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How to Optimize Human Biology:

Where Genome Editing and Artificial Intelligence Collide

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SUMMARY

Genome editing and artificial intelligence (AI) could revolutionize medicine in the United States and globally. Though neither are new technologies, the discovery of CRISPR in genome editing and advances in deep learning for AI could finally grant clinical utility to both. The medical use of these technologies individually could result in their eventual combined use, raising new and troubling ethical, legal, and social questions. If ongoing technical challenges can be overcome, will the convergence of AI and CRISPR result in practitioners 'optimizing' human health? And could viewing human biology as a machine result in a willingness to optimize biology for reasons other than health alone? Given the rapid technical progress and potential benefits of genome editing and AI, answering these questions will become more pressing in the near future. Such concerns apply not only to the United States, but to the international medical community. Notably, China has demonstrated its desire to be a global leader in both genomics and AI, which could indicate the potential of these technologies to converge in China soon. What form should the international governance of these technologies take and how will it be enforced? To ensure responsible progress of genomics and AI in combination, a balance must be struck between promoting innovation and responding to ethical, social, and moral quandaries.

GENOME EDITING IN MEDICINE

The term 'genome editing' has reemerged as a hot topic in the last five years. Recent breakthroughs in the gene editing technology CRISPR have invigorated the biotechnology community with the promise of precisely manipulating the genome of any organism, including humans[1]. While many scientists express interest in this technology for basic research, the potential impact of genome editing in medical treatments looms in the distance. Decisions about the clinical use of CRISPR are coming.

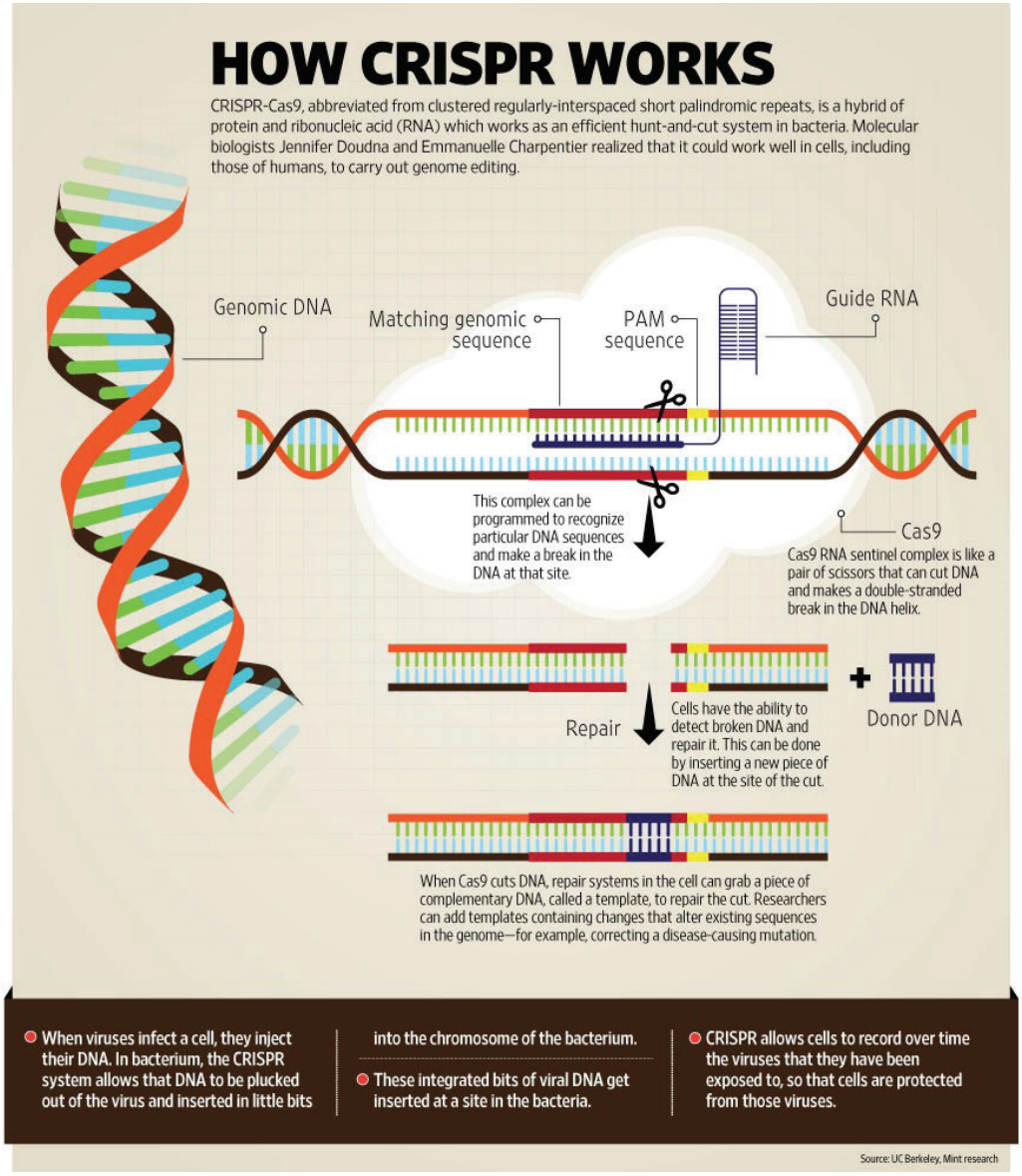
Knowledge of clustered regularly interspaced short palindromic repeats (CRISPR) arose from years of initial research on bacterial immunity, but experts have begun to recognize the power and potential of this technology in broader gene editing.[2] The new method found in CRISPR offers significant advantages over existing methods like zinc finger nuclease (ZFN) and transcription activator-like effector nucleases (TALENs). Experts now tout CRISPR as more efficient, simpler to use, and more able to edit many genes at once than older methods.[3] Interest in this technology has grown exponentially in the last 5 years since scientists first demonstrated it could successfully edit DNA alone[4] as well as DNA inside cells.[5]

