Invited Review

Ethical issues of CRISPR technology and gene editing through the lens of solidarity


†Section of Genetics, Department of Pediatrics, University of Oklahoma Health Sciences Center, Suite 12100, 1200 Children’s Avenue, Oklahoma City, OK 73104, USA, ‡Department of Bioethics, Dalhousie University, 5849 University Avenue, Room C-312, CRC Bldg, PO Box 15000, Halifax, Nova Scotia, Canada B3H 4R2, §Department of Human Genetics, Centre of Genomics and Policy, McGill University, 740 Avenue Dr. Penfield, Suite 5200, Montreal (Quebec), Canada H3A 0G1, **Centre for Biomedical Ethics, Yong Loo Lin School of Medicine, National University of Singapore, Level 2 Block MD11, Clinical Research Centre, 10 Medical Drive, Singapore 117576, Singapore, ††Faculty of Science, Department of Philosophy and Science Studies, Radboud University Nijmegen, P.O. Box 9010, NL-6500 GL Nijmegen, The Netherlands, and ‡‡School of Law, University of Manchester, Williamson Building-2.13, Manchester M13 9PL, UK

*Correspondence address. Section of Genetics, Department of Pediatrics, The University of Oklahoma Health Sciences Center, Suite 12100, 1200 Children’s Avenue, Oklahoma City, OK 73104, USA. E-mail: John-Mulvihill@ouhsc.edu.

Abstract

Background: The avalanche of commentaries on CRISPR–Cas9 technology, a bacterial immune system modified to recognize any short DNA sequence, cut it out, and insert a new one, has rekindled hopes for gene therapy and other applications and raised criticisms of engineering genes in future generations.

Sources of data: This discussion draws on articles that emphasize ethics, identified partly through PubMed and Google, 2014–2016.

Areas of agreement: CRISPR–Cas9 has taken the pace and prospects for genetic discovery and applications to a high level, stoking anticipation for somatic gene engineering to help patients. We support a moratorium on germ line manipulation.

Areas of controversy: We place increased emphasis on the principle of solidarity and the public good. The genetic bases of some diseases are not thoroughly addressable with CRISPR–Cas9. We see no new ethical issues, compared with gene therapy and genetic engineering in general, apart
from the explosive rate of findings. Other controversies include eugenics, patentability and unrealistic expectations of professionals and the public.

**Growing points:** Biggest issues are the void of research on human germ cell biology, the appropriate routes for oversight and transparency, and the scientific and ethical areas of reproductive medicine.

**Areas timely for developing research:** The principle of genomic solidarity and priority on public good should be a lens for bringing clarity to CRISPR debates. The valid claim of genetic exceptionalism supports restraint on experimentation in human germ cells, given the trans-generational dangers and the knowledge gap in germ cell biology.

**Key words:** CRISPR, ethics, gene editing, genetic engineering, germ cell mutation, solidarity

**Background**

CRISPR–Cas9 is a gene manipulation technique that emerged recently after a decade of quiet, incremental discoveries.1–6 Standing for ‘Clustered, Regularly Interspaced, Short Palindromic Repeats’ in association with the Cas9 DNA-cutting enzyme, the system in nature provides bacteria with immunity from viruses and phages, and silences genes that make molecular surface markers.7–9 This cut-and-paste function has given rise to the moniker ‘gene editing’, effectively replacing ‘genetic engineering’ and connotes a widely available tool for altering and even correcting DNA. It has enormous scientific potential, was dubbed ‘The biggest biotech discovery of the century’,10 and has evoked commentaries on ethical implications along with legal, reputational and financial consequences.11,12

At first glance, many of the ethical issues associated with gene editing appear the same as those raised about genetic engineering two decades ago. Although gene editing is not new in this respect, CRISPR–Cas9 significantly reduces the time required to conduct experiments that have previously taken years. The pace and scope of research, along with possible clinical applications, place it as a ‘disruptor’ technology.13 The supercharged scientific and ethics commentaries that have followed14,15 give contestations over the potential applications of CRISPR–Cas9, especially in modifying human embryos for developmental research16 and germ line gene therapy.17 In 2015, an International Summit on Human Gene Editing (hereafter, the Summit), sponsored by the (US) National Academy of Sciences and National Academy of Medicine, the Chinese Academy of Sciences, and the Royal Society of the UK,18 issued a concluding statement and endorsed the establishment of an international deliberative group to further assess the implications of CRISPR–Cas9.19 Soon, the Nuffield Council on Bioethics called for evidence on the ethical issues emerging from this ‘family of biological techniques for making precise genetic alterations to living cells’ that have applications in agricultural and livestock, industrial biotechnology, ecology, biomedicine and reproduction; and has recently published its findings.20

