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Implications of CRISPR-Based Germline Engineering for Cancer Survivors

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Abstract

Cancer survivors can carry germline mutations that will be transmitted to their progeny. Today, many of these mutations have been identified and can be tracked. With the recent development of genome-editing technologies and CRISPR (clustered regularly interspaced short palindromic repeats), the possibility of genetically modifying the human germline—gametes and embryos—has never been closer. This perspective has sparked a controversy within the scientific community with reactions ranging from calls for a ban on germline modification to cautious approval of further research. This Editorial analyzes the possible adoption of CRISPR-based germline engineering to prevent the spread of cancer predispositions in the human population. We discuss whether the genomic edition of human sperm and eggs would contribute to rectifying or altering the heritable genome. We anticipate the emergence of a new form of liberal eugenics fueled by a logic of offer and demand from stakeholders such as cancer survivors and their relatives and offspring, but also from fertility clinics, biotech firms, insurers, and clinicians. From a regulatory perspective, validating the clinical safety and utility of CRISPR-based germline engineering is an essential step. However, with time, gradually perfecting the technology and assessing the economic benefits for stakeholders could soften society's resistance and align opinions in support of genomic decontamination of human germlines. This progressive shift would be justified in the name of cancer prevention as well as a moral obligation to facilitate the conception of cancer-free children at a cost that is acceptable to individuals and health systems.

Keywords

CRISPR, germline, eugenics, cancer survivor, economic burden.

Introduction

Cancer survivors strive to rebuild their lives despite the many obstacles they face in obtaining bank loans, resuming their careers, or finding reasonably priced insurance policies.[1] Many wish to have children but are concerned about passing on their genetic predispositions to cancer to their offspring. Why not directly edit the cancer survivors' germline DNA to rid them of these mutations and preserve their lineage?

Our understanding of the biology of cancer has expanded exponentially in the last decade, and with it the awareness of its extreme complexity. With cancer's basis in genomics now established, there have been extensive efforts to characterize the main driver mutations and biological pathways, especially through The Cancer Genome Atlas (TCGA).[2,3] In a review of the cancer genome landscape, 84 known oncogenes and 54 tumor suppressor genes have been fully validated.[4] Unquestionably there will be more; the total number of genes involved in pivotal mutations is estimated at close to 200.[5] However, with the recent development of genome-editing technologies such as CRISPR, genetically modifying cancer predispositions has never been closer.

Genome-editing techniques allow the custom-synthesis of DNA fragments—the insertion, deletion, or expression of genetic variants in a targeted, simple, and efficient manner.[6] The most recent version of these molecular cut-and-paste technologies, CRISPR is based on two components—an enzyme (Cas9) that functions like molecular scissors, cutting out certain genes while inserting others, and an RNA molecule that guides these scissors toward a specific DNA sequence.[7] Other techniques exist, such as Zinc Finger Nucleases (ZFN) and Transcription Activator-Like Effector Nucleases (TALENs), but today CRISPR engineering stands out through its speed, accuracy, ease of use, and low cost.[8]

Genome editing already has a wide range of applications in infectiology, the prevention of new HIV infections,[9] and the neutralization of malaria-carrying mosquitoes[10]; in agriculture,

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with the transgenic editing of rice,[11] oranges,[12] transgenic livestock,[13] and hypoallergenic chickens[14]; in pharmacology, with the production of organoids that can accelerate cancer drug screening[15]; and in biomedicine, to correct mutations that can cause hereditary diseases[16] such as Duchenne muscular dystrophy,[17-19] cataracts,[20] hereditary deafness,[21] β thalassemia,[22] and cystic fibrosis.[23,24]

In oncology, genome-editing technologies are already being applied in a wave of clinical trials to conditions ranging from leukemia,[25] metastatic non-small cell lung cancer[26] and melanoma, to sarcoma and myeloma.[27] All these clinical trials are conducted on somatic cells, but CRISPR is already being considered for use on germline stem cells, which could make it possible to modify the DNA of spermatogonial stem cells.[28] Genome engineering of spermatogonial stem cells would free descendants from the symptoms of the targeted disease.[29,30] It would also ensure that individuals would not become asymptomatic carriers of these mutations that, from an epidemiological standpoint, would significantly decrease the disease's frequency in the human population.[31] In theory, these mutations could eventually disappear over generations, thereby eradicating hereditary diseases whose main genetic markers have been identified, such as cystic fibrosis and Huntington disease.

The debate over CRISPR-based germline engineering is generally framed from an ethical and scientific perspective. The economic dimension is often overlooked. In this editorial, we analyze the industrialization of this technology and anticipate that CRISPR will both create and meet demands on the individual and collective levels. Economic stakeholders—biotech and medtech firms, public payers, health insurers, fertility clinics, parents-to-be, cancer survivors, their relatives and offspring—may share converging interests in preventing the spread of cancer predispositions in the human population.