CRISPR edits DNA by acting as a pair of "molecular scissors" to 'cut' and 'paste' DNA in the genome (see Figure 1). To accomplish this, the CRISPR-associated (Cas) protein uses a short segment of RNA to find the genomics sequence of interest.[6] This feature makes this technology easy to use, as experts only need to change the guide RNA to locate different genes and can utilize the same CRISPR-Cas unit. Once the CRISPR-Cas system arrives at the target gene, the Cas unit can edit the DNA using a variety of mechanisms to insert, delete, or replace DNA at that site.[7] This function should prevent CRISPR-Cas from making edits on other genes, as it should only edit once it arrives at the target. The variety of genome editing functions this technology can perform also contribute to its wide applicability.

Medicine for the Next Generation(s)

Some of the most significant applications of genome editing include medical uses for humans, as CRISPR could be deployed to repair disease-causing mutations.[9] Practitioners could deploy this technology in the clinic in two broad ways, somatically or in germline modifications. Somatic therapy refers to editing the DNA in the cells of a human after birth, rather than during prenatal development.[10] New types of therapy for existing diseases like cancer could appear when utilizing this technology, including editing immune cells to better target cancer.[11] This application of CRISPR represents another kind of gene therapy, which is not unprecedented and presents less controversy than other uses of the technology.[12] CRISPR as gene therapy may appear in clinics in the

Figure 1. "How CRISPR Works." (UC Berkley, Mint Research, and Mehta, N.) as originally appearing in "How genes are edited using CRISPR-Cas9"[8]



short-to-medium term, especially as clinical trials may begin soon in the United States[13] and many more have already begun[14] or will start soon[15] in China.

Both the greater controversy and potential around CRISPR comes from the future potential to perform germline genomic editing. This form of therapy could prevent genetic risk or disease before it occurs by editing the genome of an egg, sperm, or embryo and then using in vitro fertilization to develop a child.[16] Rather than simply treating cancer

as it arises in adults, CRISPR promises the ability to edit out mutations from genes such as BRCA1 to lower the cancer risk of children even before birth.[17] Genome editing similarly could correct mutations which cause debilitating genetic conditions including Huntington's disease or cystic fibrosis, ensuring future generations will not suffer from such ailments.[18]

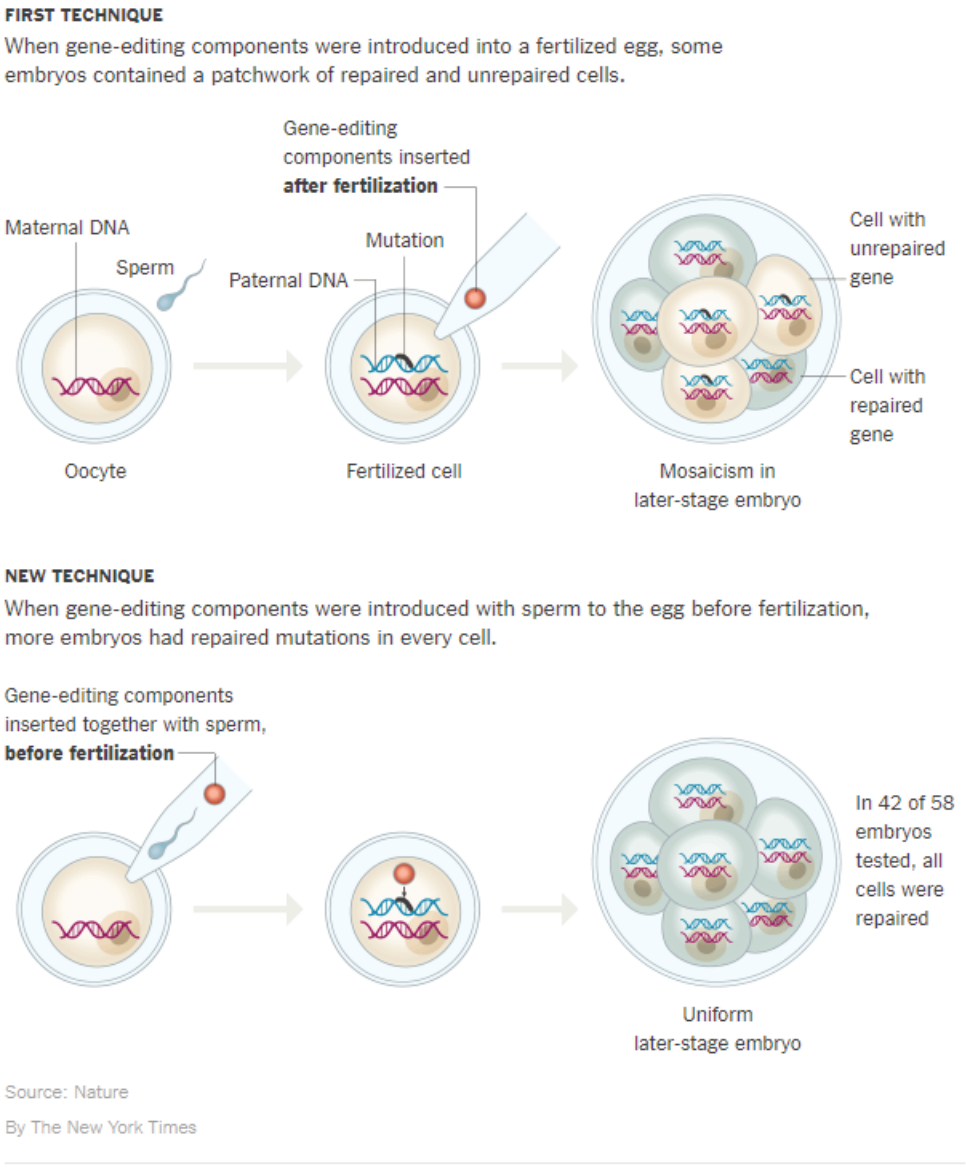
However, techniques for germline editing poses safety and ethical issues both for the child born and for any children they have, as these genetic modifications will appear in subsequent generations.[19] Off-target effects, or the possibility of altering unintended parts of the genome, have presented an increased concern since a publication in Nature Methods suggested such effects occur more often than previously thought.[20] Germline CRISPR use can result in mosaicism, where successful genome edits occurs in only a fraction of an embryo's cells.[21] Such non-uniform edits may fail to prevent a disease from occurring or could pose novel health complications. A recent development in methods involving earlier exposure of an embryo to CRISPR may aid in reducing off-target effects and mosaicism (see Figure 2),[22,23] though these groundbreaking findings will benefit from further study. Epigenetic effects may further complicate germline editing, as epigenetic factors augment an organism's genome after conception to impact whether, where, and how the body expresses genes.[24] Somatic therapies may have effectiveness problems as well, as the human immune system could potentially (and correctly) recognize the CRISR-Cas9 enzyme as non-human and develop antibodies that inhibit these gene editing tools.

