HUMAN GENOME EDITING:
AN EVOLVING REGULATORY CLIMATE

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ABSTRACT: Human genome editing is the most consequential genetic technology for precision medicine to emerge in many years. Although genome-editing techniques have been available for more than a decade, the recently developed CRISPR-Cas9 system, in particular, has become the genome-editing technology of choice because of its ease of use and efficiency. Theoretically, the uses of genome-editing technology in humans can be divided into two major branches: the use in somatic cells for treating or preventing disease, and the use in gametes or embryos for research or germline modification in human reproduction. From that division, these branches diverge in terms of ethical, social and political impacts, and they also diverge with respect to regulatory responses from governments and professional organizations and the development of consensus norms. Already, genome-editing technologies are in human clinical trials, and genome-editing experiments on viable human embryos have been conducted. This article will situate genome editing in the lineage of human genetic modification technologies that originated in the 1970s. It will then briefly describe the major branches of application for human genome-editing technology, summarize the state of technical developments as of this writing, and provide a short overview of the relevant U.S. regulatory responses to date and those that may develop in the future.


I. THE TECHNOLOGY
OF HUMAN GENETIC MODIFICATION

Modern biological science is defined by an understanding of living organisms through a detailed investigation of their underlying genetic and biochemical structures and mechanisms. Once DNA was revealed as the central repository of genetic information,¹ and proteins defined as the biochemical outputs of these genetic instructions, the driving imperative of biological research has been to deconstruct living organisms into their molecular components and

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¹See Oswald T. Avery et al., Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types, 79 J. EXPERIMENTAL MED. 137, 152 (1944).
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model their interactions. Deeper cellular investigation revealed the machinery of DNA replication and repair, and specific enzymes capable of splicing and ligating DNA were isolated. Additionally, the processes by which DNA undergoes endogenous recombination were being explained, and the mechanisms by which new genetic materials could be delivered into cells were being unraveled. All of these insights provided a foundation for the development of methods for the deliberate rearrangement and design of DNA molecules and for direct delivery of these products into target cells. Thus, the era of recombinant DNA (rDNA) (or genetic engineering) began. A recurrent theme in this emerging field of molecular biology was the reliance on research with microorganisms—bacterial, viral or fungal—to elucidate basic biochemical processes, followed by extrapolation to identify similar mechanisms in higher organisms, including humans.

A. Gene Transfer

Gene transfer refers to the first conceptual approach for deliberate molecular genetic alteration of a cell through the delivery of exogenous genetic material (often a gene) in order to confer new properties on a cell. The first methods for altering the native DNA in a cell involved the delivery of exogenous nucleic acids (DNA) to a target cell, often carried on a plasmid. The added gene(s) would rely on the native cellular machinery to transcribe and translate the DNA and produce the cognate protein. Thus, the new protein would provide a new function to the cell (phenotype). Further research led to the development of alternative methods for delivering genes into the cell, including the use of mechanical methods or viruses. A virus could be used as a vector to carry other genetic material and deliver it through an infective process. The research on vector development led to identifying which viruses could be optimal for a specific delivery task, depending on carrying capacity, cellular target, and whether the virus would integrate into the cellular genome.

All of this research set the technical stage for considering how gene transfer could be used to alter or enhance the genetic properties of target organisms, whether microbial, plant, animal or human. The modularity evident in genetic

2. See generally BRUCE ALBERTS ET AL., MOLECULAR BIOLOGY OF THE CELL 237–66 (6th ed. 2015) (detailing the cellular processes of DNA replication and repair, and the enzymes required). The “central dogma” in its most simplistic form referred to the sequential transfer of genetic information from DNA to RNA to protein, and that relay linked the concept of genotype (the DNA sequence) to phenotype (the expressed protein, and its biological function). Id. at 299.
3. Id. at 266–98 (describing the cellular processes of DNA recombination).
4. Recombinant DNA (rDNA) refers to DNA molecules that contain artificial combinations of DNA sequences; these molecules can be used to study a gene of interest, for example, or to transfer DNA to a target cell, including between species. As genes and their regulatory elements were isolated and relocated, their functions could be elucidated. See id. at 464.
5. A plasmid is a small DNA structure found in bacteria into which exogenous DNA can be added and then carried by the plasmid into a target cell. See id. at 468.
6. Id. at 495–96 (describing genetic alteration of a cell by gene transfer).
7. Id. at 18.
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manipulation meant that a gene could be chosen from another species and provided to the target organism, or a defective native gene could be augmented or corrected by supplying a wild-type (normal) copy of a gene.\(^9\) When applied to human clinical treatment, the general field of gene transfer studies was also characterized as “gene therapy,”\(^10\) although that term is actually broader and, over time, has included other approaches to clinical genetic alteration.\(^11\) The transfer of genetic material is useful for the treatment of some genetic diseases, but many clinical objectives of genetic repair might necessitate more precise alterations, such as correcting a genetic mutation in place. Direct intervention and manipulation of a target gene would be desirable if the components for performing such an operation could be identified and employed.

### B. Genome Editing

The identification of enzymes that cut DNA at specific sequence sites (site-specific nucleases) provided the basis for harnessing such enzymes in experiments to achieve the deliberate editing of a target gene in a cell.\(^12\) In the early 2000s, zinc-finger nuclease (ZFN) technology was the first technique developed for genome editing.\(^13\) This was followed by the development of transcription-like activator effector nucleases (TALENs).\(^14\) The use of either ZFN or TALEN technology requires the synthesis of artificial nuclease proteins specifically targeted to the DNA site of interest; thus the ease of such protein synthesis is a factor in selecting either method for genome editing.\(^15\)

In 2005, it was recognized that some bacteria create a genetic record of infectious viral assaults by storing viral DNA sequences within clustered regularly interspersed short palindromic repeats (CRISPRs) in their genome\(^16\)

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9. The modifier “transgenic” was often applied to an organism if it had received a new gene from another species.


11. For example, a technique known as RNA interference (RNAi), in which RNA molecules are delivered to a cell to inhibit gene expression is technically another example of a gene therapy, in that the expression of a gene is deliberately neutralized. See Alberts et al., supra note 2, at 433.