From Hereditary Risk Assessment to Clinical Interventions

Cancer is a genetic disease whose pathogenesis is influenced by hereditary and environmental factors. Genetic susceptibility and predisposition to cancer depend on the penetrance of the inherited germline and allele mutations, which are classified in three groups: high, moderate/intermediate, and low. Low penetrance alleles predispose carriers to cancer risks that are slightly higher than those observed in the general population. Moderate penetrance alleles increase the risk of disease by a factor of roughly two to five.[32] High penetrance alleles predispose an individual to the risk of cancer throughout their life, with a risk often 10 times that observed in the general population. This is the case of colorectal cancer, for which 5% of cases can be explained by germline mutations in high penetrance alleles such as APC, MLH1, or MSH2.[33] For breast cancer, BRCA1 and BRCA2 susceptibility genes are involved in roughly 25% of cases of families affected by hereditary breast cancer. For carriers of these genes, the assessed cumulative risk of breast cancer at age 80 is approximately 80%.[34]

The following question therefore arises: what would the clinically acceptable risk threshold be for using CRISPR to prevent the transmission of alleles associated with cancer? Should usage be strictly limited to high or intermediate penetrance alleles? While low penetrance alleles correspond to a polygenic model in which many of them are tied to a very low genotypic risk (factor of 1.5 to 2), their accumulation can have a multiplier effect on susceptibility in the general population.[35] Thus, individuals carrying a large number of low penetrance alleles may be exposed to a cumulative risk of cancer of close to 50% throughout their lifetime—hence the importance of identifying low penetrance alleles that are responsible for genetic susceptibility.[36] In other words, even for low penetrance alleles, genome editing could theoretically have a clinical utility both for cancer patients and their descendants who may inherit these predispositions.[32]

One possible usage of CRISPR to prevent hereditary cancers would involve a multidisciplinary approach to assess the probabilities of germline mutations in cancer-susceptibility genes, and then cross-checking these probabilities with the history of an individual and their family. The possible identification of *Variants of Uncertain Significance* (VUS) further complicates the outlook for genome editing, and although next-generation sequencing technologies will probably help to gradually reduce the number of VUSs, for the time being the use of CRISPR reflects an ethics of uncertainty.[37]

Although the utilization of CRISPR is still experimental for cancer patients, several investigational protocols may prefigure targeted therapeutic approaches in oncology. In a clinical trial for metastatic non–small cell lung cancer, a Chinese team from Sichuan University is extracting immune T cells from the patient's blood and using CRISPR technology to knock out a specific gene that encodes a protein called PD-1, which normally blocks the cell's capacity to launch an immune response.[26] The edited cells will then be multiplied in vitro and reintroduced into the patient's bloodstream, where they are expected to target cancer cells. Although CRISPR-Cas9 can result in edits at the wrong places in the genome—with potentially harmful effects—the US National Institutes of Health's (NIH's) Recombinant DNA Advisory Committee issued a positive recommendation in 2016 for a similar study designed to combine gene editing and immunotherapy to treat melanoma, myeloma, and sarcoma.[27]

In practice, before using CRISPR germline editing on carriers of cancer predispositions, the technology's analytical and clinical validity needs to be demonstrated, as does its clinical utility, that is, its capacity to accurately and reproducibly target one type of cancer over several generations. Such a demonstration represents a tremendous challenge, especially since the clinical utility of genetic testing for moderate penetrance genes is still a controversial issue.[38] This demonstration must meet the requirements of the *Evaluation of Genomic Applications in Practice and Prevention* (EGAPP) drawn up by the US Centers for Disease Control and Prevention and used by many health care systems, as well as the American Society of Clinical

Oncology (ASCO).[39] EGAPP establishes four evaluation criteria that could apply to CRISPR: analytic validity, clinical validity, clinical utility, and ethical, legal, and social issues. To some extent, the clinical utility of CRISPR-based germline engineering could be compared with artificial reproductive technologies currently used to prevent the transmission of cancer predispositions in families at risk. Validating CRISPR's clinical utility would require demonstrating that this approach leads to improved clinical outcomes and enhanced quality of life, which represent added value not only for patients but also for asymptomatic carriers of cancer predispositions and their descendants.

