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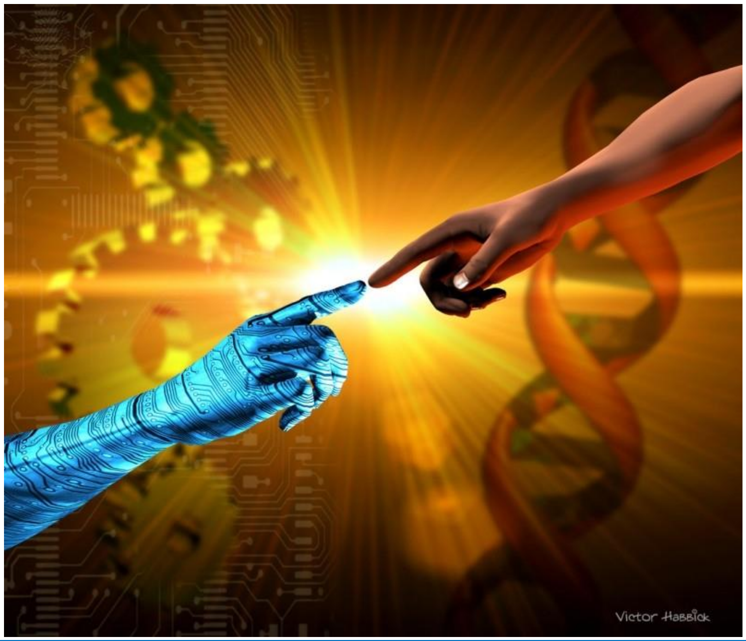

Superhumans: Implications of Genetic Engineering and Human-Centered Bioengineering

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Abstract

Humans have long pursued different ways to improve themselves and gain advantages, whether through information, technology, or physical enhancement. Recent advances in genetic engineering and human-centered bioengineering (which covers more than cyborgs) offer unprecedented capabilities for humans to modify and enhance themselves. This report describes recent advances in these areas of research, and identifies implications for the US military, as these technologies arrive in the hands, figuratively and literally, of the average person.

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Executive Summary

Throughout history, humans have pursued ways to improve themselves and gain advantages, whether through information, technology, or physical enhancement. Although advancements in machine learning offer the promise of computers with "superhuman" capabilities, two other advancements will soon offer options that only science fiction has envisioned and explored. Biotechnology—specifically, the physical modification of biology with technology—has a trajectory that goes beyond reversible "human-machine teaming" and ends with cyborg-like possibilities of endless enhancements and modifications. And genetic engineering, particularly with the accessibility offered by CRISPR[1] (clustered regularly interspaced short palindromic repeats) and related technologies, has a trajectory that promises smarter, stronger, and "better" humans from birth, heralding the advent of "homo superior."

Although the US military has made advances in exploring the applications of human engineering with robotics and human-machine teaming, the applications of genetic modifications and biotechnology to human physiology have received less attention. Meanwhile, genetic engineering and human-centered bioengineering are already seeing effects in society. This paper examines the trajectory of advancements in these areas, and it derives relevant issues and considerations for the military.

To put these latest technologies into perspective, we examined the **history of human modification** and observed that humans have been extensively modifying themselves for a long time, and they will continue to do so. The latest human modifications focus on the human "hardware": the neural, somatic, and germline, as well as things fused with the body; these human modifications are different from those that have come before. And various newly formed groups want to choose deliberately the path that humanity takes as it explores these modifications.

We examined the **trends in research of genetic engineering and "human-centered bioengineering"** (our term for cyborgs that also encompasses a few more technological options). Advances in the nuclease[2] family of gene editing tools, of which TALENs (transcription activator-like effector nucleases) and CRISPR-associated (CRISPR-Cas) are the latest members, have enabled ever more precise and flexible options for researchers. And

[1] This report describes most terminology as it arises in the main text, but for reference, Appendix A contains a glossary of terms.

[2] Enzymes capable of cleaving DNA (deoxyribonucleic acid) and RNA (ribonucleic acid).

advances in prosthetics (including sensory and organ parts), brain-machine interfaces, and wearables (including exoskeletons) continue to make smaller, lighter, cheaper, and more "restorative" technologies possible. In the near term, we expect the trends for these research areas to continue focusing on correcting human diseases and injuries. As researchers work through nontrivial safety issues, expanding options and availability will transform the lives of those who need them. In the longer term, these research areas have the potential to expand from corrective applications to enhancement applications; both research areas stand at this threshold, with human-centered bioengineering perhaps a bit further ahead. While the United States, China, and Russia continue to invest heavily in these research areas, the biohacker community plays an important role. With the connectivity of the internet, the sharing of information and procedures, the providing of equipment and alternatives, and a passion to explore and experiment (sometimes on themselves), biohackers are helping to push the envelope of research. From advanced laboratories to garage setups, we identified three trends that will shape the future of these many technologies:

- **Adaptability**. These technologies are becoming more powerful, more capable, and relevant to more problems. In genetic engineering, we observed that DNA (deoxyribonucleic acid) manipulations (e.g., reading, writing, editing) have seen great advances in the last few decades as the discovery of new tools has given researchers ever further control and precision in editing genomes. In human-centered bioengineering, we observed similar trends across the wide diversity of applications: devices are becoming smaller, more portable (or transportable), more capable, and more flexible.
- **Accessibility**. These technologies, like many others, will become cheaper and more accessible over time. The proliferation of these technologies into every aspect of life will continue to increase the availability and affordability of these products.
- **Acceptability**. The trend of acceptability, meaning whether society will approve of and adopt technological developments, has the greatest uncertainty and will likely be the slowest of the three trends. In general, society and research institutions appear to accept the employment of genetic engineering and human-centered bioengineering technologies for **corrective** applications. The consensus is less clear for **noncorrective enhancements**, or for how **convenience** will play a role. In both genetic engineering and human-centered bioengineering, we are at the threshold of achieving alterations that can enhance human characteristics, with the furthest of such advancements occurring in human-centered bioengineering. Although medical communities have largely refused to conduct such modifications, the biohacking community and some start-up companies have largely taken matters into their own hands. For these three trends, the biggest wildcard will be the thousands of garage and basement laboratories around the globe.

We then examined the **current regulations** that the US military has, or does not have, concerning genetic engineering and human-centered bioengineering, particularly as they pertain to individual service members. Perhaps not surprisingly, few military regulations appear to directly address these topics at an unclassified level. The services do have regulations on uniforms (and personal appearance) that could potentially touch on some of the human-centered bioengineering technologies.

Based on our observations of the history of human modification, our analysis of the trends in research, and our review of the current military regulations, we arrived at the following implications and recommendations:

Over time, more humans will modify themselves, or will come "pre-modified." Initially, humans will choose to modify themselves. Eventually, parents will be able to make modification decisions for their children. Human-centered bioengineering modifications are available now and will be more prevalent earlier than genetic modifications.

- **Recommendation**. The Department of Defense (DOD) should establish guidance for service members who may be interested in self-experimenting with genetic engineering, receiving chip implants, or making other modifications with these technologies.

Any difference in the availability and acceptability of these technologies will increase the likelihood of black markets and other illicit activities. In other words, if the technology is available but society (or DOD) does not accept or allow it, people will be more likely to pursue the technologies illicitly.

- **Recommendation**. DOD should keep close watch on the differences between the availability of these technologies and the societal acceptance of them. The sports industry might provide the best benchmark, since athletes will be particularly susceptible to genetic/technology enhancements on physical performance.

These technologies are no longer issues only for Science and Technology organizations; they affect all areas. Organizations such as DARPA and the service research labs may not find the information in this report surprising. But that message does not appear to have yet made its way to all parts of DOD. The advances in genetic engineering and human-centered bioengineering are beginning to affect the general population, which means that these technologies will soon affect all aspects of an organization, including personnel, training, logistics, operations, and more.

- **Recommendation**. DOD and the services should identify cross-organizational oversight for the integration of these technologies. Because these technologies touch on nearly all aspects of an organization, oversight should likely reside at the service headquarters and the Office of the Secretary of Defense. They will require extensive coordination with all parts of their organizations.

These technologies will introduce new threats—to all people, not just service members. There will be threats *by* the new technology as well as threats *to* the new technology. As an example, the proliferation of AI and machine learning research and technologies has introduced entirely new forms of adversarial attacks, vulnerabilities, and threats. We will see a similar evolution for genetic engineering and human-centered bioengineering.

- **Recommendation**. DOD should begin preparing for and understanding these potential vulnerabilities, and determining when they may become serious threats. Red teaming, war gaming, "fiction intelligence" (FICINT), and other methods provide great avenues for identifying and exploring these issues.

DOD has no frameworks or strategies to weigh the ethical and legal implications of the military applications of these technologies. Global research and interests, including national ambitions and strategies, are currently driving the trajectories of genetic engineering and human-centered bioengineering. DOD needs to engage as part of the voice of the United States in these global conversations as the entire world deals with the implication and direction of these technologies.

- **Recommendation**. DOD needs frameworks and strategies for navigating these discussions and engagements. These frameworks will need to adapt to the technologies as they evolve, as new and unforeseen technologies emerge, and as unforeseen issues ripple out from their employment.

Contents

Introduction

Throughout history, humans have pursued ways to improve themselves and gain advantages, whether through information, technology, or physical enhancement. Although advancements in machine learning offer the promise of computers with "superhuman" capabilities, two other advancements will soon offer options to humans that only science fiction has envisioned and explored. Biotechnology—specifically, the physical modification of biology with technology—has a trajectory that goes beyond reversible "human-machine teaming" and ends with cyborg-like possibilities of endless enhancements and modifications. And genetic engineering, particularly with the accessibility offered by CRISPR and related technologies, has a trajectory that promises smarter, stronger, and "better" humans from birth, heralding the advent of "homo superior."[3]

Although the US military has made advances in exploring the applications of human engineering with robotics and human-machine teaming, the future promise of genetic modifications and biotechnology, as applied to human physiology, has received less attention. This paper examines the trajectory of advancements in human-centered biotechnology and genetic engineering, and it discusses relevant issues and considerations for the military.

Background

Recent advances in artificial intelligence (AI), particularly machine learning and deep neural networks, have garnered much attention and headlines over the last decade. Researchers have greatly improved algorithms for image classification[4] [3-4], demonstrated the ability of an algorithm to defeat a world champion at the ancient strategy game Go [5-6], and even used algorithmic methods to create art and music [7-8]. In the wake of Putin's declaration in 2017 that the leader in AI will rule the world [9], many of the world's nations have published their AI visions and strategies. By the end of 2018, at least 18 nations had published AI strategies, with half of those plans also receiving funding [10]; by 2020, that list had expanded to 36

[3] Olaf Stapledon coined the term *homo superior* in his 1935 science fiction novel *Odd John: A Story Between Jest and Earnest* [1].

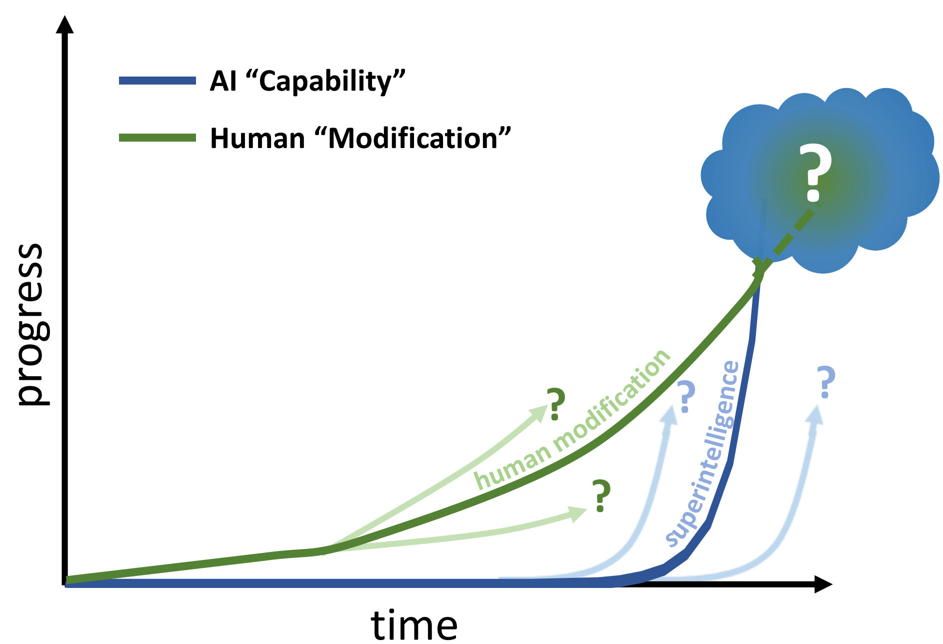
[4] At the ImageNet Large Scale Visual Recognition Challenge in 2012, the success of AlexNet rekindled interest in deep neural networks [2]. The fields of image and pattern recognition has made dramatic improvements since then.

nations [11]. Organizations, businesses, and institutions have followed suit, including the US Department of Defense and its services (for example, see [12]).

Meanwhile, the fields of genetic engineering and bioengineering have made similarly significant advances, but these fields have received comparatively less attention. Though some nations have published strategies that mention biotechnology, such as China's Made in China 2025 strategy [13], we have not seen the same rush to publish in-depth strategies on biotechnology.

Researchers in AI are striving to create an Artificial General Intelligence (AGI) that mirrors the broad intelligence and adaptability of humans. Some researchers have also predicted the possibility of creating "superintelligence," which includes the possibility that such a superintelligence will rapidly improve itself, resulting in an intelligence explosion [14-15]. Figure 1 shows a qualitative depiction of this sudden increase in capability for AI. Researchers disagree about whether or when such a thing might occur. Some predict 20, 50, or 100 years or never [16], hence the ambiguity of the "time" axis in the figure.

Figure 1. A very qualitative comparison of progress in AI and genetic engineering research



Source: CNA.

In the meantime, the trajectory of genetic engineering and bioengineering suggests that the likelihood of humans modifying *themselves* may be much closer, and is indeed beginning to happen right now. How does this improvement in human modification look, in comparison to the progress in AI, if we can even compare them? The increase in capability for human modification will likely not see an exponential explosion—at least, not with the current slower rate of biological iteration. And, of course, other researchers have predicted the potential fusion of human and machine life (with countless permutations of possibilities), so at some point, the two curves may "merge" into one [17].

As this report will describe, we are beginning to witness significant advances in genetic engineering and bioengineering, which will dramatically alter the progress of human development. Governments and organizations will soon have to consider how to treat individuals who are augmenting themselves through genetic and technological means. AI has been in the spotlight over the last decade, and significant advances in genetic engineering and bioengineering may greatly affect human life before the arrival of any superintelligence. Hence, this paper puts a bit of the spotlight back on the state of biotechnology in order to identify issues that may soon arise.