12. Id. at 464–66.


employing a specific enzyme (from the Cas family, e.g., Cas9) to identify and cleave incoming DNA from invading viruses in a process called adaptive immunity. In the bacterial system, the Cas9 protein is guided by a guide RNA molecule specific for the desired target. By 2012, scientists had recognized that the Cas9 enzyme could be redirected to any DNA sequence by specific design of the guide RNA, and therefore, a “programmable” complex based on the CRISPR strategy could be produced for deliberate alteration of a gene; thus, the CRISPR-Cas9 technique for genome editing was developed. When the guide RNA directs Cas9 to cleave target DNA, the native DNA repair mechanisms in the cell are activated, and various molecular alterations to the target DNA are possible: for example, deletions, insertions, corrections, or replacements. Although CRISPR-Cas9 originates as a bacterial defense system, the genome-editing method was shown to work in eukaryotic cells (which include human cells). CRISPR-Cas9 complexes can be delivered to cells in several ways: as an RNA/protein hybrid (ribonucleoprotein, RNP), on a DNA-based vector(s), or the Cas9 can be delivered as an RNA molecule for translation, along with the guide RNA. Several technical limitations have been observed in many CRISPR-Cas9 studies: off-target enzyme activity, where the Cas9 enzyme cleaves DNA at nontargeted sites, and an uneven distribution of repair outcomes, known as mosaicism, where incomplete or diverse editing occurs, creating a heterogeneous cell population. The off-target activity is particularly undesirable, as unintended Cas9 cleavage of DNA in a cell can create genetic

19. A note on nomenclature: the CRISPR-Cas9 methodology is often abbreviated “CRISPR” as a shorthand in the field; this Article will use that convention when describing the general use of this technique. CRISPR-Cas9 terminology may be used for specific experiments performed as such.
21. The CRISPR-Cas9 system activates the endogenous cellular DNA repair mechanisms which are recruited to facilitate the editing operation; two specific mechanisms, homology-directed repair (HDR) and nonhomologous end joining (NHEJ) are available. Doudna & Charpentier, supra note 15, at 1258096-2.
22. Id. at 1258096-5 fig.4A. CRISPR-Cas9 can also alter gene expression through other mechanisms. For the editing of epigenetic DNA methylation, see, for example, X. Shawn Liu et al., Editing DNA Methylation in the Mammalian Genome, 167 CELL 233, 233 (2016), and for the manipulation of gene transcription, see, for example, Silvana Konermann et al., Genome-Scale Transcriptional Activation by an Engineered CRISPR-Cas9 Complex, 517 NATURE 583, 587 (2015).
24. Matthew H. Porteus, Towards a New Era in Medicine: Therapeutic Genome Editing, 16 GENOME BIOLOGY 286, 289 (2015). With respect to nomenclature, the delivery of a Cas9 enzyme by DNA or RNA transfer is a kind of gene transfer; however, it is the delivery of an enzyme that will target a native gene in the cell for editing, rather than the delivery of a gene to a target cell to supplement or correct a defective version of that same gene.
25. Christof Fellmann et al., Cornerstones of CRISPR-Cas in Drug Discovery and Therapy, 16 NATURE REV. DRUG DISCOVERY 89, 95 (2017).
alterations elsewhere in the genome, undercutting the rationale for the originally intended genome-editing intervention.

Since 2012, CRISPR-based methods for genome-editing experiments have been widely adopted across biological science, and the widespread application of genome editing to studies in animals, plants, and microbes is underway. Significant financial investments and specific initiatives to commercialize genome editing have accompanied the excitement in the scientific community. A recent inventorship dispute between the University of California at Berkeley (UC Berkeley) and the Broad Institute of the Massachusetts Institute of Technology and Harvard University has centered on which institution was entitled to foundational patent rights for the commercially significant use of CRISPR-Cas9 methods in eukaryotic cells (such a dispute is resolved in a specialized and complex patent law proceeding known as an interference). In its adjudication of the conflict, the United States Patent and Trademark Office Patent Trial and Appeal Board (PTAB) declared no conflicting patent rights between a pending UC Berkeley patent application and the already issued patents of the Broad Institute; therefore, the existing grant of patents to the Broad Institute for the use

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27. A full accounting of all genome-editing applications to date is beyond the scope of this article, which focuses on the uses in humans. See infra Part II. For a general overview of work in the biological sciences, see generally Rodolphe Barrangou & Jennifer A. Doudna, Applications of CRISPR Technologies in Research and Beyond, 34 NATURE BIOTECH. 933 (2016) and Doudna & Charpentier, supra note 15. The current wave of xenotransplantation research uses genome editing in animals to generate immune-compatible organs for human transplantation. See Daniel R. Salomon, A CRISPR Way to Block PERVs—Engineering Organs for Transplantation, 374 NEW ENG. J. MED. 1089, 1089 (2016). It is important to note several dimensions of the wider use of genome editing that are shaping the broader regulatory climate for the technology. For instance, the production of genome edited food products may avoid the current regulatory scheme for genetically engineered foods, which has been largely focused on gene transfer, but that may change. See Genome Editing in New Plant Varieties, 82 Fed. Reg. 6564 (proposed Jan. 19, 2017). The production of gene-edited animals may encounter heightened review by the Food and Drug Administration (FDA). See Regulation of Intentionally Altered Genomic DNA in Animals, Draft Guidance for Industry, 82 Fed. Reg. 6561 (proposed Jan. 19, 2017). And finally, genome-editing research has led to the development of gene drives, which are CRISPR-based strategies to accelerate the inheritance of altered DNA; for example, gene drive techniques used with gene-edited mosquitos in malaria research could accelerate the spread of disease-resistant genetic elements. See, e.g., Valentino M. Gantz et al., Highly Efficient Cas9-Mediated Gene Drive for Population Modification of the Malaria Vector Mosquito Anopheles Stephensi, 112 PROC. NAT’L ACAD. SCI. E6736, E6741 (2015).

28. A number of startup companies have formed to specifically commercialize the applications of CRISPR/Cas9. See Bruce Booth, Riding the Gene Editing Wave: Reflections on CRISPR/Cas9’s Impressive Trajectory, FORBES (May 31, 2016, 6:55 AM), http://www.forbes.com/sites/brucebooth/2016/05/31/riding-the-gene-editing-wave-reflections-on-crisprs-impressive-trajectory/#640b9197141c.

29. In January 2016, the United States Patent and Trademark Office (USPTO) declared an interference proceeding between claimants from the University of California, Berkeley and claimants from the Broad Institute at the Massachusetts Institute of Technology and Harvard University to the patent rights for a number of patents related to CRISPR-Cas9 technology, with the rights to the most commercially significant application (use in eukaryotic cells) at stake. See Broad Inst., Inc., v. Regents of the Univ. of Cal., No. 106,048 (P.T.A.B. Jan. 11, 2016) (declaration).
of CRISPR-Cas9 in eukaryotic cells was upheld, and the UC Berkeley application for the use of CRISPR-Cas9 in all cells could continue prosecution.\(^{30}\) In response to the PTAB ruling, UC Berkeley filed an appeal with the U.S. Court of Appeals for the Federal Circuit.\(^{31}\)

Beyond the formal assignment of patent rights in foundational technologies, the genome-editing field is also shaped by the licensing practices of the patent holders. The current predominance of exclusive CRISPR licenses issued by academic patent holders to a handful of genome-editing companies has drawn criticism for unduly constraining the development of many human therapeutic applications of CRISPR.\(^{32}\) As specific genome-editing products are developed in coming years, patent rights to such products will certainly be sought, and the management of those patent rights will determine product access for researchers, clinicians, and patients.

