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New Developments

CRISPR-Cas9 and the non-germline non-controversy

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INTRODUCTION

On April 5, 2015, the first genome editing of human embryos was reported. The genome of an organism is the sum total of its DNA; to edit a genome is to make a highly specific change to it. The paper, by a group of Chinese researchers, used a new technology known as CRISPR-Cas9 (the embryos in question were intentionally chosen to be non-viable). This application came just three years after the technology's genesis.[1] Although the possibility of modifying genomes had been around for several decades, CRISPR-Cas9 is on the verge of making this a much more powerful reality. Not only is the technology effective, it is also very low cost and accessible.

The existence of such powerful technology has fired up a debate calling for urgent international policy discussion. This debate has centered on germline modification. Germline cells are those that have the potential to be inherited by the next generation—for example eggs and sperm: changes that are introduced to germline cells enter the gene pool of that species. Editing of a fertilized egg cell is an example of a germline application. Non-germline cells are referred to as somatic cells. Editing the genome of a child or an adult would be a somatic application. Any changes that are introduced to somatic cells will not be propagated to future generations. Somatic genome editing is

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1 Martin Jinek et al., *A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity*, 337 SCIENCE 816, 821 (2012).

most familiar in the context of gene therapy, which rests on the idea of making modifications to correct for those born with disease-causing genetic variants.

Applications of CRISPR-Cas9 to somatic cells have not attracted attention, and indeed have been largely dismissed in the debate. In this paper, we discuss issues that arise uniquely in these applications. While we do not doubt the importance of the recent debate surrounding human germline modification, we argue that somatic genome modifications entail a unique set of social and legal implications which merit attention. This is not an academic point: whereas germline modification is banned in most countries, somatic modification is not. This fact combined with the huge potential clinical benefits of somatic modification suggests that we are likely to see these issues arise in the short term.[2]

In Section I of this paper, we introduce the CRISPR-Cas9 and set it in context. In Section II, we use three examples to draw out issues unique to somatic modification. In Section III, we pick out some common themes and discuss policy implications.

I. A GAME-CHANGING NEW METHOD FOR EDITING GENOMES

In this section, we give an overview of genome editing, the introduction of CRISPR-Cas9, and the debate on germline modification that has followed.

I.1 The introduction of CRISPR-Cas 9

Genome-editing technologies rely on proteins called nucleases, the 'molecular scissors' of DNA, for their ability to precisely target areas of the genome. Several promising genome-editing technologies have been based on nucleases.[3] CRISPR stands for clustered regularly interspaced short palindromic repeats. These sequences of DNA are observed in many single-celled organisms.[4] Cas genes (CRISPR-associated genes) include genes whose products are nucleases, such as Cas9. First observed in 1987, it was not until 2005 that the function of CRISPRs and their associated genes began to be understood: they are part of the bacterial adaptive immune system, whereby bits of invading virus DNA are cut out and spliced into the bacterium's genome.[5] It did not take long for researchers to realize that the system could be used to make precise cuts at more or less arbitrary points in the DNA of any organism, and indeed, by February 2013, the CRISPR-Cas9 system was demonstrated as a genome-editing tool in human cells.[6]

Although CRISPR-Cas9 is not the first of the genome-editing technologies, it is more accurate, cheaper, safer, and more technically accessible than technologies that came before. In the words of Jennifer Doudna of UC Berkeley, co-discoverer in 2012

[2] Motoko Araki & Tetsuya Ishii, *International Regulatory Landscape and Integration of Corrective Genome Editing into in Vitro Fertilization*, 12 REPROD. BIOL. ENDOCRINOL. 108 (2014).

[3] David Benjamin Turitz Cox, Randall Jeffrey Platt & Feng Zhang, *Therapeutic Genome Editing: Prospects and Challenges*, 21 NAT. MED. 121, 131 (2015).

[4] Y. Ishino et al., *Nucleotide Sequence of the iap Gene, Responsible for Alkaline Phosphatase Isozyme Conversion in Escherichia coli, and Identification of the Gene Product*, 169 J. BACTERIOL. 5429, 5433 (1987).

[5] C. Pourcel, G. Salvignol & G. Vergnaud, *CRISPR Elements in Yersinia pestis Acquire New Repeats by Preferential Uptake of Bacteriophage DNA, and Provide Additional Tools for Evolutionary Studies*, 151 MICROBIOL. READ. ENGL. 653, 663 (2005); Francisco J. M. Mojica et al., *Intervening Sequences of Regularly Spaced Prokaryotic Repeats Derive from Foreign Genetic Elements*, 60 J. MOL. EVOL. 174, 182 (2005); Alexander Bolotin et al., *Clustered Regularly Interspaced Short Palindrome Repeats (CRISPRs) have Spacers of Extrachromosomal Origin*, 151 MICROBIOL. READ. ENGL. 2551, 2561 (2005).