Medical use of CRISPR germline editing would almost certainly necessitate Congressional action. Current appropriations forbid the National Institutes of Health (NIH) from funding research which creates or destroys human embryos and provide no funding for the Food and Drug Administration (FDA) to review germline editing products.[27] These barriers functionally prevent medical research on human germline editing in the US. While clinical use will require the above issues to be resolved, it remains likely that CRISPR germline editing may appear as clinically available in the medium-to-long term.

Biology as a Machine

The advent of molecular biology, genomics, and now CRISPR have promoted a conceptualization of biology as a machine. This view describes cellular and genomic functions using comparisons to engineering or software concepts.[28] Scientists describe mitochondria as "powerhouses,"[29] kinesins as "motors" that move "cargo,"[30] and insulin producing microorganisms as "factories."[31] Understanding natural and synthetic biology in these terms allows for simplified communication of complex ideas without steeping the discourse in field-specific jargon. This presents benefits for scientists intending on communicating with others outside of their field, the public, or decision makers.

Figure 2. Description of earlier embryo editing methods versus methodology in the recent US study (Nature, The New York Times, Belluck, P.) as originally appearing in "In Breakthrough, Scientists Edit a Dangerous Mutation from Genes in Human Embryos"[26]



However, expressing biological concepts primarily with engineering analogies may have second order effects on how the researchers view their work and how these fields advance.

Viewing biology as a machine arises from the core philosophy of synthetic biology – the engineering concept of design applied to assembling new biological systems to perform a task.[32] Practitioners conceptualize building new organisms by using living 'building

blocks' and genetically 'programming' the living machine to perform a wide spectrum of tasks.[33] This programmability of genomes in living machines allows for synthetic biologists to design novel functions into their biological machines, which may not appear in nature,[34] and gives way to a problem solving mentality towards living systems. Scientists have similarly embarked on work to utilize DNA for data storage, with a group succeeding in storing a movie and computer operating system in DNA.[35] This exposition of biology into computer science reflects a larger shift of conceptualizing biology as a machine, which can be programed and designed to perform tasks, as any other machine.

OPTIMIZING THE HUMAN BIO-MACHINERY

Genome editing may have human medical applications, which could open possibilities in the 'optimization' of human biology. Viewing biology as a machine could result in somatic CRISPR therapies conceptualized as the equivalent of software 'patches' to improve an existing system. But CRISPR also may enable germline editing on human embryos, potentially yielding experts greater ability to design and optimize the 'software' of human biology at an early stage. A university hospital recently described genetically modifying immune cells to better combat cancer as "manufacturing" the cells and reported work on "the problem of manufacturing T-cells in a process that is easy to control, understand, and scale up."[36] The presence of a mechanical conceptualization of biology amongst citizens and medical practitioners could promote the acceptance of CRISPR applications in humans. Viewing genome editing applications in therapeutics as software 'patches' or prelaunch 'debugging' could make this technology appear less foreign to the end-users.

Artificial Intelligence Could Revolutionize Genomics

Artificial intelligence (AI) represents an emerging technology with the potential to significantly impact the medical field. Progress in deep learning has enabled this shift, in which AI can learn by experience.[37] This type of learning bears similarities to how children acquire new information, and the technology functions by utilizing program architecture that resembles the human brain.[38] Such an approach involves machine intelligence recognizing patterns in data and learning from its mistakes to better identify or classify new information.[39] Deep learning specifically supports this function of AI by allowing the machine to recognize many layers of patterns; like identifying an animal by first recognizing its outline, then focusing on more specific details like fur.[40] This technology continues to find use in a variety of settings from recognizing cats in YouTube videos[41] to predicting RNA splicing patterns in mouse cells.[42] AI technology can additionally utilize optimization tools and even contribute to new optimization methods.[43] These capacities of deep learning to identify patterns from large datasets and optimize systems may provide a powerful tool when combined with genome editing.