Here, we review the literature on these issues and present the position of the Committee on Ethics, Law and Society (CELS) of the Human Genome Organisation (HUGO) on CRISPR–Cas9, with our continuing emphasis on the neglected ethical principle of solidarity and the priority on public good. HUGO’s CELS is a mechanism for HUGO to proactively initiate and facilitate dialogs on the ethical, legal and social issues related to genetics and genomics. The CELS undertakes projects to understand conceptual issues that underlie genomic sciences in practice and policy. This review expresses the views of the HUGO CELS. We focus on CRISPR’s applications in human biology and medicine, not at all to diminish its importance in other areas that also affect human beings. After stating our methods, we group our views into four sections: areas of agreement, areas of controversy, growing points and areas timely for developing research.
Sources of data

This is not a systemic review, but relies on our review of research, clinical, and popular media sources, aided by PubMed and Google searches using the keywords ‘CRISPR AND ethics’ and other similar terms for the years 2014 to present (August 2016). Other helpful websites were those of the Nuffield Council on Bioethics,20 the University of Washington’s Science and Society program21 and the (US) Centers for Disease Control and Prevention.22 This discussion expresses the consensus of HUGO’s CELS. Our use of ‘we’ indicates the Committee members’ agreement and draws on our previous statements published by the Committee.

Areas of agreement

The enthusiasm of laboratory researchers seems to arise from the specificity, ease of use and speed of the CRISPR technology. Most spectacular seems to be the quantum change in the rate of new findings that CRISPR–Cas9 permits; experiments that would have taken a few years can now take weeks. With the speed of lightning (and the inevitable but delayed roll of thunder), the awareness and speculation about CRISPR–Cas9 have spread more rapidly and broadly than other recent advances, far beyond the involved molecular geneticists, to other biomedical scientists, clinicians and the public. Perhaps not since the arrival of simple karyotyping has a technical advance been so rapidly and widely disseminated from a few research crannies to diverse laboratories worldwide, large and small. Plenary presentations have been made at national meetings of geneticists, cancer researchers and bioethicists. PubMed hits for ‘CRISPR’ doubled since 2012, from 149 to 350, 669 and 1399 in 2015. Annualized based on 7 months, the number in 2016 should total around 1588. As a scientific step, it stands out with events like the cloning of Dolly in 1996, and the contentious derivation of stem cells from human embryos and fetuses in 1998, with such an explosion of attention to developments in biomedical sciences that have prominent ethical implications.

The leap from gene editing in ‘somatic’ cells (e.g. normal liver cells or pathogenic mutations in cancers) to performing it in ‘germ’ cells, may seem trivial, for the same laboratory procedures with CRISPR–Cas9 would be used. But, we agree with others15,19,23 that the step crosses an ethical Rubicon. The process of snipping out a deleterious mutation, inserting a ‘normal’ DNA sequence, and then zipping the DNA back up again sounds clinically advantageous, but that assumption belies the complexities of taking technologies from bench to bedside. In this respect, a difficult challenge surrounding the technique is the task of separating hype from reality, and distant possibilities from early, practical applications. We are far from the clinical realization of ‘genome surgery’.24

The Summit organizers did not recommend a moratorium on research using CRISPR for human germline manipulation.19 Early experience from China,17 before regulatory and ethical debate, seemed to polarize opinions on whether such a step should proceed as the hazards may be too great to further such efforts. We agree with the concerns raised at the Summit about the unknown consequences of altering a genome that, if inherited, would persist in future generations. One could say, ‘If scientists are smart enough (or ignorant enough) to correct a mutation that, despite their best forethought and intention, proved deleterious in a later generation, their scientific heirs will be smart enough to reverse it.’ Such thinking seems to be hubris. Moreover, the genomic traits targeted for ‘rewriting’ are also a potential concern: past abuses of genetics that must never be forgotten are the idols of eugenics that captivated the much of the world in the early twentieth century;25 they must remain in the past. Hence, we go further than the Summit to endorse a moratorium on experiments with CRISPR–Cas9 and related technologies aimed toward germ cell mutations.