Methodology

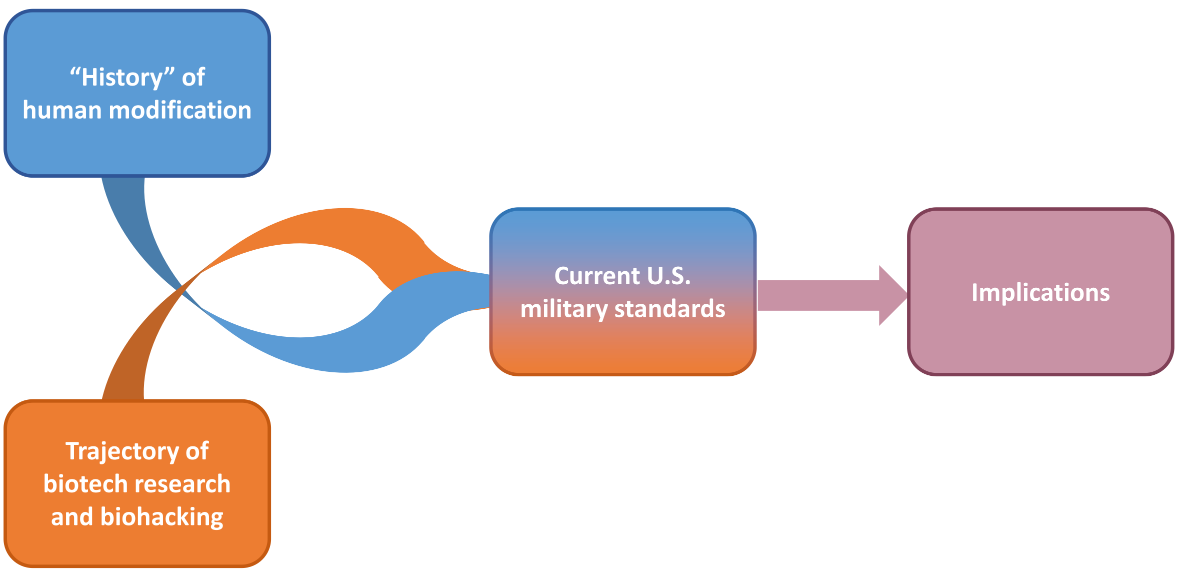
This report examines the *near-term* trends in genetic engineering and human-centered bioengineering, and it then identifies the implications of these trends for the US military. We approached this topic by answering a series of questions:

- What is the history of human modification, and what lessons can we draw from it?
- What is the trajectory of research in genetic engineering and human-centered bioengineering? How are the United States and other nations viewing research and applications in these areas?
    - What advances and innovations might we see in the near future?
    - What potential issues might these current and future applications portend?
    - What are the implications of increasing the accessibility of information and technology in these areas of research?
- What are the current US military standards and regulations regarding genetic engineering and human-centered bioengineering?

- Based on these findings, what are the considerations that the US military will need to address (1) with its own personnel, (2) with technology development, and (3) in light of global and adversary intent and progress?

The major sections of this report address each of these questions in turn. Figure 2 depicts how this information will come together to inform the implications.

Figure 2. Overview of methodology



Source: CNA.

Assumptions and caveats

In exploring the answers to the questions, we consulted a wide variety of academic publications, newspaper articles, popular writings, blogs, videos, social media postings, and other sources of information.[5] The field of biotechnology has seen rapid progress over the last few decades, and this report will describe some of the latest research breakthroughs; however, exciting new research will likely appear even while the ink is drying on these pages. In general, we sketch the larger arc of the progress in the field to ensure this report is not affected by new research breakthroughs in the near future. Barring any astounding and unexpected

[5] These sources have varying degrees of timeliness and verifiability.

advancement, this analysis should provide reasonable insight into expectations for the next few years.

This report provides examples to describe specific technologies or capabilities; however, these examples do not indicate our endorsement of any particular product or claims of its effectiveness.

Topics not covered

We focus this discussion on applications of biotechnology and bioengineering that directly affect the physical nature of human beings—specifically genetic engineering and human-centered bioengineering. The broad field of biotechnology, however, encompasses many other important topics and applications that intertwine with each other. Other resources cover these topics at length, and they remain active areas of research. This report will *not* cover these topics, including the following:

Biotechnology to create new general technology (non–human-centered). Biotechnology has application to a wide variety of fields. For example, biotechnology might enhance the production or composition of agricultural products, or it might lead to the creation of stronger, lighter materials with exotic properties, such as self-healing body armor.

Biological weapons or **bioweapons**. The 1972 Biological Weapons Convention bans the development and use of biological weapons [18]. The United States, China, Russia, and many other nations are signatories. Most current bioweapons involve the use of biological toxins or infectious agents, but advances in genetic engineering may make possible gene-tailored weapons that have the ability to target particular genetic markers (e.g., possessing a higher likelihood in a particular race or individual). Because these weapons are currently theoretical, they have no formal name, but they may be referred to as ***ethnic bioweapons*** [19] or ***genetic weapons*** [20].

Biodefense. *Biodefense* covers the defense of biological threats (see bioweapons), typically under the umbrella term CBRNE (chemical, biological, radiological, nuclear, and explosive) defense [21]. The United States released a *National Biodefense Strategy* in 2018 [22]; however, the strategy identified no resources or action plan and so has seen little implementation [23].

Bioethics. Issues of ethics and morals weave heavily into nearly all of these topics. Unlike AI and machine learning, bioethics has a more established presence and infrastructure. Many organizations have oversight panels or consultants for bioethical issues, particularly related to human subject research.[6] This report will mention a few of the ongoing controversies and discussions, but it will stay away from any discussion of "should."

Cloning. *Cloning* describes the process of creating organisms with identical DNA (deoxyribonucleic acid), whether through natural or artificial means. Some organisms may naturally produce identical offspring through asexual reproduction, but in biotechnology, cloning refers to creating copies of organisms through replicating their DNA. **Human cloning** falls into roughly two groups: **therapeutic cloning** and **reproductive cloning**. Therapeutic cloning seeks to clone cells for organ transplants and other medical purposes, while reproductive cloning involves creating a whole human [25]. Many nations have laws governing and prohibiting the research and cloning of human beings; the United States has not banned human cloning at the federal level, though individual states have passed their own laws [26-27]. Scientists successfully cloned the first mammal, Dolly the sheep, in 1996 [28], and scientists in 2018 cloned macaque monkeys [29].

Classified research. This report uses only open-source information. We recognize that the US military may have ongoing classified research and programs in genetic engineering and other modifications of warfighters [30-31]. We assume that appropriate oversight and councils exist for such programs. Even so, such potential programs do not alter our findings, since we identify issues resulting from the broad adoption of these technologies by the general population.

Eugenics. *Eugenics* describes "the study of how to arrange reproduction within a human population to increase the occurrence of heritable characteristics regarded as desirable" [32]. Although the idea of eugenics has origins as early as ancient Greece [33], the eugenics movement experienced a surge of interest in the late 19th and early 20th centuries [34], which largely resulted in the persecution (e.g., forced sterilization) or murder (e.g., the Nazi eugenics program) of populations of people that governments deemed "unfit" to reproduce or to continue living [35]. The atrocities of World War II led to the decline of the popularity of eugenics programs. The potential of genetic engineering in humans has created a resurgence of interest in the topic, at least from the "positive" perspective of enhancing genetic potential. This resurgence is sometimes called ***new eugenics*** or ***liberal eugenics*** [36], though some people prefer terms such as ***germinal choice*** [37], which refer to parents and individuals making choices about themselves and their offspring. As an area of active debate, it remains to be seen how this discussion will evolve.

Transhumanism, bioconservatism, and bioluddism (or neo-Luddism). Ideologies and philosophies have formed around the role and nature of the "future human" and humanity's

[6] See for example the *International Compilation of Human Research Standards*, a compilation from the Office for Human Research Protections [24].

relationship with technology. ***Transhumanism*** describes a philosophy of transforming the human condition to enhance both body and mind [38]. The term likely derives from Julian Huxley, brother of author Aldous Huxley, who wrote on the idea of "man remaining man, but transcending himself, by realizing new possibilities of and for his human nature" [39]. Transhumanists aim to address the place of humanity in the world and the long-term trajectory of intelligent life [40].[7] In contrast, ***bioconservatism*** takes a "hesitant" stance toward the merging of humans and technology, often with a focus on the unnatural and uncertain ends of such merging [42-43]. And ***bioluddism*** (or neo-Luddism, for technology in general) rejects emerging biotechnology and passively or actively opposes its effects on the environment, individuals, and communities [44-45]. Because these ideologies derive from personal perspectives and preferences, we do not address them further.

[7] As a philosophic idea, transhumanism (as well as bioconservatism and bioluddism) has many sub-variants, which this report will not cover. For example, see extropy [41].

The History of Human Modification

Before we discuss the current state of research in genetic engineering and human-centered bioengineering, we first examine the history of human modification from a broad viewpoint. This approach places current and new technologies in perspective with what has come before, and it highlights what makes the present and expected future research so different.

A framework for human modification

One of humanity's distinguishing characteristics throughout history has been the multiplicity of ways in which humans shape themselves and their environment. We wanted to create a framework to organize and describe the modifications that humans make to themselves. We considered a "human modification" to be anything beyond what a human has at birth, encompassing tools and physical objects, such as a pair of glasses, as well as cognitive modifications related to information and knowledge.

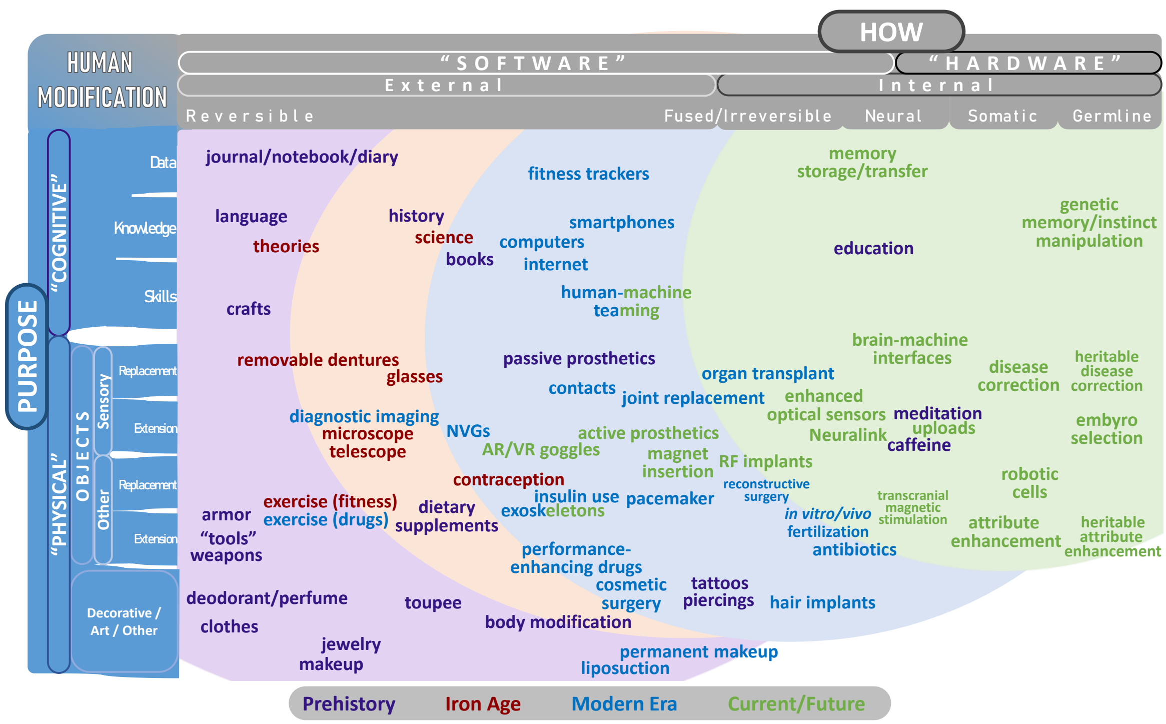
We have attempted to create such a framework by identifying two properties of modifications that humans make: **what purpose** does the modification serve, and **how** does the modification interact with the human? Figure 3 shows this framework, and we next describe its pieces. Appendix A describes some of the entries in Figure 3 in more detail, and it provides a larger version of the figure with even more entries.

What purpose? We have chosen to represent the purpose of human modifications using two broad categories: **cognitive** and **physical**. The cognitive category contains ideas such as data and knowledge. The physical category contains **objects**, which can serve as a **replacement** for a human function (such as a prosthetic device replacing a missing limb), or they can provide the human an enhancement, or **extension**, of normal human capabilities (such as a microscope extending regular human eyesight). We further divide these objects into **sensory** (related to the five senses) and **other** (everything else). Finally, we include a category for **decorative** items. This category can include modifications that serve an artistic, sacred, cultural, or other purpose.

How? We have chosen to represent how humans modify themselves by starting with two broad categories of **software** and **hardware**. This approach uses verbiage similar to that introduced by Max Tegmark in *Life 3.0*, in which he describes categories of life around living organisms' ability, or lack of ability, to modify their software (their culture and environment, which includes things such as language and tools) and their hardware (their genetic code, or the entity that they inhabit) [17]. We further divide this axis into modifications **external** and **internal** to the entity. And then we divide yet again into modifications that are **reversible**, **fused/irreversible**, **neural**, **somatic**, and **germline**.

Neither of these properties—how and purpose—represent a true linear spectrum, but they serve their role in differentiating the various aspects of human modification. Note that the external and internal categories do not split quite evenly between software and hardware, and that the fused/irreversible category bridges the divide between external and internal.

Figure 3. Human modification framework



Source: CNA.

Note: See Appendix A for a larger version of this figure with additional entries, as well as definitions.

Having established this framework, we then populated it with human modifications, which resulted in Figure 3. We describe a few additional caveats about this framework:

- **Not exhaustive.** We have not listed every possible modification. We ensured that we included major categories and concepts, but we could always add more detail.
- **Detail versus broader categories.** Because of the wide variation of types of modifications, we did not use the same level of detail for every category. For example,

we listed “tools” instead of hammer, saw, scissors, and so on. But we identified specific types of medical procedures, such as pacemakers and organ transplants, rather than using a broader term.

- **Exact placement**. We placed the modifications roughly in the location, based on the how/purpose descriptors; however, some modifications span multiple categories or do not fit neatly into one spot.
- **Color coding**. We colored the modifications based *roughly* on when humans first started using them, using four general time periods: prehistory (purple), Iron Age (orange-red), modern era (blue), and modifications currently under development or future ideas and concepts (green). We could likely color a number of other modifications green based on likely future advances in materials (such as armor, weapons, tools, prosthetics), but we chose to reserve the distinction for truly innovative modifications. This color coding revealed general groupings, which we then denoted by coloring in the background.

