), and 6 human genes were inserted and overexpressed to reduce inflammation, complement activation, and hypercoagulopathy. Although the current long-term survival of porcine cardiac xenotransplants is limited, the concept of application of gene editing in xenotransplant has the long-term potential to address organ shortages in end-stage disease.

FROM TESTING TO TREATMENT: CHALLENGES IN THE CLINICAL UTILIZATION AND APPLICATION OF GET

The complexities of genetic testing in CVD

Many CVDs have a genetic basis, although often the genetics are under-recognized because of multiple inheritance patterns, variable expressivity, reduced disease penetrance, and clinical overlap with nongenetic forms of disease. The often poorly understood role of modifier genes and variants of uncertain significance adds further complexity. Some inheritance is monogenic with near complete penetrance, and in these cases, it is much easier to clinically recognize the cause and effect of a genetic variant and subsequent disease. However, many CVDs have genetic underpinnings that are highly heterogenous with the involvement of multiple genes, variable penetrance, and significant lifestyle and environmental influences. Hyperlipidemia is a prime example. Homozygous FH can present early in life with severe disease and striking clinical features (eg, tendon xanthomas), and typically a strong family history is seen. The more common, less severe, heterozygous FH can be difficult to differentiate from the also common acquired hyperlipidemia, because phenotypic overlap results from lifestyle, environmental factors, and comorbid conditions.

Another complexity inherent in genetics is the problem of phenotypic variability and reduced penetrance. In recent years, larger population studies as well as genome-first initiatives (ie, those using identification of a genomic risk variant rather than a clinical phenotype to ascertain a

case) have expanded our understanding of the true prevalence of inherited variants. Based on the presence of a genomic risk variant, these studies have shown a higher prevalence than previously expected—roughly 1 in 250 to 300 for FH[55-58] and 1 in 230 for ATTRv-CM[59] globally with lower penetrance rates than previously reported. Because wide variability in phenotype for a particular genotype can occur, these studies also provide more nuanced information regarding expected clinical features.[60] For example, FH attributable to variants in *APOB* generally presents as a milder form of disease compared with FH associated with genetic defects in the *LDLR*.[56,61] However, the issue of predicting the true penetrance of a particular inherited variant and resultant phenotype is critical in the application of GET, particularly if the treatment of younger and less affected individuals is being considered.

Access to genetic testing

Although genetics clearly has a crucial role in the development of CVDs and existing guidelines recommend genetic testing for many forms of inherited CVDs,[62-65] recent studies have shown that only approximately 1% of patients receive appropriate genetic testing.[66,67] In fact, some genome-first studies have shown that most patients (upward of 90%-95%) were unaware of the genomic risk variant.[60,68-71] The reasons for low genetic testing rates are multifactorial. Provider education as to which diseases have known heritability, referral access to genetics specialists, and order access to specific genetic tests remain significant barriers. In addition, institutional and payor support for such testing is highly variable. Finally, although cascade testing for asymptomatic family members has been widely recommended, uptake has been limited because of concerns for patient privacy, higher premiums for life/disability/long-term care insurance, and potential for increased health anxiety. The greater ethical questions and societal costs of extended family genetic testing have been unanswered.

Furthermore, improved understanding of the optimal approach to broader genomic screening and the potential opportunistic identification of pathogenic CVD variants is needed. In 2013, the American College of Medical Genetics and Genomics released its first recommendation for screening of secondary findings in the context of clinical exome and genome sequencing (ie, variants with medical actionability unrelated to the reason for testing).[72] Since that first version, genes for CVDs have remained a substantial proportion of that list[73,74] including the 3 genes for FH and *TTR* added in 2022 (version 3.1).[75] Additionally, population genomic screening through clinical and research programs have expanded, allowing individuals to ascertain genomic risk for various conditions, often including genes for CVDs. Although studies show that these approaches help identify individuals,[71,76,77] additional work is needed to understand the short- and long-term clinical and financial utility for the patient, family, institution, payors, and healthcare systems. In addition, the ethical and societal obligations to asymptomatic individuals who have genomic risk also need to be addressed (**Central Illustration**).