[6] Le Cong et al., *Multiplex Genome Engineering Using CRISPR/Cas Systems*, 339 SCIENCE 819, 823 (2013).

of how to use CRISPR-Cas9 for genome editing: 'Any scientist with molecular biology skills and knowledge of how to work with [embryos] is going to be able to do this'.[7] Genome editing has been democratized: CRISPR-Cas9 is inexpensive and easy to experiment with. Although technical issues do persist, many of the barriers that have been holding back human genome editing have been removed.

I.2 Synergies between genome editing and genome interpretation

We understand only a tiny fraction of the consequences of genetic variation over the 3 billion bases of the human genome. However, the development of CRISPR-Cas9 coincides with substantial advances in genome interpretation, our ability to understand what genetic variation underpins which phenotypic variation (the observable traits of an organism). As the cost of sequencing genomes has plummeted, the sequencing of individuals has been moving beyond the research lab and into the clinic, and our understanding of the genetics underlying human genetic disease improves apace. The same technology also enables large-scale studies that correlate genetic variation with rich phenotypic information—information that may or may not be clinically relevant. For example, BGI (formerly the Beijing Genomics Institute), which owns the largest sequencing facility in the world, has under way a large study on the genetic underpinnings of intelligence.[8]

These recent and potential improvements in genome interpretation, enabled by falling sequencing costs, mean that we are rapidly gaining an understanding of what genetic modifications may be desirable. These modifications are not necessarily restricted to curing genetic disease.

I.3 CRISPR-Cas9 and the 2015 germline controversy

Human germline modification has always been controversial. The fact that it affects future generations is the principal objection to the technology. For example, the American Medical Association's guidelines, last updated in 1996, hold that germline engineering should not be done because it 'affects the welfare of future generations' and could cause 'unpredictable and irreversible results'.[9] An additional concern is that babies not yet born are unable to consent to changes to their DNA. Because of these concerns, germline editing is explicitly forbidden in many countries.[10]

A debate over the revolutionary potential of CRISPR-Cas9 unfolded via several commentaries in 2015, with an emphasis entirely on germline modifications.

1. January 24, 2015: Jennifer Doudna convenes a meeting in Napa of leading figures in the genome-editing field, to discuss emerging risks and opportunities

[7] Antonio Regalado, *Engineering the Perfect Baby*, 118 MIT Technology Review, no. 3, May–June 2015, at 26.
[8] Ed Yong, *Chinese Project Probes the Genetics of Genius*, 497 Nature 297, 299 (2013).
[9] American Medical Association, *Opinion 2.11 Gene Therapy*, Issued December 1988; Updated June 1994 based on the report "Prenatal Genetic Screening," adopted December 1992 (Arch Fam Med. 1994; 2: 633-642), and updated June 1996. http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion211.page? (accessed April 3, 2016).
[10] Araki and Ishii, *supra* note 2.

in the face of the rapidly maturing technology, and rumors of its use to edit human embryos.[11]

2. March 5, 2015: The MIT Review publishes an article by reporter Antonio Regalado called 'Engineering the perfect baby'.[12] The article stresses the controversial nature of human germline modification. It quotes George Church, an eminent genomicist at Harvard, distancing himself from human germline editing, while stressing the advantages that consenting adults could take from genomes optimized to, for example, never succumb to dementia. Church's lab works on somatic editing of non-human animals using CRISPR-Cas9.
3. March 12, 2015: A paper, whose authors all have a stake in the clinical application of somatic genome editing, appears in *Nature* calling for all human germline modification to be outlawed.[13] Their reasoning:

> In our view, genome editing in human embryos using current technologies could have unpredictable effects on future generations. This makes it dangerous and ethically unacceptable. Such research could be exploited for non-therapeutic modifications. We are concerned that a public outcry about such an ethical breach could hinder a promising area of therapeutic development, namely making genetic changes that cannot be inherited.

   It seems clear that they use the article deliberately to distance themselves from germline modification, in the hope of reducing the chances that their own (somatic) editing will be questioned. They also explicitly raise the concern that germline modification opens up the possibility of non-therapeutic intervention: 'Many oppose germline modification on the grounds that permitting even unambiguously therapeutic interventions could start us down a path towards non-therapeutic genetic enhancement. We share these concerns'. The authors do not even countenance the possibility of non-therapeutic somatic modifications, and the issues that might arise.
4. March 19, 2015: *Science* publishes a call for a moratorium, led by Doudna.[14] The letter, which arose out of the January meeting, was co-authored by a broad array of individuals from across the field, and made four calls:

   a. Voluntary moratorium on human germline editing for clinical applications
   b. Continued research to understand the basic science
   c. Education sessions
   d. A large international meeting

   These suggestions fall short of what (2) called for, and can be read as focusing more on our lack of knowledge for not contemplating germline modification, rather than on less fact-sensitive ethical concerns. The focus is still very much on germline modifications.