Due to advances in AI, this technology holds new potential uses in the clinic and in medical research. Deep learning software has demonstrated its ability to diagnose images of skin cancer[44] and microscopy images,[45] and predict disease in hospitals after reviewing patient medical records.[46] These AI learn to diagnose medical conditions by utilizing experiential knowledge, resembling how physicians are trained during residency.[47] Beyond the clinic, the technology can provide powerful analyses of currently available scientific information to model the molecular mechanics of how genetic variation causes disease.[48] Similarly, AI appears set to analyze a large number of genetic datasets, in a partnership between Google and Genomic England.[49] This capacity of deep learning to diagnose, predict, and find new patterns in how genetic disease operates could make AI an invaluable companion to clinical medicine. Access to cloud computing stands to further bolster these abilities as well as patient accessibility.[50] As AI continues to expand into the medical realm, the tool could have a powerful effect on how practitioners utilize genome editing. Since the new biology aims to optimize living machines to best perform their intended functions,[51] gene editing practitioners may take this mentality to maximizing a patient's ability to live a healthy life. Particularly if human biology is viewed as a machine, deep learning could find use in instructing experts on where to use technologies like CRISPR in the genome to 'optimize' the human body.

Limitations in Artificial Intelligence

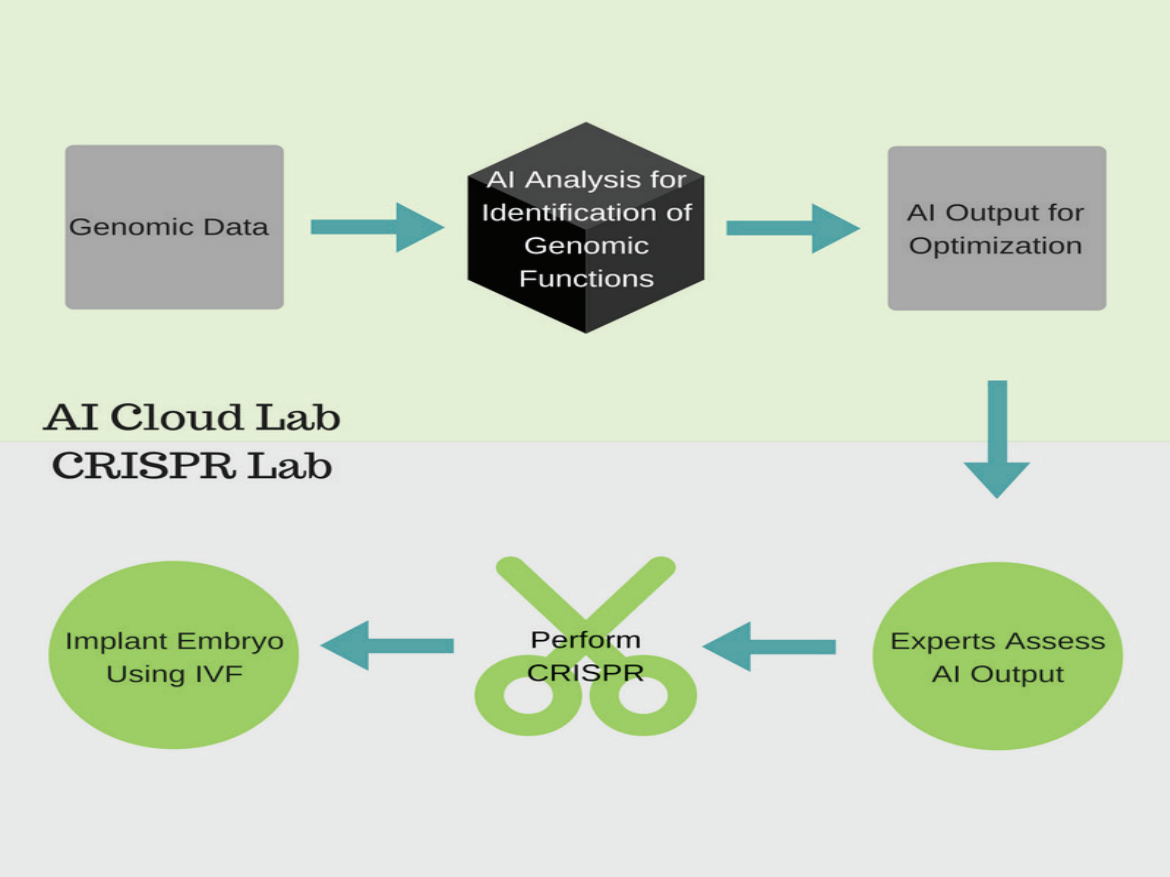
Applying deep learning to genomics and gene editing does come with limitations. While AI promise powerful new analytical and diagnostic methods in medicine, current machine learning software and their developers lack the capacity to explain how the programs arrive at their conclusions.[52] This curious "black box" character of the technology could complicate risk assessments, as an inability to understand how AI "thinks" creates issues in identifying possible areas where the machine could fail or make mistakes.[53] Should a program provide an incorrect diagnosis that influences patient and physician medical decision making, understanding why the technology made an error could pose a challenge. Furthermore, the quantity and quality of scientific information available could restrict the accuracy of deep learning projects attempting to model human biology and make predictions from those computations.[54] Additional accuracy challenges to these AI-based computational biology projects may also arise from an incomplete understanding of the natural plasticity of biology, obscured by such factors as epigenetics, gene-environment interactions, and other variations between patients.[55] These informational bounds on the models produced by AI create a need for time-intensive research to confirm their conclusions about the clinical significance of genes, as the type and amount

of information fed to deep learning software limits its potential outputs.[56] Validating AI predicted medical phenomena could rise in prevalence and importance moving forward, especially as the current knowledge of the clinical significance of disease causing mutations continues to evolve.[57,58]

