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The Era of Purposeful Manipulation Begins

AUTHOR
Carol Kuntz

A Report of the CSIS Strategic Technologies Program

CSIS | CENTER FOR STRATEGIC & INTERNATIONAL STUDIES

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Contents

Abstract 1

1 | Overview 2

2 | Tradition, Technology, and War 15

3 | Editing the Human Genome 22

4 | Databases and Their Discontents 31

5 | Useful Molecules 41

Conclusion 45

About the Author 48

Endnotes 49

Abstract

The purposeful manipulation of genomes is now possible. Such manipulation has great promise and broad strategic implications; it is creating useful molecules of various sorts and, over time, it could eliminate genetic disease. Like many emerging technologies, genome manipulation could grow into an important economic sector, contributing to a replicating cycle of innovation and enabling the United States to favorably shape its strategic future at home and abroad. Advances in these technologies are fueled by a global commercial and academic community. The United States should ensure that it fully remains a member of that community, but also that key capabilities—such as large, well-curated databases and biofoundries—are created and sustained domestically. The United States needs to rationalize its policy on heritable human genome editing, allowing legitimate types of edits but contributing to international norms against illegitimate ones. A robust biotechnology sector at home would yield many benefits—economic, technological, medical—and provide the critical reservoir of expertise within which national security interests could be secured. The Department of Defense needs to make structural reforms in its approach to emerging technologies, particularly by creating career paths for uniformed practitioners. Otherwise, it will continue failing in its effort to incorporate emerging technologies into its operational concepts, budgets, and programs—leading to diminished capabilities in the United States, particularly as compared to China. In time, falling behind on these key areas of science could lead to many problems, including failures in deterrence and, ultimately, in war.

1

Overview

DNA, coiled in its double helix, holds promise and portent. The promise is of new creation; the portent is of risk.

Today, DNA remains coiled in its double helix, but its implications have been transformed. A remarkable convergence of technical advances is enabling molecules of DNA to be purposefully manipulated to create new organisms with specific desired traits. This capability to modify genomes can create "useful" molecules leading to new materials like self-repairing fabrics, plastics that are not made of petroleum products, or biosensors of various sorts.[1] It can edit genomes to produce proteins that distill rare earth elements from wastes like coal ash.[2] It can even produce tailored therapeutics for new diseases and use precision medicine algorithms to optimize treatment strategies for a particular individual.[3] These edits could become ever more transformative as advances in machine learning and bioinformatics proceed to illuminate the genetic roots of more traits. They could eliminate genetic disease or create individuals with previously unrealizable genetic potential.[4]

Taken together, the ability to edit DNA could build a multi-trillion-dollar annual economic sector around "useful molecules" that are genetically engineered so as to produce new or specialized materials, precision medicine and tailored therapeutics, and national security capabilities that could transform war.[5] However, current U.S. programs are failing to benefit fully from the progress of science. Critical biotechnologies—and the machine learning systems that support them—are being advanced by a globalized commercial and academic sector; despite the United States' status as a leader in discovery and innovation, it lacks the training databases, biofoundries, and technical workforce to sustain its lead and to translate discoveries to cutting-edge applications.

Making up the gap in U.S. technological capability will require a healthy civilian sector in these emerging sciences. Civilian efforts are driving the rapid pace in innovation; any effort to replicate such a sector inside of the U.S. Department of Defense (DOD) would be doomed to fail, as it would inevitably lag behind the advances generated outside.

The DOD needs a two-pronged strategy. First, it should make structural reforms enabling it to swiftly incorporate cutting-edge technologies from the academic and commercial sectors into its operational concepts, programs, and budgets. Second, it should strive to ensure the health of the civilian and academic sector in the United States, particularly when it comes to machine learning and biotechnologies—an outcome the DOD, like so many other segments of U.S. society, has a fundamental interest in cultivating.

All these reforms—in the DOD and in U.S. policy more generally—are needed for the many economic, scientific, medical, and national security benefits they would generate. Of course, formulating and implementing these reforms would be difficult, even in the best of times—and these are not the best of times. China is rising as a strategic competitor to the United States. It seems poised to take advantage of delays or missteps in U.S. policy. There is still reasonable hope of avoiding military conflict with China; doing so, though, would require many deft policies of various sorts, including the construction of effective military deterrence.

Crafting and implementing such policies seem difficult in the current political context. Any U.S. scientific leader observing the Covid vaccine debates would probably be disinclined to play a large public role advocating for the creation of genomic databases, for example, even if demonstrating their necessity and underscoring that they would be crafted in a fashion consistent with national values.[6] Progress seems hard to secure in the current, riven system of government in the United States; such progress would require new organizational structures, laws, and regulations.

Convergence of Technologies

The ability to purposefully manipulate genomes comes from the convergence of three technical advances: DNA sequencing, CRISPR-Cas systems, and machine learning algorithms. DNA sequencing, which emerged at the end of the twentieth century, enables the specific DNA sequence of an organism to be determined. DNA consists of pairs of nucleotides containing four bases—A and T, G and C—whose bonds help build the double helix and create the blueprint for every living organism. The human genome is 3.2 billion base pairs in length, and most of it was first fully sequenced in 2003. Since then, the cost and time needed to sequence human DNA has plummeted, making sequencing and analysis a realistic part of research and treatment strategies; the complete human genome was finally mapped in January 2022.[7]

CRISPR-Cas systems—so named for the distinctive features of their genetic code, "clustered regularly interspaced short palindromic repeats," and their associated enzymes—are the second critical technology for this new capability. Discovered more recently, these programmable genetic sequences provide a precise, technically straightforward way of editing DNA.[8] CRISPR-Cas systems exploit a natural defense mechanism that bacteria developed over millennia to protect from virus attackers. The CRISPR sequences in the bacteria's DNA remember the genetic sequence of every virus previously encountered and use this record to evaluate new molecules and determine whether they represent a

threat. If there is a genetic match with the record of a previous attacker, the bacteria use Cas ("CRISPR-associated") enzymes to destroy the new virus by cutting its DNA.

Once scientists understood the natural function of this mechanism, they were able to make slight modifications to create a useful laboratory tool. Researchers can now use a programmable CRISPR-Cas system to specify the location of the genetic sequence they want mutated and the change they want made, a vastly easier and more precise technology than previous methods of DNA editing.

The third essential advance that has brought this era of purposeful genetic manipulation is machine learning. While the CRISPR-Cas system enables edits to DNA, there is still a limited understanding of which edits will achieve which outcome in the characteristics of the resulting organism. Increasingly, machine learning algorithms—with their ability to identify subtle correlations in extraordinarily large quantities of data—are being used to reliably predict the genetic edits required for specific traits.

Machine learning is also deepening the understanding of the causes of genetic diseases. While there was a broad recognition of the extent to which diseases had a genetic root by the 1970s, it remained very difficult to specify those roots given the enormous size of the human genome and the relevant data.[9] As one example, consider having one database that contains the genomes of individuals with a type of cancer and another of those without.[10] Given the size of the genomes, comparing them by hand to identify the differences would be an intractable problem.

Machine learning, however, is extremely good at making these types of comparisons and correlations. Using various mathematical techniques, it examines a large number of entries in a database—both the input and the output—to build a single algorithm which is posited, refined, and optimized to reliably translate each of the inputs into its corresponding output—for example, using weather information for one day as the input and the weather the following day as the output. The algorithm would improve in predictive power as it is trained on more entries. Once the algorithm was well trained, you could combine it with the weather information for today and, with high confidence, predict tomorrow's weather. All things being equal, the larger the training database, the stronger the results; one of the major challenges in the United States is the difficulty of building the large training databases needed to develop robust machine learning algorithms.[11]

Two important caveats are needed. First, mapping the genetic components of complex traits or diseases has only begun. This mapping will take many decades to complete, particularly for traits or diseases resulting from the action and interaction of a very large number of genes.[12]

The second caveat is more powerful. Biology is becoming more like engineering as an academic discipline—a shift sometimes denoted by referring to a new discipline of synthetic biology. But the engineering parallel is not exact, and biology is far from revealing all its secrets. It is not a matter of advanced technical inquiry, for instance, to observe two identical twins as adults and recognize that they are not identical despite having been born with the exact same genome. Answering the question of why they are different as adults is now an active area of research; genome regulation, cellular circuitry, and epigenomics are among the technical hypotheses put forward to explain these differences. Research efforts are only starting to map the effects of these emerging areas of biological study.

Taken together, these two caveats provide a caution. Eliminating a genetic disease, particularly one caused by relatively few genes, could be the work of a single generation. Enhancing genetic potential,

with its greater risk of unforeseen interaction effects, poses a much greater technical challenge. Ambitions of creating an adult human with a particular preselected set of physical or intellectual traits would likely be the work of many generations, if it could even be accomplished. And as so many fairy tales and myths have warned, one fears that those wishes, once fulfilled, may prove vastly less satisfying than anticipated.

Thus biology, even with the ordering of the genome conquered, retains some of its mystery, particularly when contemplating its most complicated of creations. The solution to many less complicated puzzles—some genetic diseases, tailored therapeutics, new materials—may be found with our current understanding of purposeful manipulation of genomes. But with puzzles and especially mysteries, one must proceed with caution.

Interaction of Technology and State Structure

Characteristics of technology and state structure always interact. Four characteristics of the Chinese state system are relevant to their advantage in the application of biotechnologies and machine learning.

First, machine learning requires large, well-curated training databases. In the United States, creating databases for the purposeful manipulation of genomes is complicated by many factors, including the fragmented healthcare system, privacy rights, and proprietary rights. These rights are important and should be protected. The outdated way they are protected, though, complicates the creation of needed databases, as do many other laws, regulations, and policies. In this era of artificial intelligence, the United States lacks an appropriate policy framework: it neither protects some types of data, such as consumer data provided to private companies in exchange for "free" services, nor makes other types of data available to responsible nonprofit organizations seeking to advance the public interest, such as improving the access to precision medicine to individuals of all socioeconomic and ethnic groups. The lack of such a policy framework also complicates—perhaps fatally—the ability to share databases with close friends and allies such as the European Union, whose data is governed by the General Data Protection Regulations (GDPR) and other acts. With clearer policies in the United States, it would be easier to sustain and extend data sharing agreements with GDPR member states.

In China, on the other hand, the government has access to proprietary data, does not recognize individual privacy rights vis-à-vis the government, and disdains foreign intellectual property rights. It can thus readily collect and consolidate databases of its own population of 1.4 billion individuals. In addition, the U.S. intelligence community reports that "for years, the People's Republic of China (PRC) has collected large healthcare data sets from the U.S. and nations around the globe, through both legal and illegal means, for purposes only it can control. . . . The PRC understands the collection and analysis of large genomic data sets from diverse populations helps foster new medical discoveries and cures that can have substantial commercial value and advance its Artificial Intelligence and precision medicine industries."[13]

Second, domestic production yields important benefits, which are overlooked when a company exclusively focuses on securing the lowest price for a service, as appropriate in a market economy. Such an exclusive focus by U.S. private sector companies has had the effect of denuding the United States of some critical domestic capabilities, including large scale, low-cost DNA sequencing.

China uses predatory pricing to locate key technical sectors in China. For example, while a U.S. company had a "near-monopoly" on producing the machines used to sequence DNA, the United States industry relied on China for the performance of such sequencing, particularly large scale, low-cost DNA sequencing.[14] Chinese dominance in this type of DNA sequencing provides China with access to U.S. genomes as health providers contract with Chinese companies to provide these services to them. The U.S. intelligence community has warned of the dangers of this exclusive focus by U.S. companies on low cost in DNA sequencing: "Chinese companies have also gained access to U.S. healthcare data by partnering with hospitals, universities, and other research organizations in America. These U.S. entities routinely seek low-cost genomic sequencing services for their facilities, which Chinese biotech firms can often provide due to Chinese government subsidies."[15]

U.S. policy thus needs to create and sustain some critical supply capacity in the United States. While this is important, it is far from easy. Far too many efforts to create or preserve domestic supply chains in the United States have ended up rewarding bureaucratic, outdated contractors.[16] Past policy failures do not alter the need; they merely demand a search for better policy tools given the importance of the objective to national interests.

Third, the source of innovation for machine learning algorithms and related biotechnologies is small nongovernmental actors—academic researchers, venture capital funders, biotech start-ups—supported by an international commercial sector investing large amounts of funds in this economic sector. These numerous actors actively share information, but the U.S. government is, by and large, not part of the conversation. Individual officials may, by dint of their experience and connections, have knowledge of these broader trends, but such individuals are relatively rare in government service. While the United States is blessed by the readiness of its leading academic and commercial technical experts to serve on advisory committees of various sorts, no participant or recipient of that advice would claim it is seamlessly integrated into government policy upon receipt.

Far too many efforts to create or preserve domestic supply chains in the United States have ended up rewarding bureaucratic, outdated contractors. Past policy failures do not alter the need; they merely demand a search for better policy tools given the importance to the objective of national interests.

The Chinese government, on the other hand, is always a part of the conversation, largely because their citizens must share information with the government, even if they can act as peers to their global colleagues outside of China. This difference means that the Chinese government can put together an integrated picture about advances in a particular technology and act upon it in a way that the United States government generally cannot. It also means that the Chinese government can target the acquisition of specific information or technologies in a way that its U.S. analogue cannot.