[11] Andrew Pollack, *Jennifer Doudna, a Pioneer Who Helped Simplify Genome Editing, NY Times* (May 11, 2015), http://www.nytimes.com/2015/05/12/science/jennifer-doudna-crispr-cas9-genetic-engineering.html (accessed April 3, 2016).

[12] Regalado, *supra* note 7.

[13] Edward Lanphier et al., *Don't Edit the Human Germ Line*, 519 NATURE 410, 411 (2015).

[14] David Baltimore et al., *A Prudent Path Forward for Genomic Engineering and Germline Gene Modification*, 348 SCIENCE 36, 38 (2015).

5. April 1, 2015: A paper by a Chinese team demonstrating the first application of CRISPR-Cas9 to human embryos is accepted for publication.[15] The study used non-viable human embryos, ie embryos that had been fertilized by two sperm and therefore could not have developed into fetuses. The main thrust of the work is that there are still many technical barriers to be overcome before germline editing ever becomes feasible. Indeed, the accompanying editorial stressed that the journal didn't view this as an endorsement of the technology, but as a call to rein it in: the editors viewed publishing the paper as a public service.
6. May 2015: The National Academy of Sciences and the National Academy of Medicine announce that the organizations are jointly launching an initiative 'to develop decision-making guidelines for human gene editing'.[16]
7. December 1–3, 2015: The US National Academy of Sciences (NAS) convenes a meeting in Washington, D.C. to 'discuss recent scientific developments in human gene editing and the range of ethical and governance issues associated with these advances'. The meeting exclusively focuses on germline modification.[17] Arising out of the meeting is a NAS study committee on the topic, due to report by December 2016, and several international forum meetings—one to be held in Paris in Summer 2016.

It seems inevitable that much debate about the ethical, legal, and social implications of the development of CRISPR-Cas9 for human germline modification will follow.

I.4 The application raising minimal controversy: CRISPR-Cas9 and somatic modifications

What has developed over the last year can fairly be described as a germline controversy. But what about the impact CRISPR-Cas9 will have on somatic modifications?

Somatic modification is most often considered a subclass of gene therapy. Gene therapy refers in general to the use of genes to treat disease; it can, but need not, imply the modification of someone's genome. Because these therapies involve a consenting patient, and because the changes would only affect a single individual, they are seen as considerably more acceptable than germline modifications. In a commentary to the *Science* letter, on which he was also a signatory, Stanford Law Professor Hank Greely says: 'The issues of somatic cell gene therapy, a.k.a. human non-germline genomic modification, have been discussed for many years and, apart from questions of safety, efficacy, hype, and research ethics, none has seemed very important. Changing the genes of one person, who will die without passing those on to anyone else, just hasn't raised deep questions'.[18]

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[15] Puping Liang et al., *CRISPR/Cas9-Mediated Gene Editing in Human Tripronuclear Zygotes*, 6 PROTEIN CELL 363, 372 (2015).

[16] Julie Jacob, *National Academies to Establish Human Gene Editing Guidelines*, 314 JAMA 330 (2015).

[17] On Human Gene Editing: International Summit Statement, The National Academies of Science, Engineering, and Medicine (Dec. 3, 2015), http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12032015a (accessed April 3, 2016).

[18] Hank Greely, *Of Science, CRISPR-Cas9 and Asilomar*, https://blogs.law.stanford.edu/lawandbiosciences/2015/04/04/of-science-crispr-cas9-and-asilomar/ (accessed Sept. 15, 2015).

The social, ethical, and legal implications of gene therapy have been debated since the idea of gene therapy was first introduced in the early 1970s.[19] One reason that that debate has largely stagnated is because gene therapy itself massively underdelivered on its initial promises: it is only very recently that results have been forthcoming, and to date only a small handful of gene therapies have been approved for clinical use anywhere in the world, none yet by the FDA. If the proponents of CRISPR-Cas9 (the same researchers who were warning against the use of germline modifications) are correct, all this is on the verge of changing.

II. EXAMPLES OF SOMATIC CELL GENE EDITING

To illustrate issues that arise uniquely in somatic genetic modification, we introduce three examples.