From the human modification framework, we draw three observations:

1. **Humans have been extensively modifying themselves for a long time, and they will continue to do so**. Other species may also use tools [46], but homo sapiens have created and used the most. Tool usage and modifications for humans go back well before recorded history (and as we have defined it, the act of recording history is itself a human modification) [47]. Research in neuroscience suggests that such behavior is a natural output of human brains as hypothesis-testing systems [48-49]. Accordingly, humans will continue to modify themselves, and they will continue to discover and take advantage of new technology.
2. **The focus of human modifications is shifting to the “right” of the framework, which is different than modifications that have come before**. These areas represent the irreversible, neural, somatic, and germline areas—or mostly the “hardware” for humans. Hardware modification has long stayed in the realm of science fiction and other tales, but science is beginning to make some of these concepts a reality. This shift represents the truly novel and different, which is why these technological advances represent such a dramatic change from what has come before.[8]
3. **Various groups want to direct the path that humanity takes as it explores the “right” of the framework**. Perhaps this observation does not leap directly from the

[8] To foreshadow some of the approaching challenges, we note that in recent years the US military services have struggled to provide guidance on tattoos, a rather old form of human modification [50-52].

framework, but it leads directly from the previous observation. Humans are beginning to explore modifications that reach into new realms, and we must make choices about how to explore and use these modifications. Some organizations, such as Tegmark's Future of Life Institute, want to ensure that humanity purposefully chooses its path [17]; however, this area is outside the scope of this discussion.

State of Research

Equipped with the context of the long history of human modification, this section explores the state of research in the areas of genetic engineering and human-centered bioengineering. Advances in a variety of areas have converged, leading to the rapid advancement of research. These advances include computational power, massive data sources (largely through resources on the internet), machine learning, nanotechnology (particularly fabrication), biotechnology, and neurotechnology. Research in these areas is progressing at a rapid rate, meaning that any attempt to describe the "state of the art" will quickly be outdated. Even so, we describe some of the latest breakthroughs to understand the likely trajectory of research in the coming years.

We divide the research discussion into two general areas: genetic engineering and human-centered bioengineering. Then we discuss the general status of research in the United States, China, Russia, and the biohacking community.

Genetic engineering

Genetic engineering involves the purposeful manipulation of an organism's genetic structure to add to, delete from, or otherwise alter the existing DNA sequence. This capability generally has two potential uses: to **correct** malfunctioning genes (e.g., diseases such as cystic fibrosis, β-thalassaemia) or to choose desired attributes, including **alterations** and **enhancements** (e.g., "designer" genes such as greater height or greater intelligence[9]). And in general, genetic engineering can apply toward somatic cells (which would affect only the organism) or germline cells (which would affect only future generations)[10] [54]. Figure 4 provides a simple comparison of these possibilities.

[9] Traits may not rely only on the sequence of a gene. Some human traits derive from one gene or a few genes. Other traits likely derive from hundreds of genes, which may have complex interactions with each other and their cellular and physical environment.

[10] **Germline** and **somatic** refer to whether genetic material can pass to future generations. Somatic cells (e.g., heart cells, liver cells) cannot pass genetic material to future generations, while germline cells (e.g., sperm or egg cells) can. Changes to germline cells are **heritable**. But, in 2014, researchers demonstrated the ability to turn skin cells into stem cells, and then into sperm and embryo cells, thus converting somatic cells into germline cells, albeit in low yield [53].

Figure 4. A comparison of roles of somatic and germline editing

	Somatic	Germline
Extension / enhancement	Change an attribute or quality for a person	Change an attribute or quality for future generations
Correction / replacement	Cure a disease or problem for a person	Cure a disease or problem for future generations

Source: CNA.

Scientists first began to modify the genes of organisms in the 1970s, starting with simple creatures such as bacteria and mice [55-56], and they have continued to do so to the present day. Over the last five decades, the largest change has been the *methods* of the genetic alteration. We describe here some direct gene manipulation methods:[11,12]

- ***Gene delivery*** involves the introduction of foreign genetic material into the nucleus of a host cell [60]. This foreign genetic material may remain separate from the host genome, or another method may incorporate the foreign material into the host genome.

[11] Breeding and mutagenesis also involve changing genetic structure, but they are not usually included as methods of genetic engineering. Traditional breeding involves the introduction of desired genetic traits through cross-breeding successive generations of offspring [57], while mutagenesis involves the (usually) random alteration of an organism's genetic sequence [58].

[12] Another method of gene manipulation involves **gene interference**, which uses RNA (ribonucleic acid) or DNA strands or enzymes to bind to specific genes or messenger molecules, thereby deactivating them. Several drugs using this technique are available, but we will not explore this topic further [59].

Some bacteria can naturally incorporate foreign DNA, but most cells require an additional process to make their membranes permeable and allow external genetic material to enter. These processes include a variety of chemical and physical methods (such as electroporation [61] or biolistics [62], see Figure 5), as well as the use of agrobacterium and viral vectors. These methods tend to insert the foreign genetic material in random places in the host genome.[13]

- ***Gene editing*** involves the direct alteration of existing genetic material. The four main methods of gene editing all use some form of nucleases, which are enzymes capable of cleaving DNA and RNA (ribonucleic acid). These methods include meganucleases [63], zinc finger nucleases (ZFNs) [64], transcription activator-like effector nucleases (TALENs) [65], and clustered regularly interspaced short palindromic repeats (CRISPR) and the CRISPR-associated (Cas) nuclease system [66]. The latter two methods have gained popularity recently [67]. TALENs tend to have greater target specificity, and CRISPR-Cas technologies tend to be easier to design and are more adaptable [68-69]. For a comparison of these gene editing methods and more information on how CRISPR works, see Appendix B. In short, CRISPR-Cas technologies allow for the relatively easy creation of knockout genes (genes that no longer function properly due to errors in the gene sequence, whether insertions, deletions, or frameshifts). They also allow for easier gene insertion or gene editing at specific sites by adding the appropriate templates or Cas variants.

[13] The location of the genetic code in the genome can matter as much as the code itself. Insertion of foreign genetic code can lead to unpredictable or not useful results.

Figure 5. An example of a "gene gun" used for biolistics

Source: Bio-Rad PDS_1000/He Particular Delivery System, picture by Xmort in 2005.

Gene editing technologies currently suffer from "off-target effects," a euphemism for editing that occurs at unintended parts of a genome. In a multi-cellular organism, an editing action may also not affect all cells equally, resulting in a **mosaic** organism, meaning an organism has a mixture of corrected and uncorrected cells. The editing (and insertion) methods often involve removing target cells of interest, editing them in vitro, and then redelivering the cells to the host. In vivo delivery is possible, most commonly with adeno associated viral (AAV) vectors, but nonviral methods are also available. Other challenges to successful gene editing include host immune response and DNA damage response[14] [68].

Historical and recent developments

China approved the first gene therapy in 2003 to treat a type of skin cancer [70]. But the first in vivo gene therapy drug for the United States did not arrive until December 2017,[15] when the US Food and Drug Administration (FDA) approved a treatment for an inherited form of vision loss [72]. The FDA has since approved 18 gene therapy treatments as of late July 2020 [73].

[14] The host's immune system may attack and destroy or alter the gene editing machinery, or the host's own DNA corrective machinery may interrupt the gene edits in unintended ways.

[15] In 1999, Jesse Gelsinger received an experimental gene therapy treatment for ornithine transcarbamylase deficiency. The treatment triggered a massive immune response in Jesse's body, resulting in multiple organ failure and brain death [71].

Other examples of gene therapy developments include:

- In May 2017, Temple University researchers reported the elimination of human immunodeficiency virus-1 (HIV-1) infection in live animals using a viral vector delivered CRISPR-Cas9 [74]. In 2019, further Temple University research, in conjunction with the University of Nebraska Medical Center, used a new slow-release delivery system to suppress HIV replication and remove HIV DNA from one-third of infected mice [75].
- In 2017, the first two chimeric antigen receptor T (CAR T) cell therapies were approved to treat advanced lymphoma and leukemia [76]. Different from nuclease therapies, CAR T cells are a form of synthetic biology, meaning that researchers use existing biological parts to design new biological systems that perform new functions—in this case, to attack and eliminate cancerous cells [77].
- In 2018, researchers preformed the first in vivo test of a gene therapy treatment using ZFN for Hunter syndrome, a genetic disorder which causes large sugar molecules to build up in the body. The treatment inserted a working copy of a defective gene into liver cells [78]. Initial results suggested that editing occurred, but not to the levels needed for effectiveness [79].
- In November 2016, researchers at Stanford University used CRISPR to correct sickle cell anemia in mice. They demonstrated that their process could correct 30 to 50 percent of diseased cells (with prior research showing that only a 10 percent correction of cells would cure the disease). According to their report, "The process will involve using chemotherapy to wipe out a patient's blood system but not their immune system, as is done in a stem cell transplant. Then, the team would inject the patient's own corrected stem cells, which the researchers hope would engraft into the bone marrow and produce healthy blood cells" [80].[16] Human trials began in 2019, and as of June 2020, the first patient to receive the treatment appears to be "alleviating virtually all complications of [sickle cell disease]" [83].
- In early 2020, a clinical trial tested the first example of an in vivo CRISPR therapy for an individual with a genetic mutation that causes blindness in childhood. Doctors injected the therapeutic mixture directly into the eye, near the affected photoreceptor cells [84].

[16] Interestingly, this procedure does not appear to correct the sickle cell defect, but instead it turns on the gene that produces fetal hemoglobin to counter-balance the sickle cell effect [81]. Early results from the first patient showed that nearly 95 percent of her red blood cells contained fetal hemoglobin, and that nearly 47 percent of her hemoglobin was fetal hemoglobin. This approach also has therapeutic benefits to β-thalassemia patients [82].

Heritable editing in humans

All of the previous research describes the editing of somatic cells, that is, nonheritable changes. The editing of germline cells, or heritable changes, in humans has largely been under a global moratorium.

In the United States, numerous publications in the early 2010s referred to a statement that the National Institutes of Health "will not at present entertain proposals for germ line alterations" [85-86], which appears to derive from the guideline document *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*. This wording appeared in at least a 2015 version of the document [87]; the April 2019 version no longer appears to contain this statement or similar wording [88].

A more formal ban on human heritable gene editing entered law with the fiscal year (FY) 2016 spending bill, which prohibited the Food and Drug Administration from funding research involving the germline editing of human embryos [89]. In 2019, the House briefly removed this wording for the FY 2020 spending bill in order to encourage fuller debate on the topic, but the House restored the wording before moving forward with the bill [90].

In February 2017, the National Academy of Sciences released a report suggesting that with proper oversight, heritable human genome editing could be permissible for serious conditions that had no other alternatives [91].

Then in September 2020, the National Academy of Sciences released a more detailed report on *Heritable Human Genome Editing*, which had input from experts in 10 countries. The report found that gene editing technology is not yet ready for clinical application, and it warned against using it until researchers could address safety concerns and have thorough discussions with the public [92-93]. In particular, they noted the same challenges we described above for somatic editing: off-site targeting [94] and mosaicism [95].

In spite of these general views, a few notable (or perhaps notorious) stories of human germline editing have appeared in the last few years:

- In 2015, a Chinese scientist edited the genome of human embryos in an attempt to correct a genetic blood disease. The scientist used abnormal in vitro fertilized embryos and destroyed them after the experiment [96].
- In late 2018, Chinese scientist He Jiankui reported the birth of gene-edited twin girls, with a second (and third) pregnancy still underway—the so-called "CRISPR babies." The scientist attempted to incorporate an edit to infer HIV-resistance, as well as an additional edit to lower "bad" cholesterol production. Global researchers condemned the announcement. Further revelations suggested that the experiment did not go as

cleanly as the research team thought. China's National Health Commission ordered an investigation into the work, and in January 2019, the university fired the lead researcher [97]. Some sources suggested that the Chinese government may have funded the CRISPR baby research; however, an investigation by Guangdong Providence claimed that He raised his own funds [98].

- In the aftermath of the CRISPR babies, at least one Russian scientist has openly announced his plans to perform a similar edit for HIV-resistance, claiming that he has a technique to eliminate off-target edits [99-100].

General trends and challenges

In a way, CRISPR is doing for gene editing what AlexNet[17] did for deep convolutional neural networks and image recognition—inspiring a sudden flood of research and funding focused on improving the technology and on exploring potential applications.[18] Even in the few years since its discovery, researchers have made various tweaks and improvements to the CRISPR tool set to improve its capabilities and reduce unwanted effects.

Near-term trends: More gene therapy treatments will become available. The techniques for gene editing will continue to improve, and the costs will decrease. As researchers understand and tweak the different technologies, gene editing will find more and more uses. More advances will happen first in nonhumans (animals, crops, biofuels, medicine) [102], and research in humans will initially focus on corrections. The biggest near-term challenges are minimizing or limiting off-target edits and increasing the success rate of corrective edits.

Far-term trends: As researchers make progress in correcting diseases with genetic editing, the focus of edits will likely expand to genetic enhancements. To make useful enhancements, scientists will need the ability to identify genes to tweak (genotypes) to achieve specific characteristics (phenotypes). Researchers are already trying to unravel these connections, such as a gene prominent in people who need less sleep [103]. However, with 20–25,000 genes in the human library, some attributes likely have complex combinations between many genes.

Challenges: Aside from the ethical discussions, the continued development and broader implementation of these technologies will reveal new and presently unknown problems. For example, CRISPR technology has introduced the possibility of implementing a "gene drive," a method that ensures a particular genetic trait always passes to progeny [104]. Although the technology could have beneficial ends, such as wiping out malaria [105], it could also have

[17] See the footnote in "Background" section for more information on AlexNet.

[18] In 2016, the Director of National Intelligence identified CRISPR as an emerging threat technology [101].

nefarious uses, or unintended consequences such as spreading beyond the intended target area. Just as AI and machine learning have introduced new categories of vulnerabilities and adversarial attacks, genetic engineering technology will also open a whole host of unforeseen problems.

Human-centered bioengineering (more than cyborgs)

Moving from the genetic modification of humans, we next explore the technological modifications of humans. These modifications span a wide spectrum, from simple chip implants to the replacement of limbs and organs with biomechanical (or fully mechanical) counterparts. To enable a meaningful exploration of the spectrum, we must first address the current available terminology.