CONVERGENCE: CRISPR AND AI

The concept of deploying AI and genome editing in combination to 'optimize' human biology could occur in the foreseeable future. Advances in deep learning already enable AI to contribute to the genetic diagnosis of cancer, through liquid biopsies,[59] and provide actionable medical recommendations to patients using their medical history.[60] And some genomics companies have already begun to pursue machine learning assets to boost their disease risk assessment potentials.[61] These developments suggest that AI could actively participate in medical decision making around germline genome editing in the future, especially considering the extent of data analytics required to interpret the human genome.[62] Employing medical germline editing may occur in the relatively near future as well, as the National Academies of Sciences, Engineering, and Medicine recently released a report recommending authorizing this technique under certain conditions.[63] Specifically, the Academies would permit human embryonic CRISPR use to prevent severe diseases which lack other operational medical therapies. This represents a departure from other evaluations of this technology, which push for further ethical review of the technique.[64] Applying gene editing to prevent genetic disease in this fashion could find significant benefit from AI tools which advise practitioners on where to use CRISPR in the genome to optimize health. The analytical power of deep learning could enable this technique by evaluating human biology and the genome similarly to an ordinary machine requiring streamlining. Figure 3 illustrates the basic steps by which this process could occur in the future.

Figure 3. Schema for the optimization of human biology using AI and embryonic CRISPR techniques in combination.



AI optimization represents a value-free process, however, and would not independently incorporate moral or ethical judgements. This could exacerbate tensions over deploying CRISPR for human enhancement – the improvement of biological abilities above the level of the average person. While the recent National Academies report delineates between using technology to perform a disease-correction or to augment biology, they do not categorically rule out human improvement.[65] The Academies called for public engagement prior to utilizing CRISPR to increase human biological abilities, but defining enhancement and distinguishing it from using genome editing to optimize human health poses challenges. For example, increasing muscle mass above normal levels likely represents such an augmentation. But altering the human genome to unnaturally decrease a patient's risk of cardiac disease presents a more challenging case to classify,[66] as could many other uses of CRISPR to lower risk and promote health.[67] Such risk-lowering alleles would contribute to patient wellbeing and AI tools designed to aid in maximizing human health would likely include these genes as advantageous targets for

CRISPR. Since current deep learning technology operates by identifying patterns rather than adhering to preprogramming, [68] the software would likely be unable to appreciate the ethical nuances of enhancement versus disease prevention.

Viewing biology as a machine could further distort the line between deploying CRISPR for disease prevention versus for augmentation. Should AI determine that editing the human genome for increased health requires the use of risk-lowering alleles, the biology-as-a-machine perspective may express agnosticism towards applicable concerns over enhancement. Since a primary goal of this engineering mentality is to optimize its target system, conducting these genomic edits may represent the best way to achieve this goal and promote patient health. Arguments for germline editing may find use in justifying these actions, as edits which maximize health may represent a durable way to prevent disease and increases autonomy in the resulting child.[69] This perspective may also apply to CRISPR use resulting in more obvious enhancements, if these edits similarly produce optimized health. If deep learning analysis determines that genetical modifications which enhance eyesight also lowers the risk of ocular disease or if bolstering human brain function leads to later onset of cognitive decline, performing such modifications would both enhance the resulting child and optimize their biology for health. Such AI-enabled uses of CRISPR in the germline could challenge the significance of distinguishing between augmentation and disease prevention.

Human Optimization Beyond Health

Just as a machine can be optimized to perform varying functions, gene editing in combination with artificial intelligence could enable the honing of human biology for purposes other than solely improved health. Recent genetic diagnostics which claim to predict the physical characteristics of a newborn[70] could herald a time when this type of information becomes applicable to CRISPR germline editing. Though experts question the clinical validity of information about the genetic nature of physical traits or personality.[71] Combined applications of AI and CRISPR may be presented as a potential to optimize human biology for physical characteristics and not solely health, prompting more classical concerns for enhancement.[72] Relatedly, conversations about optimizing humans for space travel have already begun,[73] including thoughts on reducing stature and boosting the body's ability to respond to radiation. Genomic testing already exists to determine if an individual possesses genetic variants which would be valuable in space,[74] a task which could be further augmented by AI analysis to identify variants which would maximize these attributes. Viewing biology as a machine influence these conversations

as well, contributing to proposals to radically modify human biology to confer photosynthetic properties – a potentially useful trait for interstellar living.[75] Engineers can grant a machine new functionalities to better perform its tasks, a mentality which manifests in discussing adding photosynthetic capabilities to humans. Such biological additions would require a great amount of data analysis and optimization to prevent negative health consequences, and fortunately both would likely be assisted by AI tools.