Determining which patients may benefit from GETs

Once the efficacy and safety of a GET for a genetically based CVD is established, the next challenge is determining which patients should proceed to GET. Several considerations are needed including patient age, disease severity, timing of treatment in the spectrum of disease, alternative treatments, and risk of treatment. Naturally, people with genetic conditions that result in severe disease without current treatment have the clearest path forward, but caution must be used if patients with genetic conditions with treatment alternatives or if more mildly symptomatic patients are being treated. In CVDs where existing treatments are available, the benefit of GET may center on the ability to be treated with a single, 1-time treatment versus repetitive maintenance dosing. As such, long-term real-time surveillance using post-approval registries will be critical, especially for younger patient populations. In addition to clinical factors, important ethical considerations are needed in the broader implementation of GET.[78-80] These include, but are not limited to, equitable access to genetic testing and treatment and analysis of the cost-benefit ratio of these treatments for patients, institutions, and healthcare systems.

Expanding the role for GET in primary prevention

The next frontier for gene editing lies not only in treating established diseases but potentially in preventing certain diseases altogether. Although current efforts have centered on reducing disease burden in affected individuals and correcting monogenic causes of disease, current tools such as CRISPR-based precision editing and emerging base and prime editors may allow for intervention before pathologic processes begin. Primary prevention through gene editing could, in the future, redefine preventive medicine.

For example, cardiometabolic risk attributable to *PCSK9*, *ANGPTL3*, and *LPA* may provide some of the first viable targets for GET as primary prevention. Somatic editing of these genes in the liver has already shown profound and sustained lipid lowering in animal models and early-phase human trials. Extending this approach to individuals at high genetic risk before disease manifestation could provide lifelong protection with a single intervention.

The transition of gene editing from treatment to prevention will require more stringent evaluation to ensure safety and efficacy in at-risk individuals. Primary prevention gene editing also invites consideration of optimal delivery mechanisms, target specificity, and potential off-target effects that may not manifest for decades (**Central Illustration**). Long-term (perhaps lifelong) registries and postmarket surveillance frameworks will be critical to capture long-term outcomes. Moreover, the possibility of germline transmission, although unintended in somatic interventions, must be rigorously excluded.

Ensuring that gene editing complements, rather than replaces, established preventive strategies as another variable in the risk/benefit equation is important. In the coming decades, well-designed early-phase studies in high-risk but asymptomatic individuals, coupled with long-term observational cohorts, will determine whether the promise of gene editing for primary prevention can be safely realized.

Societal and ethical considerations in the implementation of GET

If gene editing is to be used in routine clinical practice, implementation frameworks and governance will be increasingly important. It remains unclear how to best assess cost and payment for a 1-time highly expensive, but definitive, treatment. The current model of healthcare for many individuals in the United States is comprised of competing private insurance companies that may only cover an individual for a limited period of time, with coverage dictated largely by employment, not health risk. As such, it is unclear at what time a patient should seek approval for treatment and which payor should be responsible for that cost. This is in contrast to single payor systems where more objective benefit for early administration of a 1-time curative treatment is more likely. Additional uncertainty exists with respect to future regulations. A payor should not deny coverage for appropriate use but also cannot become overwhelmed by interventions that carry extremely high cost. Additionally, it will be critical to ensure that employers do not limit hiring or insurance coverage for individuals with genetic diseases who may incur high treatment costs related to GET. Moreover, the financial burden of GET may have a significant burden on healthcare systems, necessitating a balance between the utilitarian benefits of care delivery to large populations versus high-cost therapies to a small number of individuals. As GETs are approved, a high potential for disparities in access may occur, underscoring the importance of transparency, oversight, and societal dialogue.