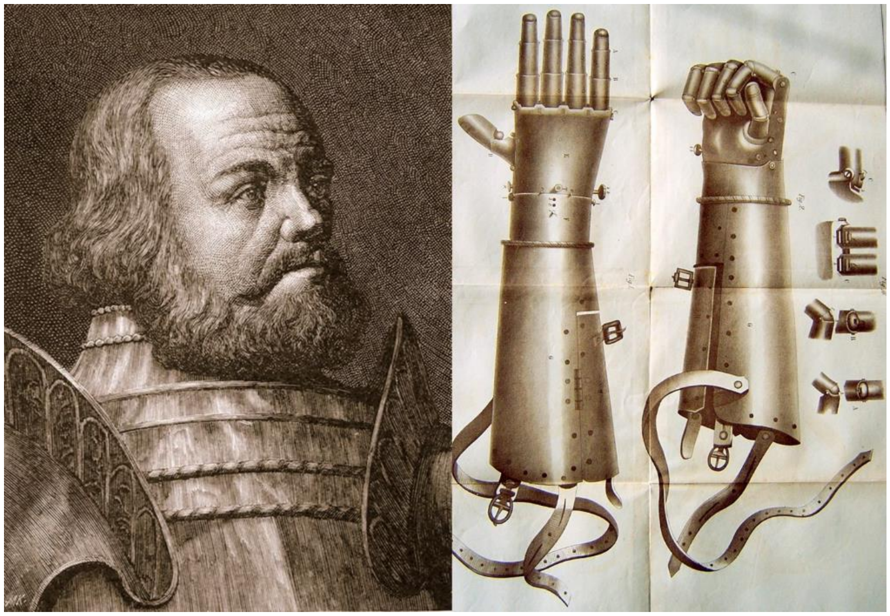
The term ***cyborg*** (short for cybernetic organism)[19] comes the closest to our intent, referring to an organism with both organic and mechanical body parts.[20] The exact definition of a cyborg can vary widely, largely depending on how one views the nature of the mechanical body parts. For example, as with genetic engineering, the mechanical parts may restore the original function of the part that they replace, or they may enhance that original function. They may or may not actively receive feedback for their function. This broad definition can lead to philosophical debates about whether a particular case "counts" as a cyborg.[21]

[19] The term ***cybernetics*** refers to the "scientific study of control and communication in the animal and the machine" [106]. It does *not* refer to, strangely enough, the types of modifications found in a cybernetic organism (although some references do use the term in that way).

[20] The term ***cyborg*** came from work by Nathan S. Kline and Manfred E. Clynes in 1960, who described enhancing a human for surviving in extraterrestrial environments rather than modifying the environments to support the human [107].

[21] There is general agreement that cyborgs represent biological organisms that have had functions restored or enhanced through technology. This definition excludes constructs such as robots and androids, which are purely artificial.

Figure 6. Götz of the Iron Hand (1480 – 23 July 1562), with an iron prosthetic hand



Source: Left, a 17th century engraving, unknown author, public domain [108]; right, prosthetic iron hand worn by Götz, unknown author, public domain [109].

Even with a broad definition of *cyborg*, we also want to include technology such as exoskeletons and wearable technology. Therefore, we use the term *human-centered bioengineering* to broaden even further the types of technology and modifications that we can include in our discussion,[22] regardless of the specific terminology that appears in the literature.

We next examine some of the latest human-centered bioengineering research. We identified, nonexhaustively, five areas to explore: prosthetics, sensory and organ parts, brain-computer interfaces, implants (or "irreversibles"), and wearables (or "reversibles").

In general, advances in other research fields have enabled progress in the development of new technologies and capabilities for human-centered bioengineering. In particular, machine learning has enabled the creation of technology that can synthesize the complex inputs necessary for robotics and brain-interfaces, and additive manufacturing (3D printing) has enabled customized part creation, rapid prototyping, and lower cost [111].

[22] We did find one term that was coined in 2012: ***cybernics*** is the "fusion of human, machine, and information." However, this word does not appear to have found common use [110].

Prosthetics

In general, a *prosthesis* is an artificial device that replaces any body part. The most common prostheses replace entire or partial limbs, including individual fingers or toes, joints, and teeth and jaw sections (such as dentures). Prosthetic devices usually have the goal of restoring the function of the missing body part, but they may also serve a cosmetic goal [112].

Prosthetic devices can be passive or powered (either internally or externally). Prosthetic arms may use a voluntary open or voluntary close mode, meaning the prosthetic naturally sits in one state (open or closed), and the user must act to switch to the other state. Myoelectric prostheses use information from the user's neuromuscular system to control an electrically powered limb; these devices tend to weigh more than their nonmyoelectric counterparts [113]. But recent developments in 3D printing have made some prosthetic devices cheaper and easier to make (Figure 7) [114].

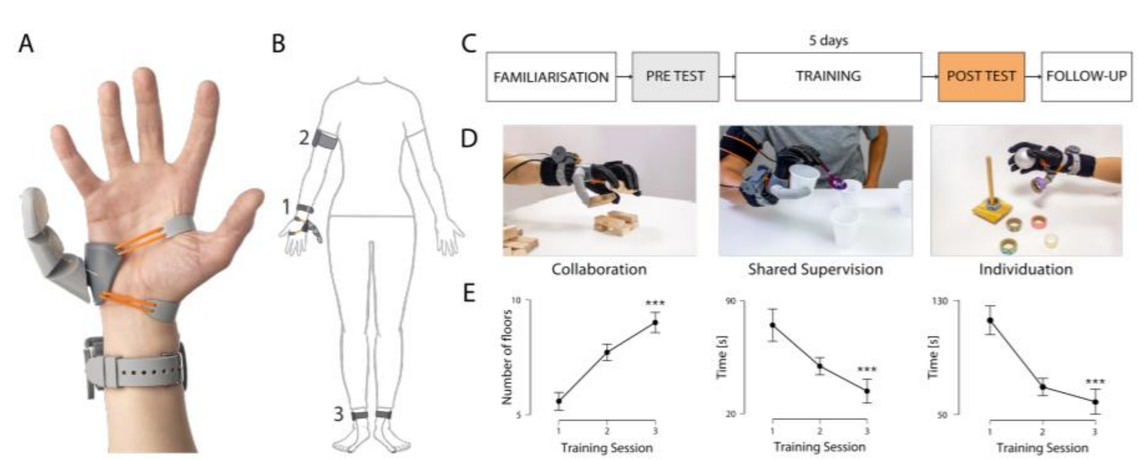
Figure 7. Raimi Davis uses a myoelectric Hero Arm with a Marvel Iron Man cover

Source: Open Bionics press images [114].

In the last couple of years, further breakthroughs in research have allowed for bidirectional feedback with prosthetic devices, which allows the user to sense what they are touching or how hard they are gripping an item [115-116].

As a glimpse into the area of augmentation, in 2020 researchers from University College London and Oxford University explored the neurocognitive impacts of augmenting the body with an additional prosthetic thumb (Figure 8). Volunteers controlled the "third thumb" with their foot, and they performed a variety of tasks using the additional assistance. Researchers found that the brain began to experience a "mild collapsing of the canonical hand structure," meaning that brain activity patterns showed a weaker representation of a traditional human hand. The research gives interesting insight into the ability of the brain to rewire when given new experiences and abilities [117].

Figure 8. "Third thumb" experiment into neurocognitive effects of augmentation



Source: [117].

Sensory and organ parts

Devices that assist human organs have been around for decades, such as dialysis machines for the kidneys (1940s) [118], pacemakers for the heart (1950s) [119], and cochlear implants for auditory systems (1950-60s) [120]; however, fully contained artificial devices that can replace major human organs have not yet arrived.

Although research is progressing on all fronts for human organs, we take a closer look at some of the recent progress in restoring eyesight [121]. In June 2019, researchers published results using Orion, an implant that bypassed the eye and optic nerve and transmitted video images directly to the visual cortex. The video images came from a camera mounted on a pair of eyeglasses. The 60-electrode brain implant allowed recipients to perceive the location of windows and doorways, as well as the differences between a sidewalk and grass [122-123]. In February 2020, researchers at the University of Miguel Hernandez reported a similar technique using an 100-electrode brain implant that enabled the visualization of a 10x10 grid [124].

As a glimpse into the future of possible developments, in May 2020 researchers at Hong Kong University of Science and Technology published the concept for an artificial eye that "sees" like a human eye (differing from the electrode approaches above). Their electrochemical eye (EC-Eye) uses a novel manufacturing method to create a dense collection of light-sensitive nanowires made of the mineral perovskite. The proof-of-concept model had a low resolution of 100 nanowires, but the researchers claim that improvements could result in resolution even better than human eyes, and with the potential to distinguish other areas of the electromagnetic spectrum, such as infrared [125].

Figure 9. The EC-Eye, a biomimetic eye, in comparison with a traditional human eye

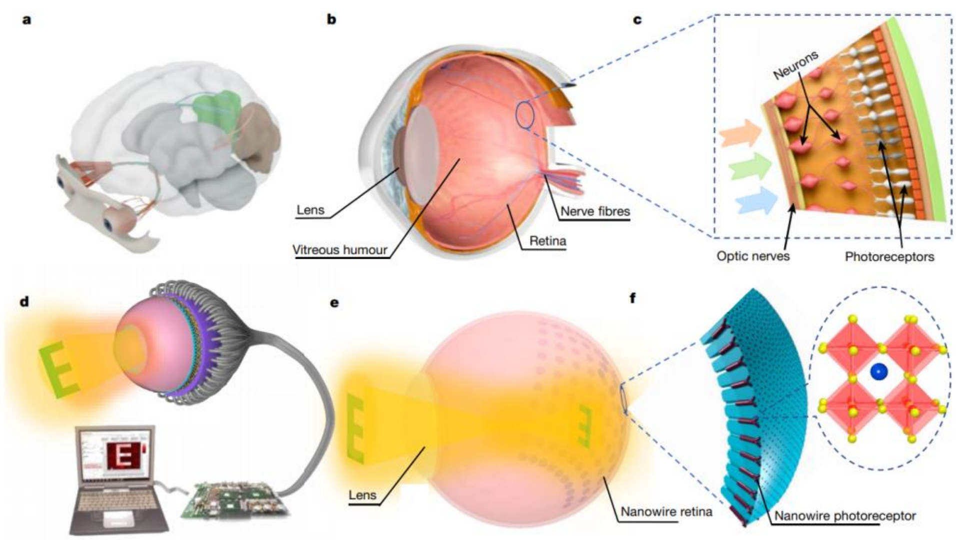


Fig. 1 | Overall comparison of the human visual system and the EC-EYE imaging system. a–c, Schematic of the human visual system (**a**), the human eye (**b**) and the retina (**c**). **d–f**, Schematic of our EC-EYE imaging system (**d**), the working mechanism of EC-EYE (**e**) and perovskite nanowires in the PAM template and their crystal structure (**f**).

Source: [125].

Brain-computer interfaces

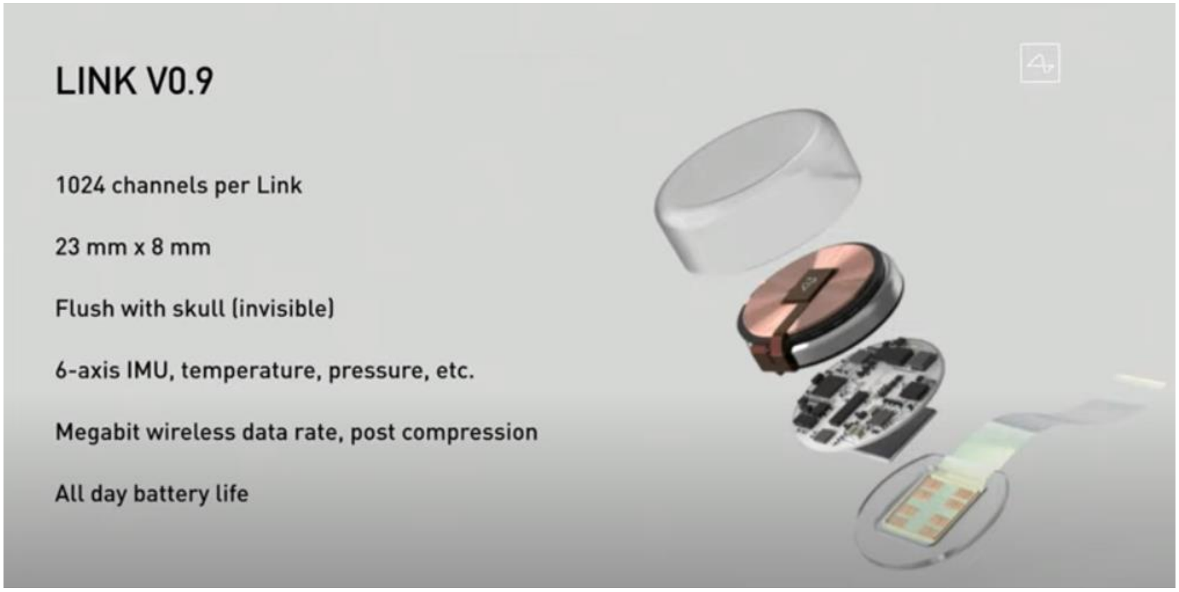
Brain-computer interfaces (BCI) (or sometimes *brain-machine interfaces* (BMI)) refer to any direct communication between a brain and an external device.[23] The connection with the brain can be invasive (with probes inserted into the brain) or noninvasive (with sensors placed on the outside of the skull). The BCI category covers a wide variety of applications, including the recent artificial eye research we mentioned in the previous section.

Research in this area has helped to shed light on the function of the brain, as much as it has helped with using the brain to interface with external devices. In particular, this research has helped to understand and explore the plasticity of the brain, which enables the brain to adapt to new signals from implanted devices [127] (which we already noted with the research using a "third thumb").

Although most BCI research involves using the brain to manipulate external devices, the technology holds the potential for the reverse—using devices to manipulate (or control) the brain. As a glimpse into possible future areas of development, Elon Musk founded the company Neuralink in 2016 to build a commercial BCI device for use in humans. An example of a general purpose BCI is the Neuralink, currently under development. The device has a number of fine electrodes that get inserted into the brain via a specialized robotic "sewing machine" [128]. In an August 2020 live update, Neuralink revealed that the organization has installed and tested the device in pigs. Demonstrations included the device identifying when the pig's (Gertrude's) snout was actively touching something, and a real-time prediction of the location of a pig's limbs from its neural information (as it was walking on a treadmill). The FDA has given approval to Neuralink as a "breakthrough device," meaning they can conduct limited human testing using the guidelines for testing medical devices (Figure 10) [129].

[23] The term ***neuroprosthetics*** sometimes gets used interchangeably with BCIs; however, neuroprosthetics tend to focus on restoring the function of impaired biological functions, such as the nervous system or particular brain functions [126].

Figure 10. An overview of the Neuralink device, from the August 2020 live update



Source: Neuralink [129]. IMU = inertial measurement units.

Other implants

We discussed the development of prosthetics in a previous section, but other devices are available that do not replace a biological function. Some of these modifications serve a cosmetic function, such as medical-grade stainless steel or silicone implants that create bumps and other shapes under the skin (so called 3D implants) [130].

