An Academic Physician-Scientist's Perspective on Genome Editing, the CRISPR/Cas9 Technology and its Potential Applications to Humans

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Executive Summary

The world is still troubled by diseases for which we have no cure. Some of the most devastating diseases for which we have no cure are monogenic diseases—disease's in which a child is born with an inherited mutation in a single gene causing a disease. Sickle cell disease, beta-thalassemia, cystic fibrosis, hemophilia, and Huntington's Disease are just a few of the most common and well known genetic diseases. It is estimated that there may be ~10,000 such diseases affecting a total of ~35 million people in the United States and >350 million people worldwide although the true health burden is unknown and could be much greater. These diseases not only have devastating impact on the patient, but incur great costs on families, communities, and societies. Most of these have no cures and finding such cures would have broad health and economic benefits. Gene therapy is one approach to finding cures and after 40 years of hard and focused work, gene therapy is beginning to pay off with hundreds of patients now having better lives because of it.

Genome editing is a more precise form of gene therapy and allows researchers to change the sequence of the DNA in a cell with single letter precision. It has generated tremendous excitement because it offers a conceptual approach to providing an ideal cure for thousands of diseases. While genome editing has been studied for >15 years, the pace of discovery has accelerated in the last 5 years with the development of new tools, most notably the CRISPR/Cas9 nuclease system. The CRISPR/Cas9 system allows scientists to correct disease-causing mutations in human cells with unprecedented efficiencies. In my lab, for example, we can correct the mutation that causes sickle cell disease in patient derived blood stem cells at a frequency of 50-80%. For severe combined immunodeficiency ("bubble boy disease") our correction frequency is 40-50%. For both the correction is highly specific and exceeds the level of correction by 5-10 fold over the efficiency that is predicted to be needed to cure a patient. We have been working closely with the FDA to bring these therapies to patients in the next 12-18 months.

We believe that the current regulatory structure has been appropriate as researchers begin to bring somatic cell editing for the treatment of disease to clinical trials and ultimately to market as an approved drug. The FDA has shown flexibility in working with researchers to expedite these therapies in a safe fashion to patients. Moving forward, as the research and medical community, private sector, and regulatory agencies, become more familiar with genome editing based therapeutics, we hope that the FDA will be flexible in its thinking such that cures can be brought to market not just for diseases for which there is a solid commercial incentive but also for diseases that are not commercially profitable.

While the application of genome editing of somatic cells to cure disease is accelerating, there are a number of other applications of genome editing that have generated headlines and controversy. These other issues, should not distract from what is needed to bring curative somatic cell based therapies to patients—including sustained, substantial financial support, excellent public/private partnerships, and an active, scientifically based and flexible regulatory structure.

The other issues surrounding genome editing, which notably are not new and have been discussed and debated for decades in the scientific, medical, bioethical community, not to mention in movies and stories. These issues include the use of genome editing to: 1) Better understand early human development as a research tool; 2) Create genetic changes that would be passed along the germline; 3) Create so called genetic enhancements in humans. Broad, inclusive and continued discussions are needed in each of these areas. The use of genome editing as a research tool for understanding early human development will likely yield discoveries about what it means to be human and improve the current practice of *in vitro* fertilization. The potential use of germline/heritable editing to treat disease is likely to be quite limited; would be obviated by improvements in somatic cell genome editing or gene therapy; and reasonable and restrictive criteria by which it might explored have been outlined by the recent National Academy of Sciences/National Academy of Medicine international study committee entitled "Human Genome Editing: Science, Ethics and Governance." Finally, the use of genome editing or any other genetic means for "enhancement" violates multiple fundamental core beliefs of our society and other societies. The FDA currently has the authority to regulate such potential applications in the United States. Ongoing international conversations and meetings will be important to gain agreement trans-nationally on the issue of enhancement.