Areas of Controversy

Extending the CRISPR debates to include solidarity

Our ‘first’ controversy is that CRISPR–Cas9 requires a complex and nuanced debate of principles of clinical and research ethics beyond what the long established one26 can guide. Solidarity is a complex term that
defies just one meaning (e.g. ‘we-ness’, as group-identify27), but which we use here to recognize the opportunities to share benefits as a public good; it helps conceptualize how disruptive technologies are also social phenomena that are subject to rapid and constant transformations. Achieving an orderly and equitable introduction of CRISPR into mainstream biomedicine requires a continued broad debate, including issues of benefit sharing versus private commercialisation. But, we postpone further explanation, specifically, of our emphasis on genomic solidarity as a way to address ethical concerns, to the section below on Areas Timely for Developing Research.

The technical improvement for non-Mendelian disorders

The ‘second’ area of concern is the ability of CRISPR to target almost any nucleotide sequence of short length, usually allowing for specific genes to be selected.28 CRISPR–Cas9 does not seem to faithfully insert new DNA sequences. This concern could extend to its handling of genomic changes beyond the level of direct DNA sequences, such as whole chromosomes (aneuploidy, as in trisomy 21 Down syndrome) and single genes mutated by trinucleotide repeats, as in Huntington disease, Friedreich ataxia and the fragile X syndrome. These conditions are high burden, neurologic disorders of some frequency with onset after the newborn period. As mutations of introns, formerly considered ‘junk’ DNA, and distant controlling elements continue to emerge as pathogenic variants, the challenge of picking out the exact disease-predisposing sequence seems formidable. Even less tractable are gene–environment and polygenic mechanisms of common disease. The presence of pseudogenes, the look-alike gene fragments left behind when evolution favored a closely related gene as the final working version, likewise can derail identifying the right clinical target for CRISPR. Some of these are likely bumps in the road, probably to be addressed by technical improvements.

The parallels to gene therapy

The ‘third’ area of concern consists in the pitfalls of genetic engineering as done under the label of gene therapy. In fact, many of the current issues about CRISPR recapitulate those about gene therapy over the last two decades—and with the same challenge of distinguishing hype from reality. Stoking early and high expectations for gene therapy led to inevitable disappointment, even distrust, of the scientific enterprise by an otherwise supportive public. Some early gene trials revealed the experimental nature, with the under-appreciated risks that all novel therapies share, and also the socio-political undercurrents that shaped them. A litany of hazards to safe and effective gene therapy considered in theory erupted, in fact, as real and fatal setbacks: childhood leukemia arising when the viral vector for gene therapy activated an ancient and latent oncogene in the human genome, overwhelming viral hepatitis from intra-arterial injection of a virus reconstructed to carry the DNA to overcome a defective urea cycle enzyme in a teenager, and the lack of a permanent fix from many protocols. In general, many years of hard work were required to achieve solid results for what had been promised to be quick by the initial hype.4,29,30

Many of the possible adverse outcomes of CRISPR technologies have been discussed at length elsewhere, including the point that gene-editing technology does not necessarily raise new issues. However, there is a growing narrative that calls for deeper understanding of the implications of CRISPR technology. The grievous lessons of racial hygienics in the 1900s need citation,31 but not elaboration. The new narrative begins with the earliest attempts of genetic engineering, where many issues arose about altering the genes of the common bacteria, Escherichia coli, including the specter that a laboratory breach could cause an epidemic of lethal gastroenteritis, worse than the occasional foodborne outbreaks that still take place with virulent strains. An ad hoc group of involved scientists met in the Asilomar Conference Center, California, for 4 days in 1975, and agreed that research could continue, but only under strict guidelines. Some laboratories shut down and new containment facilities were built for the highest level of risky experimentation.32 Given this favorable strategy, no one would expect CRISPR to be developed without peer
oversight, and the international scientific community has already exerted itself.