Rectifying or Altering Our Inheritable Genome

While the ethical debate has revealed a relative consensus on the use of CRISPR on somatic cells for scientific or therapeutic purposes, no such common ground has been reached on the issue of modifying human germlines.[40,41] Countries such as Japan, China, and India forbid it through declarations that are legally nonbinding,[42,43] while the Council of Europe has made its prohibition a legal requirement for its member states.[44] In 2015, the United Kingdom (UK) drew attention by authorizing the manipulation of gametes carrying mitochondrial DNA defects, which is a type of intervention on the human germline.[45]

The use of CRISPR on nonviable human embryos has sparked a sense of urgency in the scientific community.[46] In reaction, an international summit was hosted in December 2015 by the US National Academy of Sciences, the Chinese Academy of Sciences, and the Royal Society of the UK to issue a warning statement on human germ cell manipulation.[47] The statement calls for a cautiousness on genome editing of human germlines for reproductive purposes. It invokes several arguments such as the risk of *technical error*; responsibility toward the *future generations* that will inherit these modifications; the difficulty in *reversing the modifications* once they have been introduced and disseminated in the population; the possibility that genetic improvements will only concern a subset of the population, thereby exacerbating *social inequities*; and the ethical and moral considerations in purposely *altering human evolution*.

Following the reading of the statement, a participant in the audience—a mother of a child suffering from a genetic disorder—spoke out, describing the disease and how it destroyed the life of her son and her family, concluding with "if you have the skills and the knowledge to fix these diseases, then do it."[48] Moratoriums and prohibitions have a hard time standing up to the real-life experiences of patients and their families when they challenge the arguments against germline modification.

The *technical risk* argument is legitimate, but as with all biotechnological breakthroughs, the risk could decrease through scientific advances. Over time, technological improvements in CRISPR could reduce the occurrence of off-target edits, and certain genetic interactions with the environment.

The argument of responsibility toward *future generations* is not as obvious as it may initially seem—future generations could just as well be indignant that nothing was attempted to prevent the transmission of genetic mutations that could potentially have been eliminated with CRISPR. Some invoke the argument that these germline modifications would be made without the consent of future generations.[49] But isn't this already the case for other commonly used techniques such as In Vitro Fertilization (IVF) and Intra-Cytoplasmic Sperm Injection (ICSI)? No parent has ever obtained the prior consent of their unborn children when deciding to bring them to life, and no children have ever consented to accepting the genetic endowment of their progenitors.

Inspired by the precautionary principle, which states that nothing must be done unless everything is completely understood, the argument that genome alterations are *irreversible* is based on the assumption that their widespread dissemination cannot be undone. But why couldn't genome editing work in both directions, like a dynamic word processor with corrective mechanisms? Technically, with CRISPR, previously removed or modified mutations can be reintroduced into the genome.[50] Reversing the modifications introduced by CRISPR would theoretically enable backtracking and correcting any biosafety accidents, which would meet the provisions of the precautionary principle.[51]

The risk of exacerbating *social inequities* is an argument commonly put forward regarding the introduction of new technologies that are costly. Yet the low cost of CRISPR could allow health care systems to propose it under universal coverage, thereby ensuring equal access to all in the name of social justice.[52]

The final argument invokes the moral responsibility of purposely *altering human evolution*. But what do we mean by "human evolution"? This argument appears to assume, on the one hand, that human evolution is simply the evolution of the genome, and on the other hand, that the human genome in its natural state cannot be perfected. If we extrapolate this logic, shouldn't doctors feel guilty about their everyday attempts to cure natural disorders affecting the human body? Shouldn't the centuries-long endeavor to extend life expectancy be considered a clear interference in the natural evolution of humanity?

The prenatal diagnosis of breast cancer illustrates the potential impact of CRISPR on health care systems. Since 2009, the British health authorities have been genetically screening embryos created through in vitro fertilization (IVF) for families with a history of breast cancer.[53] As in many countries, in the UK the National Health Services covers the cost of this procedure, which is invasive and risky for women because it involves ovarian stimulation to collect the oocytes,[54] and for unborn children because the IVF technique combined with intracytoplasmic sperm injection (ICSI) can cause premature births with an increased prevalence of congenital disorders.[55] The recent

introduction of the noninvasive prenatal diagnosis (NIPD) allows the DNA circulating in a mother's blood to be analyzed to detect aneuploidy in a fetus while limiting iatrogenic risks for both mother and child.[56] In general, health professionals view NIPD as a positive advance in prenatal diagnosis.[57] However, although some urge caution in the use of NIPD to detect *BRCA1* and *BRCA2* genes in unborn children, other health professionals believe that NIPD offers parents-to-be who already have a disease the guarantee that it will not be passed on to their descendants.[58]

As a disruptive approach, genome editing could eventually eclipse standard birth screening techniques if CRISPR succeeds in eliminating BRCA mutations from the parents' germline. It would also avoid creating surplus embryos and destroying the affected ones. Genome-editing technologies usher in a preventive logic that is similar in some respects to vaccination campaigns that seek to gradually eradicate a targeted disease in a population. The use of CRISPR could gradually prevent the dissemination of *BRCA* genes in the population, avoiding hundreds of thousands of hereditary cancers, and ruined lives, while relieving health care systems from a significant proportion of the heavy economic burden of cancer.