The Relationship of Genetics to Human Disease and Human Traits

The instructions or code for the actions of a cell are embedded in the DNA sequence of the cell's genome. DNA consists of a series of nucleotides (letters (A, C, G, T)) and it is the order of these four letters that the cell decodes. The primary unit of the genome is a gene which consists of two major parts: 1) The coding part of the gene gives instructions to the cell about how to make a protein (proteins are the machines that carry out the work of the cell) and 2) The non-coding part of the gene gives instructions as to when and where the cell should make the protein. A basic example of how a gene works is the human beta-globin gene (named *HBB)*. The coding part of the *HBB* gene instructs the cell to make the beta-globin protein in a certain way. The beta-globin protein is an essential part of a complex that carries oxygen from the lungs to the tissues (such as brain, heart, muscles, intestines…). The non-coding part of the *HBB* gene instructs the cell when and where to make beta-globin protein. For the *HBB* gene, the instructions tell the cell to only make beta-globin protein in red blood cells but not in any other cell types, such as brain cells or even other blood cell types.

Every cell in a person has a DNA sequence that is nearly identical but not exactly identical to the sequence created when the sperm fertilized the egg and the sperm DNA combined with egg DNA to make the full DNA complement needed for a human cell to function. The sequencing of the human genome revealed that each cell has ~6 billion total nucleotides in the DNA (~3 billion from the egg and ~3 billion from the sperm). Except for the X chromosome and Y chromosome in males, every person has two copies of each gene.

Since DNA is a chemical, the nucleotides (letters) can be changed by exposure to other chemicals creating DNA variants (or "mutations"). This mutation process is ongoing and each day it is estimated that a cell acquires between 1-100 new mutations per day. Thus, every cell in the body has its own unique sequence of DNA. Moreover, cells often intentionally create changes in their DNA. In the development of the immune system, for example, the cells rearrange their genes ("VDJ recombination") that help fight infection in order to create a strong and robust immune system to deal with the world we face. In the development of sperm and egg (our germ cells), there is the regulated rearrangement of the DNA ("meiotic recombination") to intentionally create genetic diversity in the next generation.

There is tremendous variation between the DNA sequence of one individual and another, thus providing the basis for the rich variation and diversity that has been an important contributor to human success and robustness. Almost all of the key features that we ascribe to being human, however, are not encoded by a single gene but are shaped by a large network of genes interacting with the environment. We have only rudimentary knowledge of these gene networks and environmental interactions and ongoing sustained and substantial funding for research is needed.

An inherited genetic disease ("monogenic disease") is caused when a person is born with a sequence in a gene (a mutation) such that the gene does not perform in a healthy way—either the gene is instructing the cell to make a protein that does not work properly or the gene instructions for telling the cell where and when to make the protein are off. Most monogenic diseases are caused by mutations that cause the gene to instruct the cell to make a disease-causing protein, rather than having the cell to make a functional protein in the wrong time and place. There are estimated to be 6,000-10,000 different genetic diseases. Sickle cell disease, cystic fibrosis, hemophilia, and Huntington's disease are all examples of monogenic diseases. All genetic diseases are classified as rare in the United States because they affect less than 300,000 people in the country it is estimated, for example, that 100,000 people in the U.S. have sickle cell disease, 30,000 have cystic fibrosis, and 30,000 have Huntington's Disease. Most genetic diseases are classified as ultra-orphan diseases because they might affect tens or less people in the U.S. at any one time point. While each genetic disease might not affect a lot of individuals, however, to the patients, families and communtities they are devastating diseases that often have no cure or even good treatment to lessen the severity.

There are other diseases, such as cancer, that are acquired genetic diseases. In acquired genetic diseases, the DNA sequence of a cell changes after a birth and that cell now receives instructions that can cause disease. In cancer, a cell may acquire mutations that instruct the cell to make a variant of a normal protein or it

may acquire mutations that instruct the cell to make a protein that it normally would not. Both types of mutations are usually present in cancer cells.

Finally, there is a fascinating interaction between the environment and our genes. Our DNA sequence may influence our health and who we are but it is not deterministic. Even in the most severe genetic diseases, such as sickle cell disease and Huntington's disease, there is tremendous variation in how the disease affects patients determined by the environment and not determined by the DNA sequence. An example is sickle cell disease, where every patient carries the same mutation. In the United States the average lifespan for sickle cel disease patients is the mid-40's whereas the average lifespan in Africa s 5-8 years of age. In this case, living in an environment where there is a sophisticated health care system dramatically alters the life of a patient.

While the sequence of the gene shapes when and how a gene will be expressed, so does the environment we live in. That is, signals from the environment also control when and where a gene is expressed, so again the DNA sequence of a genome is not deterministic.