Without doubt, CRISPR will be used in the clinic, likely with oversight similar to that used for gene therapy. After the Asilomar agreement and when it appeared that the first human gene therapy was likely to occur at the US National Institutes of Health (NIH) campus in Bethesda, Maryland, NIH founded the Recombinant DNA Committee, labeled the RAC (evoking Inquisition tactics in the opinion of some). This time, other stakeholders besides the involved scientists had seats at the table. Again, the oversight plan seemed to work, by and large, but did not prevent some deaths of volunteer patients. Each time, lessons were learned and led to patches in the process, for example, to improve transparency on investigators’ possible conflicts of interest and to appreciate that cancer due to gene editing was a real, not just theoretical hazard. The RAC has now approved its first CRISPR protocol.

There are precedents to the hazards of hype, such as CRISPR has engendered. The race to completely sequence the first reference human genome was achieved despite battling ideologies of some key players representing private and public investment. Yet, ‘The Genomic Era’, characterised by high-throughput sequencing, deep coverage and large-scale bioinformatics, has not fully met the early expectations sparked by early optimism. In fact, the narrative of most pioneering innovations— involving mavericks and considerable money at their disposal, the competition and clashes of private interests and public goods, media influence over public perceptions, and political intrigue—more or less plays out with each scientific advance. Underlying this narrative is an imperative to commercialize and downplay the risks of conflicting interests, and these pressures, in turn, drive researchers to focus on the economic returns rather than the public good (and, as discussed below, solidarity). Thus, they become beholden to private interests who want to use the hype, which risks the capture of public goods through privatization and commodification; that is, technologies become the exclusive property of a few rather than being shared by many. The issue is not about the reasonable licensing that successful researchers deserve; the patent system is designed to do so. Unduly limiting the use of technologies to a privileged few slows progress and makes access to the fruits of research harder and more expensive. Whether CRISPR should be freely available to all given its potential is one thing, but given the wide interest in CRISPR and the broad spectrum of its possible uses, such potential limitations on who and how people experience its benefits need to be carefully managed by research institutions and international agencies. In retrospect, the Human Genome Project teaches that private interests—the personal and often corporate role in investing in science and securing personal benefits—are sometimes at odds with a solidary ideal of benefit sharing.

Patent issues

Commercialisation also works in other ways. In 2013, after a decade of controversy, the US Supreme Court ruled that human genes could not be patented because DNA is a ‘product of nature’. Granting that there will be jurisdictional differences, CRISPR technology also raises the questions, ‘Is it novel? An invention or merely nature discovered?’ CRISPR technology might not be considered a ‘product of nature’, since it can be modified to function in animal and human cells where it does not naturally occur. To some, it is not clear that CRISPR was invented; it came from bacterial systems where it was discovered, but, the discovery and the subsequent steps necessary to make it a functional tool are also subject to patent claims. The US Patent and Trademark Office awarded Zhang (of the Broad Institute) the first patent rights to CRISPR–Cas9 based his ability to alter, control, and modify CRISPR to function in animal and human cells, a cellular system in which CRISPR does not function naturally. Doudna (University of California), however, filed an interference claim against Zhang, in essence, challenging the date when each party claims to have discovered CRISPR–Cas9 and adapted it to work in non-bacterial cells. In late 2015, Zhang et al. announced their discovery of an improved version, called CRISPR–Cpf1. In short, a complex competitive environment that could last for years has developed,
perhaps diverting focus from benefiting the public good. Based on past experience in this field (e.g. patents on DNA sequences, stem cells or genetic variants used as diagnostic tools), this situation could have a negative effect on research, development and access to CRISPR technologies.

Patenting varies among countries. Much of Europe has ratified the European Patent Convention and Biotechnology Directive and its additional condition that commercial exploitation is not contrary to ‘ordre public’ or morality, which could be used to challenge and invalidate morally objectionable patent subjects. Other countries, such as the USA and Canada, hold that patent morality ought to be regulated through a distinct process, independent from the market-oriented intellectual property system. In spite of this ‘neutral’ position, courts of justice will often seek to prevent patents of morally controversial innovations through a more restrictive application of classical criteria of patentability. For instance, who will own the guide RNA libraries that the CRISPR–Cas9 system uses to reference for its precise edits? If a guide gene was made that repairs Huntington disease (which might be a modified cDNA sequence and therefore patentable), then that sequence might require the purchase of a license, thus impairing access to its use.