More Research and Development Needed for Germline Editing with AI

These technological applications at the convergence of CRISPR and deep learning would require further strides in research and development, as current tools could not perform these functions. The connections between many genes and disease remain poorly characterized, especially given the countless alleles with unknown impact on disease which experts continue to discover.[76] The scientific community has thus criticized researchers claiming to have found relatively simple connections between genetic factors and complex diseases.[77,78] Scientists have similarly disputed the merit of using genomics to give potentially overconfident counsel on preventing disease and improving health.[79] This evolving subsection of the genomics industry often offers genetic sequencing directly-to-consumers and can provide advice on anything from diet modification to boosting soccer performance.[80,81] Genetic tests which predict physical characteristics of newborns have received even harsher criticism from experts.[82] And recent research in CRISPR suggest that adding a new gene to a human embryo may present more challenges than originally thought.[83] In experiments that tried to replace paternal DNA with a new gene, the embryo instead copied the DNA from the maternal gene, which could pose new challenges for editing embryos with two copies of diseased genes or for making progress in enhancement.[84,85]

The "black box" and insufficient data (quantity or quality) limitations on AI similarly restrict the possibility of machine learning optimization of human biology without further work. Advances in deep learning techniques alone may prove insufficient to improve the capacity and address the limitations of AI,[86] and new approaches to the technology demand time and resources – potentially delaying the use of machine intelligence in genomics further. Ultimately, a successful medical product using germline editing (with or without AI) and FDA approval would almost certainly require more comprehensive genomics and machine learning research, substantial clinical testing, and the mitigation of remaining uncertainties.

THE US-CHINA RACE

Patient Perspectives in the U.S.

A recent meta-analysis[87] of polls on United States citizens helps in clarifying sentiments on human genome editing from the broader American public. For somatic gene editing, the studies found Americans generally support using technologies like CRISPR in treatment of inherited or acquired disease, but disapproved of enhancement. The public largely condemned any type of germline modification, worse for germline edits resulting in human augmentation. Of note, the study also identified relatively low scientific literacy on genome editing, finding a majority of U.S. citizens rarely hear of the technology and lack familiarity with terms used to describe it. These data suggest that the general American public would disapprove of AI-based genome optimization at this time, even to maximize human health and specifically to maximize other traits.

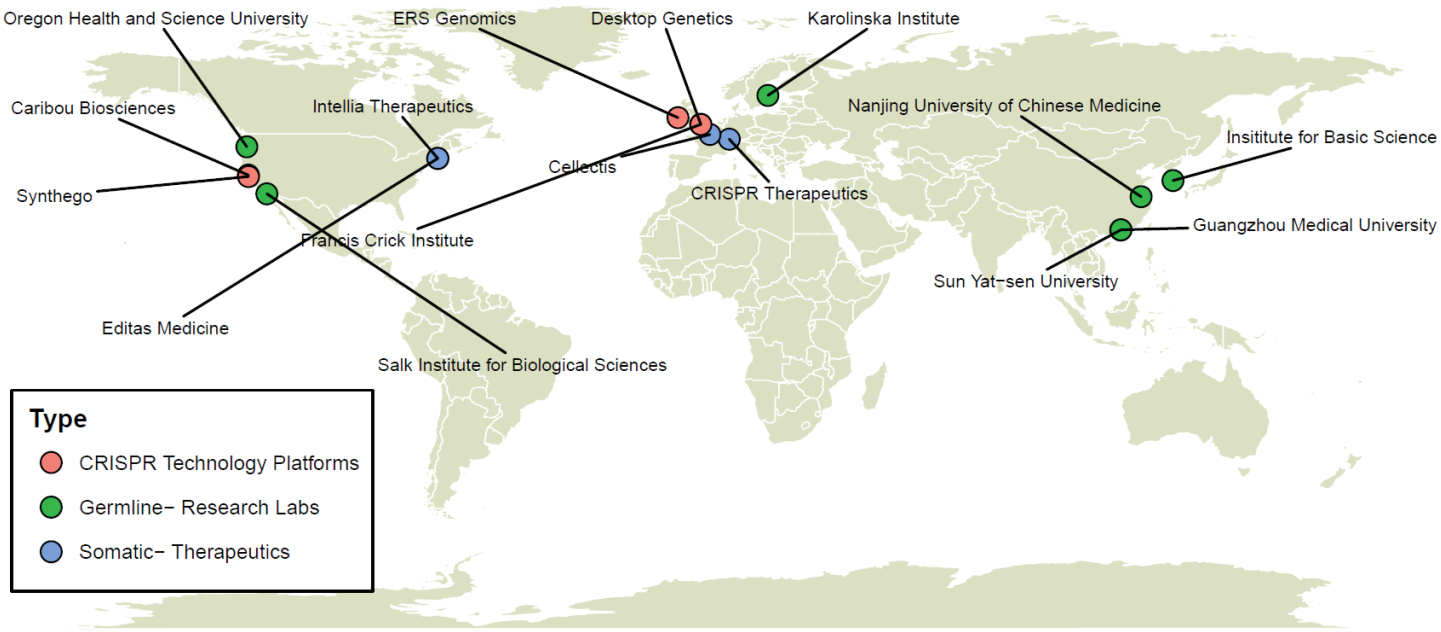
However, citizens did not universally oppose germline editing[88] and subpopulations within the broader public may be more inclined to back such technologies. Patient community and advocacy groups may serve as supporters for embryonic genome editing to improve health. The patient community for the autism spectrum has demonstrated considerable interest in genomic sequencing and research, even if testing does not directly aid in selecting therapies.[89] Should genome editing provide a method of preventing such conditions, patient communities could advocate more strongly for these techniques than the average citizen. Especially in rare disease patient communities, whose future progeny could potentially benefit greatly from germline editing,[90] some citizens may more readily support AI-optimized CRISPR interventions for better health. The recent argument that using CRISPR to replace a diseased gene inherited from one parent with a healthy one from another represents "genetic correction" and not "modification" could similarly promote more positive views of human genome editing.[91]