Fourth, genome editing of humans raises profound and disquieting ethical and cultural issues to which various governments and societies may respond differently. These different responses can constrain some national programs, leaving them able to pursue neither legitimate uses of this technology nor defenses against illegitimate uses by others. In the United States, there are prohibitions on most heritable human genome editing (HHGE) research, including research that would be allowed under most recommended scientific norms. Meanwhile, China did punish scientists who modified the genomes of twins in a controversial 2018 case, but it nonetheless permits research on HHGE that would not currently be permitted in the main research venues of the United States.[17]

Furthermore, ethical and cultural differences also may change the time scale on which results—programmatic and strategic— need to be secured, and multi-generational projects that seem worthy and reasonable to some states may not to others. China has the longest continuous history of any country in the world, reaching back more than 5,000 years with a written history of 3,500 years. An effort that would be the work of generations must seem vastly more plausible in that context than in the United States with its much more recent founding. The countries are different not only in the length of their history but in their cultural priorities. A renowned scholar of China observed that "It could be that no people have ever outdone the Chinese in ascribing moral virtues to the state or in deprecating the worth of the individual."[18] Multi-generational projects can serve the state in a way in which they could never serve an individual; the United States, with its foundational Enlightenment ideals focused on the individual, may put less value in multi-generational projects.

These observations are not meant to imply that the Chinese state structure is superior to that of the United States; on the contrary, the core U.S. values of liberty, equality, and diversity remain precious and worthy. They are simply meant to highlight that machine learning—with its need for large databases—and some aspects of biotechnology pose unique problems. The government of the United States needs to implement new policies that advance these technologies but in ways consistent with its broader values as a nation.

Four Needed Reforms

Given this broader context, this study makes four recommendations. The first seeks to enhance the DOD's ability to benefit from advances in the commercial and academic sector, and the latter three aim to ensure that the domestic sector in the United States flourishes. The U.S. government should:

- Make structural reforms inside the DOD to facilitate its ability to incorporate cutting-edge technology. The most important of these reforms would be to create uniformed career paths for experts of the new technologies, as such uniformed experts would empower senior leaders seeking change; give this change staying power; and facilitate change being woven into new operational concepts, programs, and budgets.
- Seek to build international norms for heritable human genome editing (HHGE)—despite the likelihood of cheating by adversaries—to enable U.S. research to go forward on legitimate uses of HHGE and on defenses against illegitimate uses by others.
- Create an environment that facilitates the creation of databases, given their increased strategic importance, while preserving national values. Change laws and incentives to make important data available that currently is inaccessible, create new organizational models for public-private

partnerships to manage sensitive data, and create a high-level advocate for data access so that newly identified problems can be adjudicated and properly resolved.

- Use "Grand Challenges"—along the lines of the Defense Advanced Research Project Agency (DARPA) competitions to develop autonomous vehicle technology—to produce a molecule that would be useful for a public purpose, such as mitigating climate change. The competition should be structured in a way that also advances other goals, such as assuring a domestic biofoundry infrastructure and technical staff; catalyzing the development of a valuable training database; and deriving process insights on how to create an overall environment supportive of database creation, maintenance, and usage, as well as the process to review the molecule's safety. The effort also could create connections between the technical community and the State Department so as to ensure that U.S. interests are represented in international standard-setting efforts.

Many of these reforms would be needed even in the absence of China as a strategic competitor. But with such a competitor, delay and missteps in fashioning and implementing U.S. policy can be dangerous, as many of these technologies are on a worrisome trajectory and time is shortening to make that trajectory more favorable to the United States.

Innovation inside the Department of Defense

The source of technical progress—a globalized commercial and academic sector—means that the DOD science and technology (S&T) ecosystem is perversely robust against integrating its advances. The ecosystem was built in the immediate post-World War II period when the DOD itself generated most technological innovation. It prized investments in labs for each of the military services; large, innovative defense contractors; and national labs that initially focused on nuclear weapons and their delivery systems. All of these institutions were staffed by excellent civilian experts who spent their careers within this classified environment.

With this inward-facing technology ecosystem and its impressive record of technical success in its past, it is natural that the DOD would turn to classified research and self-reliance to solve technical problems. But today, the reflexive application of this strategy is counterproductive. Despite the passage of time and the shifts in technology and their origin, the DOD S&T ecosystem has remained far too internally focused. It is poorly adapted to understanding, harvesting, or applying cutting-edge advances in technology developed by the civilian, commercial, and academic sectors.[19] In peacetime, this results in planning to fight out-of-date challenges with outmoded technical countermeasures. In wartime, the unhappy implications of this outdated perspective would be laid bare.[20]

Hence, the DOD-specific recommendation seeks to strengthen the DOD's ability to incorporate technologies that are being rapidly advanced outside of it. The most important reform would be the creation of career paths for uniformed practitioners of the new technologies.[21] The objective would be to ensure that there are at least a small number of positions at the top of a career path for technical experts at the mid and senior officer ranks, defined as the ranks of 0-5 (lieutenant colonel in the Air Force and Army and commander in the Navy) and above, possibly extending to a single position for a technical expert at the two-star level who would directly advise the chairman of the Joint Chiefs of Staff.

0-5 is the rank where officers often shift from managing current capabilities to participating in department-wide deliberations about the nature of future wars and the characteristics of

future programs and budgets. Bringing technological expertise into the mid and upper reaches of the uniformed military—and weaving those officers throughout the wargaming, planning, and programming staffs in the services, the combatant commands, the Joint Staff, and the Office of the Secretary of Defense—could make major strides in integrating emerging technologies into the myriad decisions that collectively yield military capability.

This reform would not obviate the importance of strong support for innovation from the officials holding the most senior civilian and military positions in the DOD. That strong support is and would remain essential.[22] Rather, these reforms would enable it to be actualized in detailed work supporting war games seeking to develop new operational concepts, or in detailed programmatic recommendations for incorporating new technologies into existing capabilities and missions.

Incorporating emerging technologies into warfare is neither easy nor straightforward. On that lesson, at least, history seems clear. In peacetime, the essential element seems to be institutionalizing the sustained, evidence-based interaction of experienced officers thinking about the changing nature of war, working with uniformed experts in new technologies, and obtaining external support for innovation from the most senior military and civilian leadership.[23] Structured wargames can work well, with famous examples being the Louisiana Maneuvers before World War II where U.S. ground commanders developed some of the tactics that would win the war, or war games at the U.S. Naval War College in the interwar years that developed strategies for the use of aircraft carriers in the Pacific during World War II.[24]

The DOD is making efforts to grow certain types of technical experts within its uniformed ranks.[25] While extremely laudable, these reforms are too narrow—both in technical and in military scope—to enable the DOD to incorporate emerging technologies into its operational concepts and programs. There are a variety of organizational strategies that could be used to maintain technical experts in the military in the mid and upper ranks necessary to participate in wargaming, planning, and programming. One strategy would be to have billets for which the competition would be only among uniformed technical experts, like the way promotions for chaplains or lawyers are handled in the services.

Promotion to 0-5 generally occurs at roughly the 20-year point in a military career. These career paths also would give this technical expertise a permanence and a credibility in the military services that the inevitably short tenure of top officials cannot sustain; they should be designed to ensure that these technology officers, through their first 20 years in the military, are having regular assignments designed to keep their technical skills up to date. Examples of these assignments could include opportunities to pursue graduate degrees in technical areas or to work in private companies or academic research labs. Examples of this type of proposal have been advocated by both the political science literature and blue-ribbon commission reports.[26] More limited but similar reforms were advocated by former secretary of defense Ashton Carter in the context of his Force of the Future proposals.[27]

This change should be the Goldwater-Nichols reform of the current strategic era, facilitating technical savvy the way the previous reform created and strengthened a joint perspective.[28] Passed in 1986, the Goldwater-Nichols Act increased the power of joint institutions and the joint perspective as opposed to that of the services. Goldwater-Nichols established the chairman of the Joint Chiefs of Staff as the principal military adviser to the president and the secretary of defense; it vastly strengthened the role of the geographic combatant commanders in the planning and execution of military operations; and perhaps most significantly, it required that before promotion to flag rank (general in the Air

Force or Army or admiral in the Navy) an officer need have completed a joint duty assignment, which generally meant serving on the Joint Staff or on the staff of a combatant commander. This change in requirements for promotion has had a significant impact on the perspective of senior military officers and demonstrates the broad effect that career paths can have in an organization that is characterized by grooming its leadership exclusively from within.

A very wise addition would be the restoration of a reserve unit devoted to military members who leave active service and go to work in the technology sector.[29] There also would need to be reforms to the service S&T infrastructure devoted to technologies that are being paced by advances in the global commercial and academic sectors. Some technologies are still guided principally by advances in the DOD technical world. But for those technologies driven by external advances, efforts are needed on five points: (1) shaping the career paths of civilian S&T staff to ensure they have regular assignments outside of the DOD to update their technical skills; (2) relying on the National Labs to help perform the translational role between excellence in the academic and commercial sector and application to national purpose; (3) providing greater hiring opportunities for short-term civilian S&T staff, including managers, on a basis perhaps analogous to DARPA's limited-term program; (4) facilitating the use of Other Transaction Authorities and other rapid investment tools; and (5) reducing the amount of research that is classified.

The DOD needs to think hard about the benefits of secrecy versus its costs. There are many benefits, of course, to secrecy for a military organization. Operational plans and some specific characteristics of weapons systems need to be classified. Critical supply chains need to be secure. But some of the DOD's demands for secrecy—and the resulting impact on its ability to remain up to date in certain technologies—lead it to lag, particularly in technologies rapidly advancing in a globalized commercial and academic sector. This is the case in the technologies of particular interest to this report: DNA sequencing, CRISPR-Cas, and machine learning to inform genotype-trait analysis. In these technologies, the DOD should shift toward an overall strategy of rapid adaptability and away from one solely of secrecy. Staying up to date in these technologies and being able to rapidly configure countermeasures to new war-fighting attacks are essential. Sacrificing up-to-date technical knowledge to preserve secret defenses against outdated threats will prove a losing strategy in this technological era.

Heritable Human Genome Editing

U.S. policy on heritable human genome editing (HHGE) seems strangely unresolved, almost as if the country had decided it was better to ignore the issue because it was so disquieting. Human genomes can be edited, and the resulting embryos can be implanted in their mothers and then allowed to grow to term. These edits could cause technical mistakes with unknown long-term implications for the child, or they could alter the genetic potential of the child in service of some goal or another—including the self-glorifying, the trivial, and perhaps even the sinister.

Allowing U.S. policy to continue to be unresolved does not make this disquieting situation go away; unsurprisingly, it is probably making the situation worse. Most worrying of all is that research that would be considered "legitimate" under proposed scientific norms is not permitted in the main research venues in the United States. This is because Congress prohibits the National Institutes of Health (NIH) from funding such research or the Food and Drug Administration (FDA) from considering clinical trials to license such technologies.[30] This is done through annual "appropriations

riders" to the bills providing the funding to these government agencies. Privately funded research is permitted, but its extent is hard to measure.

Despite these prohibitions on public funding at home, the U.S. government is not working to develop norms in the international context. Hobbling progress at home while not even opening discussions about norms abroad seems a poor balance. Two gene-edited babies were born in China in 2018.[31] While these births were met with the broad-based opprobrium of the international life science community—including in China—there has not been a focused effort outside the technical community to develop international norms.

That said, elite scientific groups have articulated some suggestions, and the World Health Organization has tried to develop a process for establishing them. One recent effort in the technical community to identify appropriate norms calls for a better understanding of potential unintended effects of CRISPR technology before undertaking human gene editing and a strong restriction on using it for anything but severe, otherwise untreatable medical conditions.[32]

These norms seem a reasonable place to start, but their broad adoption needs diplomacy as a national priority, led by the U.S. Department of State. Calls for international norms need to avoid naivety: cheating is probably inevitable. The technology has such low entry costs and is, at the basic level, so widely available that it cannot be controlled through technology or export controls. As using genome-editing technology does not appear to provide any external markers, an inspection regime would not be useful, unlike the valuable if imperfect inspections conducted by the International Atomic Energy Agency (IAEA) under the provisions of the Nuclear Non-Proliferation Treaty (NPT).[33]

Many of the objectives that are posited for HHGE in the military context—extending endurance, improving eyesight, increasing strength—are probably better advanced in the near and medium term through other technical strategies. For enhanced strength, one should remember that this is an era where robotic exoskeletons seem not only plausible but inevitable. For enhanced vision, one can consider augmented reality headsets. These strategies seem very promising and are likely to be successful on a vastly shorter timeline than HHGE.

On balance, this paper argues that seeking international norms would reduce the overall incidence of HHGE, an outcome that would be beneficial particularly in the near and medium term as the implications of HHGE become better understood and the methods to avoid technical mistakes become clearer. International technical elites could shape behavior through the awarding or withholding of valued opportunities like funding for research, publication in elite journals, or fellowships and post-doctoral appointments.[34] Norms can help limit the incidence of bad behavior and thus enable the focusing of limited intelligence, police, and diplomatic powers on those incidents of bad behavior that do emerge. Raising the professional and diplomatic costs of illegitimate HHGE through international norm construction seems worthwhile on balance.

The risks of participating in such norms become greatest, however, if policymakers forget how easy it is to cheat and how inevitable it is that some actor will eventually do so. The surest defense resides in a deep reservoir of U.S. commercial and academic technical excellence focused on legitimate uses of the technology, with secure supply chains of commercial and academic biofoundries, the technical staff to run them effectively, and strong and sustained DOD uniformed and civilian connections with that healthy domestic sector.

Databases

The United States lacks the large databases that are essential for training machine learning algorithms in many fields, including life science research and public health.[35] This problem needs solving if the United States is to benefit from artificial intelligence (AI).

The U.S. government should create an environment that facilitates the creation of databases, recognizing their greater strategic importance given the recent advances in machine learning. It should not, as a rule, take to itself the responsibility to create particular databases. Instead, it should change laws and create incentives to make important data accessible for use in databases while still protecting the data from inappropriate use.

The two types of data of particular importance in the present case are protected health information and proprietary information owned by pharmaceutical companies. There should be technical methods to make patient data more widely available for machine learning while preserving patient privacy and enabling informed consent for research. Similarly, some set of economic incentives for database access should be created to entice the sharing of pharmaceutical data for machine learning purposes.