II. OVERSIGHT OF GENETIC MODIFICATION IN HUMAN SOMATIC CELLS

A. Gene Transfer

The first experiments to produce recombinant DNA (rDNA) molecules began in the mid-1970s, and the recognition by participating scientists that such constructs might pose unforeseen risks to personnel or to the environment helped to initiate the design of an oversight mechanism for such research.\(^{33}\) The Recombinant DNA Advisory Committee (RAC) was established in 1974 as an advisory body for the National Institutes of Health (NIH) (which funds much of biomedical science) on research involving rDNA.\(^{34}\) The first focus was on rDNA experiments that produced genetically engineered microorganisms. The Asilomar Conference on Recombinant DNA in 1975 gathered the leading practitioners to draw up guidelines for the safe management of rDNA experiments.\(^{35}\) In 1976, the NIH published the Recombinant DNA Research Guidelines, which were applicable to all experiments performed at, or sponsored by, any institutions receiving NIH funding.\(^{36}\)

\(^{30}\) The recent decision from the PTAB found no interference between the patent claims of the two parties, thus the UC Berkeley retains its pending patent application on the use of CRISPR-Cas9 in any cell type, while the Broad Institute keeps its issued patents on CRISPR-Cas9 use in eukaryotic cells (which includes humans). See Broad Inst. v. Regents of the Univ. of Cal., No. 106,048 (P.T.A.B. Feb. 15, 2017) (judgement). Looking forward, it is possible that the coexistence of the UC Berkeley patent (upon issuance) and the Broad Institute patents could require licenses from both patent holders for the use of CRISPR-Cas9 in eukaryotic cells by third parties, and cross-licenses between the patent holders for such use.


\(^{34}\) Id.


The application of gene transfer techniques to human clinical medicine was recognized as a possibility by the 1980s. As a methodology directed at clinical improvement of human patients, the initial concept of gene transfer was aimed at somatic, not germline, cells. Traditional clinical genetics, now aided by molecular detail, had established that many human diseases and conditions had genetic origins. The simplest paradigm was a case where a mutation in a single gene led to the development of a specific disease; cystic fibrosis is one such example and the critical gene for the disease has been identified. Could the defective gene be replaced with a “normal” copy of the gene provided through gene transfer? Could the gene be delivered with a viral vector or other method? Depending on a particular gene transfer objective, the genetic material could be transferred to cells removed from the body (ex vivo) which are then transplanted into a patient, or it could be directly administered to a patient (in vivo), often by using a viral vector into which the gene of interest has been inserted. The distinction between ex vivo and in vivo methods is critical, because in vivo gene therapy must contend with designing a gene therapy vector or using other methods to deliver the gene of interest in a manner that can be safely tolerated by a patient.

Since the 1980s, authorization for human gene therapy clinical trials have required the submission of a protocol for approval to the RAC, an Investigational New Drug Application (IND) submitted to the Food and Drug Administration (FDA), and institutional approvals from the local Institutional Review Board (IRB) and the local Institutional Biosafety Committee (IBC). The NIH Guidelines have evolved over the years to their current iteration, and include specific details for investigators seeking approval to conduct gene transfer protocols in humans. The first gene therapy clinical trial in the United States was approved in 1990, with successful results reported in 1995. In 1998, the gene

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37. Anderson & Fletcher, supra note 10, at 1293.
38. NAT’L INSTS. OF HEALTH, supra note 38, at 100.
40. Naldini, supra note 8, at 353 (describing both in vivo and ex vivo techniques).
41. Id. (discussing some of the challenges, such as immune response, that in vivo editing techniques face).
43. NAT’L INSTS. OF HEALTH, supra note 38, at 2, 100.
44. See supra note 10, at 99–105.
45. R. Michael Blaese et al., T Lymphocyte-Directed Gene Therapy for ADA SCID: Initial Trial Results After 4 Years, 270 SCIENCE 475 (1995).
therapy field was shaken with the death of a patient in an in vivo gene therapy trial at the University of Pennsylvania, in which the lack of informed consent and transparency in the design and management of the trial were identified as underlying causes. In spite of that setback, gene therapy research has progressed over the years, and the number of gene therapy trials worldwide to date is around 2,000. In the United States, FDA approval, evaluating both safety and efficacy, is required to bring any gene therapy product to market. Although numerous clinical trials have been conducted, no gene therapy product has yet been approved for the U.S. market. However, efforts to enter the European market have succeeded, and several gene therapy products have been approved by the European Medicines Agency.

As gene transfer science has matured, the complex regulatory scheme for gene therapy clinical trials has been criticized for redundancy and inefficiency. A recent study commissioned by the NIH from the Institute of Medicine (IOM) to assess whether RAC oversight should be reconfigured concluded that future RAC review should be reserved for gene transfer protocols posing novel technical issues. The IOM Report also suggested that the RAC could be redefined as a more general oversight committee for emerging life science technologies, with one commentator noting such positive attributes of the advisory body as “transparency and inclusive engagement.” The NIH adopted the recommendations of the IOM Report and announced a streamlined review process for human gene transfer protocols in 2014.

B. Genome Editing

Over the last decade, basic research in the field of genome editing, accelerated by the development of CRISPR technology, progressed to the point where it was possible to explore clinical applications. Preclinical (animal) studies have demonstrated effective genome-editing therapeutic strategies for potential use in human genetic diseases, such as the CRISPR-Cas9-mediated repair of the dystrophin gene to treat Duchenne’s muscular dystrophy in mice.56 There are numerous reports of the use of genome-editing techniques to edit genes ex vivo in mammalian, including human, cells.57 Genome-editing experiments in human induced pluripotent stem cells can expand the therapeutic portfolio by offering the possibility of ex vivo genetic alteration coupled with differentiation into cell types specific for the repair of a target disease.58

The first clinical trial of genome editing was approved by the FDA in 2009, and involved editing of the CCR5 gene in T cells ex vivo using ZFN technology; disruption of the CCR5 gene could render T cells resistant to HIV infection.59 Published results from the trial demonstrated that the infusion of the ZFN-edited T cells was safe and that partial genetic resistance to HIV infection was observed in patients who were treated with the genetically edited cells.60 Other clinical trials of ZFN-based ex vivo genome editing are underway.61

In 2015, the FDA approved the first in vivo genome-editing protocol, submitted by Sangamo BioSciences, to use ZFN technology to edit Factor IX into a genetic locus in the liver to produce therapeutic levels of the protein to treat hemophilia.62 In 2016, the FDA approved a clinical trial of ZFN technology for

oversight-clinical-gene-transfer-protocols. This decision affects RAC review only; it does not change any FDA oversight.