II.1 CRISPR-Cas9, behavioral genetics, and criminal therapeutic intervention

Although our current understanding of the genetic basis of behavior is minimal, part of the picture now emerging is that the violent conduct of some individuals results from the interaction between their genes and certain triggering life events. This growing understanding, in combination with CRISPR-Cas9's precision and accessibility, may create preventative or rehabilitative gene therapy options for people who have the risk factors in both their genes and personal history. This would be an application unique to somatic, rather than germline, modification.

Some estimate that as much as half of the tendency towards aggression is genetically inherited.[20] One gene has taken center stage in our understanding of the role of the genetic basis of antisocial behavior: monoamine oxidase A (MAOA), a gene encoding an enzyme responsible for metabolizing neurotransmitters such as dopamine, serotonin, and noradrenaline.[21] Extreme antisocial behavior observed in a Dutch family was traced to a genetic variant that caused MAOA to cease functioning.[22] This association has been reliably reproduced via genetic engineering of mice: if MAOA is knocked out in mice, they become highly aggressive; when the gene is reintroduced, they return to their normal behavior patterns.[23]

More recently, common genetic variation in a region of the genome involved in the expression of MAOA was found to have functional consequences: the variant an individual possesses has a strong influence on the amount of the MAOA protein produced in the cell.[24] Like much genetic variation, the prevalence of the low-activity MAOA

[19] Joseph Fletcher, *Ethical Aspects of Genetic Controls. Designed Genetic Changes in Man*, 285 N. ENGL. J. MED. 776, 783 (1971).

[20] Terrie E. Moffitt, *The New look of Behavioral Genetics in Developmental Psychopathology: Gene-Environment Interplay in Antisocial Behaviors*, 131 PSYCHOL. BULL. 533, 554 (2005).

[21] J. C. Shih, K. Chen & M. J. Ridd, *Monoamine Oxidase: from Genes to Behavior*, 22 ANNU. REV. NEUROSCI. 197, 217 (1999).

[22] H. G. Brunner et al., *Abnormal Behavior Associated with a Point Mutation in the Structural Gene for Monoamine Oxidase A*, 262 SCIENCE 578, 580 (1993).

[23] Olivier Cases et al., *Aggressive Behavior and Altered Amounts of Brain Serotonin and Norepinephrine in Mice Lacking MAOA*, 268 SCIENCE 1763, 1766 (1995).

[24] S. Z. Sabol, S. Hu & D. Hamer, *A Functional Polymorphism in the Monoamine Oxidase A Gene Promoter*, 103 HUM. GENET. 273, 279 (1998).

variant varies across ethnic groups.[25] Crucially, this genetic variant has been found to have little effect on antisocial behavior by itself. Rather, it was found to have an effect in individuals who experienced maltreatment during childhood: maltreated children with a genotype conferring low levels of MAOA expression were more likely to develop antisocial problems.[26]

Prior to the discovery of CRISPR-Cas9, the emerging debate about the legal implications of the relationship between MAOA and violent crime focused on whether such information should mitigate offender culpability, or whether it should increase length of detention as it suggests that an offender is a poor candidate for rehabilitation.[27] CRISPR-Cas9 could shift this debate, as direct intervention becomes possible: the technology could provide a tool to help prevent violent crime, or deal with repeat offenders.

Unlike the gene therapies that seek to improve a patient's health outcomes for their own benefit, this example demonstrates the possibility of gene therapy not chosen by the individual for his or her own benefit, but potentially mandated by the criminal justice system. The technological feasibility of such modification is not far off. Even if the criminal justice system is reluctant to adopt such interventions, their mere existence would raise novel questions in criminal law: What do we think of someone who was aware that they had both the genetic and environmental risk factors and chose not to undergo a low cost, or insurance covered, CRISPR-Cas9 treatment which would lower the risk of a violent outburst? Should violent offenders who are candidates for gene therapy be regarded as less culpable and more likely to be rehabilitated than other offenders who have committed similar violent crimes? It may be that the availability of such rehabilitative treatment would render many violent offenders better candidates for early release and reduce the incidence of violent recidivism.

There is an important policy debate to be had about the possible role in the criminal justice system for CRISPR-Cas9 MAOA editing. Leadership is needed to guide responsible public discussion on the development and applications of such therapies. This is particularly important given findings that the low-activity MAOA variants have a higher incidence rate in certain ethnic populations.[28]

II.2 CRISPR-Cas9: mutable versus immutable traits

Somatic genetic modification can affect an individual's physical traits. This challenges our views on which traits are immutable. In the context of disability law, some conditions that were once thought *de facto* immutable, such as genetically influenced deafness, become mutable via genome-editing techniques. CRISPR-Cas9 technology may

[25] Reviewed in Rod Lea & Geoffrey Chambers, *Monoamine Oxidase, Addiction, and the 'Warrior' Gene Hypothesis*, 120 N. Z. Med. J. U2441 (2007).