China: A Rising Superpower in Genomics and AI

The United States will not be the only nation who could utilize human genome editing, with or without AI optimization. Many other countries in Europe and Asia conduct work on CRISPR, with China as a notable example. Largely as a result of its industry's work in DNA sequencing, China has emerged as an international giant in biomedical research and precision medicine in recent years.[92] The Chinese biomedical science community may soon overtake U.S. scientists in the number of research articles published in well-known academic journals[93] and China's biotechnology industry has discovered an increasing number of drugs in recent years.[94] China has rapidly expanded its funding of synthetic biology research and could surpass American funding by 2020.[95] Chinese scientists have

aggressively moved forward with research on CRISPR in this context, and upset the international community in the last two years when groups reported using CRISPR in human embryos on three separate occasions.[96,97,98] Suboptimal data transparency has further confounded efforts for outside parties to evaluate Chinese medical research on CRISPR.[99] However, following these firsts in China, other groups in Sweden, the U.K., and now the U.S. (without federal funding) have also pursued genome editing in human embryos.[100,101] Figure 4 presents a map with the locations of laboratories with lead investigators known to be pursuing research on human germline CRISPR techniques, overlaid with locations of companies pursuing other uses of CRISPR.

Figure 4. Map of primary laboratories engaged in human germline CRISPR research and companies pursuing somatic therapies and other CRISPR uses (Dunlap, G.).



The United States and China hold different social perceptions of the use of CRISPR in human embryos as well. The Chinese public largely responded positively to the use of genome editing in human embryonic stem cells by research teams in China.[102] Both professional and social media celebrated the work for its contributions to the scientific field and most, but not all, did not express significant ethical concerns over the use of CRISPR. In contrast, many Western stakeholders maintain that these experiments demonstrate lax regulation of emerging biotechnologies in China. Others have argued China remained within appropriate ethical bounds while performing these experiments and note that the group received ethical approval from its home institution.[103] Current

Chinese patent law prevents patents on human germline modification due to moral principles, however other legal and regulatory structures in China may not be adequately prepared to address moral and ethical concerns arising from human CRISPR use.[104]

These trends in biomedicine mirror the significant recent increases in Chinese investment in AI research, both at home and in international groups.[105] Top technology firms in China employ machine intelligence technology of comparable caliber to leading American companies.[106] Further, the Chinese computing industry has surpassed U.S. efforts with two different supercomputers, hinting at a considerable potential for machine intelligence.[107] The prioritization of AI research may find use in the healthcare sector, as a new collaboration in China has embarked to utilize this technology to interpret massive amounts of health information including personal genomics.[108] This resembles recommendations made by the Chinese Academy of Sciences to prioritize genomics research, and even to accelerate work in this field by exploiting computer modelling to optimize synthetic living systems.[109] Such policy recommendations for optimization of biological machines in combination with projects to use AI to understand genomic and other health data could foreshadow a time where AI-based optimization of human embryonic CRISPR procedures becomes acceptable in China.

Potential Futures for Human Optimization in China and Abroad

Applications of genome editing with an AI companion may find uses beyond maximizing health. A genetics firm recently announced a newborn DNA sequencing service in China which will offer interpretations not only for disease risk, but also for various physical characteristics.[110] This interpretation will include deterministic predictions about likely physical appearance, personality traits, and even more obscure items including musical ability – following trends in emerging pseudoscientific genetic counseling.[111] Independent of whether this type of interpretation is useful today, providing and accepting genomic empowered predictions of physical characteristics could lead to considerations of gene editing at those loci in the future. Social acceptance of such medical predictions or interventions in China could press Chinese AI-based CRISPR use to optimize human biology for physical characteristics, not solely for improved health. The possibilities for this type of optimization could have further ethical consequences should scientists better understand the genetics behind cognitive function and emotional capacity, with recent studies finding some genetic connections to intelligence[112] and empathy.[113]

Should China permit the use of CRISPR germline editing, with or without AI analysis, citizens of other nations could potentially access this technology through medical tourism. The concept of medical tourism involves patients travelling to another jurisdiction with the intent to receive medical treatment,[114] and could have a role in the accessibility of germline genome editing. High profile medical tourism for embryonic

procedures has already occurred in recent years with mitochondrial donation, a technique which functionally replaces diseased mitochondria in a human embryo with healthy ones.[115] In 2015, an American physician performed the technique for a Jordanian couple in a Mexican medical institution.[116] Mitochondrial donation was not legally permitted in many Western nations at the time, though no prohibitive legal barriers existed in other jurisdictions like Mexico. Reports exist of mitochondrial replacement occurring in other nations, including China and Ukraine.[117] The reality of patients and physicians engaging in medical tourism to perform embryonic treatments with emerging biotechnologies suggests the same could occur with CRISPR germline editing, and one U.S. based scientist has already suggested a willingness to consider this.[118] Obtaining access to a medical intervention, illegal in one's jurisdiction and not another, can motivate patients to participate in medical tourism.[120] The significant hype present in media coverage of the medical potential of CRISPR in combination with U.S. citizen perceptions of slow regulatory approval of medical innovations could exacerbate medical tourism for genome editing.[121]