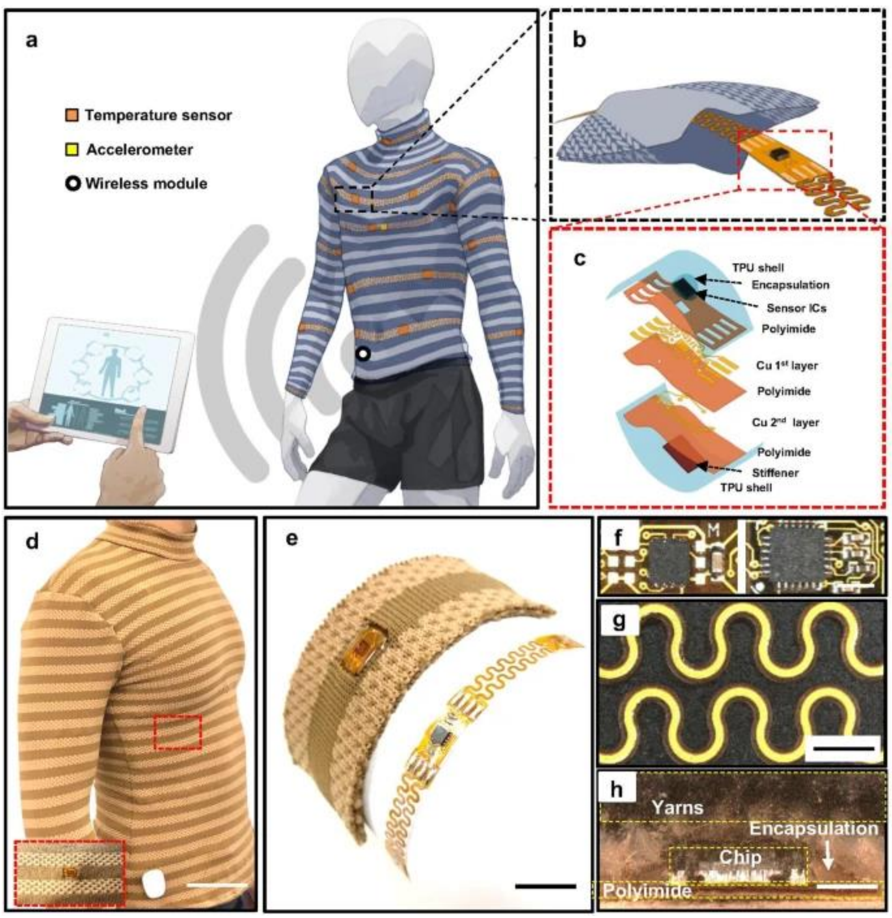
Other implants can serve an endless variety of functions. Because these devices tend not to serve a medical or "restorative" function, they also tend to find more of a home with hobbyists and other interested individuals. As such, we will discuss these devices more in the section on biohackers.

Wearables

Like implants, wearable devices can also cover an endless variety of functions. In this category, we include things such as fitness trackers, smart watches, and perhaps even smartphones (depending on how tightly people are holding on to them). Virtual reality goggles and altered reality goggles count as well. And we could include an electroencephalograph, which records electrical activity in the brain. Rather than discussing every device in the extensive zoo of wearables, we take a closer look at two particularly interesting areas: stretchable electronics, and exoskeletons.

Stretchable electronics. The dynamics of the human body can cause challenges for rigid devices, depending on the situation. Stretchable electronics, sometimes called *elastic electronics* or *elastronics*, have a variety of potential applications; for human modification, however, "smart garments" provide the most interesting applications [131] (Figure 11). They have the usual decorative and leisure applications, but smart garments could also provide medical monitoring functions such as detecting glucose levels or other biometrics [132].

Figure 11. Example of stretchable sensors incorporated into clothes for health monitoring



Source: [133].

Exoskeletons are wearable machines that typically increase the strength and endurance of the user. They can be passive or powered. Passive exoskeletons typically use springs or dampers to help bear heavy loads, while powered exoskeletons use an energy source to assist the user in various actions [134].

Exoskeletons tend to have a military connotation, thanks to popular science fiction stories and movies such as Iron Man. However, exoskeletons have important applications to medicine (in the convalescence of injured patients), industry (reducing worker injuries, assisting in moving heavy loads), recreation (such as skiing and snowboarding [135]), and other uses (such as helping firefighters carry heavy equipment [136]).

Special Operations Command (SOCOM) started a project in the early 2010s to create a tactical assault light operator suit (TALOS) [137-138] (Figure 12). The project intended to create a rugged exoskeleton for increasing speed, endurance, and range of movement of operators, with integrated sensors and communication. In 2019, SOCOM put the TALOS project on hold because the original goal was "too far ahead of what's possible." Instead, SOCOM made use of component parts of the project that had promising technologies (such as lighter body armor with more area of coverage) [139].

Figure 12. Prototype TALOS suit

Source: Revision Military.

General trends and challenges

Near-term trends. As was true of genetic engineering, the initial focal points of human-centered bioengineering are corrective and replacement applications. The technology itself will slowly become cheaper and more accessible, transforming the lives of individuals who benefit from these corrections or replacements.

Far-term trends. Again, similar to genetic engineering, we will likely see human-centered bioengineering move into enhancement and extensions of human capabilities. From eyes that can sense more than the visual spectrum and at higher resolutions, to ears that can hear a greater span of frequencies and at softer levels, the possibilities for enhancement beyond biological human limits could potentially extend to nearly every facet of human activity and function.

Very far-term trends. Humans might merge with machines (see Figure 1).

Challenges. Each of the areas mentioned in the previous sections have their own unique technological challenges and hurdles, whether needing smaller components, better power sources, stronger or more flexible materials, frequent upgrades, and so on. Advancements in science will likely continue to conquer each of these issues in turn. It is less clear how society will adopt and integrate these technologies. At present, the general stance of researchers is to consider application of nonreversible technology for only individuals with missing or malfunctioning body parts. It remains to be seen how attitudes will change as enhancement and extension technologies arrive. Will *healthy* individuals desire to use the technology (e.g., decide to remove a healthy biological arm and replace it with a bionic version)? Or will wearables advance to a stage that makes such choices moot, except for the individuals who desire to meld with metal?

Global interest and research

Most countries have regulations governing genetic research and human-centered bioengineering (particularly with medical applications). In particular, a number of countries have prohibitions against germline gene editing for reproductive purposes, though somatic gene editing generally has fewer restrictions. We discussed some of these restrictions in the previous section on genetic engineering.

This section examines the status of general research in genetic engineering and human-centered bioengineering in the United States, China, and Russia, and it describes the activities of another important group: the biohackers.

United States

The United States Department of Defense has no specific biotechnology research strategy [140], and thus no strategy regarding genetic engineering or human-centered bioengineering technologies.[24] Some of the services have explored possible future concepts through analysis and science fiction writing [141-143].

At the unclassified level, the Defense Advanced Research Projects Agency (DARPA) has a Biological Technologies Office, which explores capabilities in threat detection; protection and countermeasures; warfighting readiness, resiliency, and recovery; training effectiveness; and nontraditional platforms and capabilities. Most of these initiatives involve applications in medicine, materials, and sensors, but a few programs mention capabilities such as noninvasive brain interfaces (targeted neuroplasticity training (TNT) program [144]) and gene-encoded therapeutics. The Safe Genes program aims to protect service members from the misuse of genome editing technologies [145]. DARPA has reportedly invested at least $100 million in gene drive research. [146]. DARPA also supports the BRAIN Initiative with research in neurotechnologies through a variety of programs, including Next-Generation Nonsurgical Neurotechnology, Revolutionizing Prosthetics, and Restoring Active Memory [147]. The Intelligence Advanced Research Projects Activity (IARPA) also has a number of biotechnology initiatives underway, including Finding Engineering-Linked Indicators (FELIX), Functional Genomic and Computational Assessment of Threats (Fun GCAT), and Hybrid Forecasting Competition (HFC) [148].

Open-source reports have indicated that the United States is actively researching other applications for enhancing military service members [30-31]; however, as the Congressional Research Service noted, the United States has no national framework or guidelines for adjudicating ethical concerns [149].

China

China's civil-military fusion structure has allowed it to aggressively explore and implement technology in general, with clear examples in machine learning technologies such as facial recognition for surveillance [150-152] and policing of minority populations [153-154]. Similarly, biotech and robotics play a key priority in China's Made in China 2025 strategy,[25]

[24] We previously mentioned a compilation from the Office for Human Protections. For the United States, most of the guideline documents are over a decade old [24]

[25] That strategy became a lightning rod for international political problems in recent years. China no longer refers to that strategy, though its principles and goals still remain [155].

though it does not specifically identify genetic engineering or human-centered bioengineering [156].

China is investing heavily in education and infrastructure to support these goals. For example, in 2016 it opened the China National Genebank for housing vast amounts of genetic information (more than 10 million samples expected) [157]; the Federal Bureau of Investigation has raised concerns about the amount of US genetic information going overseas [158].

The nation has frequently prioritized power over ethics, such as making ethics boards optional at hospitals, but making mandatory the presence of Communist Party branch offices [159-160]. These priorities tend to place it at odds with the ethical practices of Western institutions and governments [161], and they have resulted in some experiments that raise the eyebrows of bioethicists around the globe [162].

According to Kania and VornDick, recent Chinese military writings emphasize the importance of biology and biotechnology, and the Central Military Commission has funded projects on a variety of topics including neurology and human performance enhancement [163]. They also cite a 2017 publication of the Science of Military Strategy, which included a section on biology as a domain of warfare, and mentioned the potential for new warfare, such as “specific ethnic gene attacks” (see the section on “bioweapons” in the Introduction section of this paper). People’s Liberation Army hospitals have also been involved in CRISPR therapy trials [164].

Russia

Russia has attempted to improve its biotechnology sector, including releasing a whole-of-government strategy called BIO2020 in 2012. It identifies the application of biotechnology to a variety of fields such as medicine, agriculture, marine life, and environmental protection, but it does not specifically call out genetic engineering (or human-centered bioengineering) [165]. As part of this effort, Russia has created the technological platform BioTech2030, which includes about 100 organizations from across industry, education, working groups, and councils. BioTech2030 seeks to create a “modern bioindustry which will provide contribution to GDP comparable to the world’s leading economies” [166].

In 2017, Russia’s President Putin stated that a genetically modified human might be “worse than a nuclear bomb” [167]; this proclamation received much less sensational coverage than his comment about AI. Russia has a moratorium on most gene editing; however, in 2019, a Russian scientist announced plans to try a modification of the notorious CRISPR baby-editing experiment [99]. Scientists rallied through *Nature* to call for a stop of such experiments, but senior Russian officials suggested that Putin would determine the outcome, possibly privately [168-169].[26]

Fewer open sources cover Russia's military interest and applications for biotechnology.[27,28] Russia's exoskeleton program perhaps has received the most coverage, with both passive and powered versions in development [172-174].

Figure 13. Example of ROSTEC's Ratnik Exoskeleton (passive)

Source: ROSTEC.

[26] In the few months from the initial announcement, the target experiment shifted from replicating He's CCR5 gene deletion to targeting GJB2 genes to prevent a deaf couple's child from inheriting their condition.

[27] Russia does have many AI and machine learning efforts underway, which may have areas that overlap with biotechnology. CNA has a series of newsletters that examine Russian publications for the latest information; see for example [170].

[28] At the beginning of this report, we noted that we would not address biological weapons. However, we note in passing that, in spite of the 1972 Biological Weapons Convention, Russia does appear to maintain Biopreparat, an extensive biological weapons program (ironically, created in 1972) [171].

Biohackers

The majority of research and funding for genetic engineering and human-centered bioengineering may reside with the usual institutions, such as governments, universities, hospitals, and industry. However, hobbyists and interested individuals have created communities to share their passion and research with each other. Though the groups as a whole have no formal name, they tend to refer to themselves as "biohackers."

Biohacking includes many types of activities: using devices (such as fitness trackers) to measure biological functions, changing eating and sleeping habits or other behaviors to tweak performance (including chemical experimentation), modifying bodies with implants or other surgical procedures, or modifying the DNA of organisms. The latter two groups have become amateur cyborgs and genetic engineers, and we discuss them further in this section [175].[29]

Biohackers have unprecedented resources that enable and empower their interests:

- Access to information via the internet, including:
  - Communication between interested participants (personal communications, topical forums, or local and global communities)
  - Open-access knowledge databases and instructional videos, built and maintained by organizations and communities
- Access to equipment and supplies, including:
  - Access to industrial or academic-grade equipment and supplies
  - Instructions on how to make home versions of laboratory equipment
  - Access to other modes of innovation, enabled through technologies such as 3D printing [176]

The internet provides a key venue for people to learn, ask questions, and discuss possibilities. As Nick Bostrom noted, internet communication played an important role for transhumanism discussions in the 1990s [40], and the internet plays a similar role today for biohackers.

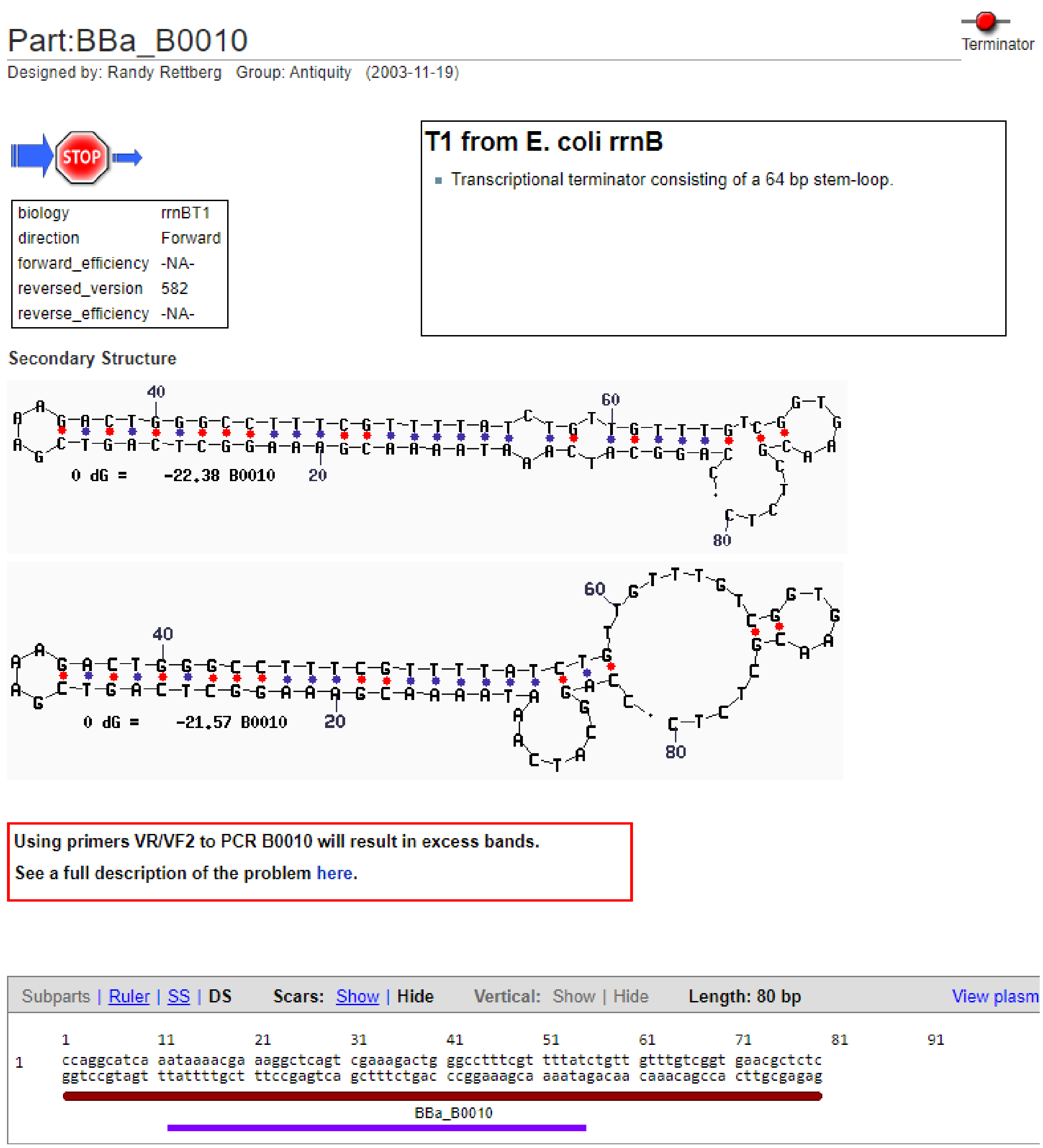
The biohacking genetic engineers

As an example of the knowledge databases available online, in the mid-2000s, the International Genetically Engineered Machine (iGEM) Foundation established a Registry of Standard Biological Parts, which provides a "growing collection of genetic parts that can be mixed and matched to build synthetic biology devices and systems" [177]. Figure 14 shows an example of

[29] This report will not further discuss the first two groups.

a "building block" for a transcriptional terminator; the library includes information on the genetic sequence and other information useful for experimentation.