[26] Avshalom Caspi et al., *Role of Genotype in the Cycle of Violence in Maltreated Children*, 297 Science 851, 854 (2002); Giovanni Frazzetto et al., *Early Trauma and Increased Risk for Physical Aggression during Adulthood: The Moderating Role of MAOA Genotype*, 2 PLoS One e486 (2007); Note that the genotype has subsequently been shown to have some effect even in the absence of mediating factors: Courtney A. Ficks & Irwin D. Waldman, *Candidate Genes for Aggression and Antisocial Behavior: A Meta-Analysis of Association Studies of the 5HTTLPR and MAOA-uVNTR*, 44 Behav. Genet. 427, 444 (2014).

[27] William Bernet et al., *Bad Nature, Bad Nurture, and Testimony Regarding MAOA and SLC6A4 Genotyping at Murder Trials*, 52 J. Forensic Sci. 1362, 1371 (2007).

[28] Rod Lea & Geoffrey Chambers, *Monoamine Oxidase, Addiction, and the 'Warrior' Gene Hypothesis*, 120 N. Z. Med. J. U2441 (2007).

soon enable grown individuals with disabilities, such as people with genetically based deafness, to effectively 'cure' themselves through low-cost gene therapy. In principle, of course, measures to eliminate the impact of genetic disabilities need not use gene-editing technology. For some conditions, medication or assistive technology may achieve roughly similar results with continued use. However, we contend that due to the common necessity of continued use, such measures are essentially palliative: they do not fundamentally challenge the existence of immutable impairment categories whereas a gene therapy treatment does. This section discusses results in recent animal studies that strongly suggest that this may soon be a viable option. If individuals with disabilities who are candidates for new treatments choose not to use CRISPR-Cas9 therapy to remedy their disabilities, they may nevertheless find that their entitlements at law to accommodations are affected by the mere availability of this treatment.

Why would someone with a disability decline treatment but demand accommodation? The view of many who subscribe to the social model of disability, arguably the most influential disability model in the modern disability rights movement, is that there is nothing wrong with those who live with disabilities. Rather, their impairments are largely the result of the way society is structured, and they resent the suggestion that individuals with disabilities need to be 'fixed'.[29] For example, a mainstream attitude in the Deaf community is that many say they would not want to hear, even if they could.[30] To some degree, this issue has been hypothetical, as real cures have not been readily available. But there is a reason to take Deaf advocates at their word: uptake on available treatments, namely cochlear implants, has been slow and stigmatized within the Deaf community.[31]

The question whether individuals with disabilities are obligated to mitigate their condition, or follow medically recommended treatments, has not been legally settled.[32] But, if what amounts to a 'cure' for deafness becomes available for adults, and it is low cost, low risk, and medically recommended, will traditional, costly, assistance to deaf employees qualify as reasonable accommodation to be expected from employers, if employees could 'cure' themselves?

Hearing loss affects approximately 1 in 500 newborns,[33] and about 50–60 per cent of this pre-lingual deafness is estimated to be genetic.[34] The first gene therapy trial to correct hearing loss was recently launched.[35] Gene therapy for treating deafness

[29] Bonnie P. Tucker, *Deafness–Disability or Subculture: The Emerging Conflict*, 3 Cornell J. L. Public Pol'y 265 (1993).

[30] N. Levy, *Deafness, Culture, and Choice*, 28 J. Med. Ethics 284, 285 (2002).

[31] Donna L. Sorkin, *Cochlear Implantation in the World's Largest Medical Device Market: Utilization and Awareness of Cochlear Implants in the United States*, 14 Cochlear Implants Int. S12, S4 (2013).

[32] Reagan S. Bissonnette, *Reasonably Accommodating Nonmitigating Plaintiffs after the ADA Amendments Act of 2008*, 50 B. C. L. Rev. 859 (2009).

[33] Albert L. Mehl & Vickie Thomson, *Newborn Hearing Screening: The Great Omission*, 101 Pediatrics e4, e4 (1998).

[34] Simon Angeli, Xi Lin & Xue Zhong Liu, *Genetics of Hearing and Deafness*, 295 Anat. Rec. Hoboken NJ 2007 1812, 1829 (2012).