REGULATORY CONSIDERATIONS

As genome editing and artificial intelligence continue to evolve, medical products incorporating one or both technologies will begin to seek market access. The FDA already approved the first diagnostic product utilizing deep learning earlier this year, which will find use in cardiology clinics.[123] Later in 2017, the agency will make a final decision on approval of two cancer treatments using somatic gene editing of immune cells, and its advisory panel recently and unanimously recommended approval for the Novartis version of this therapy.[124] As the agency continues to consider how to address these technologies in medical products, it may be appropriate to deliberate over adequate oversight for future products which involve both genome editing and AI. This is especially important for germline genome editing applications, as no medical product performing human germline modifications has sought FDA approval before and experts remain uncertain about how FDA would classify and then regulate germline technologies. For somatic uses, the Novartis immune-editing therapy would receive drug status if approved[125] and somatic gene therapy applications of CRISPR likely fall under existing FDA biologics oversight.[126] Human embryonic gene editing may be treated differently, though the precedent of FDA drug regulation for assistive reproductive technologies could result in drug oversight for germline CRISPR.[127] Others question if FDA might apply device regulation to genome editing.[128]

Regulation of AI in genomics presents another set of challenges for FDA, falling under medical device regulation and the evolving oversight category of software as a medical device (SaMD). FDA has expressed interest in establishing a digital health unit to

address products including SaMD, and the potential enactment of the proposed 2017 medical device user fee legislation could advance this goal.[129] However, the agency has refrained from establishing or discussing policies specific to artificial intelligence to date. Abstaining from setting hard regulations would prevent regulatory lock-in and potentially onerous or inappropriate industry oversight, though some have suggested FDA is currently agnostic to "black box" concerns arising from deep learning in medical diagnosis.[130] In the case of AI-based CRISPR use, such black-box issues could present unique safety and effectiveness challenges and may require further consideration. Especially if germline editing becomes regulated as a drug, the FDA's companion diagnostic oversight may present a method of assessing safety and effectiveness of genomic sequencing and AI analysis of that data. This option, however, would not currently capture laboratory-developed tests, which represent a large percentage of genomic diagnostics.[131] The FDA has further indicated its interest in advancing international harmonization of software medical device oversight, including with International Medical Device Regulators Forum.[132,133] Such international efforts could present opportunities to resolve ethical and legal dilemmas across jurisdictions over items such as AI-driven genome editing.

Several other agencies could support appropriate regulation of AI-enhanced germline editing. The Centers for Disease Control and Prevention (CDC) houses an established office for assessing public health with respect to genomics,[134] and may find increased utility over genome editing. This agency could potentially aid in coordinating or evaluating longitudinal studies into the health of individuals born using germline modification techniques – an important step required for safety oversight.[135] The Federal Trade Commission (FTC) could play a role in the regulation of genomic/machine learning technologies by leveraging its expertise in educating consumers and tackling misleading or inaccurate claims on products. This agency has already taken an interest in direct-to-consumer (DTC) genetic testing[136] and could support other regulatory activities around genome editing. While not a classic regulatory agency, the NIH can influence the direction of genome editing and AI technology by making policy-based decisions about research fund. This could include funding studies to determine the clinical significance of poorly understood genes, evaluating the capacity and limitations of deep learning in a clinical setting, and social science investigations into the impacts of AI-based germline editing.

POLICY RECOMMENDATIONS

- The United States Congress should commission a study on the ethical, legal, and social implications of employing AI to augment the medical use of genome editing. Creating appropriate oversight mechanisms will depend on evaluating the various potential consequences of these two technologies converging. Assessing public sentiments and perceptions about the prospect of AI-driven genome editing will support this process.

- The U.S. government should fund research in human genomics and artificial intelligence which will aid in risk assessment and mitigation of medical interventions utilizing one or both technologies. Research is needed in multiple areas including in improving the accuracy and effectiveness of CRISPR, cultivating a better understanding of the clinical significance of various genetic loci and variants, demystifying the "black box" of deep learning to investigate how AI makes decisions, and evaluating the impacts of AI diagnosis on medical decision making.

- Federal regulators, industry members, scholars, and other experts around genomics and artificial intelligence should begin to converse about suitable oversight mechanisms for germline genome editing and diagnostic AI, especially when used in tandem. Striking a compromise between safety and innovation is key to protecting public health while allowing these emerging technologies to develop and maintaining U.S. leadership in these technological realms. Which regulatory bodies to involve and their roles and responsibilities in oversight should be deliberated.

- The current administration should consider how to collaborate on research and industry endeavors with leading nations in both genomics and AI, including China. International collaborative research development efforts may allow for more collective decision-making on how to proceed ethically with investigations into these technologies, especially at the interface of genomics and deep learning.

- The United States government should consider beginning dialogues with leading nations in genomics and AI, including China, on harmonizing governance approaches to these technologies – both individually and at their convergence. The Office of Science and Technology Policy or another appropriate body could engage these conversations to identify and make recommendations on balancing varying values and norms.

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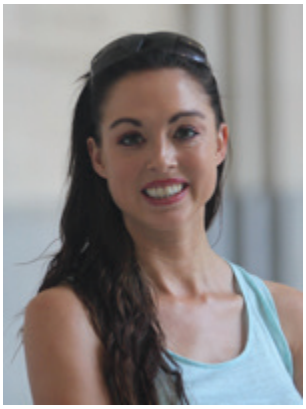

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