Such patent questions will extend to subsequent products of CRISPR–Cas9, such as genetically engineered organs for human transplant. As an example of down-stream consequences, gene-editing technologies have rekindled the debate on xenotransplantation (from pigs to humans), which paused in the 1990s, notably due to the risks that endogenous retroviruses in the pig genome could become reactivated when transplanting organs to humans. In theory, gene editing could be used to eliminate such risks. Pig genes that may cause infection or rejection can be much more quickly and accurately erased with CRISPR–Cas9 than was possible in the past. The pig genome could be ‘humanized’, as it were, so that organs could be transplanted safely. A company, eGenesis, has been established to transform xenotransplantation into ‘an everyday life-saving procedure’.

An overarching finding of the Human Genome Project is that life and its blueprint are more complicated than envisioned at the outset, when initial expectations of genetic determinism prevailed. The same trap should be avoided when predicting the products of CRISPR–Cas9 and similar technologies.

Growing points

Given the ongoing ethical assessment of CRISPR, we urge that such debates include a narrative that clearly specifies the relationships among all stakeholders in the research endeavor that we outlined—from oversight of scientists, clinical application and commercialisation—and a vision of equity based on solidarity and responsibility in research for the public good.

We can illustrate this approach by explaining a large concern, not advanced to our knowledge, regarding the science of germ line genetic engineering by CRISPR–Cas9 and related techniques. Human germ line biology is a neglected area of biomedical research with a plethora of unanswered clinical and scientific questions. To parents with a baby with a disorder arising from a de novo mutation, e.g. achondroplasia due to a FGFR3 mutation or autism due to copy number variants, the clinician often says, ‘Your child has a spontaneous mutation; it just happens.’ The answer is clinically harmless, but contradicts a scientific and clinical drive to have an explanation, a cause and a mechanism. Certain chemicals, viruses and ionizing radiation do cause mutations in human somatic cells, both in vivo and in vitro, as well as hereditable germ line mutations in mice, in a dose-dependent fashion. Hence, there is good reason to be concerned that in vitro experimentation via CRISPR–Cas9 could do so in human germ lines, despite the novel advantage of having an allegedly exact localization for the insertion of new DNA.

But, contrary to expectations, no environmental exposure has been proved to cause new, spontaneous heritable disease in human beings. No excess of genetic disease has been seen in offspring of parents exposed to atomic bombs or nuclear accidents, nor in children born to cancer survivors, despite
their large doses of chemo- and radio-therapy.\textsuperscript{53} The current absence of attributable excess of heritable disease in humans is puzzling because germ line genomes do mutate, and those of humans are no exception, as witnessed by evolution itself and by the many patients with ‘spontaneous’ genetic diseases seen in genetics clinics. An excess of sporadic genetic disorders due to environmental determinants can reasonably be inferred from the association of advanced maternal age with aneuploidies, like Down syndrome, and advanced paternal age with certain dominant single gene traits, like Apert syndrome, and with autism spectrum disorders, verified by a predominance of de novo copy number variants from the paternal genome.\textsuperscript{54}

With the issue of germ line mutagenesis being so uncertain, it would not be prudent to ignore the animal and experimental data that confirm the somatic cell mutagenicity of ionizing radiation and of most chemotherapeutic agents.\textsuperscript{55} The provocative discordance is astonishing and begs for an explanation. A parallelogram of the relationships between the findings in somatic mutagenesis in human versus experimental systems and germ cell mutagenesis in mice is as true today as when it was first stated by Sobels two decades ago (Fig. 1).\textsuperscript{56} The scientific unknowns about human germ line mutagenesis, whether induced by nature or by human experimentation, are sufficient reason to support a moratorium on germ line manipulation by CRISPR (and other technologies).\textsuperscript{11,12,14,15,19,20,23,37–60}

Thus, three questions emerge. Firstly, do CRISPR and related technologies present new and pressing ethical issues? If so, secondly, is an oversight group needed, even a global one because of the transnational work of scientists and medical tourism of patients? Thirdly, who can act as rapid, trustworthy, authoritative and well-informed overseers, an existing panel or a new one? The Nuffield Council on Bioethics and sustaining participants from the Washington Summit have made initial statements,\textsuperscript{10,61} and other stakeholders will doubtless respond whether with satisfaction or cavil. If CRISPR–Cas9 raises no new ethical or policy concern, but is merely an acceleration and dissemination of techniques that have already been addressed or anticipated, no new entity is needed; rather, existing ones can be asked to monitor with greater frequency. If a new oversight panel is needed, can the primary scientists, whether they are genomics, researchers of other disciplines, members of prestigious associations, societies or academies, be considered neutral enough to play the part of honest brokers? What other stakeholders should be heard, and how loud should their voices be, from government officials, politicians, patients, families or their advocates?

