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**Facing ethical concerns in the age of precise gene therapy: Outlook on inherited arrhythmias**

Carbone F *et al*. Ethics of gene therapy in inherited arrhythmias

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**Abstract**

This editorial, comments on the article by Spartalis *et al* published in the recent issue of the *World Journal of Cardiology*. We here provide an outlook on potential ethical concerns related to the future application of gene therapy in the field of inherited arrhythmias. As monogenic diseases with no or few therapeutic options available through standard care, inherited arrhythmias are ideal candidates to gene therapy in their treatment. Patients with inherited arrhythmias typically have a poor quality of life, especially young people engaged in agonistic sports. While genome editing for treatment of inherited arrhythmias still has theoretical application, advances in CRISPR/Cas9 technology now allows the generation of knock-in animal models of the disease. However, clinical translation is somehow expected soon and this make consistent discussing about ethical concerns related to gene editing in inherited arrhythmias. Genomic off-target activity is a known technical issue, but its relationship with ethnical and individual genetical diversity raises concerns about an equitable accessibility. Meanwhile, the cost-effectiveness may further limit an equal distribution of gene therapies. The economic burden of gene therapies on healthcare systems is is increasingly recognized as a pressing concern. A growing body of studies are reporting uncertainty in payback periods with intuitive short-term effects for insurance-based healthcare systems, but potential concerns for universal healthcare systems in the long term as well. Altogether, those aspects strongly indicate a need of regulatory entities to manage those issues.

**Key Words:** Ethics; Inherited arrhythmias; CRISPR/Cas9; Gene therapy; Equitable accessibility

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**Core Tip:** As for other diseases, inherited arrhythmias may take advantage from gene editing. Even we are still far from clinical translation, ethical issues need to be considered in order to proceed in this research field avoiding any misconduct. Off-target effects, equitable accessibility of life-saving gene therapies and economic burden for healthcare systems are key issues that need to addressed by regulatory entities.

**INTRODUCTION**

The manuscript “Inherited arrhythmias and gene therapy: Are there any ethical considerations to take into account?”, summarizes current evidence regarding potential application of gene therapy in the context of inherited arrhythmias[[1](#_ENREF_1)]. This class of diseases aligns well with the application field of gene therapy meeting the clinical needs of monogenic disease with no or few therapeutic options available through standard care[[2](#_ENREF_2),[3](#_ENREF_3)]. The quality of life for patients with inherited arrhythmias remains an unmet clinical need[[4](#_ENREF_4)]. Young individuals engaged in agonistic sports often find themselves compelled to cease any practice following diagnosis. Despite a general consensus from the European Society of Cardiology and American Heart Association to continue sport activities, local laws usually restrict them from any competition[[5](#_ENREF_5),[6](#_ENREF_6)]. Even a life-saving device like International Classification of Diseases is burdened by the negative effects of recurrent shocks, leading to the occurrence of electrical storms triggered by the catecholamines release after each shock[[7](#_ENREF_7)].

**OVERVIEW AND OUTLOOK ON GENOME EDITING FOR INHERITED ARRHYTHMIAS**

Throughout the manuscript the authors review the theoretical applications of genome editing for the treatment of inherited arrhythmias. Advances in CRISPR/Cas9 technology have broadened the potential for generating knock-in animal models[[8](#_ENREF_8),[9](#_ENREF_9)]. However, current challenges lie in the development of delivery methods and ensuring editing efficiency while minimizing off-target effects[[10](#_ENREF_10)]. In addition to technical limitations, ethical concerns are worth considering. One such concern arises from genomic off-target activity which is actively being addressed through the development of prediction assays capable of identifying unwanted editing events[[11](#_ENREF_11)]. Furthermore, on- and off-target effects may be influenced by the individual genetical diversity, potentially limiting the equitable accessibility of life-saving gene therapies. Similarly, the cost-effectiveness may further limit the equal distribution of gene therapies. While this impact is intuitive for insurance-based healthcare systems, a similar effect is anticipated for universal healthcare systems in the long term[[12-14](#_ENREF_12)]. In the real word, this is a poignant aspect as many patients may have to put their homes and life savings at risk[[13](#_ENREF_13)]. This underscores the need for a regulatory entity to prevent misconduct. Leading scientists, politicians and economists are called upon to promptly update the first genome editing-specific guidance documents release by the United States Food and Drug Administration and European regulators in 2022[[15](#_ENREF_15),[16](#_ENREF_16)].

**CONCLUSION**

In this context, the research of gene therapies for inherited arrhythmias is still in its infancy and lacks translation into a clinical setting. However, it must continue on a well-established track that adheres to defined ethical standards.

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