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PERSPECTIVE

Is Enhancement the Price of Prevention in Human Gene Editing?

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Abstract

New gene-editing tools challenge conventional policy proscriptions of research aimed at either human germline gene editing or human enhancement by potentially lowering technical barriers to both kinds of intervention. Some recent gene-editing reports have begun to take up the prospect of germline editing, but most experts are in broad agreement that research should prioritize medical applications over attempts to enhance human traits. However, there is little consensus about what counts as human enhancement in this context, or how to deal with the issues it flags. Moreover, several influential reports interpret medical applications to include disease prevention as well as treatment as a goal for gene-editing research. This challenges the current policy consensus because using gene editing to prevent disease would incidentally facilitate human enhancement applications in a variety of ways. If such research efforts are penalized by policy concerns about enhancement, then their preventive health benefits could be lost. To avoid being caught off guard by such challenges, science policy makers will need to think more carefully about what "prevention" might mean in the gene-editing context, and develop research governance that can anticipate and address the human enhancement concerns it will raise. To accomplish the latter, the scope of policy making will need to expand from its narrow focus on human clinical trials to engage with basic researchers driving the translational pipeline toward preventive gene editing and the science policy makers who have to address its "off-label" uses.

Introduction

Spurred by the remarkable advances in CRISPR* technology and preliminary studies to test the feasibility of engineering human embryos, the past three years have yielded more than 60 position statements and policy proposals on the governance of human gene-editing research (Fig. 1).[1] Multiple international initiatives have also emerged to sponsor dialogue among the authors of these statements and proposals.[2] The Second International Summit on Human Genome Editing, taking place in November 2018 in Hong Kong, will draw experts from around the world to discuss the parameters of responsible research in this domain.[3] Among the key questions is whether human gene-editing research should restrict itself to medical goals or also seek ways to improve on normal human traits.

This concern is not a new one. Society has been debating the ethics of enhancement as a boundary problem for medicine for decades. Cosmetic surgery, using biosynthetic growth hormone to increase children's stature, or the use of steroids to improve athletic performance have all raised similar concerns. These practices pose the question of whether they stray from the goals of proper medicine to implicate physicians in different social vices, from sexism and unfair competition to unnecessary health risks.[4]

Genetic enhancement has been debated since the prospect of human genetic modification first appeared on the horizon because of its potential to create irreversible and undetectable changes in the body. For example, gene doping has already been added to the World Anti-Doping Association's list of prohibited practices in elite sports, and ''designer babies'' have become a stock worry in

*Clustered Regularly Interspaced Short Palindromic Repeats.

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Table 1. Limits of Human Genetic Modification

	Treatment	*Enhancement*
Somatic cells	Yes, proceed with caution	No, on moral grounds
Germline cells	No, on safety grounds	No, on moral and safety grounds

After Walters and Palmer.[8]

gene-editing debates—long before either practice is feasible.[5,6] However, just as the relative safety and specificity of the new gene-editing tools are rekindling earlier debates over the moral merits of germline genetic interventions,[7] the breadth of application via CRISPR-based gene editing is also bringing new urgency to a longstanding question about the meaning of enhancement. How will we know ethically problematic enhancement interventions when they are proposed as research topics?

Across the dozens of gene-editing position statements published so far, there is a general consensus that both somatic and germline gene-editing research should remain restricted to efforts to combat disease.[1] So far, most of these statements continue to temporize by focusing on the most imminent applications and restricting research to less controversial protocols to treat severe disease in somatic cells. In doing so, they follow the traditional categories for the governance of human gene therapy, first outlined by Walters and Palmer in 1997 (Table 1).[8]

However, few reports offer any clarity on how that conviction might apply in practice. One common approach in the reports that do address this issue is simply to defer the definition of acceptable applications of gene editing to the public in an effort to ''democratize'' this aspect of science policy.[9] Presumably, until the public decides which applications of gene editing raise prohibitive enhancement concerns, research protocols aimed at improving the efficacy and safety of any applications would be free to proceed apace in the name of scientific freedom.

At the same time, several influential reports, such as those of the U.S. National Academy of Sciences[9] and of the Health Council of the Netherlands,[10] actually complicate the issue by expanding their interpretation of ''combating disease'' to explicitly endorsing disease *prevention* as a goal for gene-editing research. On the surface, this seems like a predictable nod toward the current enthusiasm for preventive precision medicine, which recent surveys suggest that the public would support.[11] But some uses of human gene editing to prevent disease would raise exactly the same ethical concerns that underlie the conventional rejection of human enhancement as a research goal.