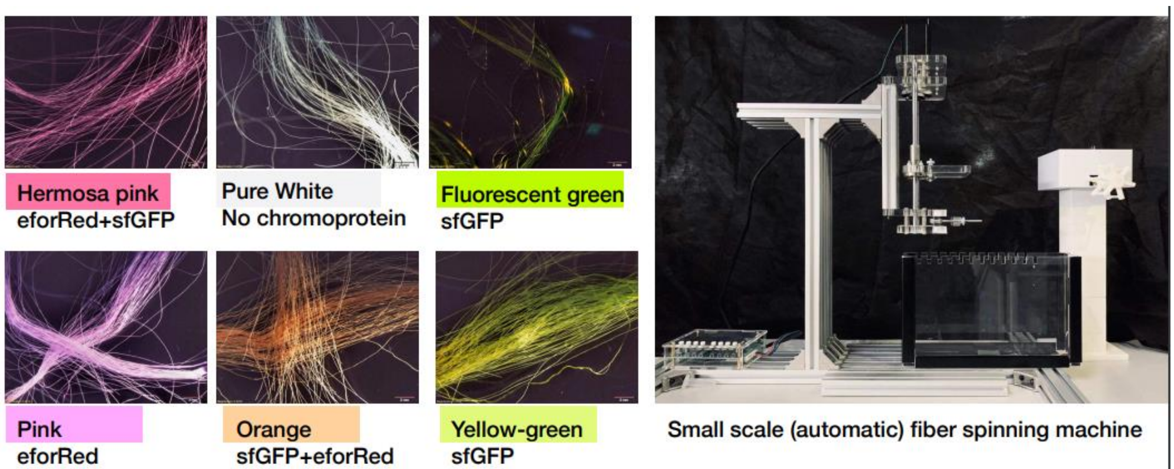
Figure 14. Example information available in the Registry of Standard Biological Parts



Source: Registry of Standard Biological Parts [178].

The iGEM Foundation also holds competitions every year for high school, undergraduate, and graduate teams from around the globe; the teams identify problems to solve and then use the genetic parts to build solutions. The organization provides all of this information, along with instructions on tools and safety, as open access. Figure 15 shows an example of the winning high school entry for the 2019 iGEM competition. The team assembled the biological building blocks to create and manufacture spider silk, and they identified chromoproteins to dye the silk in a variety of colors.

Figure 15. Great Bay Shenzhen High School team's spidersilk project for 2019 iGEM competition



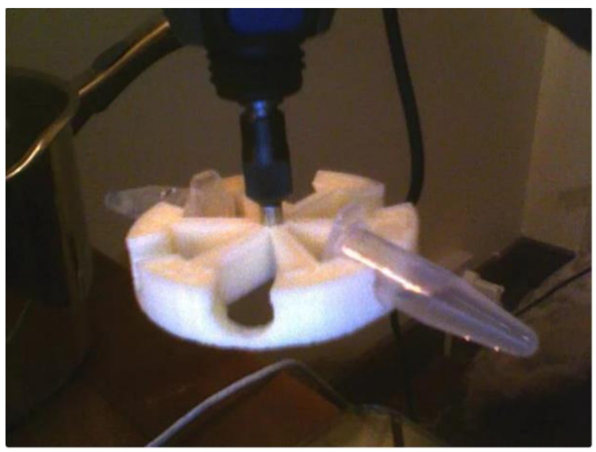
Source: Great Bay Shenzhen High School, iGEM 2019 High School Grand Prize Winner [179].

Numerous websites offer equipment and materials for starting a biology lab in the basement or garage [180-182]. For biohackers with fewer resources, some websites offer do-it-yourself (DIY) instructions on how to build makeshift lab equipment (for example, see the home-built centrifuge in Figure 16; see [183] for more resources). For those with even fewer resources, some areas have community laboratories for people to use (for example, [184]). Many other such tools and community groups are available [183, 185-187], including educational sites [183, 188].

DIY genetic engineers tend to focus on synthetic biology building blocks, cuttlefish, or beach hoppers, and the availability of CRISPR has made genetic editing more affordable (and more repeatable) than TALENs and other editing tools [189]. Some DIY biohackers have turned their attention toward hacking the human body, sometimes tinkering with their own gut bacteria and personal microbiome [190], but also sometimes attempting to edit their own DNA [191] or experimenting with other methods [192].

In some cases, CEOs or other entrepreneurs take matters into their own hands, whether for personal reasons or to demonstrate the value of a potential method or product [193-194]. In one very visible case, a CEO of a biotech firm injected himself with an experimental herpes treatment in front of a live audience at Body Hacking Con in 2018 [195]. The FDA has released a statement about "Self-Administration of Gene Therapy," which highlighted the legal procedures for clinical studies, noting that the "sale of ['do-it-yourself' kits to produce gene therapies for self-administration] is against the law" [196]. Proponents have countered that their experiments are legal if nothing is for sale, and they cite a long history of self-experimenting scientists [197-198]. Ultimately, the FDA has little control over the activities of experimentally-inclined hobbyists in their private garages and basements.

Figure 16. Image of a free 3D-printable tube holder for rotary tools



Source: DremelFuge [199].
Note: The maker claims that with a Dremel 300 tool, the "DremelFuge" can achieve 33,000 revolutions per minute, putting it in the "ultracentrifuge" category [199].

As a further example of the resources available, one website offers equipment such as a USB-powered polymerase chain reaction (PCR) thermocycler that can amplify DNA, and a genetic engineering home lab kit (including a centrifuge capable of 10,000 revolutions per minute, a gel electrophoresis box, a variety of pipettes, and more; see Figure 17). Other offerings include a bacterial genetic engineering CRISPR kit (which modifies a nonpathogenic E. coli strain to survive on a normally preventive media) and kits for growing and modifying human cells.[30] Most of these kits costs a few hundred dollars or less.

Figure 17. An example of genetic engineering products available for online purchase

Source: The ODIN (https://www.the-odin.com).
Left: bioengineering kit to make brewer's or baker's yeast fluoresce (under black light) [202]; right: genetic engineering home lab kit.

The biohacking cyborgs[31]

For healthy humans, *cyborg biohacking* mostly involves incorporating technology into the body via subdermal implants. These implants tend to have two general functions: serving as an information and communication device, or providing an additional "sense" to the user (or both).

Information and communication. Chip implants have been around since the late 1990s [204]. The most common implants use radio-frequency identification (RFID) tags, near-field

[30] This website also offered a human CRISPR knock-out kit to target exon 1 of the myostatin gene, presumably to increase muscle mass [200]. The offering included a note that the product was not meant for human injection because the DNA needed purification and replication (as well as additional chemicals to get the CRISPR system into cells). The product is no longer in stock. It is unclear whether that is due to the FDA restriction on selling unapproved human gene therapy products or for other reasons [201].

[31] Let's face it, "biohacking cyborgs" sounds a lot cooler than "biohacking human-centered bioengineers." Sometimes the biohacking community uses the term ***grinder*** to refer to people engaged in changing and enhancing the ways their bodies function, but this term also generally refers to the full suite of options [203].

communication (NFC) tags, or other integrated circuits (such as transponders), usually sealed in silicate glass or biopolymers. These tags can store small bits of information and operate in the same way as tags on a credit card, security badge, or any other related technology. The implants, as small as grains of rice, operate passively and do not contain any power source. Some implants contain power-harvesting light emitting diodes (LEDs) that light up when exposed to the proper electromagnetic field (Figure 18) [205]. In 2017, for example, a Wisconsin-based company offered chip implants to its employees for accessing the office building, logging into computers, and purchasing food and drink at office markets and vending machines; around one-third of the employees have used the technology [206].

Figure 18. NFC implants with LED (left) and installed in a hand (right)

Source: Dangerous Things [207].
Note: The implant (shown left) measures 15mm x 2.1mm.

Sensing. Implanted devices may give extra senses to the users. Perhaps the most popular choice involves the implanting of magnets into the hand, which saw a surge of interest in the early 2010s; the magnets give the users the ability to sense magnetic fields in the environment[32] [208]. Another type of device offers users the ability to sense when they are facing north by providing haptic feedback [209], though this particular device is bolted onto the outside of the chest, not embedded. Another device, the North Star, offers users the ability

[32] It also prevents users from certain activities, such as entering a magnetic resonance imaging machine (MRI).

to control an electronic device through hand gestures (Figure 19) [210-211]. The cyborg artist Neil Harbisson, who was born with achromatopsia (total color blindness), had an antenna implanted in his skull in 2004, which he uses to hear and feel colors as audible vibrations sent through his skull [212]. He has made other modifications to his body, including a Bluetooth tooth that can communicate via vibrations to another tooth [213], and a "solar crown" that marks solar time by a point of heat that rotates around his head [214].

Figure 19. Early version of the North Star implant

Source: Grindhouse Wetware, Ryan O'Shea.

The biohacking cyborgs and grinders (biohackers who alter their own bodies via chemical or technological means) have established many communities and places for sharing information, whether locally or on the internet [215]. Websites offer implants and other tools for device installation, though these websites recommend professional installation.[33] Not surprisingly,

[33] Professional installation in these cases typically refers to tattoo parlors and piercing studios. These businesses may not use any form of anesthetic, which would constitute the practice of medicine. These procedures also fall into the area of "consented assault."

they also come with disclaimers such as "[these devices] have not been tested or certified by any government regulatory agency for implantation or use inside the human body. Use of these devices is strictly at your own risk" [216].

General trends and challenges

Near-term trends. Research will continue apace, whether in government institutions, academic and industrial laboratories, or home garages and basements. The biohacking movement will likely remain "fringe" in the short term. But nations must begin to address concerns about ethics and oversight, particularly as individual nations (or scientists or biohackers) push the boundaries of technology and human interaction.

Far-term trends. Historical trends suggest that society embraces an increased adoption of technology over time, sometimes slowly and sometimes rather abruptly (as in the case of smartphones). Adoption of these technologies will likely also increase, particularly as products become smaller, more adaptable, and more affordable. The need for upgrades will pose some interesting dilemmas for users, as will the disposal or recycling of used technology. Adoption may see a bit more traction in countries more comfortable with the technology and information sharing [217].

Challenges. Aside from the general technical challenges in each of the fields of research, the primary issues and challenges will likely occur in the areas of ethical concerns, regulation, and societal integration. There have already been calls for greater regulation and oversight of biohacking (particularly genetic biohacking), or in some cases greater exercising of current regulations and authorities [218]. As with genetic engineering, the topic of implants carries a variety of ethical concerns, such as data privacy or the morality of enforced implants [219]; however, no regulatory framework currently exists [220]. Notably, the FDA did approve the chip implants that the Wisconsin-based company previously mentioned offered to employees. In addition, society will face challenges about integrating people who have utilized these technologies. For example, the UK Passport Office rejected Neil Harbisson's passport photo in 2004 because of the presence of his antenna. Neil responded that he identifies as a cyborg and that the antenna counts as part of him, not as a device. After correspondence, the UK Passport Office accepted the photo, resulting in stories that he was the first cyborg to be recognized by a government [221]. There have also already been instances of assaults on people with attached technology [222-223].

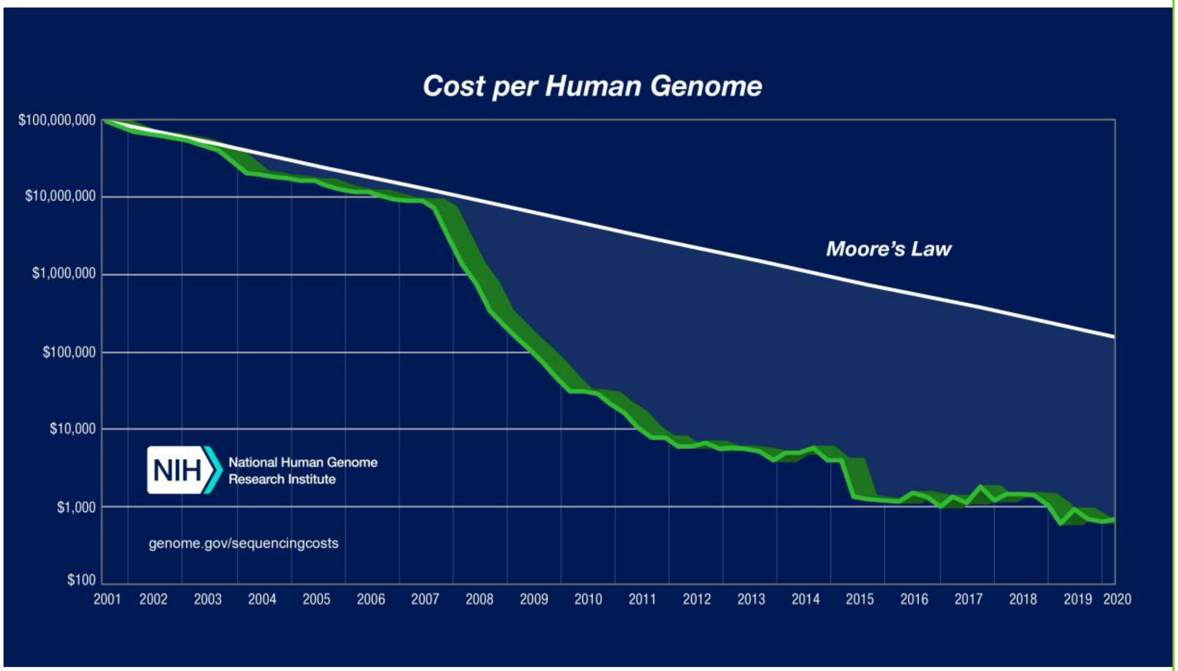
Summary of research and trends

This section provided a glimpse into the state of research for genetic engineering and human-centered bioengineering. A true accounting of all ongoing research would require volumes more material, but these snapshots help describe the general direction and trends of these research areas. Perhaps not surprisingly, the different research areas are all encountering similar general trends and challenges. We group these observed trends under the umbrellas of adaptability, accessibility, and acceptability:

Adaptability. These technologies are becoming more powerful, more capable, and relevant to more problems. In genetic engineering, we observed that DNA manipulations (e.g., reading, writing, editing) have seen great advances in the last few decades as the discovery of new tools has allowed ever further control and precision in editing genomes. In human-centered bioengineering, we observed similar trends across the wide diversity of applications: devices are becoming smaller, more portable (or transportable), more capable, and more flexible.