The relationship of the environment with the genome also shows how there is no such thing as one "best" genome. Instead different DNA sequences may be better in one environmental situation but worse in others. One important example is the *CCR5* gene, a gene that helps regulate how our immune system responds to infection. A small number of people have mutations in the *CCR5* gene that make them resistant to infection by HIV. But these same people are more susceptible having severe infections when they get West Nile Virus or other infections. Thus, in an environment with high prevalence of HIV, it might be beneficial to have a *CCR5* mutation. In an environment with a high prevalence of West Nile Virus, however, it would be a disadvantage. We usually do not know into what environment we are going to be born into or what environments we will end up in as we live our lives. I never expected in my lifetime to be testifying in front of the Senate HELP committee, for example.

We are just beginning to understand the complex ways that the environment and genome interact and any predictions about how changing the DNA sequence of a healthy individual would impact the life of that individual should be taken with a large spoonful of humility.

In sum, for most people the DNA sequence of a person shapes but does not determine their health. For certain individuals with monogenic diseases, however, they had the unfortunate luck, through no fault of their own, to be born with a sequence in a gene that causes them to have a severe disease, usually a disease for which we currently have no cure or even treatment to lessen its severity. Finding transformative therapies, such as by using genome editing, is of tremendous importance.

Genome Editing is a Precise Form of Gene Therapy to Treat Human Disease

Gene therapy is based on the idea that changing the DNA of a cell can be a way to cure diseases. Genome editing is a more precise form of gene therapy. Genome editing is the ability to change the sequence of the DNA of a cell with both spatial and nucleotide precision. A list of changes that can be done using genome editing include, but are not limited to the following: 1) making precise mutations in genes in order to inactivate them; 2) deleting specific segments of DNA, 3) simply changing one letter/nucleotide of DNA to another or; 4) inserting large DNA segments into precise locations in the genome. Each of these uses of genome editing has potential applications in the treatment of human disease.

While there are ways of performing genome editing without making a specific DNA break, the current most efficient method of performing genome editing is to use a DNA double-strand break. In this method, a nuclease is designed to bind to a specific DNA sequence in the genome and after binding to cut both strands (thus creating a DNA double-strand break). The double-strand break then activates the cell's own machinery (a complex of proteins) to repair the break. It can repair the break in two primary ways.

1) In non-homologous end-joining (NHEJ) the cell glues/stitches the two-ends back together. Usually this stitching is accurate but sometimes there is a loss or gain of extra letters during the joining which then results in an INDEL (for insertion/deletion) mutation at a specific location in the genome. This NHEJ mediated genome editing usually results in a mutation—thereby inactivating or breaking the gene. For example:

Original Sentence:	THISISAHARMFULGENETICSEQUENCE
Sequence after a break:	THISISAHARM/ /FULGENETICSEQUENCE
Sequence after NHEJ:	THISISAGENETICSEQUENCE

2) In homology directed repair (HDR) the cell finds a piece of DNA that is nearly identical to broken DNA, makes a copy of the undamaged DNA and then uses the new DNA to paste into the damaged site (cut, copy and paste). For example:

Original sequence:	THISISASENTENCEWITHOUTAYPOGRAPHICALERROR
Sequence after a break:	THISISASENTENCEWITHOUTAYPOG/ /ARPHICALERROR
Copy of Undamaged DNA:	NTENCEWITHOUTATYPOGRAPHICALERR
Sequence Genome after HDR:	THISISASENTENCEWITHOUTATYPOGRAPHICALERROR

   Using HDR mediated genome editing, therefore, one can create precise changes in the letters for the genomic DNA.

There are multiple different tools to design an engineered nuclease to make a specific DNA double-strand break. These include homing endonucleases, zinc finger nucleases (ZFNs), TAL effector nucleases (TALENs), and RNA guided based nucleases including variations such as the CRISPR/Cas9 nuclease (please see briefing from ASGCT on November 21, 2016 for more details). There are likely going to be even more tools developed in the future. In the U.S. and Europe, all currently approved genome editing clinical trials use either ZFNs or TALENs—CRISPR/Cas9 based trials will likely begin in 2018 and 2019. Nonetheless, the CRISPR/Cas9 system is currently the best tool to perform genome editing because of its simplicity of design, its high activity, and when used carefully, its high specificity. The CRISPR/Cas9 tool has opened the field of genome editing to a much broader swath of investigator both in the US and around the world and as a consequence has transformed the field. With prior nuclease tools there was a substantial barrier to scientists entering the field because of a small number of gatekeepers who had the necessary expertise for that nuclease. With the simplicity of the CRISPR/Cas9 tool, the role of gatekeepers to using genome editing has essentially disappeared. While the use of CRISPR/Cas9 is not as simple as it is sometimes described (that it can be easily used to genetically engineer cells in a garage), it is a simple enough that a reasonably staffed and equipped lab can use the tool quite easily. The thousands of publications in the last four years from small and large institutions in the United States and across the world are an objective marker of the broad utility of CRISPR/Cas9 based genome editing. While CRISPR/Cas9