Since the U.S. government is not going to be creating or curating databases, in general, it needs to create a new set of public-private organizational models. These are necessary because databases intended for public purposes—particularly those containing sensitive information, like patient data—need to be managed by a nonprofit organization, perhaps a national laboratory or a consortium of research universities, to assure proper protections and uses for the data. That said, they also need to have a significant private sector component, largely because the expertise to curate data largely resides in the private sector. Data is collected with all sorts of different definitions; for large databases, the process of resorting this data into common definitions is extremely complicated.

Finally, the government should create a high-ranking data advocate. As researchers identify new questions, they should have a place to appeal for access to new data sets. Being placed at a high level in the executive branch, this advocate could effectively cut through bad reasons to restrict the data from being available for research purposes. There are of course good reasons for controlling data, but this new officer would be able to give a request a proper hearing and evaluate the issue in the context of the greater strategic importance of constituting new databases.[36]

The government should create a high-ranking data advocate. As researchers identify new questions, they should have a place to appeal for access to new data sets. Being placed at a high level in the executive branch, this advocate could effectively cut through bad reasons to restrict the data from being available for research purposes.

Handling private health data in the United States is governed by the Health Insurance Portability and Accountability Act (HIPAA). HIPAA's value of protected health information should be preserved, but the allowed methods to do so should be updated to accommodate the data being stored and handled by these private-public partnerships and used for research and precision medicine.

Useful Molecules

The government should speed the development of genetically modified molecules that advance public purposes through organizing and funding one or several Grand Challenges. Grand Challenges incentivize teams to integrate cutting-edge science and technology to solve a specific ambitious but achievable national goal. A Grand Challenge should incentivize the design and production of a useful genetically modified molecule. These molecules are useful because of the valuable roles they can play, including parsimoniously storing data, extracting valuable raw materials, or making products in a way that is more sustainable.

In addition to the creation of the molecule, the competition should be designed to generate several further benefits: (1) the training database used in the competition will itself be useful; (2) the process lessons learned from the competition can inform both the package of organizational, legal, and regulatory reforms needed to create an environment that makes it easier for databases to be created and used for public purposes (as discussed earlier) and an evaluation of the efficacy of the current framework for evaluating the safety of genetically modified molecules and the identification of any needed changes; (3) the competition will advance the goal of creating and sustaining a domestic biofoundry sector; (4) funding will catalyze apprenticeship programs and scholarships to train technical staff at all levels for the biofoundries that support the competition; and (5) identification of U.S. government preferences on biofoundry standardization will inform government participation in international negotiations and standard-setting agencies.

The DARPA Grand Challenges for autonomous vehicles in 2005 and 2007 could be used as a model.[37] The 2005 test took place in a deserted terrain where the vehicles had to navigate to a particular point on a desert road. Two years later, the test was comprised of the more difficult challenge of navigating in a simple urban landscape where the cars had to monitor the movement of other cars and make various decisions, including when they could turn left safely at stop signs. These challenges are credited with spurring significant advances in the development of autonomous vehicles.

Conclusion

These recommendations strive to ensure the health of the domestic sector in the biotechnologies and machine learning. Efforts to build and preserve domestic infrastructure need to be balanced with the recognition of how critically important it is for the United States to remain engaged with the international science community and the global commercial and academic sectors in developing these technologies.

It also is critical that the DOD improve its ability to benefit from any advances in international science and the domestic infrastructure. If it fails to gain from the advances of technical communities outside the Pentagon, the DOD will continue to lag in these key technology areas—likely dooming its efforts to construct a credible deterrent. The lack of a credible deterrent means that war becomes more likely.

The challenge facing the DOD today is not only China's rising power, but the U.S. government's difficulty in crafting and implementing needed policies, including those to shore up its capability in the complex technology areas of bioengineering and machine learning.

DNA, coiled in its double helix, shows promise and portent. So too do societies, where their promise of advancing the common interest is so often paired with the worrisome portent of being consumed by arguments over whether that interest is worth preserving—or, indeed, whether it ever existed at all. History sometimes asks whether the ability to shape policy in the national interest has drifted away from a nation-state. As time passes, history invariably gets its answer.

2

Tradition, Technology, and War

Few successful professionals must celebrate tradition as fervently, and yet incorporate technical change as urgently, as a combat military officer. Longbows and the defeat of the French at Agincourt in 1415 and super cannons and the defeat of Constantinople in 1453 are still studied by military officers.[38] These historical episodes underscore the disquieting lesson that failing to recognize and properly incorporate technical change leads to defeat on the battlefield. In peacetime, there is a lot of theorizing about which technologies should be incorporated and how. In wartime, however, there is generally less theorizing and more regret.

This report urges structural reforms in the U.S. DOD to strengthen its ability to incorporate cutting-edge technologies into its operational concepts, programs, and budgets. The principal recommendation is to create career paths for uniformed practitioners of new technologies. This reform would speed the ability of the military to evaluate and incorporate emerging technologies by bringing more technical experts into its traditional structure, leading to a blended understanding of war-fighting problems and technical possibilities.

These reforms are needed now because of the faster and more transformative rate of advance in defense-relevant technologies generated by a global commercial and academic sector. The DOD's S&T ecosystem was built in a different era and sometimes is remarkably robust against incorporating technologies that emerge outside of its large, contractor-based ecosystem. The rate of change and its transformative nature mean that there are fewer officers at the rank to shape planning about the future nature of war who understand these technologies and their possibilities. This problem remains despite many worthy pilot projects, limited reforms, and talented individuals within the DOD.

The reforms proposed in this paper also assume that there will be advocates for incorporating cutting-edge technologies among top civilian and military officials and excellence among civilian S&T staff. The efforts of these civilians should be enabled by embedding technical experts in the military. Similarly, uniformed military experts can help civilian technical experts better understand the military problems that need solving.

There are two particular efforts that these technical officers could advance: developing new operational concepts incorporating cutting-edge technologies and supporting the work of the department by weaving new technologies into ongoing programs and budgets. The first effort changes parameters, while the second optimizes the work of the department within its existing parameters.

Operational Concepts

As at Agincourt and Constantinople, victory is secured not merely by using a new technology but by developing an operational concept that puts it to a war-winning use. Any student of war has been cautioned that having the best technology is not enough. The winning military generally had a better theory about the nature of the war they were fighting, having more accurately incorporated technological and strategic calculations. Figuring out that new theory is generally difficult and greatly contested.

Consider the use of tanks in the 1920s and 1930s in Europe, and then in 2022 in Ukraine. The tank-based blitzkrieg is a particularly famous example of an operational concept, as it was the British, not the Germans, who first developed the tank and an early version of effective tank tactics. But by the outset of World War II, the British had abandoned the tactical aspect of their innovation. Instead, they used tanks in a combined format with the much slower infantry (walking or marching soldiers) and artillery (large-caliber weapons like cannons operated by crews and often pulled by tractors).[39]

The French did a little bit of everything and hence nothing particularly well. They were defeated in part by the simple device of the German tanks driving around the putatively impregnable French Maginot Line, even as the French had more and better tanks than the Germans at the time of their defeat in 1940. The French thought that mobility on the battlefield would be more like the trench warfare that characterized World War I and hence put faith in the stationary defense offered by the Maginot Line. When developing doctrine for their maneuver forces, they emphasized tight central control and the integration of tanks with other, slower force elements such as infantry.[40]

By the end of 1940, it seemed clear that a tank should be used as part of an offensive mechanized force moving swiftly to surprise, pierce, and overwhelm enemy defensive lines. This seemed clear because that was how the Germans—with their blitzkrieg operational concept for tanks—swiftly won many victories in Belgium, the Netherlands, and France in 1939 and 1940.

When Russia invaded Ukraine in 2022, technology had again transformed the battlefield. Although the Russian army may have planned a blitzkrieg, it certainly failed to execute it. There are multiple factors that caused this outcome in the early weeks of the war, but principal among them were technical advances: commercial satellite imagery, available over the internet, that made the tanks' precise location obvious to their adversary; and javelins and other shoulder-fired anti-tank missiles, which made the vehicles easy targets for a small group of Ukrainian foot soldiers to destroy once they were in range.[41] Tanks, which in 1939 and 1940 had been an instrument of unstoppable offensive attack, were rendered into large vulnerable targets in the early weeks of the war in Ukraine in 2022.

These ideas about how a war should be fought are called operational concepts. Identifying and developing a new operational concept requires a strange alchemy. The process generally includes iconoclastic military leaders who are troubled by the challenges of the next war and have been exposed to new technologies. Generally, top supporters in Congress, the DOD, or the military services provide a protected bureaucratic enclave so the iconoclasts can develop, test, refine, and demonstrate their new concept. An intellectual environment requiring evidence-based evaluation and comparison of competing ideas is often also present.[42]

Uniformed practitioners of a new technology could help provide exposure to it by serving as a member of the iconoclast's immediate staff or as a colleague in a unit devoted to thinking about the future of war, like a staff devoted to conducting wargames. The technical officers also could ensure the rigorous testing of the new idea and its competition against other candidate ideas. Accurate testing of candidate operational concepts is often a critical component of them being accepted by the larger military organization.

Explicit imposition of the "right" operational concept during peacetime from outside this military competition could short-circuit the process of refinement and competition. If the civilian leadership specify the "right" answer, it could transform the process from an evidence-based competition to a performative celebration of the high-ranking civilian's idea. These performative celebrations occur when all the military services adopt at least the trappings of the defense secretary's avowed preference so as to secure more money out of the budget allocation process.

In peacetime, top civilians might do best to help favored ideas by building higher walls around the bureaucratic enclave protecting the idea's military supporters, enabling them to develop evidence for their new operational concept before it must compete against other candidate operational concepts.[43]

In wartime, on the other hand, the need to create this intellectual environment is removed because the outcome of battles provides feedback about which ideas are the best. If the military is failing to adapt, despite sustained losses in battle, the civilian leadership needs to intervene. This may be an example of what Secretary of Defense Robert Gates confronted as the casualty numbers from improvised explosive devices (IEDs) in Iraq and Afghanistan continued to go up and the military continued to fail to respond.[44]

Therefore, the first way that uniformed technical experts could contribute would be through helping develop new operational concepts. The process of identifying a new war-winning operational concept does not seem to have a precise recipe but invariably includes sustained interaction among individuals with knowledge of new technologies and of war-fighting problems, as well as a notable dash of iconoclasm. These new operational concepts often change the parameters of the department's business and can lead to victory in war.

Program and Budget Processes

The second way that technical military officers could contribute would be quite different: through participating in the formal processes that the DOD conducts to optimize the department's efforts around existing parameters.

The DOD has formal processes for proposing, evaluating, and approving the draft annual budget that, upon the president's approval, is submitted to Congress.[45] It also has separate but related processes

to identify needs (called "requirements" in DOD vernacular), particularly needs to be filled by new equipment.[46] The term "program" usually refers to a multi-year plan to develop, procure, and deploy equipment to meet a requirement.

These DOD processes are extraordinarily complicated, cumbersome, and acronym-laden, and they certainly have their own share of flaws, including misaligned incentives. Regardless, they do provide centralization of decisionmaking power with a structured way to consider and adjudicate alternatives.

The program and budget processes are adversarial in the sense that proposals are made by one office and then critically evaluated by other offices, who sometimes will offer a specific alternative. The revised program or budget proposal moves up the bureaucracy through increasingly senior evaluative councils. Eventually, the proposal and its alternatives reach the most senior level, and a decision is finally made. Final decisionmakers are generally the deputy secretary of defense or the vice chairman of the Joint Chiefs of Staff.

Staff from many different organizations in the Pentagon actively participate in this process, including the Office of the Secretary of Defense, the Joint Staff, the combatant commanders, and the military services. The geographic combatant commanders are four-star generals or admirals in charge of planning for and, if necessary, executing military operations in a particular geographic theater. Their planning uses the forces and equipment "as is" which generally gives them a practical, relatively near-term focus.

The new under secretary of defense for research and engineering (USD(R&E)) would have leading responsibility to ensure that the proposals sufficiently incorporate the looming implications of emerging technologies.[47] It may be a surprise to most outsiders of the DOD that the new under secretary does not control most of the people or money concerned with research or engineering. The military services, in general, hire the people and spend the money themselves.[48]

The under secretary has a great deal of power, but that power lies largely in the ability to define a compelling vision, to use the funds they do control to advance and demonstrate the correctness of this vision, and then to use some mix of persuasion with the services and direction from the secretary of defense to get the service activity largely aligned with that vision. The under secretary needs to persuade, lead, and occasionally demonstrate tough tactical skills in a bureaucratic fight.

The USD(R&E) recently created the first post of assistant director for biotechnology. Although this new position is a positive step forward, the individual assigned to it will similarly not control much of the money or hire many of the people involved in research.

Uniformed Technical Experts

Technically trained military officers could make valuable contributions as members of the staff who draft and review materials in support of program and budget processes. For example, many of the military officers who set the requirements for the biodefense program have not had biology since high school. The officers are generally curious, intelligent, and deeply responsible individuals, but the unhappy reality for anyone who has been out of high school for 20 years is that biology has changed a great deal in the intervening time. It generally takes civilian technical advisers several years to build up personal credibility, explain some of the remarkable advances in biology, and build support for

innovative changes in long-standing DOD programs with these officers. Usually, some progress is made eventually. But within a few years, consistent with military norms for the length of assignments, the officers are reassigned. The newly assigned officers arrive and are generally curious, intelligent, and deeply responsible . . . but haven't had biology since high school.

Increasing the technical expertise of internal DOD staff might enable an expert with a requirement in one office to identify new strategies to meet it, with "useful" genetically engineered molecules being a good candidate for meeting many requirements. Some useful molecules can, for example, sense effluents from landmines and fluoresce when they do so, drawing attention to the location of the landmine.[49] The DOD has lots of different substances it would like to sense: Could this technology be adapted to things like the effluents of biological weapons programs? Fissile material enrichment programs? Precursors for improvised explosive devices? Currently, the DOD has weak processes for identifying biological solutions for non-biological problems, a severe weakness in a time of change such as this.