Consider the recent study reporting the successful use of gene editing to increase the production of Klotho protein in human cell lines.[12] The stated goal of this research is to develop somatic human geneediting interventions to prevent

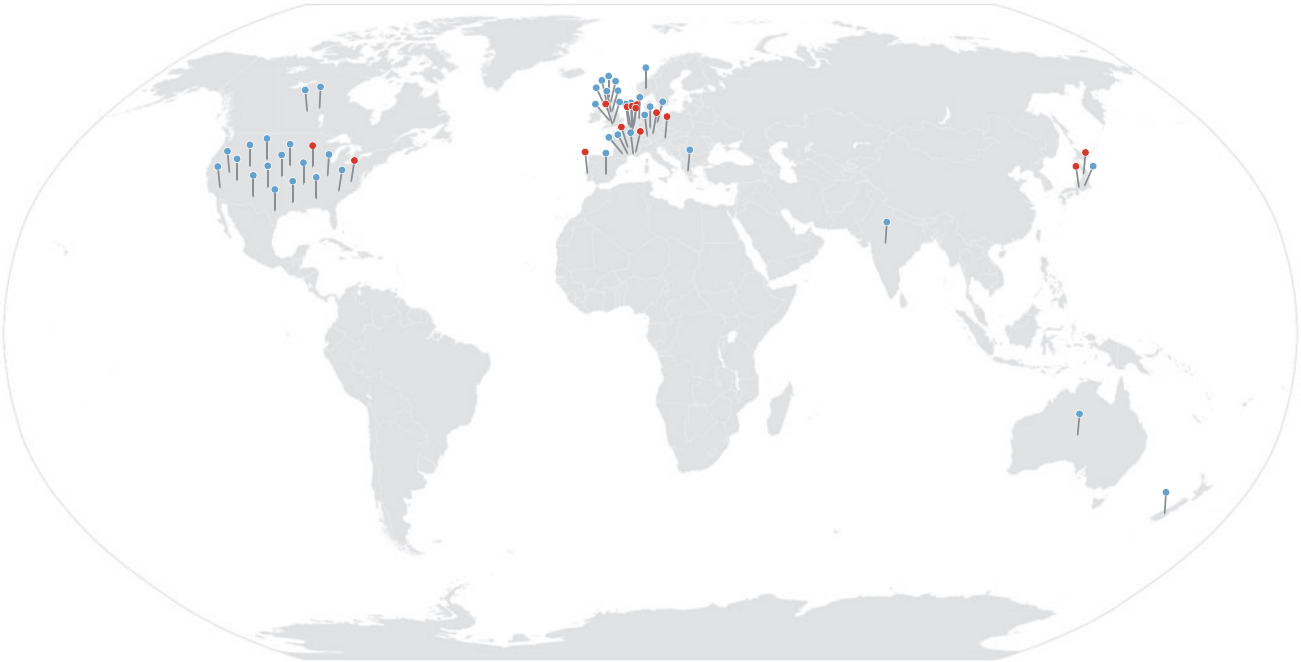

FIG. 1. Professional and governmental policy statements on human gene editing since 2015. (Red = multinational scope, Blue = national scope.)

age-associated degenerative neurological conditions such as Alzheimer's disease by controlling and reversing neurological demyelination. However, upregulating the Klotho gene has also been shown to enhance cognition in mice and to increase murine life-span by as much as 30%.[13,14] If the same pleiotropic effects were predictable for Klotho editing in humans, it might mean that in the course of preventing neurological decline, we could also improve people's cognitive capacities, as well as extend their life-spans. These ''incidental enhancements'' would raise the same worries about competitive advantages, equality of access, authentic agency, and the traditional human life cycle that they would raise outside the preventive medicine setting.[15] Does that set human trials of such interventions outside the limits of responsible gene-editing research? Or should such sequelae be celebrated as serendipitous side effects of successful disease prevention?