56. See, e.g., Chengzu Long et al., Postnatal Genome Editing Partially Restores Dystrophin Expression in a Mouse Model of Muscular Dystrophy, 351 SCIENCE 400, 400 (2016); Christopher E. Nelson et al., In Vivo Genome Editing Improves Muscle Function in a Mouse Model of Duchenne Muscular Dystrophy, 351 SCIENCE 403, 406–07 (2016); Mohammadsharif Tabebordbar et al., In Vivo Gene Editing in Dystrophic Mouse Muscle and Muscle Stem Cells, 351 SCIENCE 407, 410 (2016).

57. See Porteus, supra note 24, at 293; see also Morgan L. Maeder & Charles A. Gersbach, Genome-Editing Technologies for Gene and Cell Therapy, 24 MOLECULAR THERAPY 430, 435 (2016).

58. See Dirk Hockemeyer & Rudolf Jaenisch, Induced Pluripotent Stem Cells Meet Genome Editing, 18 CELL STEM CELL 573, 575 (2016).


60. Pablo Tebas et al., Gene Editing of CCR5 in Autologous CD4 T Cells of Persons Infected with HIV, 370 NEW ENG. J. MED. 901, 902 (2014).

61. See Maeder & Gersbach, supra note 57, at 434–35.

the in vivo treatment of mucopolysaccharidosis type II using a viral vector to deliver an enzyme to affected patients. 63

As of this date (mid-2017), the first U.S. clinical trial using CRISPR-Cas9 genome editing could be near, and it emerges from the field of cancer immunotherapy. 64 In 2016, the RAC approved a genome-editing protocol for study in human patients, which involves CRISPR-Cas9-mediated editing of T cells from cancer patients for ex vivo immunotherapy targeted against their cancer cells. 65 FDA approval will also be required for the clinical trial to proceed. A scientifically similar clinical trial with CRISPR-Cas9-edited T cells for ex vivo use in lung cancer patients is currently underway in China, and this trial represents the first administration of CRISPR-edited cells to a human patient. 66

As of this writing, proposed genome-editing protocols and clinical trials have been absorbed into the preexisting U.S. regulatory framework for gene therapy, whose overview is largely derived from gene transfer studies. Although the recent redesign of RAC oversight shifts more responsibility to local IRB and IBC boards, that shift is likely most relevant to the incumbent field of gene transfer as it is regarded as a field with established technical norms. However, the new field of genome editing is emerging just as RAC oversight is being reconfigured. Therefore, the reservation of RAC review for protocols involving novel technical issues will likely mean that any proposed genome-editing protocols will automatically trigger public review by RAC for the foreseeable future (e.g., first RAC approval of a CRISPR-Cas9 human genome-editing protocol). 67

As noted above, the FDA has not approved any gene transfer-based products in the United States despite decades of research and clinical trials, and that fact suggests that the more recent field of genome editing is unlikely to generate commercial products any sooner. At least one commentator has questioned whether the formulation of a genome-editing product for FDA approval would invoke either a product or device regulatory framework as a matter of technical classification. 68 Genome-editing applications in clinical medicine share some

64. Sara Reardon, First CRISPR Clinical Trial Gets Green Light from US Panel, NATURE (June 22, 2016), http://www.nature.com/news/first-crispr-clinical-trial-gets-green-light-from-us-panel-1.20137; see also Andrew D. Fesnak et al., Engineered T Cells: The Promise and Challenges of Cancer Immunotherapy 16 NATURE REV. CANCER 566, 575 (2016) (describing how CRISPR-Cas9 can be used to genetically edit a cancer patient’s T cells, which are then infused into the patient to attack cancer cells).
66. David Cyranoski, CRISPR Gene Editing Tested in a Person, 539 NATURE 479 (2016).
67. See Kaiser, supra note 65.
68. Barbara J. Evans, Presentation at the NAS International Summit on Gene Editing, Panel: Governance at the Institutional and National Levels (Dec. 2, 2015), http://nationalacademies.org/gene-editing/Gene-Edit-Summit/Slide-Presentations/index.htm. Because the CRISPR-Cas9 complex delivers an enzyme that will target and cleave DNA, it has some attributes of a device, which could be relevant to FDA regulatory classification. Id.
continuing technical concerns with gene transfer applications, especially where in vivo approaches are used, because the delivery vehicles for either technique can be a source of clinical complications.\textsuperscript{69} However, the serious genetic side effects specifically observed in genome-editing experiments to date (off-target enzyme activity, mosaicism) will likely warrant a heightened level of scrutiny and monitoring in any proposed therapeutic uses in human somatic cells.

In 2015, the National Academy of Sciences (NAS), along with the National Academy of Medicine (NAM), announced the Human Gene Editing Initiative to allow all stakeholders and official authorities an opportunity to take stock of the progress of genome editing and define where ethical, legal and political issues were emerging as the technology was more widely adopted.\textsuperscript{70} An International Summit on Human Gene Editing (NAS International Summit) was held in December 2015;\textsuperscript{71} this was followed by a consensus study by an expert committee convened by the NAS which issued its report in early 2017 (NAS Report).\textsuperscript{72} The study endorsed the use of somatic cell genome editing in human clinical medicine;\textsuperscript{73} however, it strongly discouraged the use of genome editing for enhancement purposes.\textsuperscript{74} The NAS Report further concluded that the oversight of human genome editing in somatic cells could rely on the evaluative and regulatory frameworks developed for gene therapy.\textsuperscript{75} Thus, the oversight of genome editing in human somatic cells to date has not required the establishment of new regulatory authorities beyond those established for gene transfer oversight, illustrating that genome editing falls on the continuum of gene modification technologies that began with the rDNA experiments of the 1970s.

\section*{III. OVERSIGHT OF GENOME EDITING IN THE HUMAN GERMLINE}

It was immediately foreseeable that the most contentious application of genome-editing technologies would be in human reproduction—namely the use of genome editing to perform germline genetic modification, leading to the establishment of heritable changes in the human genome. As a practical matter, no germline genome editing for reproduction could be undertaken until substantial

\begin{itemize}
\item \textsuperscript{69} See generally Porteus, supra note 24.
\item \textsuperscript{70} See Human Gene Editing Initiative, nat’l acad. sci., eng’g & med., http://www.nationalacademies.org/gene-editing/index.htm (last visited Mar. 9, 2017).
\item \textsuperscript{73} Id. at 110 (“At this time, regulatory authorities should authorize clinical trials or approve cell therapies . . . for indications related to the treatment or prevention of disease or disability.”).
\item \textsuperscript{74} Id. at 159.
\item \textsuperscript{75} Id. at 110 (“Existing regulatory infrastructure and processes for reviewing and evaluating somatic gene therapy to treat or prevent disease and disability should be used to evaluate somatic gene therapy that uses genome editing.”).
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basic research on genome editing in human embryos has been conducted. However, as a threshold policy matter, genome-editing experiments on human embryos (for studies in developmental biology or as a predicate to reproductive applications) are not universally accepted. Thus, there are two undercurrents of debate that emerge when deliberating the policy frameworks for germline genome editing: the propriety of genome-editing research with human embryos and the acceptability of using germline genome editing in human reproduction.