The DOD should thus create career paths for uniformed practitioners of new technologies. The Army has started to do this with cyber officers. This report recommends creating a technical corps within each of the services, with a small number of service and joint billets at the flag officer rank. The creation of these service tech corps would be a transformative step on the level of magnitude of the Goldwater-Nichols reforms which transformed the officer corps. Much as those reforms gave rise to the incentives that strengthened joint forces, these proposed reforms would create the technically able cadre of military officers so necessary for this strategic era.

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Career paths would keep more technologists in the military, encouraging them to rise to ranks 0-5 and above (about the 20-year mark, as described earlier). This is roughly the rank where officers move beyond managing service technical programs and start participating in planning and war games, both of which are focused on the nature of future military capabilities. Although creating service tech corps is not the only way to achieve this strategic objective, this report favors it for four reasons.

First, it creates the kind of culture and community of shared expertise that is so characteristic of the military, the informal channels of information and allies that are a key part of getting things done. These informal channels would be within the technical corps, so that an artificial intelligence expert would probably have been in a service school or a previous assignment with a biotechnology expert and could reach out to get informal advice about how to proceed on a biology issue, for instance. There

would also be channels of communication within the service, so that warfighters (infantry officers, helicopter pilots, etc.) would get to know technical corps officers and would feel comfortable reaching out and trying out ideas. While it relies on formal processes to frame, adjudicate, and implement decisions, the DOD—like any large bureaucracy—relies on personal relationships to share information, build alliances, and conduct informal but invaluable vetting of ideas.

Second, creating service tech corps would create a deep reservoir of technical expertise that would help the DOD, both those individuals who leave at more junior ranks and those who stay to become flag officers. The individuals who choose to leave as captains or majors probably would have received their undergraduate and graduate training at government expense; increasing STEM experts is good in general, and each of these graduates would leave with a better understanding of the military and its needs and culture. The department should create reserve units that retain as many of these individuals as possible in positions to assist the department with special projects over time. These veterans also would be more effective interlocutors in their civilian jobs than individuals who had never served in the military.

The number of lieutenant colonels that the department would need to retain would be a small proportion of the lieutenants it would need to attract. Small numbers of individuals would presumably choose to stay for an entire career, for the same reason as many other talented officers: that it is fascinating to work as part of a talented team to solve complicated, important problems with a rapidly growing personal scope of substantive and management responsibilities. The DOD has retained many officers who could command high salaries in the private sector. The military services have long experience with incentive programs to keep the sub-populations that they want, as the lengthy histories of special pay and early promotion attest.

The third advantage of a military technical corps is that it could provide tangible support to the chairman and the combatant commanders, at least some of whom do want to incorporate cutting-edge technologies but lack the personal knowledge and staff support to sort through the many complicated details needed to put together an executable plan. At the four-star rank, officers generally identify priorities and empower subordinates to pursue those priorities. In the current situation, many four-stars are identifying innovation as a priority but do not have the staff with the needed technical expertise. It could make sense to have a small number of joint billets for one- and two-star technical officers. For example, there might be a single two-star technical officer who serves as the science adviser to the chairman of the Joint Chiefs and associated one-star flag officers who serve as science advisers to the heads of the military services and to each combatant commander.

Whatever their technical weaknesses, these four-stars are more than equal to the task of identifying new priorities, directing subordinates to develop detailed plans actualizing those priorities, and rigorously evaluating those plans before endorsing them or directing that some revisions be made. The use of reserve status and other special authorities could jumpstart the creation of a senior cadre of uniformed technical officers even as the slower process of growing them from 0-1s proceeds over time.

Fourth, there are ways to structure the joint S&T billets and the requirements to meet S&T status that would increase service interest in cultivating and taking ownership of their own technical corps. For example, the civilian leadership could specify the number of S&T officer billets in each service and the requirements for having S&T designation. The service leadership could determine the mix of different technical disciplines within the cap set by the civilian leadership. Service chiefs may take little interest

in biology, but they invariably take an interest in the allocation of officer billets. Allocating the officer billets within the service tech corps between academic disciplines would prompt consideration of where the service's future lies, and which innovations may prove most important for that future. Those discussions, as well as the resulting decisions, should themselves be helpful to the broader goal of promoting service thinking about incorporating technical advances.

Top civilian officials—perhaps the under secretaries of personnel and readiness, or of research and engineering—should set the requirements for having an S&T designation. The years between 0-1 and 0-5 ranks should consist of a mix of receiving graduate degrees from civilian universities; working in service staff positions on programs, budgets, and wargames; and working in academic, commercial, service, or national labs.

This recommendation has focused exclusively on an officer technical corps. Any observer of the U.S. military is deeply aware of how much its effectiveness depends on enlisted personnel. Supporting reforms in enlisted personnel would be needed as well, but this report defers to the judgment of the military services to identify them.

Conclusion

This report urges the creation of career paths for uniformed practitioners of new technologies. This is not to say that this reform alone would enable the DOD to properly incorporate emerging technologies into operational concepts, programs, and budgets; the support of top civilian and military leaders would continue to be essential. Indeed, the efforts of those top leaders would be strengthened by the presence of uniformed technical experts.

The pace and extent of technical change has been so great, and it has occurred in commercial and academic sectors so far removed from the DOD, that uniformed practitioners are particularly necessary to incorporate its implications now during peacetime. Such officers could increase the probability that the somewhat amorphous process of developing a new operational concept could occur successfully, and they could certainly facilitate the incorporation of these technologies in the programs and budgets of the department.

A military combat officer in peacetime has the oddest of jobs. They study Clausewitz and Sun Tzu, for each has enduring wisdom about the interplay of tactics and strategy. Then they must consider fluorescent biosensors and unrealized genomic potential. And of course, their principal business is commanding troops who drive tanks or fire artillery, with all the tactical complexities those tasks involve. Uniformed technical officers, particularly in an era of rapid, transformative, and private sector-driven technical change, are needed. It is too far from Clausewitz to fluorescent biosensors for the combat officer to travel entirely alone.

3

Editing the Human Genome

Evolution has wandered its way through the eons, balancing between the constancy of heredity and the variation of mutation and evolution. The convergence of three technologies—DNA sequencing, CRISPR, and machine learning—now makes the purposeful manipulation of genomes possible, including the human genome. Such editing holds the prospect of speeding evolution and substituting human choice for the forces of constancy and variation that have thus far shaped the human species. [50]

Only the creation of nuclear weapons seems to have frightened its inventors as much as the creation of the tools to enable purposeful manipulation of the heritable portions of the human genome.[51] But then, as now, it is not clear how to uninvent the technology; the only realistic option seems to be to create a policy context to manage and shape its use, to seek cooperation to facilitate legitimate uses, and to build deterrent and defensive capabilities against illegitimate uses.

Only the creation of nuclear weapons seems to have frightened its inventors as much as the creation of the tools to enable purposeful manipulation of the heritable portions of the human genome.

The decision to edit the genome in a human embryo, implant the embryo in a mother, and then allow the embryo to grow to term could spring from different motives. Compassion might guide efforts to cure debilitating genetic diseases that have no other treatment and have caused great pain and tragedy in preceding generations. A certain carelessness would be required to proceed now, though, before further research reduces the risk of technical mistakes and resolves questions about unintended off-target effects of the new CRISPR technology. The humanitarian costs of such errors—to the resulting babies and their families—could be enormous. Even once this risk of technical errors is reduced or eliminated, one fears other motives, as researchers and prospective parents may be motivated by profit, fame, self-glorification, celebrity by means of trivial fads, or even more sinister motives of unreasonable individual or national advantage.

This paper argues that current U.S. policy does not advance the nation's or humanity's best interest. This is perhaps understandable because making policy in this area is so disquieting and cuts across so many profound values. This paper recommends that legitimate HHGE proceed within the major research venues in the United States and that the United States lead international norm construction efforts to discourage illegitimate HHGE.

An international scientific report from 2020 defines "legitimate" HHGE as that which corrects serious diseases for which there is no other treatment; "illegitimate" HHGE would thus be any other editing, including editing for enhancements.[52] Of course, no editing, however legitimate, should be pursued until there is a better technical understanding of precisely how CRISPR-Cas systems and other related technologies work so as to avoid technical mistakes in procedures that could cause unknown risks for the affected children.

2018 Case in China

A certain carelessness was present in the only known case of HHGE resulting in live births, which occurred in China in 2018. He Jiankui, a researcher in China, edited two human genomes and then implanted the resulting embryos in their mother.[53] The babies were born in 2018 and are known by their pseudonyms of Lulu and Nana.

He Jiankui explained that he sought to edit a particular gene, CCR5, to enhance the babies' resistance to HIV. There are, though, effective and vastly less risky treatments to avoid a baby receiving HIV from the father (as was the risk here).

In addition to their questionable necessity, the edits appear to have been marred by technical errors. Among other things, the insertions and deletions appear to make the twins more vulnerable to influenza, and their effectiveness against the babies' vulnerability to HIV is uncertain.[54]

Amid his work in the lab, He Jiankui evidently consulted a high-end Manhattan fertility doctor about opening a fertility clinic in a lightly regulated tropical locale to perform such embryo genetic manipulation as medical tourism. He would manipulate embryos and implant them in their mothers. Then, the mothers would return home, having renovated their embryo to match their aspirations.[55]

The work of the Chinese researcher was greeted with widespread opprobrium from the life science community. The researcher was convicted of violating Chinese regulations and sentenced to three years in prison and a lifelong ban from working in reproductive health.[56]

Proposed Norms

International groups of technical experts have sought to outline appropriate norms to shape the use of this technology. A 2020 study by scientific advisory groups in the United States and the United Kingdom suggested a set of norms to guide the use of HHGE:

- The research community should not conduct HHGE until it has a significantly better understanding of unintended effects of the use of CRISPR;
- Such editing should only be used to treat severe, otherwise untreatable conditions;
- HHGE should never be used for "enhancements"; and
- HHGE use should only proceed in the context of robust ethical and public deliberations.[57]

There is much of merit in these proposed norms. Meanwhile, the United States has a strange patchwork policy. Indeed, it is possible that the current, implicit U.S. stance on HHGE is the worst possible policy, as it prevents advances in what would be considered legitimate research under the 2020 proposed norms, fails to pursue international efforts to increase the political and scientific costs of conducting illegitimate research, and denudes expertise in the United States thus leaving it less likely to be able to detect or defend against the illegitimate uses of this technology by adversaries.

There are several important distinctions to make when thinking about these issues. The first is between genome editing that is not heritable as opposed to editing that is heritable. Within heritable genome editing, there are discussions about what might be considered "legitimate" as opposed to "illegitimate."

Heritable and Non-heritable

The core issue of whether an edit is heritable or non-heritable is whether the edit is reflected in the DNA contained within egg, sperm, or embryo cells that are passed onto descendants. HHGE often occurs when the embryo is a single-cell entity. As it differentiates, the edits appear in all cells, including those that ultimately are differentiated into sperm or egg cells.

Non-heritable editing would be done to a child or adult where the cells have already differentiated into different functions, such as a liver cell or a heart cell. Edits to the genes of those differentiated cells would not be passed onto descendants.[58]

Non-heritable edits, also known as edits to somatic cells, hold tremendous promise to cure human disease and are generally called "gene therapy." There appears to be broad agreement that manipulating the somatic cells of an adult or child to cure disease in them is appropriate, if it proceeds consistent with the rigorous standards for medical research and treatment of humans.

This is an area of active investment and drug development for research and biotech start-ups.[59] Several promising gene therapies are in clinical trials and three have successfully emerged from such trials.[60] For cancers caused by a genetic mutation, using that genetic anomaly to target cells—either to limit growth of the cancerous cells or to create a proliferative advantage for the normal cells—should provide an effective treatment for an individual's disease.

Advances in these areas hold great promise for medical treatment, benefiting those sick with these diseases and their loved ones. These treatments also are expected to be a significant source of profit

and a reinforcing cycle of innovation for the global pharmaceutical companies that are first to market with them.

Legitimate Heritable Genome Editing

Many of the scientific studies on heritable genome editing make a distinction between "legitimate" and "illegitimate" editing. There is no broad societal agreement on what constitutes "legitimate" editing. These debates have principally been confined to technical committees, but they should properly reside in a broader discussion in society.

A 2017 study done by the U.S. National Academy of Sciences argued that once certain technical issues surrounding off-target effects had been resolved, HHGE would be legitimate in a small number of cases of serious, otherwise untreatable diseases. The report offered the example of two parents, both with cystic fibrosis (CF), who wanted to have children genetically related to them.[61] CF meets the two criteria: it is serious, causing severe damage to the lungs, digestive system, and other organs in the body; and it is not treatable under current technologies. Most people with CF live only into their thirties or forties.

The 2020 scientific study that outlined the proposed norms above similarly recommended that edits to prevent serious, otherwise untreatable diseases would be "legitimate." There are other genetic diseases that are serious and that are not treatable with current technologies, and both studies urge that these types of edits would be legitimate once the off-target effects of CRISPR-Cas systems were better understood and could be avoided. However, "enhancements" of any sort—the editing of a genome to make an individual more intelligent, attractive, or athletic—would be "illegitimate" under the proposed 2020 norms.

The 2017 study included a more nuanced discussion, noting that there is a category of genetic changes that fall between curing a serious illness and enhancements. These could be editing the genome to reduce the vulnerability to serious diseases like Alzheimer's or the tendency to process cholesterol poorly which leads to heart disease. The 2017 study speculated that these types of edits could be ethical under a robust set of constraints and after significant public debate and consensus-building.