The Economic Burden of Cancer

Numerous studies have assessed the considerable socioeconomic impact of cancer, in particular the financial burden for patients[59,60] as the result of their loss of employment or productivity at work.[61,62] The financial repercussions of cancer also impact access to care and the survivor's capacity to meet the basic necessities of everyday life.[63] A further factor is the frequent inability of insolvent patients to pay for the cost of cancer-related medical expenses not covered by their insurance.[64] The difficulty in obtaining insurance coverage exacerbates the financial distress of survivors, in some cases leading to a deterioration in health or even a higher mortality rate.[65,66]

Beyond the individual challenges encountered by survivors, cancer represents a tremendous economic burden on health care systems. In the United States, the NIH evaluated the cost of treating cancer in 2010 at $125 billion, and project the 2020 cost at $207 billion.[67] In 2012, the total cost of cancer in the 28 countries of the European Union was €143 billion, of which 40% was directly tied to care.[68,69]

Health care systems are struggling to keep up with these soaring costs, especially for anticancer drugs. "High cancer drug prices are affecting the care of patients with cancer and our healthcare system," declared a patient-driven initiative and petition to curb prices of anticancer drugs.[70] In 2015, the average gross household income in the US was $56,000 per year.[71] For an insured patient with cancer who needs a drug that costs $120,000 per year, "the out-of-pocket expenses could be as much as $30,000—more than half their average household income," according to the authors of the petition. The average price of new cancer drugs has risen between 5- and 10-fold over 15 years to more than $100,000 a year in 2012. As a result of these rising prices, the cost of drugs for each additional year lived rose from $54,000 in 1995 to $207,000 in 2013.[72]

How is this price escalation justified? Fortunately, technological disruptions often result in lower prices. In genomics, next generation sequencing (NGS) technologies have enabled an exponential drop in sequencing costs, which fell from $100 million in 2001 to approximately $1000 in 2016.[73] This same phenomenon could occur with CRISPR: at €34.4 per genetic target, CRISPR costs 10 times less than RNAi technology (€337.0 per target) and 64 times less than TALEN technology (€2.360 per target).[74] In terms of technological performance, CRISPR-Cas9 has already leapfrogged TALEN technology, mostly because Cas9 offers an unprecedented simplicity to target a large variety of functional domains to various genomic sites.[75] While RNAi has dominated the mammalian gene expression manipulation field for the past 15 years, the recent rapid growth of CRISPR-Cas9 raises the question of whether RNAi will become a tool of the past.[76]

CRISPR illustrates what the economist Joseph Schumpeter coined "creative destruction": genome-editing technologies could carry "everlasting storms of innovations" that will disrupt market structures.[77] Eventually, CRISPR could drastically alleviate the economic burden of cancer by revolutionizing two models currently used by health care systems: cancer screening programs and precision medicine.

The prevention strategy used by health policy makers to fight cancer mainly consists in cancer screening programs to detect tumors as early as possible and rapidly begin treatment. But with CRISPR, prevention campaigns would make it possible to intervene even earlier, detecting and correcting genetic mutations before they produce tumors. This would offset the costs of periodic screening exams (eg, mammographies, colonoscopies) and the treatments (eg, chemotherapies, radiotherapies). With germline engineering, CRISPR could also offset the costs of artificial reproductive technologies for cancer survivors who wish to give birth to cancer-free children (eg, IVF, ICSI, preimplantation genetic diagnosis).

For colorectal cancer, population-based screening programs are evaluated in terms of budget impact and cost effectiveness.[78] In Australia, for instance, a study shows that—at AU$12,405 per life-year gained and an average lifetime expectancy of 16.084 years—five-yearly colonoscopy screening was the most cost-effective strategy.[79] Medico-economic evaluations have also been conducted in other countries such as Belgium, with similar results.[80] Currently based on the early detection and treatment of colorectal cancer, these public health strategies could be upended by CRISPR. Rather than investing in a national colonoscopy program, budgets could be reallocated to edit genomes in the population—in particular for families at risk—with a view to eliminating the main hereditary predispositions of colorectal cancer in order to reduce its prevalence and eradicate its transmission to future generations.