Germline genome editing for reproduction could be accomplished, for example, by introducing a CRISPR-Cas9 complex into a gamete (egg, sperm) or embryo to perform a desired editing operation in the targeted DNA. Theoretically, the genetic edit embedded in this germline DNA will become a heritable modification in the developing offspring. In contrast, the use of genome editing in somatic cell applications will alter the targeted cells, but the genetic changes will not be passed on to offspring of the individual under treatment.

It is not surprising that it was the first public announcement of CRISPR genome-editing experiments on human embryos in 2015 that focused global attention on the rapid rise and incorporation of CRISPR technologies into scientific research. The first published experiments were from China, and detailed the use of CRISPR-Cas9 to edit the genomes of nonviable human embryos; one laboratory reported an editing of the HBB gene, which encodes β-globin in beta-thalassaemia, and a second laboratory reported the editing of the CCR5 gene to carry a mutation that is known to make T cells resistant to HIV infection. In addition to reporting the relative inefficiency of the editing process in the embryos, both publications also catalogued deleterious consequences of the genome editing: the off-target activity of the Cas9 nuclease, and the mosaicism of the edited embryos. The choice of nonviable embryos for these experiments, while less controversial than using viable embryos, also diminished the possible relevance of the data to understanding genome editing in a normal embryonic environment.

In early 2017, the first publication of CRISPR-Cas9 genome editing on viable human embryos appeared; the results suggested that a higher editing efficiency was achieved compared to nonviable embryos; however, significant mosaicism was observed in the study. In August 2017, the first U.S. genome-editing experiments using CRISPR-Cas9 on viable human embryos carrying a

76. See id. at 44.
78. Id.
79. See id.
81. Xiangjin Kang et al., Introducing Precise Genetic Modifications into Human 3PN Embryos by CRISPR/Cas9-Mediated Genome Editing, 33 J. ASSISTED REPROD. & GENETICS 581, 583, 588 n.19 (2016).
82. Id. at 585; see Liang et al., supra note 80, at 364.
83. Lichun Tang et al., CRISPR/Cas9-Mediated Editing in Human Zygotes Using Cas9 Protein, 292 MOLECULAR GENETICS & GENOMICS 525, 532 (2017).
specific genetic mutation were published.\textsuperscript{84} In addition to a relatively high efficiency of genetic correction of the mutation, the study reported low off-target activity of the Cas9 enzyme due to an optimal delivery method, and further reported that mosaicism in the edited embryos could be reduced by manipulating the cell cycle stage at which the CRISPR-Cas9 is introduced into the embryo.\textsuperscript{85} Notably, these U.S. experiments solely relied on private funding.\textsuperscript{86} Beyond China and the United States, scientists in other countries are also engaged in genome editing of viable human embryos.\textsuperscript{87}

Following the first reports of genome editing in human embryos in 2015, several responses emerged from the U.S. government. The White House issued a statement opposing any attempts at genome editing of the human germline.\textsuperscript{88} Congressional hearings on genome-editing technologies were held,\textsuperscript{89} and a specific amendment added to the 2015 appropriations bill prohibited the FDA from using any federal funds to take administrative action regarding “research in which a human embryo is intentionally created or modified to include a heritable genetic modification.”\textsuperscript{900} This provision is especially important because it could apply to other genetic technologies in addition to genome editing. An existing law already impacts any genome-editing embryo research: since 1996, the Dickey-Wicker amendment has been an annual rider to the appropriations bill in Congress that bans the use of federal funds to create embryos for research or for research in which an embryo is destroyed or discarded.\textsuperscript{91} In 2015, the NIH

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\item \textsuperscript{84} Hong Ma et al., \textit{Correction of a Pathogenic Gene Mutation in Human Embryos}, \textit{Nature} (Aug. 2, 2017), https://www.nature.com/nature/journal/vaop/ncurrent/pdf/nature23305.pdf.
\item \textsuperscript{85} Id. at 3, 5.
\item \textsuperscript{86} Id. at 7.
\item \textsuperscript{87} In the United Kingdom, the Human Fertilisation and Embryology Authority (HFEA) issued a formal approval to the Francis Crick Institute for genome-editing experiments on viable human embryos in order to study early embryonic development. Press Release, Human Fertilisation & Embryology Auth., HFEA Approves Licence Application to Use Gene Editing in Research (Feb. 1, 2016), http://hfeararchive.ksouth.cloudapp.azure.com/www.hfea.gov.uk/10187.html [hereinafter HFEA Press Release]. The HFEA, however, noted that “no research using gene editing may take place until the research has received ethics approval,” and “[a]s with all embryos used in research, it is illegal to transfer them to a woman for treatment.” Id. Developmental biologists at the Karolinska Institute in Sweden are currently performing genome-editing experiments on viable human embryos, although no formal publication has issued. See Rob Stein, \textit{Breaking Taboo, Swedish Scientist Seeks to Edit DNA of Healthy Human Embryos}, NPR: SHOTS (Sept. 22, 2016, 5:07 AM), http://www.npr.org/sections/health-shots/2016/09/22/494591738/breaking-taboo-swedish-scientist-seeks-to-edit-dna-of-healthy-human-embryos.
\item \textsuperscript{88} John P. Holdren, \textit{A Note on Genome Editing}, \textbf{WHITE HOUSE: BLOG} (May 26, 2015, 10:40 AM), https://obamawhitehouse.archives.gov/blog/2015/05/26/note-genome-editing [https://perma.cc/D2B3-YLLG].
\end{itemize}
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announced that it would not provide any federal funding for research that involved the use of genome editing with human embryos. Beyond the federal sphere, various state laws prohibit or restrict research on human embryos. Finally, and more generally, it has long been the official policy of RAC that it will not review any protocols for germline genetic modification.

The scientific community reacted to the first reports of genome editing on human embryos in 2015 with a series of cautionary statements. A call for an immediate voluntary moratorium on any genome-editing experiments with human embryos was published, and a call for more discussion on the use of genome editing on human embryos was also published. In contrast, an endorsement of genome-editing research on human embryos emerged from an international bioethics consortium.