Observables and Detection

This study has argued that norm construction should proceed but warned that cheating by other nation-states on the norms would be virtually inevitable. This section provides one example of why inspections or other technical measures could not assure any norms are uniformly observed abroad. Recall, too, that if the United States for its own reasons decided to forego the use of this technology, it is not plausible that other countries would similarly forego its use.

For cases where only one parent carries a genetic disease like CF, many couples use prescreening to identify embryos that do not have the genetic error. This procedure is called "pre-implantation" screening. Only embryos without the genetic disease would be selected for implantation. The couple would then use in vitro fertilization to implant that embryo in the mother, who then carries it to term. In vitro fertilizations have become increasingly common as a technique to overcome many

different types of fertility problems. In the procedure, the egg and sperm of the biological parents are combined in a petri dish and then the fertilized egg is implanted in the mother.

For those contemplating methods to prevent cheating on any agreed norms, one confronts the conundrum that it is extremely difficult to distinguish between HHGE and closely related procedures like pre-implantation screening of embryos. In vitro fertilization is a standard part of fertility treatment. Editing human embryos and keeping them until day 14 but not implanting them is permitted research in labs in the United States, Europe, and China.[62] Assuring that these techniques are not improperly combined, as He Jiankui did in his lab in 2018, seems impossible.

Some biologists have urged the adoption of a moratorium on germline editing for at least five years. This would enable progress on understanding the off-target effects of CRISPR and perhaps enable the growth of international institutions to build norms.[63]

Genetic Potential

Genome editing of an embryo could alter its genetic potential, raising profound questions about what changes parents (or governments) might seek.

Non-heritable genetic editing in children and adults could not affect genetic potential in the same way, as such non-heritable editing is done after the various cells have already differentiated to serve different functions. However, edits to the genome of an embryo could. As an example, an embryo might have the genetic predisposition to be a short adult. Genome editing could alter the genetic predisposition to instead be a tall adult.

Realizing such genetic potential for complex traits is expected to be the work of several generations of research. This is because of both the complexity of current research in genome regulation, cellular circuitry, and epigenomics and the reality that many of these complex traits arise from the interaction of many, perhaps several thousand, genes. In contrast, these complexities are much less daunting for more simple traits, such as genetically modified molecules creating new materials or diseases caused by a small number of genes.

National Strategy

Appropriations riders from Congress prevent the NIH from funding any research on germline edits in human embryos and bar the FDA from considering any clinical trials using this technology.[64] Private research is not prohibited, but its scope is difficult to discern. Research by other government agencies is not forbidden by this legislation, but it would still be covered by a more general prohibition in the United States against the implantation of an edited human embryo. (There is also a moratorium on implantation in Europe; China likewise reports that such actions are against its regulations, which formed the basis of its conviction and imprisonment of He Jiankui.)[65]

Appropriations riders from Congress prevent the NIH from funding any research on germline edits in human embryos

and bar the FDA from considering any clinical trials using this technology. Private research is not prohibited, but its scope is difficult to discern.

The United States should permit legitimate HHGE research in its main research venues once the remaining technical questions about off-target effects of CRISPR are resolved. It also should lead the development of international norms along the lines of the 2020 study outlined above, raising the diplomatic and professional costs as high as possible for illegitimate human gene editing. These costs will have the greatest impact in the labs where technical mistakes are most likely to occur; decreasing the incidence of HHGE accompanied by technical errors or pursued for trivial reasons would have a great humanitarian benefit.

International adoption of norms against illegitimate HHGE is a worthy goal but should not be perceived to equate with eliminating illegitimate HHGE entirely. National participation in norm construction must recognize that cheating against the norms is inevitable. The technical entry costs to the technology are very low, both in terms of the price of needed equipment and the difficulty of attaining the needed technical knowledge. The use of the technology also does not generate any explicit observables that would be useful for the construction of an inspection or verification regime.

The persistent reality that cheating against these norms could—and probably would—occur reinforces the importance of maintaining a healthy domestic sector in the United States in legitimate HHGE. Any norms should preserve the ability to pursue legitimate HHGE research and to pursue defenses against illegitimate uses by others.

These illegitimate uses by others could be an attempt to secure a military advantage. Even setting aside ethical considerations, such attempts on balance do not seem likely to yield a meaningful military advantage in the near or medium term given current expectations about the pace and nature of technical advances. For the near and medium term, advantage is likely to lie in mechanical extensions of human capability. The U.S. military should energetically pursue such mechanical extensions, such as robotic exoskeletons and augmented reality headsets. There seems too much technical uncertainty, about both epigenetic effects and the interaction of many genes for traits of interest, to confidently create a better super soldier through genetic engineering than through mechanical augmentation in the near and medium term.

As for the long term, mysteries sometimes do reveal themselves. Biology, in several generations, may have fully explicated even its most complicated of creations. On balance, this seems unlikely. But if it does occur, the healthy U.S. domestic sector on legitimate HHGE will be technically able to construct any necessary deterrent or defensive capabilities. And the cooperative norms built in the intervening period may reduce the risk that those defensive capabilities would be needed.

The next section explains for a layperson how CRISPR—the technology that is a critical enabling technology for this revolution—works. CRISPR enables precise edits to be made at a particular spot in a genome. Its fundamental source is an eons-old struggle by bacteria to defend against the predations of viruses.

CRISPR-Cas Systems

CRISPR-Cas is a revolutionary technology because of the vastly greater ease with which it allows the precise editing of DNA. The two researchers who modified this natural mechanism to become a useful laboratory tool, Emmanuelle Charpentier and Jennifer Doudna, were awarded the 2020 Nobel Prize in Chemistry for their work on CRISPR-Cas9.

CRISPR-Cas is more of a discovery than an invention. Bacteria have been using CRISPR genes to fight off viruses for countless millennia. The notion behind CRISPR-Cas has two parts: first, a capability in bacteria to recognize a virus that has previously attacked it or its ancestors, and second, the ability to destroy the virus by cutting up its genetic information before it can reproduce.

Viruses are odd and sturdy things that attack cells, including those of microorganisms, plants, and animals. Viruses cannot reproduce on their own, and instead hijack the cell's machinery, tricking it to reproduce the virus. Often, the cell produces so much virus that it eventually bursts, flooding the surrounding area with the newly produced viruses, each intent on attacking yet more cells.

CRISPR is a part of the bacteria's ability to defend against viruses. After defeating a virus, bacteria incorporate a short, distinctive portion of the virus's genetic material into their own genome—the CRISPR genes. This reference copy of the virus genetic material is retained in every descendent of the bacteria, enabling that line to compare the genetic material of previous virus attackers with the genetic material of a new, unidentified invader. If the genetic code matches, the bacteria have confirmed the invader is a virus and swiftly deploy the cutting function of the Cas system to destroy it.

By continually updating its reference copies of defeated attackers, the bacteria are speeding their ability to recognize an attacker and launch the cutting phase of their defenses. Because repeat encounters with the same virus are common, the reference genes often contain multiple copies of the short distinctive genetic material for a particular type of virus, each separated by a few spacer cells.

One can easily imagine why this portion of bacterial DNA drew the attention of researchers looking at the bacterial genome. The acronym "CRISPR" simply describes what researchers observed, before the function of these genes was even understood: short repeating sequences or "clusters" of 20 or so base pairs of DNA, which were palindromes (reading the same backward or forward, like the words "wow" or "mom"), and which had a small number of spacer cells between each repeating sequence. In other words, "clustered regularly interspaced short palindromic repeats"—CRISPR.

Thus, the term CRISPR describes the portions of the bacteria's genome that contains the reference copies of the virus genetic material. This allows bacteria to identify DNA they come into contact with and determine whether it matches a previous virus attacker, at which point the second part of the capability—"CRISPR associated" enzymes, abbreviated "Cas"—sends nucleases to destroy the virus. The designation "Cas" is then generally followed by a number to indicate which of several Cas nucleases are being used; the earliest identified and most widely used version is CRISPR-Cas9.

Once this function of the CRISPR-Cas system was identified, it was natural that researchers would want to adapt it to human purposes. It soon proved straightforward to substitute the reference copies of virus genetic material for any DNA sequence that researchers wanted to manipulate. CRISPR therefore allows researchers to edit the genome of a target cell by introducing the CRISPR machinery, the info about target location, and the info of the intended new DNA sequence.

The CRISPR-Cas system can cut, exchange, or add to existing DNA, and thus it is being optimized to support purposeful genome manipulation. This chapter is focused on the use of CRISPR to edit the heritable portions of the human genome, but CRISPR capabilities have wide application as they can manipulate the genome of all sorts of cells—from those that consume toxic industrial chemicals and render them inert to those engineered to become biosensors for the effluents of landmines.[66]

Cooperation and Its Challenges

This paper urges that efforts be made to build international norms surrounding HHGE, as this is likely to raise the technical and diplomatic costs of violating them and thus lead to significant humanitarian and health benefits. The norms outlined in the 2020 report seem a good place to start. There exists a continuum of possible organizational models for any agreement on norms.

For one example, a permanent organization could be an international scientific cooperative effort that shares information about HHGE and builds norms to guide its use throughout the world. It would be a clearinghouse of information about off-target effects, and participation in the work of this consortium would develop norms among technical experts. It could be modeled after the IAEA, which was created to implement the trade at the core of the NPT.

In the NPT, technologically advanced states agree to share civilian nuclear technology with less technologically advanced states in exchange for intrusive inspections to ensure that the recipient states are using the technology only for civilian purposes and not diverting it to build a nuclear bomb. The existence of the IAEA has catalyzed the development of a small international community of technical experts. Their shared perspective brings credibility to the findings of the IAEA and contributes to their countries adopting the desired norm. The NPT and the IAEA have been far from fully successful at halting the proliferation of nuclear weapons, but they have slowed such proliferation and increased the political costs of nuclear use.

A new organization created to oversee HHGE could provide technical training to researchers from less advanced states while inculcating them with the agreed norms on the appropriate uses of the technology. It could serve as a central hub for information, assuring that all life science community members benefit from research conducted on these particularly sensitive topics.

Unfortunately, intrusive inspections cannot be effective and probably in this case should not be attempted. There is also the concern that the information sharing intrinsic in an international HHGE technical effort would raise the level of genomic expertise in less technically advanced states, raising the risk over time that they could cheat on the very norms they are vowing to uphold. After all, the provision of technology for civilian nuclear power plants has been harshly criticized by some observers who argue that it sped the acquisition of nuclear weapons technology by these less-developed countries.

The creation of a central agency is not the only way forward for international standard-setting on HHGE. Other models could include the United Nations adopting norms, either in the Security Council or the General Assembly, and then directing each member state to advance the norms in the context of their own national laws and regulations. Technical and civil society organizations could then play a role of monitoring the extent to which nations were implementing the norms. This is the structure used for implementation of United Nations Security Council Resolution 1540, a resolution that calls

on nation-states to strengthen their domestic laws and regulations to complicate efforts by terrorist groups striving to get precursors for chemical, radiological, biological, and nuclear weapons. This structure enables the articulation of the norm by the international community, while relying on the police powers of each nation-state to enforce that goal and on civil society to monitor enforcement efforts. A great weakness of this approach, of course, is that it exerts little leverage against authoritarian governments.

Finally, the third and loosest type of agreement might be an international scientific cooperative effort, perhaps analogous to the Human Genome Project.

There are many legitimate criticisms of all these approaches. The international system defaults to competition, not cooperation. If the risks of cheating by an adversary are managed as described elsewhere in this report, one could responsibly try to entice cooperation, which could minimize technical mistakes and trivial uses of this technology as well as speed the availability of its many benefits to the citizens of more nation-states. But that cooperation is more likely to endure if the vulnerability to competition is recognized and the benefits of cheating are minimized—if not eliminated.

Conclusion

HHGE raises difficult choices. One observer commented that the stewardship of human DNA would be "the ultimate test of knowledge and discernment for our species."[67]

The benefits of cooperation should be carefully considered. Avoiding a nationalist competitive race seems very desirable, but such efforts must recognize and manage the risk of cheating. As urged here, a plausible strategy is to build domestic technical abilities in legitimate HHGE and to pursue a robust research program in detectors and treatments of illegitimate use. It is also important that HHGE not proceed until the technical issues of its potential off-target effects can be further investigated.

The worst outcome would be one where the current moratorium in the United States is not lifted as the off-target effects are resolved. While moving forward cooperatively with other nations could be a good outcome, lagging behind other countries in the application of this technology could be disastrous.

The United States needs to ensure that it retains robust, broad-based technical expertise in the agreed legitimate uses of this technology as well as active research and development in detectors against HHGE. This combination could build deterrence and needed national security capabilities. One close observer of this new technology muses: "Our genome has negotiated a fragile balance between counterpoised forces, pairing strand with opposing strand, mixing past and future, pitting memory against desire."[68] The past unhappily holds the memory of the competition between nation-states and the future holds only a small prospect for cooperation, but one worthy of pursuing. Much as the strands of DNA are counterpoised against each other, so hopes and fears must be counterpoised, striving for an outcome that balances national interests and shared human heritage. Humanity must strive to do well on this "ultimate test."[69]

4

Databases and Their Discontents

In the United States, databases supporting life science research and public health are too small, too fragmented, and too difficult for legitimate researchers to access. Enabling access to needed data would be extraordinarily complicated. Such an effort, though, is essential to ensure that the United States can remain at the forefront of innovation.

Large, well-curated databases are essential to train machine learning algorithms. These algorithms can support extraordinary advances in precision medicine and tailored therapeutics. This chapter makes three recommendations to facilitate the creation of large databases in the United States: change laws, policies, and regulations to make more data available; create new types of public-private partnerships to manage such databases so a nonprofit organization can assure their proper use but can benefit from private sector expertise in data curation; and establish a data ombudsman to facilitate the availability of needed data to researchers. These recommendations would advance a core objective of this report: correcting worrisome trajectories in U.S. machine learning capabilities in medical and life science research.