Finally, informed shared decision-making between patients and their providers will be critical to the implementation of GET in CVDs. Clinicians must be prepared to provide evidence-based guidance to contest both positive and negative misinformation with respect to the role of genetics, gene editing, and potential "cures" to disease. Ultimately, GET may allow for a transition from reactive disease management to a model of durable, molecular disease prevention of disease, but this will only be possible through the application of scientific rigor, cautious optimism, and sustained ethical reflection. Researchers face many unanswered questions regarding off-target effects, including potential for malignancy and germline mutations, which must be transparently addressed to preserve trust in these novel interventions.

CONCLUSION

The rapid evolution of CRISPR-Cas9 technology is finding applications in and out of medicine—most notably with the recent approval of gene editing as a definitive treatment of sickle cell disease. It has similar potential in CVD. Preliminary application of GET in ATTR-CM and lipid disorders shows great promise, but additional work fine-tuning and innovating GET delivery vehicles for this technology is needed to expand to other cardiovascular conditions. As gene editing technology advances, it will be critical to concurrently address the societal implications and ethical considerations of such interventions. Cardiovascular clinicians will be key stakeholders in this process because they will be the ones who ultimately implement the treatments. As such, cardiovascular clinicians must stay at the forefront of the application of GET to CVD to ensure this evolution is applied equitably to the right patient at the right time and with ethical integrity for both the individual and our greater society.

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APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—GENE EDITING THERAPY IN CARDIOVASCULAR DISEASE: 2026 ACC SCIENTIFIC STATEMENT

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Amrut V. Ambardekar, *Chair*	Professor of Medicine, Cardiology; Director of Cardiac Transplantation; Director of Cardiac Amyloidosis Program, University of Colorado	None	None	None	None	None	None
Ami Bhatt	Chief Innovation Officer, ACC	None	None	None	None	None	None
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Kiran Musunuru	Barry J. Gertz Professor for Translational Research; Director, Genetic and Epigenetic Origins of Disease Program; Scientific Director, Center for Inherited Cardiovascular Disease, Perelman School of Medicine, University of Pennsylvania	■ Capstan Therapeutics* ■ Lexeo Therapeutics* ■ Verve Therapeutics†	None	■ Variant Bio*	None	■ Beam Therapeutics ■ Nava Therapeutics	None
Pradeep Natarajan	Director of Preventive Cardiology, Massachusetts General Hospital; Paul & Phyllis Fireman Endowed Chair in Vascular Medicine, Massachusetts General Hospital; Associate Professor of Medicine, Harvard Medical School	■ AiRNA ■ Allelica ■ Apple ■ AstraZeneca ■ Bain Capital ■ Blackstone Life Sciences ■ CRISPR Therapeutics ■ Foresite Capital† ■ Foresite Labs† ■ Genentech† ■ GV ■ Magnet Biomedicine ■ TenSixteen Bio†	None	■ MyOme ■ Preciseli ■ TenSixteen Bio† ■ Vertex‡	■ Allelica† ■ Amgen† ■ Apple† ■ AstraZeneca† ■ Boston Scientific† ■ Novartis† ■ Silence Therapeutics†	None	

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*No financial benefit.

†Significant relationship.

‡Spousal relationship.

ACC = American College of Cardiology.

APPENDIX 2. PEER REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (COMPREHENSIVE)—GENE EDITING THERAPY IN CARDIOVASCULAR DISEASE: 2026 ACC SCIENTIFIC STATEMENT

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*No financial benefit.
†Clinical trial enroller: Relationship with this company is limited to enrolling patients in clinical trials. This disclosure was entered under the Clinical Trial Enroller Category in the ACC's disclosure system. To appear in this category, the author acknowledges that there is no direct or institutional relationship with the trial sponsor as defined in the ACC/AHA Disclosure Policy for Writing Committees.

ACC = American College of Cardiology; AHA = American Heart Association.