A more recent position statement issued by a coalition of professional genetics organizations not only endorsed genome editing research on human embryos, but recommended public funding of such experiments.

There have been several formal deliberations sponsored by the National Academy of Sciences as part of their Human Gene Editing Initiative. At the NAS International Summit in 2015, a consensus statement from the participants endorsed genome-editing research, including on human embryos. The NAS convened an expert study committee to consider all “clinical, ethical, legal, and social implications” of human genome editing; it concluded that genome-

94. See Nat’l Insts. of Health, supra note 38, at 100 (“The NIH will not at present entertain proposals for germ line alterations but will consider proposals involving somatic cell gene transfer.”). That has been the position of NIH (through the RAC) since 1985. See generally Barbara J. Culliton, Gene Therapy Guidelines Revised, 228 Science 561 (1985).
96. See David Baltimore et al., A Prudent Path Forward for Genomic Engineering and Germline Gene Modification, 348 Science 36 (2015). Many of the authors were organizers of the NAS International Summit held in 2015.
99. See supra notes 70–72 and discussion therein.
editing experiments on human embryos could proceed with appropriate precautions, citing the benefits of such research to the study of infertility and embryonic development.102

The endorsement of genome-editing research on human embryos does not equate to automatic support for its application in human reproduction. The consensus statement from the NAS International Summit concluded that it would be “irresponsible” to conduct any clinical germline genome editing at present, until technical and safety issues were resolved and “broad societal consensus about the appropriateness of the proposed application” was achieved.103 The NAS Report did not call for a prohibition on the use of genome editing in human reproduction, noting that “[h]eritable germline genome editing trials must be approached with caution, but caution does not mean they must be prohibited.”104 The NAS Report then defined an extensive set of predicate conditions that would need to be met before germline genome editing could proceed.105 Professional research organizations have also issued policy statements on reproductive applications, including calls for a moratorium on any use of germline genome editing in clinical practice.106

102. NAS REPORT, supra note 72, at 82 (“Existing regulatory infrastructure and processes for reviewing and evaluating basic laboratory genome-editing research with human cells and tissues should be used to evaluate future basic laboratory research on human genome editing.”). The report further noted: “Important scientific and clinical issues relevant to human fertility and reproduction require continued laboratory research on human gametes and their progenitors, human embryos and pluripotent stem cells.” Id. at 81.


104. NAS REPORT, supra note 72, at 189.

105. Id. at 102–03. The conditions for the use of genome editing in the germline for human reproduction include the following:

- the 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 that 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;
- the availability of credible preclinical and/or clinical data on risks and potential health benefits of the procedures;
- during the trial, ongoing, rigorous oversight of the effects of the procedure on the health and safety of the research participants;
- comprehensive plans for long-term, multigenerational follow-up that still respect personal autonomy;
- maximum transparency consistent with patient privacy;
- continued reassessment of both health and societal benefits and risks, with broad ongoing participation and input by the public; and
- reliable oversight mechanisms to prevent extension to uses other than preventing a serious disease or condition.

If genome editing is defined simply as a more recent set of techniques for genetic modification in human reproduction, the caution and resistance encountered are somewhat familiar from earlier technical advances that posed the potential for the genetic design of human offspring. Earlier genetic modification technologies with the potential for use in human reproduction elicited controversy and debate. Several recent examples are helpful for illustration.

When somatic cell nuclear transfer (SCNT) was used to produce a cloned sheep in 1997, the field of reproductive medicine encountered a technology that could be used in the deliberate genetic design of offspring. SCNT could be used to generate a cloned embryo in human reproduction (reproductive cloning), or to generate cloned embryonic stem cells for therapeutic uses in diseases of cellular deterioration (therapeutic cloning). The possibility that a new technology could produce a cloned human motivated international and national authorities to consider whether human reproductive cloning should be banned or regulated. In the United States, the White House banned the use of any federal funds for reproductive cloning, the National Bioethics Advisory Commission recommended a ban on reproductive cloning, and federal legislation to ban the technique was introduced into Congress. The FDA asserted its jurisdiction over research leading to reproductive cloning. On an international level, although a proposed treaty failed, the United Nations passed the Declaration on Human Cloning in 2005 (supported by the United States), calling on member nations to ban all cloning procedures. Although such an international statement of ethical principles on reproductive technologies is noteworthy and even novel, commentators have noted that its effect is minimal if not accompanied by implementing policies.

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108. See NAT’L BIOETHICS ADVISORY COMM’N, CLONING HUMAN BEINGS 13 (1997), https://bioethicsarchive.georgetown.edu/nbac/pubs/cloning1/cloning.pdf. Reproductive cloning is a technology that allows for genetic design of offspring, albeit transmitting an existing (unaltered) genome from the donor of choice. Id. at 15.


111. Id. at 87, 104 tbl. 1.


114. G.A Res. 59/280, Declaration on Human Cloning, ¶ (b) (Mar. 8, 2005).

In a recent study, a survey of thirty-nine countries revealed that twenty-nine formally ban human germline genetic modification (the United States does not), including the use of criminal sanctions for violations; most of these laws were enacted after the controversy over reproductive cloning arose in the late 1990s. Although the likelihood that reproductive cloning will be used in reproductive medicine has abated since the late 1990s, the acute responses (domestic and international) provide a yardstick for public mobilization in the face of a perceived threat from a new reproductive technology. The intensity of opposition likely revealed a widespread resistance to the deliberate genetic manipulation of the genome of offspring, a more general theme that transcends the specific technology of cloning.

Not all reproductive genetic modification has been met with such staunch resistance. Mitochondrial genetic diseases are maternally transmitted and occur in some families when diseased mitochondria are transmitted from mother to child by the egg. Research into reproductive techniques that would allow affected women to avoid the transmission of mitochondrial diseases has increased in the last several decades. Mitochondrial replacement therapy (MRT), a more recent assisted reproductive technology, has emerged for the treatment of these forms of genetic diseases and is encountering a more permissive climate. In one illustration of mitochondrial replacement therapy (MRT), the nucleus of a woman with mitochondrial disease is transferred to the enucleated egg of a healthy donor (carrying healthy mitochondria), and that hybrid egg is then fertilized. This MRT has been shown to work in mice, and researchers in the field have sought FDA permission to conduct human clinical trials.

In 2015, the FDA asked the Institute of Medicine (IOM) of the National Academy of Sciences, Engineering and Medicine to consider all of the relevant regulatory issues raised by MRT. The IOM convened an expert panel that issued a report in February 2016, in which it declared that it would be “ethical” for the FDA to consider clinical trials of MRT. To date, however, the FDA has not approved any such clinical trials of MRT, and the agency is now currently prohibited from engaging in any such review because of a rider in the

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116. Motoko Araki & Tetsuya Ishii, International Regulatory Landscape and Integration of Corrective Genome Editing into In Vitro Fertilization, 12 REPROD. BIOLOGY & ENDOCRINOLOGY, art. no. 108, 2014, at 1, 8.