From a broader, national perspective, these recommendations would constitute only a portion of a proper policy framework. Such a broader framework would both facilitate the creation of databases for worthy purposes such as outlined here and provide some type of privacy and individual rights over the use of personal data by private sector algorithms. Current uses of machine learning in the United States are generally by private companies who harvest data about users from "free" services to power the companies' profitable ad-targeting and related businesses. The lack of U.S. policy has left the country and its citizens confronting many of the ills of machine learning without enjoying its many potential benefits.

Both the European Union and China have policy frameworks in place, albeit both remain a work in progress. The effect of even those nascent policy frameworks is to create usable databases in the life sciences that dwarf those of the United States (particularly in China) and from which the United States increasingly is excluded (particularly in the European Union). Creating well-curated, large databases relevant to important subjects needs to become a strategic priority for the United States. The value of large databases has greatly increased over the last decade and thus many policies need to be updated to reflect their importance.

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Comparative Policy Frameworks

In the United States, there are essentially no laws at the national level to shape the use of artificial intelligence. The public debate in the United States has focused on the many ills of machine learning algorithms by private companies like Facebook to micro-target advertising and entice users into unhealthy information silos; and these ills are worrisome indeed, including concerns about the loss of privacy, the effects on adolescence, and the spread of extremism.[70] The laissez-faire U.S. approach does little to protect individuals from these ill effects of machine learning algorithms. Some states and counties have passed laws for these purposes, with the most notable example being the 2018 enactment of the California Consumer Privacy Act (CCPA).[71]

Other laws prohibit the use of facial recognition software because of the demonstrated difference in its error rates for members of different ethnicities or because when coupled with dense networks of close circuit cameras they enable surveillance.[72] Although the United States government should create a policy framework to manage the harms of machine learning, this important effort is not the subject of the current study. More pertinent is the lack of a policy framework to facilitate the creation of databases for public purposes like precision medicine algorithms that could optimize treatment for patients while preserving their privacy.

While the United States has a largely lax policy regarding artificial intelligence, the European Union and China both are constructing a thorough-going domestic set of rules and norms. In different ways, these structures abroad are making more acute the self-imposed disadvantage in the United States of failing to craft a policy environment that facilitates the creation of databases consistent with national values.

The European Union has put in place a broad framework to govern the use of artificial intelligence called the General Data Protection Regulation (GDPR), which has been supplemented with recent data acts. The GDPR gives EU citizens significant rights.[73] The Digital Services Act and the Digital Markets Act coming into force will add demanding requirements, including for additional algorithm transparency.[74] While the legal framework has been established, the fine-grained details of implementation are still being sorted out. The principal implication of the GDPR for the purposes of this study is that it provides significant limitations on sharing data with non-EU states, unless certain protections for the data are in place in the receiving country. Considering the laissez-faire nature of U.S. policy, demonstrating that these protections will be in place in the United States is extremely difficult, and so the prospect of data sharing is very limited.[75] Given the strong correlation between the size of the training data and the strength of the resulting algorithm, crafting a U.S. legal regime to enable data sharing with the European Union and other countries should be an objective.

China, in an authoritarian mirror image of U.S. policy, is providing its citizens with privacy rights from private companies but incorporating all sorts of personal data into government databases for many purposes, including the dystopian "social credit" system which in some regions is planned to reward behaviors like properly sorting your recycling and punish behaviors like jaywalking.[76] More relevant to this report, the Chinese government is building an enormous genomic and public health database at BGI with limited transparency or availability to foreign researchers. Estimates of the number of genomes the database contains vary widely, but even the most conservative estimates make it vastly larger than Western research data bases. As previously noted, the U.S. intelligence community warns that the Chinese government has subsidized a low-cost, large-scale DNA sequencing capability by Chinese companies and secures many foreign genomes from their companies' work providing services to U.S. and other foreign public health providers. A prenatal test used around the world also is reported to have provided China access to genomes of eight million women.[77]

Machine Learning

The strategic importance of databases grows out of the critical role they play in training machine learning algorithms and the extraordinary insights that machine learning algorithms can bring to previously intractable high-impact problems. Made possible by the extraordinary advances in available computing power of the past 70 years, machine learning can identify patterns, perceive subtle correlations, and make predictions.[78]

In 1965, Gordon Moore, a cofounder of the computer chip maker Intel, predicted that computing power would increase exponentially each year while decreasing in relative cost. The subsequent period has proven his prediction to be true. This extraordinary rise in computational power enabled theories from the 1950s about machine learning to finally be implemented, and the internet facilitated the creation, curation, and sharing of the large data sets needed to train algorithms.[79]

Each entry in a training database has both an input and an output. All things being equal, the more entries in the training database, the stronger the resulting algorithm.[80] An example of a training database could be the genomes of individuals with a particular polygenetic disease (a disease caused by the interaction of many genes) and the genomes of individuals without that polygenetic disease. The "input" would be each individual's genome, and the "output" would be that corresponding individual's status as either having or not having a particular cancer.[81] Each human genome is 3.2 billion base

pairs long, so a hand-by-hand comparison of the inputs with cancer and without cancer would be intractable, even if one hired an army of willing graduate students.

Hence, prior to machine learning, the genetic source of some monogenetic diseases, or diseases caused by a single gene, was identified through idiosyncratic means, such as a visual cue that could be seen through an electron microscope. But systematically identifying the genetic cause of all monogenetic diseases—and of the more complex polygenetic diseases—was unfeasible until the advent of machine learning algorithms.[82]

The type of machine learning described above is called "supervised" learning. It is "supervised" by the labeling of the data into broad categories of possible outputs, in this case "cancer" and "not cancer." Supervised learning is the most common type of machine learning and relies on this type of structured or labeled data.

Large amounts of data can achieve high degrees of accuracy. The necessary size of the training database varies significantly, but trends high: for example, in a supervised learning category where the algorithm was sorting images into three categories—cats, dogs, or elephants—you would need to have 10 million items of each category to match or exceed human-level sorting accuracy.[83]

Artificial intelligence is a large category of techniques to train computers to perform human-like functions of various degrees of sophistication. Machine learning is a subset of that large category and is an approach that relies on learning from databases. While there are additional artificial intelligence techniques being developed in research venues, machine learning is the only artificial intelligence technique widely used in applied contexts outside of the lab today.

National Values and the Value of Databases

Efforts to create well-curated databases will require access to data that is currently unavailable. Access is blocked for different reasons, many of which will require a unique solution. For the public health and life science communities, the strongest examples are protected health information, which has significant legal constraints on sharing, and data owned by pharmaceutical companies, which is intellectual property. Current laws and regulations generally were crafted before the emergence of machine learning and hence fail to value the benefits that could emerge from such algorithms.

PROTECTED HEALTH INFORMATION

Protected health information is a good example of an area that needs to be updated to preserve national values while allowing studies to improve public health. Technical experts report that there are strategies that could preserve patient privacy and informed consent while creating large databases appropriate for research purposes. Some technical strategies, for example, would scramble the data to preserve individual privacy, while still properly training the algorithm.[84] The inflexibility of the current rules on protected health information has stymied efforts to investigate this and other technical options.

The largest official genomic database in the United States is the Million Veteran Program (MVP) at the Department of Veterans Affairs. It has the genome and medical records of 870,000 veterans who agreed to join. It meets high standards of patient privacy and informed consent. The program has many technical strengths, but it is very difficult for researchers to access.[85] The NIH is developing a database

for research purposes, called All of US, that is gathering genomes, medical records, medical samples, and consent for research. That database contains about 350,000 genomes.[86]

The size of these databases seems strange when compared to the 26 million individuals who provided genetic information to one of two private sector companies—Ancestry.com and 23andMe.[87] It is strange to contemplate those 26 million individuals effectively waived their rights to privacy and provided a profit center to private companies in exchange for information about their ancestry, while similar numbers did not support the NIH program which provides full privacy protections, contributes to improved health care, and does not cost anything to participants. The situation raises questions about whether the NIH knows how to market their program or understands the interests of their potential contributors; whether individuals don't care or don't know about the benefits of patient privacy or informed consent for research; or whether individuals are vastly more comfortable giving this type of information to a private company than to the government.

The norm for informed consent is handled by 23andMe in a much more casual fashion than is permitted in NIH-funded research. When samples are initially submitted, consumers are asked if their material can be used for research purposes and 80 percent agree. Their consent for any subsequent research is assumed. 23andMe says it is transparent about the uses to which the genetic information is put and that the individuals have the right to remove their genetic information from research. But this right appears to be hard to exercise.[88] This broad granting of initial consent is very different from the pre-use consent for each research project that is considered the gold standard in medical research. GSK, a large pharmaceutical company, has secured access to genetic information held by 23andMe by purchasing a portion of the company in 2018.

Patient data—including both an individual's genome and their treatment history—is covered by the 1996 Health Information Privacy Protection Act (HIPPA) in the United States. This law seeks to ensure that protected health information is not shared by an individual's physician or hospital without the permission of the patient.[89] Patient histories combined with their genome is the type of data particularly needed for precision medicine and other types of algorithms. Informed right of consent is a norm in human subject research. It states that individuals must understand the nature of the research and agree to it prior to their personal information being used in the context of that research. The genetic data provided to Ancestry.com and 23andMe is not covered by HIPAA because it is shared in a commercial, not a medical, transaction.

While privacy and consent should remain core objectives, there needs to be acceptance of more flexible and creative ways to secure them. The current implementation of these values has made it extraordinarily difficult to use patient data for research purposes; most is stored in pre-certified data channels which are created and managed by the government but accessible only to their health care providers. The HealthIT initiative has extended the use of electronic health records, with 95 percent of hospitals and 88 percent of private practice physicians using them.[90] Its objective largely is to stovepipe the data, consistent with the rights enumerated in the HIPAA law. It has some small pilot studies underway to create the type of databases needed to develop precision medicine algorithms and tailor treatment strategies while preserving privacy and consent, but these are the exception, not the norm.

While privacy and consent should remain core objectives, there needs to be acceptance of more flexible and creative ways to secure them. The current implementation of these values has made it extraordinarily difficult to use patient data for research purposes.

One option that should be considered for a usable genomic database is a nonprofit organization on the model of the UK Biobank. This is one of the most successful sets of genomes and medical data: it holds about 500,000 genomes and extensive medical histories, all of which are made widely available for research.[91] A national lab or a consortium of major research universities in the United States could manage the creation and sustainment of a similar public health database. Such a nonprofit organization could establish responsible technical strategies to maintain privacy and consent. It could oversee the database and evaluate research to be conducted on it, even as there was access for private sector companies so the nonprofit organization could benefit from their expertise curating the data and performing other technical tasks.

Further, U.S. citizens, when having their genomes sequenced for medical or other purposes, should be required to use companies owned by U.S. persons. A ban on sequencing of U.S. genomes by any companies other than those owned by U.S. individuals could increase the probability that these genomes would be handled in a way consistent with best practices on privacy and informed consent, while also contributing to demand for services to sustain the advanced biotechnology sector in the United States and to a database on public health. Surreptitious sequencing of retrieved hair or saliva by foreign intelligence services would of course continue to be possible.

Requiring that the sequencing data be held more carefully and handled by U.S. companies could eliminate a risk to individuals and groups of Americans; help build up the private biotechnology sector in the United States; and align U.S. policy with China and Russia, neither of which permit samples or genomes of their citizens to be shared abroad.[92] While choosing the low-cost sequencing option made sense for each individual company in the United States that sought large-scale DNA sequencing services from Chinese companies, it's much less clear that these choices made sense for the U.S. national interest.

PROPRIETARY DATABASES

One of the challenges to building the database needed for public health and life sciences is that a significant amount of valuable information is owned by pharmaceutical and other private sector companies—for example, the pharmaceutical companies who used to create molecules and screen them against a particular disease to see whether the candidate drug was effective. This hit-and-miss strategy was necessary in the era before the current "design-build-test-learn" phase of biology. This screening data would be valuable for data sets for machine learning about cause and effect between drugs and diseases. Companies currently do not have an incentive to share the data, precisely because it is valuable; perhaps even worse for the functioning of a market economy, they are unsure how to price the data, given that the development of machine learning algorithms is still in an early stage.

Any proposed policy package needs to create incentives for these companies to share this data with the nonprofit organizations building and managing life science databases. Compensation is an obvious candidate strategy, but other approaches could include more creative ideas like patent benefits, or perhaps an exchange of access to proprietary data for access to large databases of protected patient data. Strategies might require some sort of "safe harbor" for intellectual property rights.

These two types of data hopefully illustrate the broader point that the government needs to facilitate the creation of large databases while balancing key values by solving known problems like protected health information and proprietary data. Each type of data is likely to need a slightly different solution to balance the competing needs of access and control.

New Organizational Entities

The second reform to government technology approaches would be the creation of new organizational structures. These structures would need to combine public and private organizations. Private sector participation is needed because that is where the expertise in turning disparate data into integrated, usable databases resides. A nonprofit organization would be required to control overall access to the resulting database, to ensure that necessary controls to protect the data are observed, and to evaluate research requests.

Usable databases require that the data be organized using common definitions or formats. One discovers soon enough though that most extant data was not collected for this purpose and hence does not use the same definitions. Resorting the data into common definitions so it can be useful as part of a larger database is very complicated. A burgeoning private sector marketplace is helping companies manage these difficult data curation challenges by providing data sets, software to curate them, and consultants versed in their complexities. New organizational options need to allow private sector companies to contribute their expertise to curating this bioinformatic data in support of public institution's research mission.