Accessibility. Although we did not generally discuss the costs of research (other than noting that CRISPR technologies are cheaper than other options), as with most technology, research will become cheaper and more accessible over time. As a general reference point, Figure 20 shows the historical cost of sequencing a human genome with a comparison to Moore's law to demonstrate the effect of a breakthrough in technology around 2008. Another example is 3D printing making prosthetic limbs cheaper and more customizable. The proliferation of these technologies into every aspect of life will continue to increase the availability and affordability of both genetic engineering and human-centered bioengineering products.

Figure 20. Historical data on the cost of sequencing an individual human genome



Source: National Human Genome Research Center [224].

Acceptability. The trend of acceptability, meaning whether society will approve of and adopt technological developments, has the greatest uncertainty and will likely be the slowest of the three trends. In general, society and research institutions appear to accept the employment of genetic engineering and human-centered bioengineering technologies for **corrective** applications. The consensus is less clear for **noncorrective enhancements**, or for how **convenience** will play a role. In both genetic engineering and human-centered bioengineering, we are at the threshold of alterations that can enhance human characteristics, with the greatest advancements being made in human-centered bioengineering. Although the professional and medical communities have largely refused to conduct such modifications, the biohacking community and some start-up companies have largely taken matters into their own hands, turning to other professional services and each other to share knowledge and perform installation procedures. The biggest wildcard will be the thousands of garage and basement laboratories around the globe.

When we examined the history of human modification, we identified a rich history of humans making new discoveries and using those breakthroughs to modify themselves and their daily lives. We expect that behavior to continue. Early adopters, whether grinders or other curious individuals, will explore the frontier of the impossible. But will people prefer "wearables" over the "irreversibles?" Even if wearables and other reversibles become equivalent options, it is possible that some people will always prefer the irreversibles. As Hughes and colleagues noted, "descriptions of a future identity state will not draw solely from biological and information technology fields. They will also be driven by philosophical concepts of how human beings and their attendant devices will interact and co-exist in ways that are nascent or novel" [225]. Moreover, people do not need to ascribe to any philosophical movement to take advantage of perceived convenience. Many of us can recall how rapidly society adapted to the technology of smartphones.

Considerations for the US Military

Given the history of human modification and the current state of research, we now examine the ramifications for the US military of the continuing shift toward human "hardware" modifications. First, we identify current relevant regulations to understand how they might apply to uses of genetic engineering and human-centered bioengineering. Second, we discuss the implications, given the current regulations and our previous discussion of the trends of research.

Current regulations

In general, US law sets the broader boundaries for the application of genetic engineering and human-centered bioengineering (for example, when a service member receives treatment for a medical condition or a prosthesis for an injury) [226]. So we examined the current military regulations that might apply to a service member who decides to experiment with genetic engineering or human-centered bioengineering as a biohacker or a hobbyist.

Genetic engineering

Perhaps not surprisingly, the Uniform Code of Military Justice (UCMJ) does not appear to address directly the use of gene editing substances, or self-experimentation with said substances [227]. Article 112 does cover the use of drugs and controlled substances, including anabolic steroids, but it does not list gene editing substances.

Human-centered bioengineering

The UCMJ also does not appear to address the topic of human-centered bioengineering devices [227]. However, service-specific **uniform regulations**, which largely address the dress code and the physical appearance of service members, may apply to aspects of this issue. For example, the United States Marine Corps Uniform Regulations under paragraph 1004, "Personal Appearance," prohibits marines from (quoted):

- a) Mutilation of the body or any body parts in any manner, and;
- b) Attaching, affixing or displaying objects, articles, jewelry or ornamentation to, through or under their skin, tongue or any other body part. Female Marines, however, may wear earrings consistent with paragraph 3010. [228]

With these restrictions, particularly the prohibition of objects "under their skin," it is unlikely a marine could have a chip implant or any enhancement that alters the body (visible or invisible). The other services all have similar restrictive clauses for jewelry and "mutilation," although the wording in the Navy and the Air Force regulations might be the most lenient, forbidding only visible or ornamental modifications [229-231]. Most of the service uniform regulations make allowances for wearing fitness trackers, which indicates flexibility with societal changes.

It is unclear whether the guidelines for Sensitive Compartmented Information Facilities (SCIFs) restrict the presence of simple RFID or NFC implants, since they do not transmit intelligence data or have any recording capability [232].

The services' regulations on prostheses are also not clear. It appears that service members who lose a limb typically take on administrative roles, if they are able. But in some cases, service members have returned to their active duty jobs, including paratroopers [233-234].

Summary of current regulations

As the brevity of this section suggests, the US military services do not appear to have many regulations that cover the areas of genetic modification and human-centered bioengineering. Regarding the uniform regulations that do prohibit objects "under the skin," it is unclear how the services would know or verify that a service member had, for example, an RFID implant in the webbing of the hand, other than voluntary disclosure or accidental exposure (e.g., while having an X-ray taken for an unrelated issue).

Implications

In this report, we established the likely trends for genetic engineering and human-centered bioengineering. Given the current regulations in place (or not in place), we next examine the implications of this information and research for the US military. Though it is exciting to think about the far-term outlook, in which robots, cyborgs, and genetically engineered enhancement may become commonplace, we have not yet arrived at that future. We therefore focus more on less flashy but still revolutionary near-term implications, which nonetheless give glimpses into the far-term implications. We find that:

Over time, more humans will modify themselves, or will come "pre-modified." Initially, humans will choose to modify themselves. Eventually, parents will be able to make modification decisions for their children. Human-centered bioengineering modifications are available now and will be more prevalent earlier than genetic modifications.

- Genetic engineering:

- **Near-term (next decade or two)**: initially, adults will choose to modify themselves. These corrections will be mostly somatic modifications, and initially they will focus on correcting diseased cells. Such modifications are happening now (e.g., sickle cell anemia), but the number of diseases with treatments will increase over the next decade or two as the gene editing tools become more precise and controllable. We will likely see parents gain access to gene editing for their offspring in the next two decades—again, with a focus on fixing known genetic diseases and defects. The capability enhancement modifications will start to appear in the next two decades, though likely through the biohacking community and more unofficial channels. Enhancement modifications such as increased muscle mass or increased endurance (e.g., red blood cell production) will likely prove particularly attractive to service members.
- **Far-term (more than two decades)**: genetic enhancements will become more commonplace, though largely dependent on social acceptability. Somatic enhancement modifications will likely be more commonplace, as tools (and knowledge of appropriate targets) proliferate. Germline enhancements may begin to be available, meaning that new recruits may start showing up having been born with genetic enhancement modifications in the next 30 to 40 years.

- Human-centered bioengineering:
  - **Near-term (next decade or two)**: technology for modifications will continue to improve for prostheses and other corrective technologies, but these technologies will likely be less relevant to active duty service members (except for those receiving prostheses for duty-related injuries). Even technologies such as exoskeletons will remain niche, as mission-specific capabilities. Simple implants (such as RFID tags) and sensory implants (such as magnets), however, are available now, and the type and purpose of implants will only increase with time. Although everybody could potentially use such implants, the extent of public adoption will depend on a combination of acceptability with perceived convenience and benefit. Other implants may offer new capabilities, or make alterations that are more dramatic to human physiology. Wearable technology, particularly devices integrated into cloth, will also see a large increase in development.
  - **Far-term (more than two decades)**: prosthetic enhancements and other modification enhancements will become more commonplace. Brain-computer interfaces will be much more common and ubiquitous. Implants will continue to do more, and possibly integrate more with biological functions. Adoption will

depend heavily on the degree of acceptance from society. Wearables and reversibles may be more common, though some individuals will likely seek fused or nonremovable installations.

- **Recommendations**. DOD should establish guidance for service members who may be interested in self-experimenting with genetic engineering, receiving chip implants, or making other modifications with these technologies.
  - What will be the guidance? If DOD chooses to restrict access to such activities, how will they monitor compliance? Gene doping and other genetic modification techniques do not leave markers as other prohibited substances do [235]. Subdermal implants would require X-ray images to reveal their presence.
  - If or when these technologies become more powerful and ubiquitous, will DOD embrace the technologies and offer standard enhancements for its service members? Will chip implants become standard issue instead of a Common Access Card or other identification? If new service members already have chip implants, will DOD remove old implants and provide military-grade implants? How will enhancements affect physical fitness tests or entrance into particular schools (such as special operations forces)? Will enhancements be restricted to mission-specific requirements (e.g., genetic modification for enhanced cold resistance) and only apply temporarily? Will modifications be available for active duty members only, or to family members and veterans? Will service members be "reset" to their arriving configuration upon discharge or retirement? These services and monitoring will require a whole new array of infrastructure to support.
  - What will be the ramifications of cyborg rights when equipment has become part of the individual?

Any difference in the availability and acceptability of these technologies will increase the likelihood of black markets and other illicit activities. In other words, if the technology is available, but society (or DOD) does not accept or allow it, people will be more likely to pursue the technologies illicitly. The greater the difference between availability and acceptance is, the more likely that people will seek black market options. At present, both genetic engineering and human-centered bioengineering are experiencing an environment reminiscent of the "Wild West," where the law may not have equal enforcement everywhere. Genetic engineering has a more formal infrastructure in place with bioethics committees and forums; however, both scientists and biohackers are pushing very firmly on these boundaries. Social acceptance and adoption will ultimately drive how ubiquitously these technologies take root.

- **Recommendation**. DOD should keep close watch on the differences between the availability of these technologies and the societal acceptance of them. Establishing guidance now will be important, with regular updates to account for inevitable technological breakthroughs. Technological enhancements related to physical fitness may be the best areas to watch. Sports professionals, often plagued with issues of performance-engaging drugs, will be particularly susceptible to misuse, with prestige, championships, and money on the line. These other communities may drive the demand for such enhancements, which would then spill over into military spheres.

These technologies are no longer issues for only Science and Technology organizations; they affect all areas. Organizations such as DARPA and the service research labs may not find the information in this report surprising. But that message does not appear to have yet made its way to all parts of DOD. The advances in genetic engineering and human-centered bioengineering are beginning to affect the general population, which means that these technologies will soon affect all aspects of an organization, including personnel, training, logistics, operations, and more.

- **Recommendation**. DOD and the services should identify cross-organizational oversight for the integration of these technologies. Because these technologies touch on nearly all aspects of an organization, oversight should likely reside at the service headquarters and the Office of the Secretary of Defense. They will require extensive coordination with all parts of their organizations.

These technologies will introduce new threats—to all people, not just service members. As an example, the proliferation of AI and machine learning research and technologies has introduced entirely new forms of adversarial attacks, vulnerabilities, and threats. We will see a similar evolution for genetic engineering and human-centered bioengineering. There will be threats *by* the new technology as well as threats *to* the new technology. We chose not to include a deeper discussion of bioweapons, but these new threats will include not only the ability to engineer new bioweapons, but also to target the genome or use genome editing as a weapon.[34] Threats may even arise from unintended side effects of genetic modifications. Similarly, technology insertion into the human body opens the door to the whole host of computer-related vulnerabilities such as snooping, hacking, virus attacks, and perhaps unforeseen threats. The threat increases from the implantation of spying devices, and in the far future, we might even have concerns about the ability to read (or write/manipulate) neural memories.

- **Recommendation**. DOD should begin preparing for and understanding these potential vulnerabilities, and determining when they may become serious threats. Red teaming,

[34] As we previously mentioned, DARPA's Safe Genes program is an effort to address some of these genome editing issues [145].

war gaming, "fiction intelligence" (FICINT) [236], and other methods provide great avenues for identifying and exploring these issues.

DOD has no frameworks or strategies to weigh the ethical and legal implications of military applications of these technologies. Global research and interests, including national ambitions and strategies, are currently driving the trajectories of genetic engineering and human-centered bioengineering. DOD needs to engage as part of the voice of the United States in these global conversations as the entire world deals with the ramifications and direction of these technologies.

- **Recommendation**. DOD needs frameworks and strategies for navigating these discussions and engagements. These frameworks will need to adapt to the technologies as they evolve, as new and unforeseen technologies emerge, and as unforeseen issues ripple out from their employment [237].

Conclusion

Science fiction stories have long dreamed of wild and fantastic possibilities, exploring futures with incredible technologies and capabilities. Although faster-than-light travel and interplanetary alliances may still be far off in the future, we now find ourselves on the cusp of possibilities that only imaginative authors have described and explored. With all of the hype and commotion, it can be easy to fixate on some future world of robots and neural uploads. But today, very real discussions and decisions need to happen. We identified concrete steps that DOD can take to prepare for the rapidly approaching future, including the creation and promulgation of guidance, the creation of oversight organizations, and the joining of a global dialogue on how humanity moves forward with these technologies. We must prepare today for that upgraded tomorrow.

Appendix A

This report defines most terminology as it appears, but this appendix provides a consolidated list of vocabulary, with short definitions, in alphabetical order. This appendix also reproduces a larger version of Figure 3 and provides definitions for the more esoteric terms listed in it. This appendix closes with a historical example of military use of modifications.

Definitions and terminology

Adeno-associated viral (AAV) vectors are used as a method for gene therapy delivery.

Base pair. In DNA, refers to a nucleotide on one strand and its hydrogen-bonded partner on the opposite strand.

Bioethics. The study of ethics in the field of biology, often with strong medical application.

Biohacking has no formal definition, since it derives from activities of individuals and communities outside of traditional laboratories (academic or industrial). The idea amounts to "do-it-yourself" biology. The "hacking" part refers to its practitioners learning by doing, and trying out ideas and seeing what happens [238]. It can refer to the biology of one's own body, or biology in general (e.g., cuttlefish). These experiments might involve physical and chemical manipulation (e.g., stimulants), but may also include genetic manipulation.

Biolistics involves the delivery of biological material into cells using a micro-projectile delivery device, or a "gene gun." Researchers coat tiny particles of heavy metals with the material of interest (DNA, RNA, proteins) and fire them at cells, typically plant cells [62].

Bionics. The application of biology to modern technology, such as adhesives based on the feet of geckos.

Biotechnology covers the broad application of biological processes in technology. The term can apply to medicine, agriculture, materials, and many other sectors. This paper focuses on biotechnology for humans proper.

Brain-machine interface. Sometimes **brain-computer interface**. A broad term that refers to any direct communication between a brain and an external device.

Cisgenic. The introduction of genetic material from the same species (see **transgenic**).

CRISPR(-Cas). Clustered regularly interspaced short palindromic repeats, and CRISPR associated systems. A family of nucleases that allow for easier gene editing.

Cybernetics. "The scientific study of control and communication in the animal and the machine" [106].