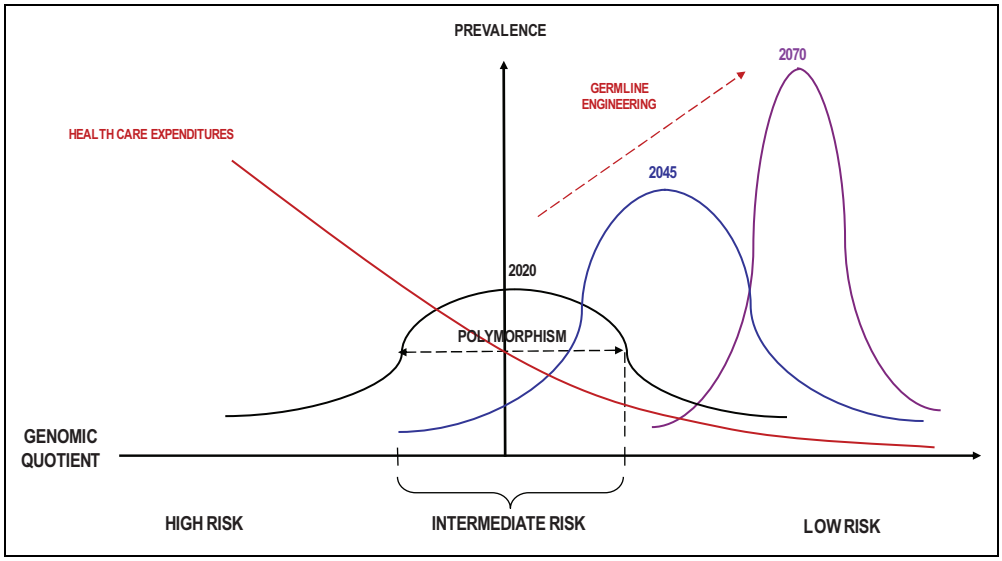

Figure 1. The genomic quotient (GQ). The GQ would be calculated by comparing the average number of pathogenic variants in a population with that of an individual. The GQ score would integrate parameters such as variant profiles and levels of penetrance. Over generations, use of germline genome editing would gradually skew the bell curve to the right, increasing the average quotient of the population and lowering health care costs, but also narrowing the population's polymorphism and impoverishing genetic diversity between humans.

CRISPR could also profoundly transform the present model of precision medicine and eventually achieve the aim of making medicine an art of precision. According to the 2008 definition of the US Office of Science and Technology, "precision medicine classifies patients into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases that may develop, or in their response to a specific treatment."[81] Is this approach cost-effective? Oncotype Dx is an example of a molecular assay with a putative value-based price of $3500 per test.[82] The major economic benefit is that it avoids chemotherapy costs and side effects (including the risk of death) in women with early stage breast cancer by identifying women with a very low risk of cancer recurrence.[83] In England, Oncotype Dx was recommended for use by NICE based on a calculation that took account of the QALY health gains from avoiding the adverse effects of chemotherapy, as well as the savings from reduced treatment cost.[84] In France, Oncotype Dx was also found cost-effective from a national insurance perspective (€2134 per QALY gained) and cost saving from a societal perspective (€602 lower than costs of standard care).[85] The approach based on value assessment in precision cancer medicine could simply disappear if CRISPR is able to eliminate the main genetic predispositions to breast cancer. If so, the disease will no longer be triggered, rendering companion diagnostics and costly treatments pointless.

The Genomic Quotient

CRISPR could make it possible to eradicate close to 3600 rare monogenic disorders caused by identified genes.[86] Theoretically, this perspective could also be extended to polygenic disorders such as cancer, with a higher level of complexity and unpredictability in terms of clinical outcomes. For each individual, assessing genetic risks will progressively mean establishing a series of scorecards at different periods in time, based on genetic predispositions, lifestyle, and exposure to epigenetic factors. As new genetic markers and their penetrance are gradually identified, it may eventually become possible to evaluate the genomic quotient of an individual, that is, the morbidity risks of a given genome based on the mutations it contains.[87] The genomic quotient—a composite score similar to the intellectual quotient—could contribute to stratify risk-adjusted profiles statistically distributed in the homogeneous subpopulations.[88] The genomic quotient of each profile would be given an economic value based partly on the risk of a disease appearing and partly on the cost of the treatments required to cure the disease (see Figure 1). As with the actuarial models used in the insurance industry, it would become possible to observe that people with a high genomic quotient get sick less often than the average person, implying lower health care costs, and vice versa.

The genomic quotient would help target individuals for whom CRISPR-based germline engineering would provide medical and economic added value. Such an approach could bring about a significant decrease in health care costs within two to three generations. The phenomenon could be accelerated through positive and negative eugenics programs where high quotients would receive economic incentives to procreate—such as tax credits or low health insurance premiums—and low quotients would be economically penalized if they refused to eliminate the cancer predispositions of their germline DNA.

This scenario would have profound consequences, as this normative approach toward human births would reduce the polymorphism of a population in a few generations, potentially putting the survival of the human species at risk. For instance, certain genetic disorders confer resistance to infectious diseases: sickle-cell anemia provides resistance to malaria, cystic fibrosis to cholera, Niemann-Pick disease type C1 prevents the filovirus infection, and Tay-Sachs disease provides protection against tuberculosis.[89] Using CRISPR to eradicate genetic disease variants would imply greater exposure of human species to infectious diseases.