Data Ombudsman

Finally, a high-level advocate for data access should be created in the executive branch. This advocate would have a forward-looking perspective, helping researchers in the future with problems they have acquiring access to needed data. Construction of databases generally is a bottom-up enterprise, based on a particular research interest. Such efforts are often halted by laws, regulations, or norms. Database builders should thus have a place to appeal the restrictions complicating their efforts to gain access to particular data. Creation of such an advocate would acknowledge the growing importance of databases and hence broad data availability. But the power to make data available would not be absolute; there would need to be a balancing of the value of large databases and other national interests. The request for access to the data need not always be granted, but at least there would be a place to make the request.

Other Types of Machine Learning

Supervised machine learning, discussed above, is not the only relevant subtype of this technology. This chapter concludes by providing some additional background on other types: unsupervised and reinforcement learning. An amplifier or accelerator for any of these three types—supervised,

unsupervised, or reinforcement learning—called deep learning, or neural networks, is also discussed. In all cases, a large and well-curated database is crucial—generally the bigger, the better—but the nature of the databases do vary, as does the optimal type of question to answer using each of these techniques.

UNSUPERVISED LEARNING

Unsupervised learning is characterized by the clustering of significant characteristics of the inputs. Consider an example of a researcher trying to optimize treatment strategies for each patient with a particular type of polygenetic cancer. The cancer could be treated by different combinations of chemotherapy, radiation, or surgery. The researcher wants to understand how to optimally use each of those treatments given each individual's precise combination of disease-causing genes.

This researcher would want a large training database that contains patient data: the genome of individuals with the cancer as well as their treatment history, particularly what combination of radiation, chemotherapy, or surgery each patient received. All that information would be different aspects of the input. The output would be some measure of effectiveness, probably something like whether the patient was cancer-free five years after treatment. Once this algorithm is well-trained, it could be used to identify the best treatment strategy for each patient.

REINFORCEMENT LEARNING

The third type of machine learning is called reinforcement learning. Reinforcement learning is trained by the algorithm receiving a reward when it makes the right selection. Reinforcement learning has a simple structure at its core but can be used for powerful purposes. In its most simple form, reinforcement learning works like training a dog: you reward successful completion of a task. In the case of a machine learning algorithm, however, you might program its core objective to be to acquire as many points as quickly as possible.

Consider, for example, how reinforcement learning could help train an algorithm to properly diagnose the results of an X-ray trying to identify cancerous tumors in the liver. The training database would have X-rays of livers and then, hidden from the algorithm, the information about whether an experienced radiologist diagnosed a tumor or not. The nascent algorithm would be told it would receive one point every time it properly designated a picture as a "cancer" or a "not cancer" X-ray. The algorithm would carefully identify and then internalize the visual characteristics that distinguished between "cancer" or "not cancer." After being trained, the algorithm could be presented with a new X-ray and reasonably be expected to properly diagnose the disease.

Reinforcement learning optimizes achievement of some goal (properly reading the X-rays) based on specified rules (what cancerous tumors look like). Like the two other types of machine learning, this has the terrific advantage that no human has to specify every instance of the differences between a cancerous and a non-cancerous X-ray. The larger the training database is, the more accurate the algorithm's prediction gets.

Reinforcement learning in particular enables the use of simulated data to train its algorithm, so this becomes a powerful way to supplement real data. Care must always be taken to look closely at the assumptions being used to generate the simulated data, however. For example, it is not clear whether it would be safe to use data generated by a simulation for autonomous driving that assumes other drivers always drive at the speed limit and stop at red lights.

DEEP LEARNING

Deep learning is a computer technique that can be used to augment any of the types of machine learning mentioned above. It can increase the accuracy of an image processing algorithm by more than 40 percent and a voice recognition algorithm by more than 20 percent.[93] Its need for a large training database is particularly voracious. Deep learning relies on a technology called "neural networks"; these terms are sometimes used interchangeably in common parlance.

Deep learning uses layers that have "tunable connection strengths."[94] These tunable connection strengths enable the relationship between each of the layers of the network to be tightened or loosened as the algorithm proceeds through the training database. As it examines each new input/output entry, the algorithm readjusts the connection strengths between each of the layers to further optimize its accuracy. This relentless optimization and the nuance provided by the multiple connection points between layers provides deep learning algorithms with their greater precision.

The layers are believed to proceed from gross features of the data (for instance, the edges of the images in a photo) to increasingly fine features of the data (such as the individual pores on an elephant). Deep learning has the somewhat disquieting quality that the substantive nature of the layers on which it sorts and tunes the algorithm is not observable, as the algorithm itself selects the layers and optimizes itself. Significant research is under way to improve the "explainability" of deep learning approaches. The most promising techniques are those that reverse engineer the impact of a particular criterion and so can identify the most important considerations for the algorithm. These efforts at "explainability" are promising but are still being refined.

This uniquely high degree of precision offered by machine learning augmented by deep learning could be clearly seen the first time deep learning participated in a competition against other types of algorithms. At the 2012 Image Net competition, all the algorithms were asked to perform image classification. This basically means that the algorithms were all trained on a large training database extracted from the Image Net database containing 15 million images labeled with one of 22,000 possible categories, such as canoe, artichoke, and sunglasses. The trained algorithms then competed to demonstrate which algorithm would most accurately label a new set of inputs with their proper category. The deep learning algorithm had almost half the error rate of its closest competitor.[95]

Conclusion

Databases possess a new strategic importance to the United States. They could enable the development of precision medicine algorithms; they could guide the development of tailored therapeutics, like vaccines for a newly emerged pathogen of pandemic potential; they could design a molecule to distill critical raw materials, like rare earth minerals, or design crops suited for a hot, dry climate.

The U.S. government should create a policy framework that reflects this new strategic importance. That said, its role would best be limited; as a rule, specifying databases and striving to manage them from the federal government level would be a mistake. The government needs to create an environment where databases can be created by new public-private organizations, and it should make data available at present and in the future, properly balancing data's many benefits against other national values.

Databases in the United States that can be used to support life science research and public health are too small, too fragmented, and too difficult for legitimate researchers to access. But that situation could be changed to better reflect the strategic importance of data in this new technological era.

5

Useful Molecules

The era of "useful molecules" has begun, where genetic engineering can purposefully create molecules to serve many purposes like helping to sequester carbon dioxide, make plastics that are biodegradable, and absorb toxic chemicals and render them benign.[96] These molecules can advance many public policy objectives and create an important economic sector: McKinsey, a global business consultancy, estimates such molecules could build a multi-trillion-dollar annual economic sector around new or specialized materials.[97]

This report recommends that the U.S. government organize a series of Grand Challenges, like the DARPA Grand Challenges in autonomous driving. The avowed objective of the competition would be to produce a particular genetically engineered molecule that advances public need. The competition should be structured so as to not only catalyze creation of the molecule but also support construction of a secure supply chain and inform related government policy.

The management structure for the competition should reflect its dual goals of creating a molecule of particular importance to the public sector and of informing government policy. A science policy committee should be constituted to distill some of the broader lessons learned from the competition. This science policy committee could perhaps be run out of the White House Office of Science and Technology Policy, or some other government office vested with this broad responsibility. A management team responsible for running the actual competition also should be created, perhaps in the science organization of an executive branch department or national lab. Both groups need to have members expert in private sector activity in this technology area to help focus on areas that the private sector would not fund.

Historically, biology was largely an observational science. More recent technical advances, including the purposeful manipulation of genomes, have revealed many of its mechanisms and enabled a shift toward a more engineering-like discipline, with a characteristic design-build-test-learn cycle: synthetic biology.[98]

For synthetic biology, the design stage generally is done using software-enabled approaches because of the complexity of deriving and specifying a genetic code with the desired characteristics. Designers could develop several molecules computationally before evaluating them in a wet laboratory setting.

The build phase for such molecules would be handled by a biofoundry. The name seeks to evoke traditional steel foundries, where steel was formed into specific tools or building components. A biofoundry, similarly, is a production facility where a common source—in this case living cells—is manipulated so as to produce precise materials to serve specific, practical purposes.[99]Far from the steel factories of history, though, biofoundries are generally clean rooms, with scientists working in hushed tones on computers, while automated robotic arms perform the labor, manipulating precursors to ensure precision and high throughput, translating the computer code specifying the desired genome to the physical construction of the specific molecule of DNA.[100]

The designer would then test the candidate molecules and optimize the design. Once the molecule had been optimized, the designer might only want it in small quantities, in which case the production capacity of the prototyping biofoundry would probably be large enough. If the designer wanted instead to produce the molecule in quantity, different commercial manufacturing techniques and equipment probably would be used.

Biofoundries are at a stage of development where there are efforts to standardize them. Standardization generally reduces per-unit cost for any type of manufacturing operation. There are significant advances in both commercial and non-commercial biofoundries. The commercial sector—in terms of venture capital and initial public offerings—is providing money in the low tens of billions of dollars annually.[101]

The Global Biofoundry Alliance was created in 2019 to develop and share best practices for non-commercial biofoundries. The organization boasts about 30 members, located in the United States and Canada, Europe and the United Kingdom, Australia, India, and East and Southeast Asia.[102] Within the United States, the National Institute of Standards and Technology and the Department of Energy have established a biofoundry that, in their judgement, has an optimal design, and they are seeking to entice research institutions to adopt their design through the provision of grants for that purpose.[103]

Shape Government Policy

As mentioned earlier, the way the competition is designed could generate many benefits. In addition to the creation of the specified molecule, there are at least five ways that the competition could contribute to government policy.

DATABASE CREATION

The bioengineering Grand Challenge could identify a molecule of public interest, but its usefulness can go far beyond, aiding to transform the biotechnology landscape of the United States. First, the creation of the databases needed to develop the molecule would itself be useful. It is extremely unlikely that the training database needed to engineer a DNA sequence in a bacterium that will be capable of

extracting lithium or cobalt from ores or other feedstocks, for example, already exists. As part of the conduct of the competition, the management team should fund some public-private partnership to create the needed database and support that partnership's efforts to get access to the data sets needed for the larger training database. Given that the competition is focusing on useful molecules in an important public area, the training database could probably be reused for many valuable purposes.

PROCESS INSIGHTS

Second, the science policy committee can derive process insights from the progress of the competition to develop the needed database and to assure the safety of the molecule.

As discussed in the previous chapter, the U.S. government needs to create an environment vastly more hospitable to the creation of databases in areas of interest to commercial or academic researchers. Thus during the process of building key databases to support the specific question under review in the competition, the science policy committee should be kept apprised of particular problems encountered in building the database, from which it could generalize to help identify broader problems that need to be fixed on a structural level. This broader suite of reforms should be distilled and secured through policy, legal, and regulatory changes.

The science policy committee also should review the process to assure the safety of the molecule and identify any needed refinements.[104]

BUILD BIOFOUNDRIES

Third, the United States needs to build and sustain a secure supply chain of biofoundry production capability.[105] The competition should be used as an initial vehicle to advance that goal. The management team running the competition should ensure that there is a biofoundry for each of the contestants that make it to a particular point in the competition, perhaps the semi-finals. The funding should be awarded in some way to ensure that the funds are supplementing private or institutional investments.

The United States needs a secure domestic capability in this area, both to produce specific molecules and to make the U.S. sector competitive for international trade. This capability would help assure the health and dynamism of this sector in the United States.

TALENT PIPELINES

Fourth, talented technical staff at all levels is a critical part of the needed domestic supply chain. The team managing the competition should provide funding to support the training of biofoundry staff as part of the support offered to every competitor reaching semi-finalist status. Management at each participating biofoundry should receive funding for apprenticeship programs for technical staff and scholarships for undergraduates and graduate students at regional universities.[106]

Much as for the database effort, the science policy committee should examine how these programs have worked after a reasonable interval. Strengths and weaknesses of the programs should be assessed, and based on the findings, they should be continued and possibly created at other places. If the programs are not working, the committee should derive some lessons for alternative methods to allocate government funding to facilitate the training of excellent technical staff at all levels.

The United States needs a larger cadre of technical experts—including those that have applied lab and manufacturing skills, such as lab technicians and senior lab managers. This technical staff is essential to applying these technologies to new applications.

PARTICIPATION IN INTERNATIONAL STANDARD-SETTING ORGANIZATIONS

Fifth, the United States has failed to participate sufficiently in recent international technical meetings, such as those for technologies like 5G.[107] These international technical meetings focus on various issues, including standardization, which is surprisingly important, as anyone trying to use a U.S. electrical appliance in Europe could attest. This gap in U.S. diplomacy should be corrected in the case of biofoundries in particular and biotechnologies in general.

The funding conditions for the competition should require that the biofoundry semi-finalists participate in government meetings to shape U.S. policy for participation in international standard-setting efforts and that they contribute technical experts to participate in U.S. delegations to such bodies, traveling to international meetings alongside State Department diplomats.

In a time of technological transition and strategic competition such as this, it is very unwise for the United States to be absent from international standard-setting groups. As biotechnology develops, the United States needs to be active in related international standard-setting agencies. The U.S. State Department needs to make a priority of attending these types of negotiations with appropriate delegations of technical experts, given the importance of such participation to the health of the U.S. sector.

Conclusion

Specialized materials and other products of modified genomes promise to be very useful. Speeding the development of such useful molecules through Grand Challenges that seek to spur the development of molecules for a public purpose—like climate remediation and critical material supply—would be a very valuable outcome. Structured properly, the competitions could yield many additional benefits, including the development of a secure domestic supply of biofoundries and the technical staff at all levels to run them effectively. It also could catalyze the creation of the supporting training database as well as insights into the types of reforms necessary to create an environment supportive of such database creation and of a review process to assure the molecule's safety. Finally, it could make important connections between the technical community and the State Department, thus enabling the framing and pursuit of U.S. interests in international standard-setting efforts. The United States broadly leads in bioengineering research but has been less successful in translating this intellectual leadership into concrete results. These competitions should help catalyze efforts in the application of this remarkable technology.

