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"Prevention" and Human Gene Editing Governance

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Abstract

The Holocaust and the racial hygiene doctrine that helped rationalize it still overshadow contemporary debates about using gene editing for disease prevention. In part, this is because *prevention* can mean 3 different things, which are often conflated. *Phenotypic prevention* involves modifying the expression of pathogenic DNA variants to forestall their clinical effects in at-risk patients. *Genotypic prevention* involves controlling transmission of pathogenic variants between generations to avoid the birth of affected offspring. *Preventive strengthening* seeks to improve normal human traits to resist disease. These distinctions have been neglected in human gene editing governance discussions and are clarified in this article.

Genetic Prevention and the Shadow of the Holocaust

The scientific racism and eugenic delusions that led to the Holocaust are widely eschewed by members of human genetics and genomics communities today.[1] Yet the Holocaust's long shadow is still evident in public anxiety about our growing ability to control human genes' expression and transmission. Today, the focus of this anxiety is on the suite of new molecular tools for gene editing that promises to revitalize the enterprise of human gene therapy. Since the first demonstration that these tools can be used to modify genetic mechanisms in human cells more precisely and efficiently than older forms of gene transfer, global organizations charged with their oversight have produced a deluge of reports and statements proposing ethical guidelines for these tools' use.[2] Most of these reports concentrate on immediate research ethics questions raised by the development of any new biomedical innovation: questions about physical risk, informed consent, and fair distribution of research benefits and burdens. But behind those deliberations, the memory of the Holocaust surfaces more fundamental ethical questions about where this research leads and the worry that we could repeat the mistake of creating genetic hierarchies from social prejudices and try again to remake our species against the backdrop of a fundamentally unjust vision of human health.

This background concern manifests itself in the new wave of gene editing governance documents that frame discussion of gene editing regulation on the presumption of 2

boundaries: (1) restricting gene editing to treating disease rather than furthering human enhancement and (2) restricting research to somatic cell rather than germline interventions.[3] The clinical uncertainties and risks of earlier gene therapy technologies have been sufficient to support widespread consensus on both of these boundaries within the scientific community since they were first articulated in the 1980s. But the improved safety, efficacy, and efficiency promised by the new gene editing techniques are now opening the way to renewed discussions of both conventional limits. If technical promises of gene editing technology can be realized, society will need to reconsider the conceptual and moral merits of these boundaries directly against the historical shadow of the Holocaust that inspired them. The concept of *prevention* has an underappreciated but potent role to play in these debates.

Medical applications that have been endorsed when drawing a line against genetic modification for enhancement purposes have traditionally been understood to be *treatments* for severe diseases. Many of the recent reports on human gene editing governance, however, go beyond treatment to include disease *prevention* as an ethically acceptable research goal,[4] which accords with precision genomic medicine efforts in genetic risk assessment and pharmacogenomics. But, in genome editing, *prevention* as a concept easily subsumes and conflates 3 interpretations of prevention goals, which I call *phenotypic prevention*,[5] *genotypic prevention*,[5] and *preventive strengthening*.[3] Each has ethical implications that should be disambiguated and clarified.

Phenotypic Prevention

Under the banners of precision and personalized medicine, advances in human genome research are making it increasingly possible to detect pathogenic genomic variants before their problematic clinical phenotypes are expressed in specific patients. One of the hopes for human gene editing research is to use our new abilities to correct or replace those variants to forestall the clinical health problems they can cause. Phenotypic prevention of this sort is not an unusual goal for biomedical research. It reflects a goal shared by many medical interventions—from drugs to surgeries and biobehavioral interventions—that attempt to intervene early enough in the course of a patient's malady to preempt the deleterious effects that the patient would otherwise experience. The only difference between preventive gene editing and the phenotypic prevention provided by other traditional medical means is the former's promise to act earlier and more completely by intervening at the genomic level.

Achieving the goal of phenotypic prevention can raise a wide range of ethical questions, as the extensive literatures on ethical challenges in predictive genetic testing and somatic cell gene therapy document.[6] But as a translational goal for biomedical research, the close alignment of phenotypic prevention with biomedicine's traditional ethical imperative to help specific patients avoid suffering gives it a widely endorsed *prima facie* moral authority. This acceptance is reflected in interventions ranging from newborn genetic screening programs and presymptomatic genetic testing for late onset disorders to efforts to use somatic cell gene therapy to forestall the clinical sequelae of cancer through "cancer vaccination" protocols.[7]

An important conceptual premise of phenotypic prevention that helps ground its medical moral authority is the assumption that its beneficiary is an identifiable individual patient whose suffering we have an obligation to address. For human gene editing protocols aimed at modifying the somatic cells of a particular patient to forestall deleterious effects of detected pathogenic variants, this criterion is easily met. But now that basic

gene editing research suggests that it might be possible to introduce the same preventive changes in *germline* cells on behalf of future patients, what does this imply?

Some would argue that gene editing interventions in early embryos that are designed to prevent diseases in later life are just as clearly examples of phenotypic prevention as newborn screening and—assuming they can be accomplished safely—should enjoy the same level of ethical acceptance. This, for example, was the line of argument that He Jiankui used to defend his effort to prevent HIV infection by editing the *CCR5* gene in human embryos.[8] Successfully defending embryo engineering as a form of phenotypic prevention, however, involves resolving a number of contentious philosophical questions about the identity, individuation, and moral status of early embryos as subjects of the intervention. For those who would rather leave those judgments to parents, it makes more sense to reframe the goal of such interventions as preventing the occurrence of a predictable health problem within a family rather than its manifestation within a particular patient.