[35] Elizabeth Dougherty, *Can We Unlock the Body's Ability to Regenerate Lost Hearing?*, Novartis, Nov. 19 2014, https://www.novartis.com/stories/discovery/can-we-unlock-bodys-ability-regenerate-lost-hearing (accessed April 3, 2016); On the Novartis-Genetec partnership: http://www.genvec.com/product-pipeline/cgf-166-hearing-loss (accessed on Sept. 14, 2015).

has also been demonstrated in combination with cochlear implants in Guinea pigs, a technique that works by stimulating neurons to grow.[36] Although this study did not use CRISPR-Cas9, the authors suggest its use as a promising future direction. Indeed, effective CRISPR-Cas9-mediated genome editing has already been shown in the mammalian inner ear *in vivo*.[37] Given these advances, and the prevalence of genetically based deafness, it is unsurprising that the correction of hearing loss has been suggested as a natural early avenue to explore the role of CRISPR-Cas9 in humans.[38]

CRISPR-Cas9 may enable low-risk, low-cost, effective 'cures' for disabilities. In the context of employment law, such a development could bolster arguments in favor of imposing an obligation on individuals living with a disability eligible for CRISPR-Cas9 treatment to mitigate their condition. Job candidates or employees with disabilities are entitled to have reasonable accommodations made by their employer to enable them to hold positions for which they are qualified. There is no direct judicial guidance as to the meaning of 'reasonable accommodation' in relation to employees with disabilities who refuse to mitigate their condition using medically recommended treatments. The ADAAA[39] says the determination of 'reasonableness' should not take into account the plaintiff's failure to mitigate. But entitling non-mitigating employees to employer-financed accommodations conflicts with the legislative intent of the ADAAA: 'The last message we would want to send to Americans with disabilities…is the less you manage your disability, the less you try, the more likely you are to be protected under civil rights laws'.[40] EEOC guidance suggests that relevant reasons for the failure to mitigate include cost and risk.[41] And while religious beliefs could provide acceptable reasons not to mitigate by following medically recommended treatment, not included in the admittedly illustrative list of acceptable reasons for refusing treatment are social or political philosophies, of which the social model of disability is an example, as well as mere personal preferences.[42]

Given the anticipated low cost and effectiveness of CRISPR-Cas9 gene therapy, relative to the high cost on employers of accommodating the deaf under many circumstances, courts may be inclined to interpret 'reasonable accommodation' as requiring gene-therapy eligible plaintiffs to mitigate their disabilities. The result would not be to force deaf individuals to undergo gene therapy, but rather to personally bear the costs of their choice not to, instead of being able to shift the cost of that choice onto other members of society.

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[36] Jeremy L. Pinyon et al., *Close-Field Electroporation Gene Delivery using the Cochlear Implant Electrode Array Enhances the Bionic Ear*, 6 Sci. Transl. Med. 233ra54 (2014).

[37] John A. Zuris et al., *Cationic Lipid-Mediated Delivery of Proteins Enables Efficient Protein-Based Genome Editing in Vitro and in Vivo*, 33 Nat. Biotechnol. 73, 80 (2015).

[38] Bing Zou et al., *The Application of Genome Editing in Studying Hearing Loss*, 327 Hear. Res. 102–108 (2015).

[39] The ADA Amendments Act of 2008, 42 USCA § 12101.

[40] Statement of Cheryl Sensenbrenner, past Board Chair of the American Association of People with Disabilities, before the United States House of Representatives Committee on the Judiciary, cited in Bissonnette, *supra* note 32.

[41] EEOC Enforcement Guidance, No. 915.002, Reasonable Accommodation and Undue Hardship Under the ADA, Requesting Reasonable Accommodation, Question No. 38, n. 106 (Oct. 17, 2002).

[42] Ref guidance on Rehabilitation Act.

II.3 CRISPR-Cas9 applications in sports

CRISPR-Cas9 will be an attractive technology for some athletes, and we argue below that they are likely to be early adopters. We use this example to illustrate issues that do not arise for germline modification.

There are several reasons to believe that there are low barriers to experimentation in the sports domain. First, many athletes have demonstrated that they are willing to take high risks, including biological modifications, in order to enhance performance. Second, sports performance is an area where our genetic understanding already suggests somatic modifications that could give an athletic edge.[43] This is partly because many genes that are relevant to sports are also clinically relevant for independent reasons, for example, the maintenance of muscle mass for patients with muscular dystrophy. Third, genome editing is likely to be incredibly hard to detect. It is unsurprising that the idea of 'gene doping' has been circulating for over a decade, and the World Anti-Doping Agency explicitly banned it in 2003.[44] CRISPR-Cas9, with its low cost and accessibility, brings the reality of gene doping much closer.

Somatic modification, unlike germline, allows you to make choices about your genome that reflect your passions and choices in life. Baseball pitchers today sometimes opt for non-therapeutic surgery in order to maximize their chances of success.[45] For many people, existing laser-based eye surgery can offer the opportunity for better than 20/20 vision, and this is technology the US Armed Forces are embracing.[46] In the future, such choices could extend to somatic modification, where you could opt, for example, for a higher percentage of fast twitch muscle if you wanted to be a sprinter.