Conclusion

"One lingered long among the dynamos, for they were new, and they gave to history a new phase. Men [and women] of science could never understand the ignorance and naivete of the historian, who, when he came suddenly on a new power, asked naturally what it was. . . . [He asked] a score of such questions to which he expected answers and was astonished to get none."

— Henry Adams at the Chicago Exhibition of technology in 1893[108]

This report has focused on the astonishing implications of the combination of three technologies: DNA sequencing, programmable CRISPR-Cas systems, and machine learning. Taken together, these technical advances enable the purposeful manipulation of genomes. Such manipulation can create "useful molecules" of various sorts, tailored therapeutics and treatment strategies, and cures for genetic disease.

Purposeful manipulation of genomes has astonishing implications, and perhaps most remarkably, it is occurring in an age where it is only one of the transformative technologies emerging. The quotation at the outset of the conclusion comes from Henry Adams describing his visit to the technology exhibit at the 1893 Chicago Exhibition. Adams taught medieval history at Harvard College in the late 1800s. His work as a historian had underscored constancy, symbolized by the medieval cathedral, but Adams also was a keen observer of his own time. He warned that the exhibit demonstrated not only profound technical change but a rapid acceleration in the pace of that change and the extent of its implications. The coal-fired steam engine powered railroads and factories, and now was supplemented by the dynamo, the first electrical generator capable of delivering power for industry. Adams judged that the convergence of these and other new technologies "gave to history a new phase."

The pace and extent of technological change today has, again, given to history a new phase. Machine learning algorithms promise to upend many inquiries, not only those about the genome. Satellites are growing ever smaller, cheaper, and more capable. Among other progress, such as nanotechnology and quantum computing, these are all dynamos powering incalculable advances.

Machine learning algorithms reveal subtle correlations and make predictions. For military purposes, they raise problematic issues about escalation into unintended war; about lacking robust training data on how a battle unfolds and relying instead on simulated data sets; and, about the disturbing but clinically efficient prospect of killer robots. But the solution for the military is not to entirely avoid machine learning because of its risks of escalation. Deterrence failure awaits any military that fails to incorporate machine learning to enhance its ability to manage logistics, to benefit from imagery, and to manage many other critical tasks.

The ever-improving capacities of small satellites are revolutionizing war, quite apart from what they are doing for internet access. Commercial companies are probably only a few years away from near-real time imagery of the entire world being available with a credit card over the internet. Coupled with artificial intelligence to efficiently sort images, this will eliminate tactical surprise for large formations of tanks or surface ships, as the Russian tanks in Ukraine in the early weeks of that war discovered. Invasions like D-Day in World War II, with six divisions of ground and amphibious forces moving together with tactical surprise, probably could never successfully occur again; the units would have been seen long before they arrived on Omaha Beach. Small-unit tactics and vastly better means of denial and deception will be needed.

The challenges and transformation in other domains of technology pose similar problems for the military, and for society. This report has outlined recommendations given the emerging ability to purposefully manipulate the genome. It seems likely that these recommendations would also be broadly applicable to other emerging technologies.

The technologies noted above are all being advanced in the global commercial and academic realms. The DOD would benefit from uniformed technology experts and from a healthy domestic sector. The U.S. government should create an environment where each of these technology sectors can flourish, where they participate actively in international science but have secure domestic supply chains and talented technical staff at all levels.

The military should be restructured to benefit from those healthy sectors, accepting that efforts to reproduce such an ecosystem inside the DOD would fail, with the DOD lagging yet further behind cutting-edge technical advances. To ensure that the DOD can incorporate these technologies, it needs uniformed practitioners of these new technologies participating in the difficult debates that optimize—and sometimes profoundly change—the department's efforts.

Historians when writing of a past age may speak of constancy and cathedrals. But of their own time, filled with new dynamos of various sorts, they may only be astonished by how many questions cannot be answered. Today similarly seems a time with more questions than answers, a time of rapid and accelerating technological change.

There is constancy of a sort, though. Many historians of past ages have shown the costs of failing to incorporate new technologies—stories of Agincourt's armor, of Constantinople's walls, of the French

Maginot Line. These are all stories of strategic defeat, of failures of operational concepts, and, more fundamentally, of governance. Effective governance requires a certain ability to come together to develop and implement national policy to respond to the new challenges of a new age, both at home and abroad. Historians may tell these stories, but it is nation-states who write their own story of effective governance or of strategic defeat.

About the Author

Carol Kuntz teaches on the policy implications of artificial intelligence at Georgetown University and conducts research as an adjunct fellow (non-resident) in the Strategic Technologies Program at the Center for Strategic and International Studies (CSIS).

Dr. Kuntz served in the United States Department of Defense (DOD) for more than 30 years. Her work particularly focused on identifying changes in the strategic and technological environment and crafting new policies and programs given those changes.

In the several years before Covid-19 emerged, she sought to embed cutting-edge biotechnologies into the DOD's biodefense program to strengthen its ability to rapidly configure vaccines to protect against novel pathogens. For the five years after the 9/11 terrorist attacks on the United States, Dr. Kuntz served as the homeland security advisor to the vice president of the United States. At the end of the Cold War in 1989, she worked with top DOD officials to craft a new defense strategy to replace the post-World War II strategy of containment.

Dr. Kuntz received her PhD in political science from the Massachusetts Institute of Technology. She received her MPA from Princeton University and her BA from Cornell University. Dr. Kuntz received numerous awards over the course of her government career, including twice receiving the Secretary of Defense Medal for Meritorious Civilian Service.

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limits of their own military knowledge and get around the bureaucratic shenanigans of their military organizations . . . those at the top of the [military] hierarchy, who have achieved their rank and position by mastering the old doctrine, have no interest in encouraging their obsolescence by bringing in a new doctrine. Thus innovation should occur mainly when the organization registers a large failure, or when civilians with legitimate authority intervene to promote innovations." See Barry R. Posen, *The Sources of Military Doctrine: France, Britain, and Germany Between the World Wars* (Ithaca, NY: Cornell University Press, 1984), 223–224. See also the discussion of MRAPS and drones in Gates, *Duty*.

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32 National Academy of Medicine, National Academy of Sciences, and The Royal Society, *Heritable Human Genome Editing*.

33 See a lengthy (really lengthy) discussion of these issues in Carol R. Kuntz, *New Forces Yet Undetermined: The Challenge of Biodefense* (doctoral dissertation, Department of Political Science, MIT, September 2009), https://dspace.mit.edu/handle/1721.1/54614. For example, on inspections see page 82: "Inspections to assure the peaceful use of biotechnologies should not be pursued. They would consume more diplomatic energy and goodwill than the security benefit they could confer. This dissertation urges instead that the diplomatic energy be invested in the development and adoption of international norms on biosafety, biosecurity and worrisome dual use research, as discussed elsewhere." On export controls, see page 48: "In the case of biotechnologies, export controls would be undercut by the diffusion of technology, lack of political consensus on controls, and the emergence of significant non-state actors, both economic and security, with interest and expertise in biotechnologies. Knowledge and materials needed for catastrophic biological weapons attack are widely diffused abroad. Entry costs for biological weapons are low (defined in term of both costs and technical knowledge)."

34 Political scientist Ernest Haas outlined the formal theory of "neofunctionalism" that argues international technical elites and other extra-national actors, like the bureaucrats who run international organizations, can play a powerful role in formulating and enforcing norms in certain international environments. See particularly Ernest B. Haas, "Beyond the Nation-State: Functionalism and International Organization," *Political Science Quarterly* 82, no. 1 (March 1967): 148–150, https://www.jstor.org/stable/2147335.

35 National Academy of Medicine, National Academy of Sciences, and The Royal Society, *Heritable Human Genome Editing*, 86. "Genes operate in functional networks and understanding the role that genes and their variants play in such networks is a challenge that will require powerful computational tools and large-scale datasets from genomics programs, including animal models."

36 For a more traditional perspective on solving the problems while agreeing the problems exist, see National Academy of Sciences, Engineering, and Medicine, *Safeguarding the Bioeconomy*, 14–17.

37 Sean Gerrish, *How Smart Machines Think* (Cambridge: The MIT Press, 2018). See in particular Chapter 2: "Self-driving Cars and the DARPA Grand Challenge."

38 Julia Martinez, "Battle of Agincourt, European history (1415)," Britannica.com, https://www.britannica.com/event/Battle-of-Agincourthttps://www.britannica.com/event/Battle-of-Agincourt; Myles Hudson, "Fall of Constantinople, Byzantine history (1453)," Britannica.com, https://www.britannica.com/event/Fall-of-Constantinople-1453https://www.britannica.com/event/Fall-of-Constantinople-1453.

39 There is an enormous literature (and an enormous number of perspectives) on World War I, the interwar period, and World War II. The core source for this section is Williamson Murray, "Armored Warfare: The British, French, and German experiences," in Murray and Millett, *Military Innovation in the Interwar Period*. On the British, see pages 17, 24–27. The author also consulted Posen, *The Sources of Military Doctrine*.

40 On the French, see Murray and Millett, *Military Innovation in the Interwar Period*, 29–34.

41 "OSINT: A new era of transparent warfare beckons," *The Economist*, February 19, 2022; "Could Ukraine's anti-tank missiles hamper a Russian invasion?" *The Economist*, January 21, 2022; "Baguette-sized flying bombs are about to enter service in Ukraine," *The Economist*, March 26, 2022.

42 There does not appear to be a precise recipe for peacetime military innovation, but many of the same

elements are present in different measure in different explanations. For an argument that emphasizes the importance of career paths for practitioners of the new technologies, see Rosen, *Winning the Next War*, 76–105. For a very useful but more multifaceted explanation, see Watts and Murray, "Military Innovation in Peacetime." For a greater emphasis on the role of civilian leaders, see Posen, *The Sources of Military Doctrine*.

43 The deleterious effects of the top civilian or military leadership declaring the right answer in peacetime has been amply demonstrated; consider the complaints of a French general about the shutting down of discussion in the French military before World War II: "'Everyone got the message, and a profound silence reigned until the awakening of 1940.'" Murray, "Armored Warfare: The British, French, and German experiences," 34.

44 Gates, *Duty*. Consider also the discussion of the difference between peacetime and wartime military innovation in Rosen, *Winning the Next War*.

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46 "Joint Requirement Oversight Council (JROC)," Defense Acquisition University, https://www.dau.edu/acquipedia/pages/articledetails.aspx#!324.

47 Congress recreated the position of under secretary of defense for research and engineering in 2016. CRS, *Defense Primer: Under Secretary of Defense for Research and Engineering*. "Over the last several years, policymakers and others have expressed concern that the long-held technological edge of the U.S. military is eroding due, in part, to the proliferation of technologies outside the defense sector, organizational and cultural barriers to DOD effectively incorporating and exploiting commercial innovations, and insufficient engagement with leading-edge companies that have not historically been a part of the DOD innovation system. The establishment of the USD(R&E) as the fourth highest ranking DOD official—behind the Secretary, Deputy Secretary, and Chief Management Officer—was intended to promote faster innovation and to reduce risk-intolerance in the pursuit of new technologies."

48 Of the FY 2020 research, development, test, and evaluation (RDT&E) funding, 74.8 percent of the funding goes to the three services, while only 25.3 percent goes to DOD-wide uses, of which only some would be for the OUSD(R&E). The total RDT&E funding in FY 2020 was $108.6 billion. This data is from John F. Sargent Jr., "Department of Defense Research, Development, Test, and Evaluation (RDT&E): Appropriations Structure," Congressional Research Service, R4471, October 7, 2020, 9, https://crsreports.congress.gov.

49 Landau, "Glowing Bacteria in the Dirt."

50 Mukherjee, *The Gene*, 495. Mukherjee uses the concepts of "constancy" and "variation" to set up the challenge posed by human genome editing. This book is beautifully written and prescient, explaining many of the issues in this chapter. It is highly recommended for those with a deep interest in the topic.

51 On nuclear weapons: "As he witnessed the first detonation of a nuclear weapon on July 16, 1945, a piece of Hindu scripture ran through the mind of Robert Oppenheimer: 'Now I am become Death, the destroyer of worlds.' It is, perhaps, the most well-known line from the Bhagavad-Gita, but also the most misunderstood." James Temperton, "'Now I am become Death, the destroyer of worlds'. The story of Oppenheimer's infamous quote," *Wired*, August 9, 2017, https://www.wired.co.uk/article/manhattan-project-robert-oppenheimer. On CRISPR: "It won't be long before CRISPR allows us to bend nature to our will in the way that humans have dreamed of since pre-history. When that will is directed toward something constructive, the results could be fantastic – but they might also have unintentional or even calamitous consequences." Doudna and Sternberg, *A Crack in Creation*, 117.

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53 Saha, "Genome Editing with Precision and Accuracy."

54 Ibid.

55 Antonio Regalado, "Disgraced CRISPR Scientist Had Plans to Start a Designer-Baby Business," *MIT Technology Review*, August 1, 2019.

56 Regalado, "He Jiankui Faces Three Years in Prison for CRISPR Babies."

57 National Academy of Medicine, National Academy of Sciences, and The Royal Society, *Heritable Human Genome Editing*.

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61 National Academies of Sciences, Engineering, and Medicine, *Human Genome Editing*.

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considerations that should be addressed prior to and during establishment. These include drivers for establishment, institutional models, funding and revenue models, personnel, hardware and software, data management, interoperability, client engagement and biosecurity issues. The high cost of establishment and operation means that developing a long-term business model for biofoundry sustainability in the context of funding frameworks, actual and potential client base, and costing structure is critical. Moreover, since biofoundries are leading a conceptual shift in experimental design for bioengineering, sustained outreach and engagement with the research community are needed to grow the client base. Recognition of the significant, long-term financial investment required and an understanding of the complexities of operationalization is critical for a sustainable biofoundry venture. To ensure state-of-the-art technology is integrated into planning, extensive engagement with existing facilities and community groups, such as the Global Biofoundries Alliance, is recommended."

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