This genomic stratification associated with a risk classification is reminiscent of the concept of "the average man" introduced in 1844 by Adolphe Quételet in his work on anthropometry and body mass index.[90] Today, health insurance is moving toward establishing the concept of "average genome," associated with nosological risks arranged in low-, intermediate-, and high-risk homogeneous groups.[91] From the insurance perspective, the average genome would represent the average risk that actuarial models would consider reasonable to cover, in the name of solidarity.[92]

Eugenic Freedom for All

With CRISPR technologies comes the resurgence of eugenics, with the instrumental capability to select humans based on their phenotypic and/or genotypic profiles. But who would dare to proclaim which hereditary standards are acceptable within a population? The State? "The individual," answers Nobel Laureate James Watson: "Eugenics is [a way to] self-correct your evolution, and the message I have is that individuals should direct the evolution of their descendants: don't let the State do it. I think it would be irresponsible not to direct your evolution if you could, in the sense that you could have a healthy child versus an unhealthy child."[1]

In Antiquity, Plato's *Republic* recommended aristocratic eugenics designed to favor mating between men and women of the elite.[1] In the 20th century, the Third Reich combined positive eugenics (*lebensborn*) with negative eugenics (*the final solution*) to promote the Aryan phenotype. With CRISPR, a new kind of eugenics could emerge in modern democracies, this time based not on social or phenotypic criteria but rather on a genotypic evaluation combining morbidity rate and economic burden. Genomic standard profiles would be defined by the citizens themselves. The State's power would be limited to guaranteeing eugenic freedom for all, without interfering in the private reproductive choices of its citizens.

Today, Great Britain illustrates this kind of approach by regularly updating an official list of hereditary diseases for which newborn genetic screening is authorized and reimbursed. In 2004, the Human Fertilization and Embryology Authority (HFEA) had included 29 diseases, including Huntington disease and Tay-Sachs disease. By January 2017, there were 415 diseases on the list, including breast, colon, and ovarian cancer, as well as other illnesses, many of which are treatable, poorly penetrant, and late-onset diseases. Within 13 years, the number of diseases for which newborn genetic screening is reimbursed increased by a factor of 14.

"Have your say on conditions awaiting consideration," the HFEA website announces: through a citizen's forum, patients and their families can make their voice heard and weigh in on the inclusion of new genetic diseases in the list, such as albinism type 2.[1] In a sense, this list sets a limit, yet at the same time, by allowing citizens to participate in the consultation, this limit is elastic and slippery. With this democratic approach, the State is not imposing eugenic norms on its citizens; it is giving them the freedom to choose the genomes they consider undesirable for the next generation.

But with CRISPR-based germline technologies, what will happen if some people refuse to decontaminate their descendants' genomes? Could the State decide to no longer pay for their children's treatment if they suffer from a hereditary disease? The estimated cost for the treatment of stage IV melanoma is up to $152,244 per year and per patient[1]: how many families could afford such an expense? In this scenario, parents would have the choice to use or refuse CRISPR in theory, but in practice, the economic consequences of their refusal would be prohibitive.

Industrializing Germinal Decontamination

CRISPR is at the crossroads of the health care and agri-food industries. Startup companies such as Caribou Biosciences, CRISPR Therapeutics, Intellia Therapeutics, and Editas Medicine have provided private equity financing for Cas9-based genome engineering firms. In all, companies with an interest in using Cas9 for applications related to gene therapy have raised more than $600 million in venture capital and public markets between 2013 and 2015.[93] The pace of this activity is remarkable given that the first granted patent for the use of CRISPR in eukaryotic cells was issued on April 14, 2014. In 2015, several high-profile investors, including the Bill & Melinda Gates Foundation and Google Ventures, invested $120 million in the genome-editing firm Editas Medicine.[94]

In October 2016, there were 1625 CRISPR-related inventions distributed in five main technical categories: components (CRISPR RNA, Cas9 enzyme, etc), activity (Cas cleavage, etc), vectors (bacterial, viral, plasmid), delivery (liposome, nanoparticle, etc), and application (gene editing, gene therapy, drug discovery, diagnosis, regulating, and targeting).[95] The 10 main patent holders include the Massachusetts Institute of Technology (MIT), Harvard, Broad Institute, NIH, Sangamo Biosciences, Cellectis, University of California, Dow AgroSciences, DuPont Nutrition Biosciences, and Editas Medicine.