Whereas germline modification happens once, at the embryo stage, it is developing and developed individuals to whom somatic modification is applied. There are certain genetic variants that are known to have an impact at particular times during development. This is to be expected: the phenotypic traits of an individual, for example, their height, are the result of a complex developmental process—a process that is continuously defined and shaped by gene products. For example, variants have been identified that affect how much of a growth spurt an individual experiences during adolescence.[47] There would be a time window for editing to get the effect of these 'taller' variants. The fact that somatic modification is time sensitive during development leads to concerns around the use of genetic enhancement using CRISPR-Cas9 on minors. Current opinion is divided over the types of health choices minors should be permitted to make and those that their guardians should be permitted to make on their behalf. For instance,

[43] See eg Lisa M. Guth & Stephen M. Roth, *Genetic Influence on Athletic Performance*, 25 Curr. Opin. Pediatr. 653, 658 (2013).

[44] The World Anti-Doping Code: 'M3. GENE DOPING The following, with the potential to enhance sport performance, are prohibited: 1. The transfer of polymers of nucleic acids or nucleic acid analogues; 2. The use of normal or genetically modified cells' (Jan. 1, 2015).https://wada-main-prod.s3.amazonaws.com/resources/files/wada-2015-prohibited-list-en.pdf (accessed April 3, 2016).

[45] Stan A. Conte et al., *Prevalence of Ulnar Collateral Ligament Surgery in Professional Baseball Players*, 43 Am. J. Sports Med. 1764, 1769 (2015).

[46] David Smadja et al., *Safety and Efficacy of Wavefront-Guided Myopic Laser in Situ Keratomileusis using a New Wavefront Sensor Technology: First 100 Cases*, 41 J. Cataract Refract. Surg. 1588, 1593 (2015); Rose K. Sia et al., *Wavefront-Guided versus Wavefront-Optimized Photorefractive Keratectomy: Clinical Outcomes and Patient Satisfaction*, 41 J. Cataract Refract. Surg. 2152, 2164 (2015).

[47] Diana L. Cousminer et al., *Genome-Wide Association and Longitudinal Analyses Reveal Genetic Loci Linking Pubertal Height Growth, Pubertal Timing and Childhood Adiposity*, 22 Hum. Mol. Genet. 2735, 2747 (2013).

there is no consensus within the medical establishment concerning the use of hormone treatment intervention for children assessed as transgender. Such treatment, applied early, would prevent them from developing secondary sexual characteristics.[48]

III. ANALYSIS AND RECOMMENDATIONS

Whereas the received wisdom is that somatic modification does not raise deep questions, we have sought to demonstrate through our examples the existence of several such questions.

Our first example concerned the existence of gene–environment interactions that modulate aggressive behavior. CRISPR-Cas9 helps us view not only an individual's environment, but also their genetics, as mutable. Somatic modification could allow for reacting to the effects of particular experiences an individual has had by altering the underlying genetics. A point we sought to draw out in our second example is the extent to which the technology calls into question the idea of mutable versus immutable traits, and how this plays out if the individual in question has the option of being 'cured'. This should lead us to consider a range of examples of societal attitudes to traits that are currently, but perhaps not for much longer, outside the control of the individuals who possess them. We used our third example of sports to point out that CRISPR-Cas9 somatic modification allows for interference at optimal stages of the development of an individual, a technology that would be tempting for use on minors. Somatic modification also allows for the possibility of an individual opting to make modifications to suit their life choices. Both of these points generalize far beyond sports and clearly have policy implications.

Of interest to note, germline modification has been regarded as ethically distinct from somatic because it affects all humanity (via affecting the human gene pool). The considerations highlighted above demonstrate that somatic modification also has consequences beyond the individual being modified: it is not necessarily just the individual modified who is affected, but rather those affected by levels of violent crime, by the cost of accommodating the 'immutable' traits of others, by how the optimizations an individual can choose to make for themselves alters how they can compete with others.

The focus of concern on germline editing and sidelining of somatic considerations makes it easy to overlook that technological development of somatic applications is charging ahead. The main drive behind developing somatic genome modification is to cure genetic disease, and research on this front is progressing at startling speed. Since 2012 there have been over 2280 articles published on CRISPR, over 1000 in the first 10 months of 2015 alone[49]; several companies have been set up to commercialize this rapidly maturing technology[50]; an online search for 'CRISPR MAOA' returns sites selling genome editing kits of this gene in mouse and in human cells; there has been a lot

[48] Norman P. Spack et al., *Children and Adolescents With Gender Identity Disorder Referred to a Pediatric Medical Center*, 129 PEDIATRICS 418, 425 (2012); Henriette A. Delemarre-van de Waal & Peggy T. Cohen-Kettenis, *Clinical Management of Gender Identity Disorder in Adolescents: A Protocol on Psychological and Paediatric Endocrinology Aspects*, 155 EUR. J. ENDOCRINOL. S131, S137 (2006); Baudewijntje P. C. Kreukels & Peggy T. Cohen-Kettenis, *Puberty Suppression in Gender Identity Disorder: the Amsterdam Experience*, 7 NAT. REV. ENDOCRINOL. 466, 472 (2011).