Worrying about these questions has been largely a philosopher's problem until now, since we've had neither the gene-editing expertise nor the genomic knowledge to realize such outcomes. But advances on both fronts are converging to make the questions a practical matter for human gene-editing policy makers. First, there has been steep increase of scientific experience with gene editing in animals, which is quickly teaching us the best ways to pursue mammalian gene editing safely and effectively. New gene-editing tools are already being used widely in the food-science industry in efforts to produce animals ''enhanced'' for the particular environments in which they are raised (e.g., cattle resistant to tuberculosis or pigs tolerant of extreme cold).[16,17] Although the use of these genetically modified animals as food is sometimes controversial, the gene-editing research that produced them faces no particular oversight hurdles and has engendered little policy debate.

At the same time, basic research in functional genomics is identifying DNA variants associated with various beneficial human traits such as superlative infection resistance; faster wound repair; psychological resiliency; metabolic efficiency, strength, and endurance; sensory acuity; or even longevity.[18] As almost any functional improvements in human biology will help prevent some disease or other, it is easy to extrapolate from this research to ideas for human gene editing in pursuit of that goal. The direction and scope of this basic genomic research, however, falls as far outside the scope of current efforts to anticipate the governance challenges for human gene editing as the animal studies that are teaching us how to do it.

Enhancement Concerns

As these advances in human and animal research converge, they will produce interventions that will raise ''enhancement'' concerns in different ways, with different regulatory and ethical implications. Some interventions might actually achieve their preventive goals by extending a recipient's capacities beyond the range of normal human function, such as gene-editing efforts to prevent Alzheimer's disease by controlling the species typical rate of senescence.[19] While this would count as human enhancement by most definitions, it would only raise the same ethical questions society already faces with other forms of immunizations and would probably not require special research governance. Other gene-editing interventions designed to prevent the development of disease might have incidentally enhancing side effects, like the Klotho example. For these cases, someone will have to decide whether such pleiotropic effects should be counted as risks or potential benefits for the purposes of research governance. Are these the sorts of decisions that public opinion should dictate, or are they professional scientific judgments? Moreover, the same interventions that act preventively in at-risk patients, such as a muscular dystrophy gene-editing protocol to preserve normal strength and endurance, might enhance the target traits beyond the normal range when applied to healthy people.[20]

Policing such ''off-label'' uses of these preventive interventions is likely to go beyond the jurisdiction of gene-editing research governance to require responses by public regulatory bodies such as the U.S. Food and Drug Administration. However, gathering the safety and efficacy evidence that such responses will require will mean conducting research on the enhancement potential of these preventive interventions. For example, in determining how best to respond to the growing off-label use of biosynthetic growth hormone (Hgh) to attempt to enhance the height of children, in 1991 the National Institutes of Health found itself conducting a study of the effects of Hgh on normal children's stature, effectively crossing the line into ''enhancement research.''[21] As similarly non-medical uses of gene editing start to emerge, this kind of risk-assessment research will become important in this domain as well. But where such research also serves to advance the development of these enhancement applications, should it be allowed or discouraged?

Anticipatory Policy Needs

Beyond their conventional disavowal of gene editing for enhancement purposes, the primary focus of recent policy discussions of gene-editing research has been the controversial prospect of editing the human germline through embryo engineering. But long before any credible proposals for human germline interventions arise, the governance of gene-editing research could face somatic-cell

human-editing proposals that are just as ethically challenging. If the scope of acceptable clinical research is expanded to include preventive strengthening interventions, the door is opened to protocols that raise enhancement concerns. Moreover, since those concerns would arise in a medical context, determining their salience in practice cannot be deferred entirely to public dialogue. How should such dialogue proceed, and how much consensus is enough to warrant permission to proceed with research? Balancing the health gains of prevention against the social costs of enhancement will require scientific reflection as well as social wisdom. Advances in both animal gene editing and beneficial genomic variant research are converging to pose this governance challenge outside the scope of the current human gene-editing debate.

Drawing temporizing boundary lines around clinical research as matters of principle will no longer help as practice draws closer for preventive human gene editing. To avoid being caught unprepared, all those involved in this debate will need to think more carefully about what ''prevention'' might mean in the gene-editing context, and develop research governance that can anticipate and address its implications.[22] The first step will be for those developing governance for human gene editing to learn more about emerging research on DNA variants associated with preventive human traits, and about the ongoing work in preventive gene editing in animals, so that they can anticipate the specific contours of the first clinical research protocols that raise the challenge of preventive human editing. As is true with so much in international science policy, ''the truth is in the nuance'' when it comes to developing responsible governance for preventive human gene-editing research.

Author Disclosure Statement

No competing financial interests exist.

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