The least settled and the most contentious biomedical area that relates to gene editing is its potential impact on reproductive science and medicine. Repeatedly, the topic has boiled with hot button issues of prenatal diagnosis, in vitro fertilization, and reproductive cloning, so it surely will do so again, around the manipulation of human germ line genomes by CRISPR–Cas9. Each day, news seems to energize tense questions, seeming imponderables, like the moment human life begins, a woman’s right to practice artifical reproductive technologies as they see fit, the children of parents who have no conventional children, and how loud should their voices be, from government officials, politicians, patients, families or their advocates?
Areas timely for developing research

Is genetics special?

Many people think that environmental factors, not genes, are the principal determinants of disease, epitomized by the microbial basis of infections; at most, heredity modifies the risk of disease and the probability of staying healthy. It is more accurate to use the word ‘ecogenetics’: each person diverges from a path of health due to a unique combination of intrinsic genetic variations that interact within cells and the person’s environment, a lifetime accumulation of prenatal, infancy, childhood, adolescent and adult exposures. With the debut of effective genomic medicine (in part, based on gene editing), concerns about the ethical, legal, political and social implications of genetics are re-surfacing in public discourse. Two extremes to be avoided are genetic ‘determinism’ and genetic ‘exceptionalism’.

- Genetic ‘determinism’ holds that the DNA sequence is the prime cause of all human traits, normal and abnormal (health and disease). It is a mistaken and wrong concept. A person’s disease is not solely the result of their genes. Environmental factors play a large role, at any time of life, whether sudden or chronic.
- Genetic ‘exceptionalism’ implies that the usual logic and rhetoric of human situations do not apply and that the typical considerations must be revised when an issue concerns genetics. We do not hold this view, ‘except’ for germ cell biology and medicine and especially germ cell mutation. The reason is simply that the outcomes or consequences of such germ line mutations affect not just one person or just one couple, but offspring for countless generations. Future descendants cannot give consent for present day scientists to change their genomes, just as they would not want current environmental trends to jeopardize their potential for health.

Genomic solidarity

As already mentioned in Areas of Controversy, the time and issues seem ripe for applying the emerging principle of solidarity into the discussion of genome editing. The HUGO CELS and its predecessors have long emphasized the role for solidarity and the public good. Of late, solidarity has been reinvigorated as a principle in bioethics. The Committee underscored the relationship between solidarity and equity, as solidarity fosters health for connected communities, and is undermined by gross disparities in health, income and access to care. We find that it is now necessary to aver solidarity as one of the pillars of ethical genomic research in the light of recent events, such as the increasing accessibility to sequenced genomes through open ‘altruistic’ initiatives, such as the 1000 Genomes Project, participant-centered research such as UK Biobank, the possible European Union Million Genomes Alliance (MEGA), and, although indirectly, the US Supreme Court decision on the non-patentability of genes. In so doing, we recognize genomic solidarity as a co-extensive commitment of scientists and clinicians, as well as the persons who donate their data, health records and biological samples to them, to sharing expected health and economic benefits of biomedical research with the communities where they reside and those who participate. Genomic solidarity encourages participation in worthy initiatives as both sharers and benefactors; it creates obligations to trustworthiness and stewardship and leads to an equitable creation of value. Solidarity provides the framework for working together—researchers, study participants and sponsors—to deliver and share experience and outcomes. It reaffirms reasons for bearing costs and burdens for others, but with acknowledgment or compensation in a reciprocal fashion. It calls for a common vision in setting goals and challenging conditions, such as commercialization, that private interests might create that conflict with the public infrastructure.