[49] Publications as listed in the PubMed database, David Smadja et al., *supra* note 46, with date ranges applied.

[50] CRISPR-based companies include, but are not limited to, Editas, Caribou, Intellia, CRISPR therapeutics, Cellectis.

of biohacker enthusiasm and activity.[51] Moreover, the maturation of CRISPR-Cas9 is synergistic with the huge advances in genome interpretation that are happening concurrently. The advances are not only technological but also economic: cost barriers are disappearing much faster than anticipated.

The rapid development of this technology is coupled with the existence of groups of people for whom it will be immediately relevant, due to the risk appetite of the stakeholders: those suffering from health issues that make them willing to risk their current state for a potential improvement, and those who operate in arenas where a small performance edge makes it worth taking on big health risks using an experimental technology.

Although the drive to develop the technology comes from therapeutic use cases, to a large extent advances apply equally to non-therapeutic uses. Much policy and discussion assumes a meaningful division between the two. But particularly in recent years, when preventative health has taken center stage in medicine, this distinction becomes harder and harder to maintain: medicine is not just about a reaction to acute disease, it's about adopting a healthy lifestyle. Is a modification that would make it harder for someone to put on weight a therapeutic intervention?

In guidelines published in 1988 and last updated in 1996, the American Medical Association said it was appropriate to limit modification to somatic only 'at this time'.[52] They outline some conditions for acceptable therapeutic somatic modification, and provided the following guidance for non-therapeutic interventions:

> At least three conditions would have to be met before it could be deemed ethically acceptable: (1) there would have to be a clear and meaningful benefit to the person, (2) there would have to be no trade-off with other characteristics or traits, and (3) all citizens would have to have equal access to the genetic technology, irrespective of income or other socioeconomic characteristics.

These guidelines are clearly limited, first in the assumption of a therapeutic/non-therapeutic divide, and second because all three of their criteria listed are incredibly hard to apply.

The guidelines do state that '[a]s genetic technology and knowledge of the human genome develop further, additional guidelines may be required'. The arrival of CRISPR-Cas9 should force this reconsideration.

Concrete policy areas where rapid clarification will be needed include defining which interventions minors should be permitted to make. This should be openly debated, public views invited, and the discussion should be based on medical evidence. Our existing frameworks for medical decision making involving minors are in some key respects inadequate, piecemeal, and inconsistent. The division between clearly therapeutic cases, such as editing the genetic variation that causes cystic fibrosis, and clearly non-therapeutic cases, such as introducing variation that is correlated with tallness, should be recognized in this discussion.

[51] See, for example, Heidi Ledford, *Biohackers Gear Up for Genome Editing*, 524 NATURE 398, 399 (2015).

[52] American Medical Association, *Opinion 2.11 Gene Therapy*, Issued December 1988; Updated June 1994 based on the report 'Prenatal Genetic Screening,' adopted December 1992 (Arch Fam Med. 1994; 2: 633-642), and updated June 1996. http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion211.page? (accessed April 3, 2016).

Another novel policy question is whether it should be legal to incentivize individuals (for example via insurance) to undergo genome modification. For example, should a woman who carries one of the BRCA1 variants known to increase risk of breast cancer be encouraged to edit out the damaging variant? What about someone who is genetically predisposed to become addicted to nicotine?

Our examples present just the tip of an iceberg of possible application areas and considerations, and this diversity will impact policy development: whereas all germline applications have in common their heritability, and thus a blanket moratorium is arguably appropriate, somatic cases are not unified by a common concern that could be the target of sensible restriction or regulation.

CONCLUSION

CRISPR-Cas9 has proven to be a revolutionary technology and has justly sparked widespread debate. To date, this debate has focused almost exclusively on using CRISPR-Cas9 to edit human germline cells. We have argued that somatic applications are not only more likely to develop in the near term than germline applications, but that somatic applications have consequences that merit consideration over and above those that arise in the germline case. There is a new debate to be had. The debate around gene therapy from the 1980s and 1990s, which some dismissed as not raising any interesting issues, rested on assumptions which have not played out concerning the cost and accessibility of gene editing. Nor did we anticipate the leaps that have been made in genome interpretation and gene–environment interactions. We hope to have highlighted some of the topics that should be covered in this renewed debate.