based genome editing can be easily used for research in the lab, translating its use to treat human disease remains a complex and sophisticated process that goes far beyond simply having expertise in the editing process itself.

For human therapeutic applications, the CRISPR/Cas9 tool does not enable theoretically applications that could not be done using other nuclease platforms. Practically, however, it makes such applications more feasible. My research program has used all of the above nuclease platforms over the last 15 years and currently uses the CRISPR/Cas9 tool because we have identified it as having the features that make translating genome editing to the cure or treatment of serious human diseases most feasible.

Genome Editing as a Research Tool

The CRISPR/Cas9 tool has enabled a broad range of researchers to use the powerful approach of genome editing as a research tool to gain better understanding of biomedical processes. This development has already resulted in important discoveries in all aspects of biomedical research including, but not limited to, cancer, infectious diseases, autoimmunity, neurodegenerative diseases, developmental diseases and monogenic disease. These applications are uncontroversial and with significant and sustained support from the federal government will likely transform our understanding and treatment of disease both in the short term (next five years), medium-term (next 5-20 years) and long-term (over the next twenty years).

There are applications of genome editing, however, that require ongoing and further broad discussion. These applications of genome editing were possible using prior genome editing tools, but have become substantially more feasible with the discovery of the CRISPR/Cas9 tool.

One such application is the use of genome editing to better understand early human development. It is clear that early human development cannot be fully understood by studying the early development of other species, particularly mice. The precision of genome editing provides a powerful tool to better understand this critical stage in human development. From a research perspective, using genome editing of human zygotes (whether at the blastocyst stage from unused embryos derived from in vitro fertilization procedures or created directly for research purposes) will lead to important discoveries. There is a discrepancy across countries and across states within the United States about the legality and permissibility of such studies. It is possible that scientists who are interested in this stage in early human development will take their research programs to places where such research is more permissive. It is also important through public discussion and debate that shared beliefs are explored such that potential appropriate agreed upon limits and guidelines are generated.

A second area for further discussion is the use of genome editing to create large animal models of human disease. Using the new tools of genome editing it is now possible to create specific models of devastating human diseases in animal models other than mice. This will result in the intentional creation of suffering in these animals. There should be a forum that allows all interested parties to participate in adjudication of the moral, scientific and cultural risk/benefit of intentionally creating and propagating such non-rodent models. Whether that adjudication should be for non-human primates only or also include the creation of models in other species, such as dogs and pigs, needs to be broadly discussed.

Genome Editing of Somatic Cells to Treat or Prevent Disease

One of the areas that generates the most excitement for genome editing is its application to treat or prevent human disease. While exciting clinical successes have now been reported for the treatment of monogenic inherited diseases (severe combined immunodeficiency, Wiskot-Aldrich syndrome, metachromatic leukodystrophy, cerebral adrenoleukodystrophy, spinal muscular atrophy, hemophilia, beta-thalassemia, congenital blinding diseases…) and cancer (engineered Chimeric Antigen Receptor T-cells) using gene therapy, there remains tremendous excitement and potential for genome editing.

Genome editing can be roughly divided into *ex vivo* and *in vivo* approaches (nicely described in the November 21, 2016 briefing documents provided by the American Society of Gene and Cell Therapy to the HELP committee). In *ex vivo* approaches, cells from a patient are removed from the body, genetically modified outside the body, and then transplanted back into the patient. In *ex vivo* gene therapy, the therapeutic product is a therapy that combines genome editing (using genome editing to modify the genomic DNA sequence of the cell) with cell therapy (transplanting the cells back into the patient). In *in vivo* genome editing, the genome editing machinery is packaged into a vector. The vector is then delivered directly to the patient with the intent of modifying the appropriate somatic cells of the body to achieve a therapeutic effect without unintentionally modifying the germline cells of the patient.