118. Id.

119. Id. at 71.

120. See id.


122. Wolf, supra note 117, at 73.

2016 Congressional appropriation legislation. The visibility of MRT at the same time that genome-editing technologies have been entering mainstream science may have converged to heighten Congressional sensitivity to germline modification in general; whether the current ban on any FDA administrative action involving heritable genetic modification will persist is unknown. Thus, there is a theoretical possibility that the United States could approve a germline genetic modification technology in the form of MRT, if the FDA decides to follow the IOM recommendation in the future. Nonetheless, in the absence of such a permissive environment, the FDA is currently monitoring any uses of MRT technology in the U.S., asserting its jurisdictional authority and identifying any noncompliant activity by researchers who are engaged in offering MRT services.

In the 1990s, the RAC encountered the issue of prenatal gene therapy, albeit not for deliberate germline manipulation. The RAC was asked to consider a proposed protocol for fetal gene transfer (in utero) in 1999, but the committee issued a statement declaring that it was “premature” to consider any in utero gene transfer experiment. However, the 2017 NAS Report does contemplate the possibility of future fetal genome editing in utero, whether ex vivo or in vivo, with specific cautions noted.

The question of whether germline genome editing would be the only approach to avoiding inherited genetic disease in offspring is a threshold question for any potential use of the technology in human reproduction. To date, there

125. Id.
130. NAS REPORT, supra note 72, at 108 (“Although fetal genome editing has potential advantages, at least two special ethical issues would need to be addressed: special rules for consent (see Chapter 2) and the increased risk of causing heritable changes to the germline by causing modification of germ cells or germ cell progenitor/stem cells.”).
is a substantial clinical history with the use of other assisted reproductive technologies to allow prospective parents with existing genetic diseases to generate healthy offspring, using, for example, preimplantation genetic diagnosis (PGD). This technique requires in vitro fertilization followed by genetic testing of embryos to select one or more embryos without genetic disease for implantation and pregnancy. Because PGD is a credible option to avoid the transmission of many genetic conditions, the scenarios where germline genome editing would be the only pathway to generating offspring free of genetic disease are quite few.

The possibility of using genome-editing technologies in human reproduction raises specific legal and ethical issues beyond those raised by the use of genome-editing technology for therapeutic objectives in somatic cells. The issues include the establishment of risk/benefit ratios, the possibility of consent for affected individuals, autonomy of prospective parents, respect for human dignity, avoidance of eugenics, the availability of alternatives to genetic modification, and the consideration of divergent views on ethical, philosophical and social implications of germline genome editing.

Widespread opposition to human germline genetic modification in the United States was evident from the response to earlier reproductive-related genetic technologies, such as reproductive cloning. Although proposed legislation that targeted cloning for prohibition in the United States failed, there has been no parallel effort to date to specifically prohibit germline genome editing. More broadly, the United States lacks any specific legal prohibition on human germline genetic modification. However, there are indirect sources of resistance. The Dickey-Wicker ban on federal funding for most human embryo research poses a significant obstacle. Other more specific obstacles to the use of germline genome editing in the United States include the NIH’s declaration that no federal funding can be used for genome editing of human embryos (echoing the Dickey-Wicker ban), the RAC’s formal refusal to consider any protocols for germline alteration, and the recently enacted legislative prohibition on the FDA’s ability to review any proposals for clinical trials of any such technology. Germline genome editing differs from MRT or reproductive cloning in that it requires the administration of a gene therapy product (e.g., CRISPR-Cas9 complex) to accomplish the genetic modifications, creating a more complex regulatory profile; the regulations for conducting clinical trials or seeking premarket approval would be different.

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132. NAS REPORT, supra note 72, at 113. The report suggests that “[c]linical trials using heritable genome editing should be permitted only within a . . . regulatory framework that encompasses . . . the absence of reasonable alternatives.” Id. at 189.

133. See id. at 114–15. The report identifies prospective parents who are both homozygous for an autosomal recessive disease, or a couple where one parent is homozygous for an autosomal dominant disease as possible candidates. Id.

134. See Dana Carroll & R. Alta Charo, The Societal Opportunities and Challenges of Genome Editing, 16 GENOME BIOLOGY 2015, at 6–9; see also Katrine S. Bosley et al., CRISPR Germline Engineering—The Community Speaks, 33 NATURE BIOTECH. 478, 478 (2015) (chronicling the answers of twenty-six “researchers, ethicists, and business leaders in the global community” on the “ethical issues raised by CRISPR engineering of the human germline”).

135. See NAS REPORT, supra note 72, at 119–30.
approval of such products that are enforced by the FDA would apply in addition to FDA’s asserted oversight of various clinical techniques used in assisted reproductive medicine.\textsuperscript{136}

A “slippery slope” to a greater likelihood that genome editing would be attempted in human reproduction is likely to be derived from the acceptance and ubiquity of genome-editing research on human embryos. As discussed above, at least four research groups have reported actual or future genome-editing experiments on viable human embryos.\textsuperscript{137} Although the NAS Report did not call for direct prohibition of germline genome editing in human reproduction, it did advocate for a substantial set of predicate conditions for the use of clinical germline genome editing which are unlikely to be satisfied anytime soon.\textsuperscript{138} As somatic cell genome-editing technologies undergo investigation and clinical use, the collection of data on undesirable side effects such as off-target enzyme activity and mosaicism will begin to define the risk profile for the technology as applied to specific targeted cells. Any genome-editing experiments with human embryos will contribute more data on the viability of genome editing with embryonic cells and tissues. Beyond formal scientific experiments, the trend toward the democratization of genome-editing tools by commercial vendors could offer another source of information emerging from unexpected real-world applications.\textsuperscript{139} Thus, at this time, accurate predictions regarding the performance of genome-editing techniques, including CRISPR, across a heterogeneous collection of cell types and organisms, are not yet possible. Even apart from ethical and legal objections, the substrate of technical accomplishment that would be required for serious consideration of clinical germline genome editing is unlikely to develop anytime soon.