Patent holders, licensors, licensees, and partners are interacting at different levels. The institutional cluster of MIT, the Broad Institute, and Harvard have granted exclusive licenses for therapeutic applications of their CRISPR-Cas technologies to their joint commercial effort, the spin-off company Editas. In addition, they offer academic researchers access through

Addgene, a nonprofit plasmid repository. UC Berkeley has granted an exclusive license to the startup Caribou Biosciences, which has in turn issued exclusive sublicenses to Intellia and Novartis for therapeutic applications, and to Dupont for agricultural applications. Yet, under pressure from their venture capital backers, these startup companies are aggressively seeking to develop new products of their own and open new markets.

CRISPR may unexpectedly expand its core market to the edition of human reproductive cells. As is already under way with crop seeds, genome editing of human gametes—ova and spermatozoa—could gradually become the next step in CRISPR's industrial application. Initially used by sterile persons and cancer survivors, gamete banks now cater to fertile couples, homosexuals, and one-parent families. Some also market services for young female employees of companies such as FaceBook or Apple that offer egg cryopreservation to allow them to build a career while holding off their pregnancy until after age 40.[96]

Polluter Pays

CRISPR could turn this century into a huge wave of genome decontamination. Like the carbon footprint, a genomic footprint disseminated in the general population could be taxed as a prejudice to the common good. CRISPR would make it possible to decontaminate a population's reproductive cells. One could choose not to do so—in the name of individual freedom—but this would spawn a new kind of polluter payer tax, since parents would be taking the risk of disseminating harmful genes in the general population, potentially resulting in costly treatments for the community at large.

Newborn screening programs are an integral part of health care policy.[1] In the United States, an analysis of newborn screening in families affected by cystic fibrosis showed that for an average medical cost of $63,127 per year and per patient and an average life span of 37 years,[1] the net savings generated if couples carrying these mutations use IVF and PGD rather than giving birth to a sick child requiring life-long treatment is estimated at $33.3 billion.[1] Genome editing would multiply these savings, given that IVF with genetic screening only covers one generation, whereas with a single action on the germline, CRISPR would make it possible to modify the DNA of all generations. Through the 20th century, the concept of prevention meant avoiding the appearance of an illness. In the CRISPR century, prevention could come to mean avoiding the appearance of ill persons.

But like other prospective parents, those who rely on donor sperm want to conceive healthy children. The donor selection process gives these parents the opportunity to minimize the risk of recessive disease inheritance by avoiding donors who carry mutations that are genetically incompatible with the reproducing parent. Yet, despite tremendous advances in variant identification, understanding, and analysis, the vast majority of disease-causing mutation combinations remain undetected by commercial carrier screening panels.[97] To overcome this situation, why not use CRISPR directly to commercialize reproductive cells with a customized genome? Today, fertility clinics offer phenotypic details about their sperm donors, from face matching to donor silhouettes, childhood photos, and audio interviews. With CRISPR, they would offer an enhanced genomic quotient to the family and its descendants.

Firms such as GenePeeks and 23&Me have filed patents on technologies that assess the probability of transmitting the genetic diseases of parents to their offspring.[98] The methods for evaluating the genome combinations of two gametes are used to draw up a score that incorporates disease probability, life span, and health care expenditures.[99] "I prefer a child with . . . a low risk of colorectal cancer" is one of the choices in the drop-down menu depicted in 23&Me's patent application.[100] The firm OvaScience is working on an experimental genome-editing technique for oocyte precursor cells that would modify their hereditary predispositions before the embryo is conceived.[101] OvaScience has set up a joint venture with Intrexon, a company specializing in synthetic biology, to accelerate clinical developments in gamete and human embryo genome editing.

The adoption of human germline engineering could be driven by the economic dynamic of supply and demand. Cancer survivors, fertility clinics, biotech firms, oncologists, malpractice insurers, employers, and health authorities are all stakeholders that may find converging interests in the use of germline genome editing, on the individual and collective levels. Figure 2 presents stakeholders' interactions and converging interests in using germline genome editing.

This stakeholder alignment would represent a powerful influence based on an industrial logic rather than an ethical or political consensus. The convergence of economic interests would also be consistent with democratic values such as individual freedom. Indeed, germline modification would represent the freedom of parents to choose the genomic quotient of their offspring at an affordable price, not in the name of "eugenics" but in the name of "hygienics," to prevent genetic pollution and contamination. From this economic perspective, using CRISPR on human germlines could become not only acceptable but also natural and rational.

Voices of Patients

Since the proposal and subsequent confirmation of the structure of DNA, countless bioethical controversies have referred to the concept of "human dignity."[102] But what have we really learned from these debates[103]? That human dignity is a moral value shared by all human beings regardless of their physical characteristics, which includes genetic predispositions. In other words, if CRISPR eliminates a mutation such as KRAS from the human germlines, human dignity will not be diminished. CRISPR children will not be less 'human' than children born through IVF or embryo screening. They will be indistinguishable from all other children. They too will be imperfect and lovable. They too will grow, and one day endure disease and eventual death.