There are a broad number of diseases for which genome editing is being developed to treat. Some of these, such as sickle cell disease, severe combined immunodeficiency, beta-thalassemia, are best approached using an *ex vivo* strategy, while others, such as congenital blinding diseases and muscular dystrophies, are probably best approached using an *in vivo* strategy. And for many diseases, more research needs to be done in order to determine whether an *ex vivo* or *in vivo* approach will give the best safety and efficacy.

In these approaches, genome editing is used to fundamentally correct a missing function. Another use of genome editing is to enhance the disease treating function of the cell. The enhancement of cell activity to treat disease should not be confounded with enhancement of traits in humans. An example of such an application is using genome editing to increase the safety and efficacy of CAR-T cells against not only leukemia but also against solid tumors, which so far have been recalcitrant to the activity of first generation CAR-T cells.

CRISPR/Cas9 based genome editing strategies to treat human disease, both genetic diseases and cancer, are likely to enter clinical trials in the United States in the next 1-2 years.

The current regulatory structure in the United States, which has been developed around the development of gene therapy, is well suited to assess which trials and products should be approved in the United States. While the field of therapeutic genome editing is relatively new, the FDA has the authority and expertise to make the appropriate judgements. For issues that may have broader issues, the Recombinant DNA Advisory Committee (RAC) has the authority to evaluate genome editing based clinical trials of somatic cells with public input and then providing advice on such trials. Finally, institutional IRBs have the authority and ability to engage relevant scientific and medical expertise as needed to evaluate risk/benefit and give ultimate approval to deliver the therapy as part of a clinical trial. ***This safety first, patient-centric regulatory structure does not need any major structural changes to handle the therapeutic application of genome editing of somatic cells.***

There are areas of regulation of somatic cell editing for disease that should be considered in order to enhance the distribution of this potentially transformative technology.

1) For first in human uses of genome editing, the current regulatory structure is appropriate. But if genome editing strategies are shown to be safe and are based on a shared platform, the regulatory agencies should have the flexibility to standardize a core set of experiments to allow investigators to bring transformative therapies in a more streamlined fashion to patients. In this way the financial resources of large pharmaceutical companies or well-funded biotechnology companies, whose fiduciary interests might not always align with a developing a therapy for a disease that affects only a small number of patients, would not be necessary. This regulatory flexibility would not preclude such companies from becoming involved in developing such therapies if they chose to, however.

2) The United States should consider developing a more flexible approval structure for cell and gene therapy products based on data from well-designed early clinical proof-of-concept clinical studies that show both safety and efficacy. This new flexible structure might be similar to what has been put in place in Japan or the pilot program at the European Medical Agency. In this structure, a conditional, time-limited approval for a product is given such that the company can generate revenues while definitive safety and efficacy data is generated. This flexibility would also facilitate the development of therapies for ultra-orphan diseases.
3) There may be certain devastating childhood diseases for which gene therapy and genome editing needs to be administered before birth to be effective. Depending on the situation and stage at which the therapy might be administered, there is a chance of the unintentional modification of cells that give rise to germ cells. The regulatory agencies should be given the flexibility to evaluate the risk/benefit of such a proposed therapy. They may need to be given the authority to evaluate the ethical risk/benefit in addition to the medical risk/benefit in certain circumstances.

In sum, the application of genome editing in somatic cells shows tremendous promise to provide cures for patients with diseases who currently often have no disease-modifying, much less curative, therapy available. While there is excellent support currently from a large variety of funding sources, the long-term success of the clinical applications of genome editing will still require the sustained and substantial financial support of basic science research—not only of the research itself but also of talented, creative, and motivated junior researchers who will discover therapies that we might not even be able to currently imagine. It should be noted for example, that the best genome editing tools we now have, were discovered from basic research that at the time was seemingly unrelated to gene therapy, genome editing or developing transformative therapies for patients.

Heritable (Germline) Editing to Treat or Prevent Disease

As therapeutic cell gene therapy and genome editing becomes better and more efficient, the number of diseases for which it might not work, becomes smaller and smaller. The consequence of such improvements in somatic cell genome editing and gene therapy, is that the need for having to make genetic modifications in cells that would then be passed along to future generations will decrease.