The rapid dissemination of genome-editing technologies (most prominently, CRISPR-based techniques) into basic and clinical biological research has opened a new era of genetic modification for potential use in human medicine and reproduction. In the five years since the first publication of the

\begin{footnotesize}
\textsuperscript{136} Id. at 100. \\
\textsuperscript{137} See Tang et al., supra note 83; Ma et al., supra note 84; HFEA Press Release, supra note 87; Stein, supra note 87. \\
\textsuperscript{138} See NAS REPORT, supra note 72, at 134–35. \\
\textsuperscript{139} Data could also emerge from unlikely sources. It is likely that genome editing is a technology with a higher do-it-yourself(DIY) profile than any earlier genetic technology with a potential application to human reproduction. As a result, the public availability of kits and protocols could also generate information regarding unexpected risk of genome-editing technologies. See Denver Hicks, Biohacker Scientist Is Selling DIY Gene-Editing Kits for $120, TIME: MONEY (Jan. 12, 2016), http://time.com/money/4177434/diy-gene-editing-kit-crispr/. The risk of rogue activities involving genome editing has been recognized by U.S. national security officials. See JAMES R. CLAPPER, STATEMENT FOR THE RECORD: WORLDWIDE THREAT ASSESSMENT OF THE U.S. INTELLIGENCE COMMUNITY 9 (2016), https://www.dni.gov/files/documents/SASC_Unclassified_2016_ATA_SFR_FINAL.pdf (“Given the broad distribution, low cost, and accelerated pace of development of this dual-use technology, its deliberate or unintentional misuse might lead to far-reaching economic and national security implications.”).
\end{footnotesize}
CRISPR-Cas9 technology, the use of CRISPR genome editing has spread rapidly through the biological sciences, owing to its ease of use and efficiency. The first experiments using genome editing on viable and nonviable human embryos have been reported, and the first human clinical trials using CRISPR-edited cells in an ex vivo protocol are underway. With respect to actual technical promise, CRISPR-based genome editing offers the most potential to date for implementing precise genetic alterations in a target cell or organism, but it is not without complications. CRISPR editing experiments to date have revealed that targeted cells can sustain off-target enzymatic activity capable of causing genetic damage and can display an uneven distribution of outcomes, leading to genetic mosaicism. These consequences could limit or delay the use of genome editing for somatic cell therapeutic applications, and they add to the objections raised against the use of the technology in the human germline. Over time, the risk metrics for CRISPR-based applications will become more sharply defined as data accumulates from the widespread adoption of the technology.

The rapid dissemination of CRISPR genome-editing technologies have been accompanied by a widespread recognition that significant policy questions arise with such a powerful technology for genetic modification. However, there is a sharp distinction in the ethical, social, and policy issues raised by the use of genome editing for therapeutic genetic correction in somatic cells or the use of genome editing on gametes or embryos for the deliberate genetic design of offspring.

With respect to the near-term use of genome editing in human somatic cells, it appears that the existing oversight mechanisms for gene transfer therapies in the United States will remain adaptable as needed to provide the same review of proposed genome-editing protocols in humans. The well-established RAC model of professional review coupled with public engagement can continue to absorb new genetic technologies for technical assessment. The RAC has also been a forum for the public airing of ethical issues accompanying new technologies, and that role may be invigorated as genome editing becomes more visible. For instance, the RAC could establish periodic Genome Editing Policy Conferences, modeled on their earlier public events regarding gene transfer technology.

Similarly, the FDA will remain as the gatekeeper to clinical trials or pre-market approval for any genome-editing products (whether derived from public or private funding). After several decades of effort, the lack of any approved gene transfer products in the United States illustrates the complexity of gene modification in somatic cells, despite formal therapeutic promise. Therefore, the forecast for any routine incorporation of genome editing in somatic cells as a component of precision medicine is hard to make at the current time. Nonetheless, it is likely that the ex vivo applications of genome editing in human somatic

141. See id.
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cells will be the most practical embodiments for near-term clinical trials, in contrast to the in vivo applications which require an efficient delivery mechanism for targeting cells in a patient.

Against an international backdrop of national laws prohibiting human germline genetic modification, the United States lacks any such official prohibition. However, the United States exhibits a patchwork of regulatory impediments that would reduce the possibility that germline genome editing could be used in human reproduction. The recent Congressional ban on FDA’s ability to take any action regarding germline modification might become another semi-permanent barrier to any use of the technology (as the Dickey-Wicker ban on federal funding of embryo research has now been law for 20 years), and the current policies of the FDA and RAC prohibit the consideration of any clinical proposals for germline genome editing. In addition, official disavowals of federal funding for genome editing in human embryos or germline genome editing evoke earlier funding bans that were issued with respect to reproductive cloning and embryonic stem cell research, and their impact could be significant.

Opponents of genome-editing experiments with human embryos argue that they increase the likelihood that reproductive applications become more socially palatable or technically feasible. Therefore, one current schism in the debate on human germline genome editing appears to center on whether genome-editing experiments on human embryos should proceed; there is more agreement at the present time that actual germline gene genome editing to create offspring is off-limits, and even where not officially prohibited, it is certainly disfavored. Nonetheless, basic genome-editing research in human embryos in the United States can proceed with private funding in any state with a permissive stance toward human embryo research. The first U.S. publication of CRISPR-Cas9 genome editing of viable human embryos in 2017 reported experiments that solely relied on private funding. Official sanctions of genome-editing experiments on viable human embryos for research into early human development have been given in the United Kingdom, Sweden, and China (to date), and the NAS Report in the United States has endorsed such research.

It is evident that the CRISPR revolution in genome editing has caught the attention of policymakers in the U.S. government and the international sphere. As detailed in Parts II and III, almost all of the relevant U.S. government agencies with a stake in biomedical research or oversight have reacted with either enthusiasm or caution (or both) to the potential that genome editing will accelerate therapeutic and preventive approaches to genetic disease. The broad adoption of CRISPR technology across the biological sciences has also generated significant participation from the scientific community in the articulation of emerging policy dilemmas and possible resolutions. While the attention of scientists to the ethical and social implications of genetic technologies is desirable and necessary, the CRISPR-inspired visibility of human genome editing has generated significant commentary on the need for collective deliberation that involves other sectors of society.142

142. See, e.g., Sheila Jasanoff et al., CRISPR Democracy: Gene Editing and the Need for Inclusive Deliberation, ISSUES SCI. & TECH., Fall 2015, at 25, 26 ("But the human genome is not
It is fair to conclude, in mid-2017, that human genome editing is the most consequential genetic technology for precision medicine to emerge in many years. Its rapid adoption and prominence in current biological research, largely driven by the development of CRISPR technology, is evidence of that assertion. For all the technical novelty that genome-editing technologies offer, however, their recent emergence conjures up very familiar debates over the propriety and management of human genetic modification in general, whether on living persons, embryos or future offspring. These questions emerged with the advent of rDNA experiments in the 1970s, and they are as relevant today as they were then. The widespread interest in and use of genome editing is likely to intensify the ongoing debates on the ethical, social, and legal aspects of human genetic interventions, and it could increase the urgency to establish robust mechanisms for oversight and accountability in the use of present and future genetic technologies.