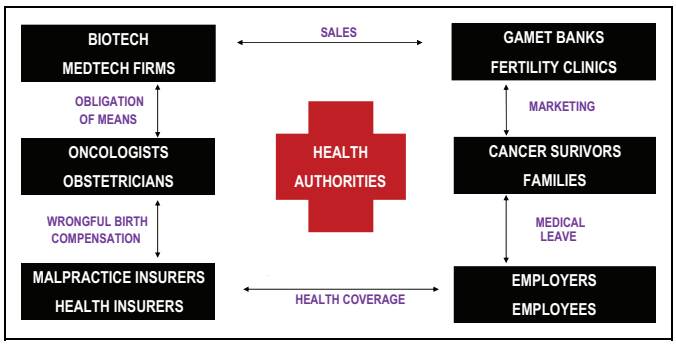

Figure 2. Stakeholder convergence on use of germline genome editing. (i) Cancer survivors could find in CRISPR a way to have children free of cancer predispositions while retaining their fertility capabilities. (ii) Fertility clinics could see in CRISPR a marketing solution that meets the demands of customers looking for reproductive cells with a specific genomic quotient. (iii) Biotech and medtech firms could industrialize their patents by marketing CRISPR to gamete banks and fertility clinics, oncologists, and obstetricians. (iv) Oncologists and obstetricians could use CRISPR to satisfy their obligation of means in order to minimize the risk of transmission of cancer predispositions to the next generation. (v) Malpractice insurers could see CRISPR as a way to avoid wrongful birth claims and costly damages to the families. (vi) Employers offering health insurance to their employees could encourage them to use genome editing to reduce cancer risks that result in medical leaves and health care expenditures. (vii) Finally, health authorities could view germline genome editing as a powerful primary prevention tool that would curtail the dissemination of hereditary diseases in the population and decrease health care costs.

The surprising element in the debate over germline modification is the absence of the voices of the patients and their families. Public opinion surveys show that most Americans are in favor of genome editing to prevent their children from inheriting serious diseases,[104] although 65% consider that modifying the genes of unborn children should not be legalized.[105] Another survey conducted in 2016 found that 49% of Americans approve the use of germline editing to reduce the transmission of hereditary diseases.[106] A caveat to these surveys is that they were conducted in the general population, where cancer survivors statistically represent only a small fraction. In these days of "patient-centricity," it would have been interesting to compare the survey results of the general population with a sample of cancer patients and their families.

"As a parent with an incredibly sick child, what are we supposed to do—sit by on the sidelines while my child dies? . . . CRISPR is a bullet train that has left the station—there is no stopping it, so how can we harness it for good?"[107] If the proper use of CRISPR should be limited to the "incredibly sick," what criteria should be used to objectively determine these extreme cases? Quality of life? The question is trickier than it may seem. For instance, some consider that autism is a hereditary behavioral trait that is an integral part of human diversity, and that this "neurodiversity" must be respected.[108]

Even before the use of CRISPR on germlines, some people with hereditary deafness or dwarfism were already deciding to selectively transmit those genetic traits to their children in order to share a common way of life.[109] Illness or disability does not necessary imply unhappiness. Several studies show that half the persons with serious diseases consider that their quality of life is good or excellent.[110] In particular, the majority of patients with locked-in syndrome—who can only communicate by blinking their eyes—declare that they are happy despite their state of complete dependence.[111] Why do many people with serious and persistent disabilities report that they experience a good or excellent quality of life when, to most external observers, these people seem to have an undesirable daily experience[112]? The mystery of resilience allows certain diseased persons to overcome the turn of fate, transcend suffering, and create a human endeavor. They succeed "despite," but also "thanks to." Yet with or without resilience, cancer patients will probably refuse to remain passive in the face of illness, forego CRISPR, and let their hereditary predispositions contaminate their descendants.

Concluding Thoughts

Many cancer survivors are quietly consumed by a dilemma: on the one hand, they disapprove of the mass eugenics that would have prevented their own deleterious genomes from coming to life, while on the other hand they wish to benefit from the individual eugenics that would spare their descendants from their own genetic predispositions and suffering. How can these two perspectives be reconciled? More specifically, how can this form of micro-eugenics be condemned when it supports a moral obligation to give our children the best chance of the best life[113]? Yet in a liberal democracy where each individual would be allowed to procreate freely, the cumulative effects of micro-eugenic decisions could eventually lead to macro-eugenics bent on favoring the highest genomic quotients. CRISPR could lead to the reemergence of what Nietzsche called "the grand politics [which] places physiology above all other questions—it wants to rear humanity as a whole, it measures the range of the races, of peoples, of individuals according to the guarantee of life that they carry within them. Inexorably it puts an end to everything that is degenerate and parasitical to life."[114]In the CRISPR century, this vision is probably not a prophecy but a possible future.

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