Our statement on benefit sharing affirmed that the human genome is part of the common heritage of humanity and that can be transformed into a public good in terms of the work needed to sequence, analyze and understand the genome. These goods—the information and products—can lead to healthier and happier lives. Solidarity further affirms the role all participants have in gaining benefits from these goods by investing in good science, taking part on fair terms and distributing the goods equitably.
Genomic solidarity and CRISPR

CRISPR–Cas9 is a tool. Its significance as a disruptor technology requires complex ethical discussions that go beyond solitary principles of medical ethics. How doctor and patient discuss gene editing may not involve a broad consideration of the public good. The idea of genomic solidarity supports the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity, which was adopted in 2010 and entered into force in October 2014. It provides a legal framework that governs access to non-human genetic resources and traditional knowledge. The Protocol became law in the European Union in 2014, calling for:

... a clear and sound framework for implementing the Nagoya Protocol that should contribute to the conservation of biological diversity and the sustainable use of its components, the fair and equitable sharing of the benefits arising from the utilisation of genetic resources and poverty eradication, while at the same time enhancing opportunities available for nature-based research and development activities in the [European] Union.

Solidarity, for example, calls for a reaffirmation that research participants are as important to successful human research as are specific aims, clear outcomes and statistical power. Such awareness deserves strengthening and might mean that the tools available for extracting public goods, such as CRISPR–Cas9, might be widely available. Patents and commercialisation might not be the end all if it is realized that patients and donors are also participants; they enable the research and become players in progress.

CRISPR–Cas9 also needs to be judged for the good of future generations. It is difficult to express any obligations to those yet born without implying something like mutuality. The principle of solidarity emphasizes taking into account the common vulnerabilities of human beings wherever and whenever they exist. Just as present generations have reasons now to have concern for the good of future ones. In this way, mutuality exists across time.

As for present day implications, solidarity suggests that scientists and researchers, with their sponsors and employers, should not just seek fame or financial profit, but also strive to make lives better. For these ends, active networks of participants and communities are needed. Solidarity means mutual sharing of costs and dividends, burdens and benefits, and not just in economic terms. For example, the scientists who quickly share findings should not lose scientific priority nor their competitive advantage. With equal expectations of participation and benefit, solidarity acknowledges and prizes collaborations, and encourages shared imagination in addressing challenges (such as compensating for the competitive and economic risks of data sharing). This common commitment precludes exclusive interests, exploitation and disingenuous frameworks of ownership and profit.

The idea that a powerful technology, such as CRISPR–Cas9 and the guide DNA can be patented and therefore become the exclusive property of a researcher (or their institution) is part of this debate. If the technology, which was isolated from naturally occurring bacteria (and not invented), can be proprietary, then many people could be denied access to its benefits outside market mechanisms. Researchers know little about CRISPR in natural systems, but patents can be used to transfer what we do know (or at least access to its benefits) to a few stakeholders. Solidarity holds that this tendency needs to be resisted.

Conclusions

We are grateful for the teachable moment that CRISPR provides for renewed public and professional awareness and education in genomics and ethics. The ethical challenges of CRISPR–Cas9 largely recapitulate those of genetic engineering and its clinical applications, and those of gene therapy. The eventual use of such techniques in oncology, neurology, pharmacology and pharmaceuticals, as well as in agriculture and animal husbandry, generate justifiably high hopes, but on a likely longer time frame.
Assuming resolution of its utility for non-Mendelian (single gene) diseases, like aneuploidies, trinucleotide repeat and imprinting disorders, and multifactorial diseases, we still hold great concern about its ethical use in human germ line manipulation, mostly because of the dearth of knowledge on human germ cell mutagenesis and, hence, the uncertain consequences in future generations. We agree with calls for recognition of the many stakeholders in the discussions and the need for oversight by their representatives and honest brokers, in a climate of transparency. The Human Genome Project holds important lessons in data sharing, team science, global cooperation, non-patentability, and good and rapid public access. The Recombinant DNA Committee of the US NIH has already cleared one CRISPR protocol for human use, a salubrious process. CRISPR’s greatest contribution will surely be the sheer pace, depth, and breath of applications and findings it permits. The principle of solidarity and consideration of the public good deserve far greater consideration in making sure that these rapid advances become shared benefits and that this view deserved ongoing discussions by many entities: scientific, clinical, and patient and family associations, governmental agencies, and interdisciplinary policy institutes. Also, we ask for responsible management of expectations with clear statements of realistic events on a conservative time frame [Two important documents support our cautious conclusions about not proceeding now with clinical applications of human germline manipulation. (ACMG Board of Directors. Genome editing in clinical genetics: points to consider—a statement of the American College of Medical Genetics and Genomics. Genet Med 2017; 26 January; http://www.nature.com/gim/journal/vaop/ncurrent/full/gim2016195a.html; and Committee on Human Gene Editing. Human Genome Editing: Science, Ethics, and Governance. National Academies Press, 2017. https://www.nap.edu/catalog/24623/human-genome-editing-science-ethics-and-governance)].

