ASK AN EXPERT

Experts in the field delved deep into various issues regarding Gene Editing and Personalized Medicine

Ronald F. Carter, MSc, DVM, PhD, FCCMG

Professor Emeritus, Dept of Pathology & Molecular Medicine, McMaster University

"Do you believe that N-of-1 trials (a clinical trial in which a single patient is the entire trial), are appropriate to evaluate the effectiveness of genomic therapies for rare and/or common genetic disorders? Do gene-editing/targeting therapies have the potential to expedite the advancement of personalized medicine?"

We can now affordably detect the molecular mutations that cause thousands of rare genetic disorders, and drugs can be designed to specifically target protein dysfunctions caused by individual mutations. Further, DNA editing techniques like CRISPR bring the promise of actually correcting genetic mutations in the human body. It is all promise, however, until we can show that personalized drugs and gene editing deliver better outcomes. How can we safely and efficiently evaluate and adopt such personalized treatment modalities, when it often costs at least $1 billion and takes many years to achieve licensing and funding for a single new drug?

The first issue is how to demonstrate safety and efficacy for novel, personalized treatments engineered specifically for truly rare genetic disorders. Drug trials typically enroll hundreds to thousands of participants before approval for use is obtained; for rare diseases, there will never be enough participants to meet the usual requirements. With some syndromes, there are literally only a handful of affected people worldwide; how few studies and participants are enough? Is one person sufficient, if the disease is devastating, very few people have it, and no other effective treatment is known? I would argue that it could be permitted if conditions were met to help us mitigate and accept adverse risk. These conditions include: a) no known alternate effective therapy; b) a severe disease outcome is expected; c) cell culture studies show evidence of cause and effect mechanisms for improvement of cellular function; d) cell culture and animal model studies show limited expectation of unacceptable toxicity; e) dosage escalation can be attempted; f) defined endpoints with measurable outcomes are set, and g) there is a legally binding framework addressing issues of informed consent and management of adverse outcomes. Any implementations must also address the fact that the cost per patient will be utterly unaffordable on a large scale if the process of drug development, testing, approval, and production remains anything like what we have now.

Gene editing also beckons as a very effective intervention for genetic disease. Gene editing techniques come with two levels of potential implementation and impact: a) somatic corrections limited to the life and scope of an individual under treatment, and b) germline corrections that become hereditary and might alter allele frequencies in the general population. Gene editing is in its infancy and we certainly need to demonstrate the safety of the technology, especially for germline editing. However, it is important to note that in biological and evolutionary terms, gene editing of somatic and germline tissues may have opposite impacts. If it is effective and broadly used for a large number of genetic conditions, somatic editing would help more patients to survive, but also to potentially pass on disease alleles to their children. In contrast, germline editing could reduce the frequencies of pathogenic DNA sequences in populations and thereby improve reproductive fitness over time. This is a critical point, because when better care gives people with genetic disease the longevity to reproduce, then inevitably the burden of genetic disease in the population increases over time. Germline editing, however, raises huge concerns about the appropriateness of altering the human genome.

While laudable and desirable on an individual basis, the more healthcare helps people with disease, the more people live with disease. Paradoxically, generations from now, despite our ethical and moral concerns, we may have to embrace the most invasive and ethically troubling version of genetic engineering in order to preserve our own ability to reproduce. If we truly want to focus on optimal health of populations, maybe we should learn from somatic editing in order to perfect germline gene editing. Of course, ethical, moral, medical, legal, scientific, and cultural perspectives should fuel vigorous debate on the merits and risks of such an approach. We will need to decide if gene editing is worth all the costs. ■

Further Readings

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Dr. Ronald F. Carter

Dr. Carter is the Director of Laboratory Genetic Services for the Hamilton Regional Laboratory Medicine Program, which has a catchment of 2.3 million people in the central south region of Ontario. He is also Head of the laboratory cancer genetics service, which provides diagnostic cancer genetic testing (cytogenetic and molecular test services, including hereditary cancer syndromes). His research is primarily based upon collaborative studies involving clinical correlations of diagnostic or prognostic genetic markers.