Nonetheless, there still could be certain diseases for which somatic cell editing may not be possible or effective—such as for diseases in which the pathologic manifestations occur prior to birth and are not reversible.

In this situation, the only way to prevent or cure the disease may be to intervene at such a stage that genetic modification of cells to treat or prevent the disease will result in the genetic modification being passed along to future generations (heritable editing).

The recent International Committee on Human Gene Editing: Scientific Medical and Ethical Considerations sponsored by the National Academy of Sciences and National Academy of Medicine, released a report "Human Genome Editing: Science, Ethics and Governance" (hereafter called the "NAP Report" and accessible at: https://www.nap.edu/catalog/24623/human-genome-editing-science-ethics-and-governance). This committee considered this possibility and outlined some very specific and relatively restrictive criteria by which one might consider such an approach (listed here):

- *Absence of reasonable alternatives*
- *Restriction to preventing a serious disease or condition*
- *Restriction to editing genes that have been convincingly demonstrated to cause or to strongly predispose to the disease or condition*
- *Restriction to converting such genes to versions that are prevalent in the population and are known to be associated with ordinary health with little or no evidence of adverse effects*
- *Availability of credible pre-clinical and/or clinical data on risks and potential health bene ts of the procedures*
- *Ongoing, rigorous oversight during clinical trials of the effects of the procedure on the health and safety of the research participants*
- *Comprehensive plans for long-term, multigenerational follow-up while still respecting personal autonomy*
- *Maximum transparency consistent with patient privacy*
- *Continued reassessment of both health and societal benefits and risks, with broad on-going participation and input by the public*
- *Reliable oversight mechanisms to prevent extension to uses other than preventing a serious disease or condition*

All of these criteria are important and need continued and ongoing discussion. I will emphasize that the first criteria, "Absence of reasonable alternatives," is quite restrictive because *In Vitro* Fertilization followed by Pre-Implantation Genetic Diagnosis (IVF-PGD) serves as an alternative to almost every situation that a couple might encounter if they desired to have a genetically related child without disease. The rare situations of both parents carrying an autosomal recessive disease, one parent having both copies of an autosomal dominant gene (such the child would have a 100% chance of inheriting one the disease causing dominant genes), or specific types of genetically based infertility are the few examples where IVF-PGD would not be an approach to having a genetically related child without disease. While the process of IVG-PGD remains quite inefficient, it is likely to improve with time (particularly as genome editing is used to further understand this stage of human development). There are strong arguments that IVF-PGD would reduce economic and healthy suffering costs for patients, parents, families, communities, and societies. In the United States the cost of IVF-PGD is not covered by insurance, however, and thus is only available to people who have the resources to pay for it directly.

Gene Therapy/Genome Editing for Enhancement

A long discussed potential application of genetic engineering, gene therapy, and now genome editing is for enhancement—the application of the procedure to genetically engineer humans who have characteristics beyond what they could achieve by hard work and careful living. I believe that such applications violate many of

the key ethical and moral beliefs of our country and society. While we should endeavor to create a society in which everyone has the opportunity to achieve their goals, I do not believe genetic tools should be used to do so. I believe that the goal of the biomedical research establishment is to create healthy babies/humans, not designer babies/humans. Using genetic methods to treat a patient to remove suffering and so that they can live in the normal range of humans is different than using genetic enhancement to give one person an advantage over another. The following are reasons for this assessment. For purposes of this document, I will use the term "genome editing" to encompass all such genetically based activities for the purpose of enhancement.

- Genome editing for enhancement involves treating people as objects, not as humans.
- Genome editing for enhancement reduces personal autonomy.
- Genome editing for enhancement violates the principle of humility.
- Genome editing for enhancement violates the principle that the human traits we consider most important are the result of the interaction of multiple gene variants and an environment and cannot be defined by a single gene or gene variant.
- Genome editing for enhancement increases the risk of structural inequality.
- Genome editing for enhancement increases the risk that we increase structural stratification with the belief that one human being is better than another.
- Genome editing for enhancement does not respect that engineering for one trait may result in compromising the long-term health of the individual.
- Genome editing for enhancement increases the risk that we make evaluations under the rubric that there is one best thing. There is no such thing as one best trait, human characteristic or feature.

The concerns listed are magnified if applied to heritable/germline genome editing.