HEART HOUSE ROUNDTABLES

AMERICAN COLLEGE of CARDIOLOGY®

KEY TAKEAWAYS

The Heart House Roundtable on **Advancing Gene Editing Therapy for Cardiovascular Disease** identified the following key takeaways.

1. Gene editing using CRISPR-Cas9 is now widespread in non-medical environments, commonly applied in agriculture and the food industry.

2. Gene editing technology, especially CRISPR-Cas9, may offer targeted approaches to address the underlying genetic causes of cardiovascular disease. The first medical application of gene editing is exagamglogene autotemcel (Casgevy), FDA-approved for the treatment of sickle cell disease. This agent is designed to edit the *BCL11A* gene to produce higher levels of fetal hemoglobin, which can prevent red blood cells from sickling.

3. Unlike traditional treatments focusing on symptoms, gene editing has the potential to offer permanent solutions by modifying faulty genes and potentially curing or preventing disease progression. Such modifications may be interruption of gene function or repair of mutations.

4. Current applications for gene editing in cardiovascular disease include targeting the *PCSK9* gene to reduce LDL cholesterol levels and the *TTR* gene to treat transthyretin amyloid cardiomyopathy. Future applications of gene editing could include genes targeting hypertension as well as treatment of genetic cardiomyopathies.

5. In vivo delivery of the CRISPR-Cas9 payload to achieve gene editing is dependent on delivery systems that are presently limited to certain organs. Future approaches may include ex vivo editing or other delivery systems that are not as organ-specific.

6. Because gene editing offers a permanent solution, it is important that there is adequate education of the public in the indications, risks, alternatives, and benefits of this approach, as well as adequate safety and regularly mechanisms in the clinical trials.

7. The economic ramifications of gene editing are unclear: how will a one-time therapy be priced, and will there be disparities in access due to high cost? On a public health level, given the anticipated high cost of therapies, should they be targeted at groups with the greatest potential benefit (primary and secondary prevention of atherosclerotic cardiovascular disease) versus conditions like ATTR-CM?

8. Gene editing, especially in vivo applications, presents potential risks like off-target editing, germ-line editing, and immune responses, requiring careful evaluation and optimization before clinical use. Systems should be put in place to ensure adequate long term follow up of previous participants in clinical trials even if the companies developing therapies close; federal oversight with a registry would be useful in this case.

9. Ongoing research and clinical trials are focused on improving the safety of gene editing by developing techniques to minimize off-target editing or vector-associated adverse events.

10. Gene editing raises ethical concerns regarding potential unanticipated effects on future generations, emphasizing the importance of establishing specific regulatory systems and education of the public.