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Author Biography

John J. Mulvihill is a pediatrician and medical geneticist. After two decades with the US National Cancer Institute, he founded, in 1990, the Department of Human Genetics at the University of Pittsburgh, and, in 1998, the Section of Genetics, University of Oklahoma. He trained at Holy Cross College, Dartmouth Medical School, University of Washington, and Johns Hopkins Hospital and is consultant to the US National Human Genome Research Institute. Medical ethics and mentoring are major commitments and his research focuses on the genetics of human cancer, with 336 articles and 7 edited monographs. Dr Mulvihill contributed this paper, in part, as a special service for the Ignatian Volunteer Corps (www.ivcusa.org) of Philadelphia and South Jersey Region to assist the poor.

Benjamin Capps is an Associate Professor at the Department of Bioethics, Faculty of Medicine, Dalhousie University. Previously, he was at the Centre for Biomedical Ethics, National University of Singapore (2008–2014), and the Centre for Ethics in Medicine, University of Bristol, UK (2000–2008). Dr Capps was previously a member of the Neuroethics Working Group of the Bioethics Advisory Committee (Singapore) and the Pro-Tem National Oversight Committee for Human Animal Combinations in Stem Cell Research (Ministry of Health, Singapore). He is currently an International Expert on the project ‘One Health, Zoonotic Diseases and Pandemic Planning: Creating a Bioethics Framework in Singapore’ (Ministry of Health, Singapore).

Yann Joly is a Lawyer Emeritus from the Quebec Bar and the Research Director of the Centre of Genomics and Policies (CGP). At McGill University, he is an Associate Professor at the Faculty of Medicine, Department of Human Genetics and cross-appointed at the Bioethics Unit. He is a member of the Canadian Commission for UNESCO. His research interests lie at the interface of the fields of intellectual property, health law (biotechnology and other emerging health technologies) and bioethics.

Tamra Lysaghts is an Assistant Professor and Director of the Phase Ill Health Ethics, Law and Professionalism Programme at the Centre for Biomedical Ethics, National University of Singapore. She has worked for the Technical Working Group on Ethics at the World Health Organization, the Translational Clinical Research Programme of the Institute of Mental Health (Singapore) and the Human Health Division of the International Atomic Energy Agency. She is currently researching the ethics and regulation of cell therapies and translational medicine, genomics and precision medicine, and One Health in Singapore.
Hub Zwart studied philosophy and psychology at Radboud University in Nijmegen, the Netherlands. In 2000, he was appointed as full Professor of Philosophy at the Faculty of Science. In 2003, he became Director of the Centre for Society and Genomics (CSG) and in 2005, Director of the Institute for Science, Innovation, and Society. His research focuses on genomics and post-genomics (synthetic biology, nanomedicine, brain research), with special attention to genres of the imagination (novels, theatre, poetry, movies) as windows into emerging technoscientific research fields. With Ruth Chadwick, he is editor-in-chief of the open access journal Life Sciences, Society and Policy.

Ruth Chadwick is Professor of Bioethics at the University of Manchester. From 2002 to 2013, she directed the ESRC Centre for Economic and Social Aspects of Genomics (Cesagen). She co-edits the journals Bioethics and Life Sciences, Society and Policy and served on the Council of the Human Genome Organisation, the Panel of Eminent Ethical Experts of the Food and Agriculture Organisation, and the UK Advisory Committee on Novel Foods and Processes. She is Fellow of the Academy of Social Sciences; the Hastings Center, New York; the Royal Society of Arts; and the Royal Society of Biology. In 2003, she won the World Technology Network Award for Ethics and, in 2014, was elected Fellow of the Learned Society of Wales.

Conflict of interest statement

All authors state no conflict of interest.

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