Genotypic Prevention

This understanding of the preventive goal of germline gene editing is even clearer when it is contemplated before conception, as interventions on gametes of prospective parents. The goal is to avoid the "vertical transmission" of pathogenic genotypes within families rather than the manifestation of pathological symptoms within a particular patient.[9] When scholars point to the availability of preimplantation screening and embryo selection to argue that embryo editing will almost always be unnecessary to prevent genetic disease, they are assuming that this form of prevention—genotypic prevention—is the goal under discussion.[10] But preventing transmission of particular genetic variants between generations is different than preventing the manifestation of a disease in a patient, with a much more contentious history.

Phenotypic prevention assumes the existence of a patient whose health problems might be forestalled. Thus, attempts to sort preventive interventions in genetic medicine into the traditional levels of primary, secondary, and tertiary prevention used in preventive medicine and public health usually locate examples of phenotypic prevention, such as newborn genetic screening, at the level of secondary prevention,[11] on the assumption that their aim is to interrupt an existing disease process in an affected patient rather than to prevent the inheritance of its causes. But the medical genetic interventions that get classified as primary prevention, such as prenatal and carrier screening, are not about keeping specific patients from acquiring disease-causing genes, as in infectious disease contexts. Instead, the goal of genotypic prevention is usually framed in terms of the interests of prospective parents by allowing them to avoid having children with foreseeable health problems. As disabilities scholars point out, this goal implies that one feature of genotypic prevention is always the tacit judgment that the burden of coping with new cases of genetic disease can outweigh any other value that individuals with the target genotypes might bring to a family or community.[12]

The tradition in modern clinical genetics has been to accept and support the reproductive decisions of prospective parents making well-informed, uncoerced decisions about their family's welfare under the rubric of nondirective genetic counseling. If germline gene editing of gametes and preimplantation of edited embryos is ever feasible, respect for reproductive autonomy should equally extend to these technologies. However, interventions aimed at genotypic prevention are also often evaluated in social and public health terms, according to their ability to reduce the

incidence of genetic disability and disease in a population. For example, famous population-wide programs of genotypic prevention, such as Mediterranean carrier screening programs for beta-thalassemia or Tay-Sachs screening in Ashkenazi communities, are deemed success stories because they have reduced the number of community members with these conditions, not because they have enhanced parental autonomy.[13,14] Should this logic also apply to germline gene editing efforts?

Expanding the preventive goals of gene editing to include population interests broadens genetic medicine's responsibilities beyond the health needs of specific families to the next generation's aggregate population. This expansion makes it easy to import public health goals into gene editing and to subordinate familial decision making to population needs. Unfortunately, genotypic prevention already has an infamous track record along these line in the excesses of 20th-century eugenic efforts to "purify and protect" idealized parts of the human gene pool from so-called contamination from immigration, interracial marriage, and the "feeble-minded."[15] The Holocaust remains history's grimmest warning against the idea that "racial hygiene" could mimic public health efforts against infectious disease to prevent the vertical transmission of particular genotypes in the name of health promotion. To the extent that germline editing is associated with professional allegiance to genotypic prevention at the population level, it inherits all the history, erroneous assumptions, and moral liabilities of this past, which dims the prospects for well-reasoned public assessments of its merits.

Preventive Strengthening

Since the inception of human gene transfer research in the 1980s, public policy and professional opinion has discouraged researchers from pursuing interventions aimed at human enhancement because of the value judgments such pursuits would entail and the questions of justice they provoke.[16] Indeed, current proposals for governing human gene editing research largely stand by 1980s research restrictions on enhancement applications.[2] But current studies of genetic variants that are benign, functional, or even beneficial suggest another way in which gene editing might approach prevention: by enhancing normal traits to build resistance to disease. Should this vision of preventive strengthening trigger worries about human enhancement or be embraced as a legitimate translational goal for gene editing research?

Under the banner of "wellness genomics," scientists are already identifying natural genomic variants they see as helping their carriers resist disease, tolerate environmental extremes, and rebound from injuries more quickly.[17] When gene editors use these variants to try to upgrade such traits in nonhuman animals, they do so in the name of preserving health and draw analogies to vaccines as human immune system upgrades that help us combat infection by certain pathogens.[3] A recent human gene editing governance report suggests that research justified in terms of preventive strengthening of humans could also be used to justify translational goals of gene editing research.[4]

But preventive strengthening interventions can also raise the same concerns about equity and human nature that haunt nonclinical conceptions of human enhancement. Some preventive strengthening interventions, such as those promising to build resistance to anticipated injury or boost the ability to better tolerate sleep deprivation,[18] might confer serendipitous social advantages to those with such physical enhancements. A preventive strengthening intervention to increase muscle mass in muscular dystrophy patients, for example, could be used "off label" to enhance healthy

people who want more muscle mass for social purposes.[19] The result is an interesting challenge for gene editing governance that has yet to be addressed: if the same interventions can serve legitimate preventive goals in some patients and be used by others for enhancement purposes, how should their development and use be managed?

In Common

To anticipate the ethical challenges that can attend the 3 senses of prevention distinguished here —phenotypic prevention, genotypic prevention, and preventive strengthening—the policies that govern human gene editing must appreciate their differences and implications. Each form of prevention sends us in a different direction for guidance: phenotypic prevention, to our emerging experience with preemptive genetic medicine; genotypic prevention, to our history of efforts to control gene flow; and preventive strengthening, to the translational pipelines of beneficial genomic variant research. What should integrate and ground these efforts is a renewed resolve to never again allow invidious genetic value judgments to undermine our commitment to our common human moral equality in the face of our biological diversity.

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