Cryonic suspension. The freezing of a living or recently deceased organism, usually in the hopes that future technology can resuscitate and cure whatever disease the organism has.

Deletion. The removal of one or more base pairs into a gene sequence.

DNA. Deoxyribose nucleic acid. A macromolecule consisting of many nucleotides, which encodes the information for generating living organisms. DNA consists of two strands in a helix formation.

Double-strand break. A break in both strands of DNA, as opposed to a single-strand break.

Electroporation involves using an electric field to open holes in cell membranes in order to allow foreign genetic material to enter; the cell's repair mechanisms close the holes once the current ends [61].

Embryo selection. The process of choosing a fertilized embryo to develop based on desired genetic characteristics.

Frameshift. A cell's machinery reads the gene sequence in groups of three. A nontriplet insertion or deletion changes the reading frame, which likely results in a completely different code sequence. Frameshifts usually lead to malformed RNA or proteins.

Genetic engineering describes the process of altering the genetic composition of an organism, whether by changing, adding, or removing a base pair or sequence.

Germline and **somatic** refer to whether genetic material can pass to future generations. Somatic cells (e.g., heart cells, liver cells) cannot pass genetic material to future generations, while germline cells (e.g., sperm or egg cells) can. Changes to germline cells are **heritable**. But, in 2014, researchers demonstrated the ability to turn skin cells into stem cells, and then into sperm and embryo cells, thus converting somatic cells into germline cells, albeit in low yield [53].

Grinders are biohackers who alter their own bodies via chemical or technological means.

Heritable. Capable of being passed to successive generations of an organism.

Homology directed repair (HDR). A repair pathway for double-stranded DNA breaks that uses a template to guide the repair.

Insertion. The addition of one or more base pairs to a gene sequence.

Knockout. The removal of genetic material from a genome, usually in reference to a specific gene.

Mosaic. In general, a mosaic refers to an organism with cells that have differing genomes. In gene editing, mosaicism occurs when the gene editing acts unequally on the population of cells.

Nanobots. Machinery on the scale of nanometers, theoretically capable of manipulation at that scale.

Nickase. (See **nuclease**.)

Nonhomologous end joining (NHEJ). A repair pathway for double-stranded DNA breaks, which uses no template (thus being nonhomologous).

Nuclease. An enzyme that cuts the phosphodiester backbone of DNA or RNA. Depending on its activity, a nuclease may cause single-strand (a "nickase") or double-strand breaks in DNA.

Nucleic acid. Another term for DNA and RNA. Nucleic acids are made of nucleotides.

Nucleotides. The building blocks for DNA and RNA.

Optical sensors. Machinery that can serve as, or replace, human eyes.

Respirocytes. A theoretical artificial blood cell [239].

Robotic cells. Machinery that serves the function of cells.

RNA. Ribonucleic acid. Single strands of nucleic acids, usually generated from DNA, and usually serving as the messengers for building proteins.

Somatic. (See **germline**.)

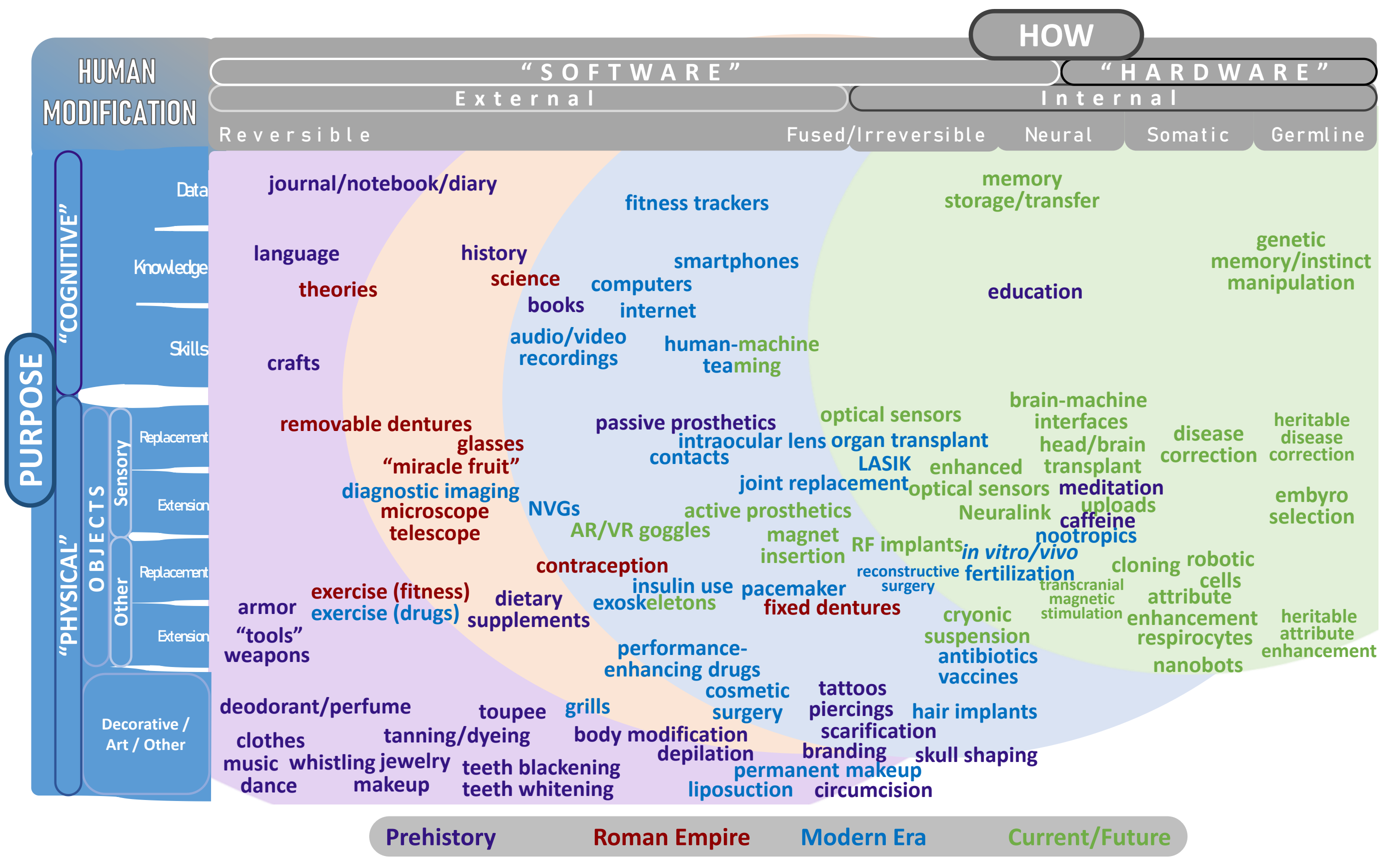
Transcranial magnetic stimulation. The use of magnetic waves to stimulate brainwaves (e.g., to reduce the need for sleep)[137].

Transgenic. The introduction of genetic material from a different species (see **cisgenic**).

Uploads. Human minds transferred to machines, as explored in *The Age of Em* [240] and countless science fiction stories.

Vector. A DNA molecule that serves as a delivery method for genetic material.

Figure 21. Human modification framework (larger version of Figure 3)



Source: CNA.

UNCLASSIFIED

A brief but relevant historical example

During World War II, both German and Allied soldiers made use of performance-enhancing drugs [241]. These drugs kept soldiers awake for days at a time. Germany used methamphetamine, which it marketed under the name Pervitin. The British War Office estimated that Germany sent 35 million Pervitin tablets to its forces during the three months of the Blitz in 1940 [242]. Upon discovering Germany's drug usage, the Allies chose amphetamine for its troops, marketed as Benzedrine (see Figure 22) in 1941.

Figure 22. Amphetamines marketed for soldiers during World War II

Source: Brave Planet Films and THIRTEEN Productions LLC [241].

Appendix B

This appendix provides more detail on the operation of the CRISPR family of gene editing tools. This information is not necessary for understanding the material in the main paper, but it may provide useful details for those who are interested. First we describe the operation of the CRISPR-Cas gene editing tools in greater detail, and then we provide a table from the literature that compares the four major categories of gene editing tools.

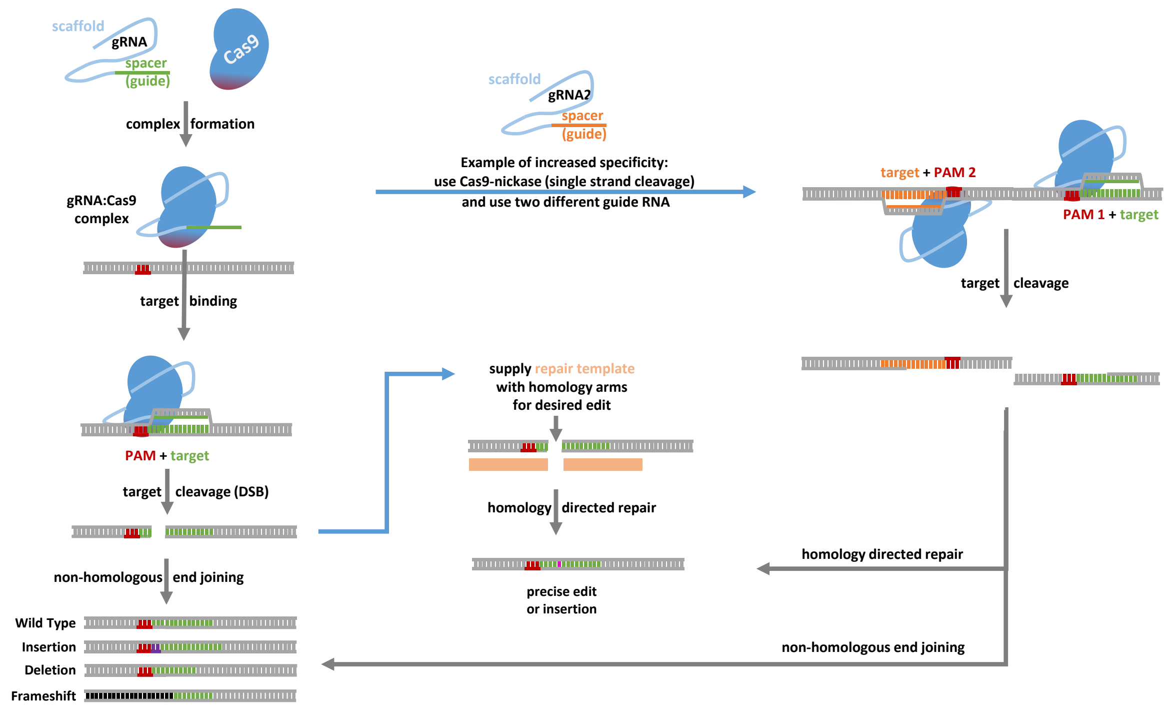
CRISPR-Cas overview

CRISPR-Cas allows for increased flexibility when editing DNA. CRISPR-Cas only needs to change the genomic target segment of the guide RNA [243]. Other members of the nuclease family, such as ZFN and TALENs, need a new design for each new nuclease pair to edit.

As shown on the left side of Figure 23, the Cas protein combines with a guide RNA (gRNA), which contains scaffolding that binds it to the Cas protein. This gRNA also contains a guide sequence (spacer), which targets a specific area of a DNA molecule.

In the presence of the proper DNA sequence, the gRNA guide sequence will bind with the appropriate strand of DNA. This binding brings the Cas protein in proximity to the DNA strand, and interactions further increase between the Cas protein and a PAM (protospace adjacent motif) on the DNA. The Cas protein contains two sites of nuclease activity; these sites will cut both strands of DNA to result in a double-strand break (DSB). Depending on the organism, molecular machinery may repair the double-strand break in a process known as nonhomologous end joining (NHEJ). This repair process can result in a restoration of the original DNA molecule (wild type), or a DNA molecule that has undergone changes (with insertions, deletions, or other frameshifts). These changes typically results in knockout genes (genes that no longer work), which allows researchers to explore the effects of a missing gene on an organism.

Figure 23. Overview of CRISPR-Cas gene editing



Source: Modified from [243].

Researchers have created variations of the Cas protein in order to tweak different attributes (such as binding locations) [244]. As an example of such modifications, researchers can disable one of the two nuclease sites on case, so that it will only cut one strand of DNA (referred to as a "nickase," because it nicks the DNA). Combining two of these Cas-nickases with *different* gRNA guides allows researchers to increase the specificity of where the proteins cut DNA, because the cuts specify two locations instead of one. The right path of Figure 23 shows this method.

As a final example, researchers can also provide a template to direct the DNA repair. This repair can involve single base pair changes, or the insertion of large pieces of a gene sequence. This process is called homology directed repair (HDR), as the middle path of Figure 23 shows. HDR repairs currently have a low efficiency, and repairs may still happen via the NHEJ pathway.

Researchers have a growing number of other tricks to increase the efficiency of HDR. For example, if only one base pair needs to change, researchers can deactivate the nuclease capability of Cas and instead attached a cytosine base editor (which causes a C to T change) or an adenosine base editor (which causes an A to G change).

Comparison of gene editing tools

Cox and coworkers provided a comparison of the nuclear family of gene editing tools in *Nature Medicine* in 2015 [245]. Table 1 reproduces their comparison of the techniques.

Table 1. Comparison of gene editing techniques

	Meganuclease	Zinc Finger Nuclease (ZFN)	TALEN	Cas9 (CRISPR)
Recognition site	Between 14 and 40 bp	Typically 9 to 18 bp per ZFN monomer, 18 to 36 bp per ZFN pair	Typically 14 to 20 bp per TALEN monomer, 28 to 40bp per TALEN pair	22bp (20bp guide sequence + 2bp PAM sequence for *S. pyogenes* Cas9); up to 44 bp for double nicking
Specificity	Small number of positional mismatches tolerated	Small number of positional mismatches tolerated	Small number of positional mismatches tolerated	Positional and multiple consecutive mismatches tolerated
Targeting constraints	Targeting novel sequences often results in low efficiency	Difficult to target non-G-rich sequences	5' targeted base must be a T for each TALEN monomer	Targeted sequence must precede a PAM [AU: please define]
Ease of engineering	Difficult, may require substantial protein engineering	Difficult, may require substantial protein engineering	Moderate, requires complex molecular cloning methods	Easily re-targeted using standard cloning procedures and oligo synthesis
Immunogenicity	Unknown, meganucleases may be derived from many organisms including eukaryotes	Likely low, as ZFs are based on human protein scaffold. FokI is derived from bacteria and may be immunogenic	Unknown, protein derived from *Xanthamonas sp.*	Unknown, protein derived from various bacterial species
Ease of ex vivo delivery	Relatively easy through methods such as electroporation and viral transduction	Relatively easy through methods such as electroporation and viral transduction	Relatively easy through methods such as electroporation and viral transduction	Relatively easy through methods such as electroporation and viral transduction
Ease of in vivo delivery	Relatively easy due to small size of meganucleases, allows use in a variety of viral vectors.	Relatively easy due to small size of ZFN expression cassettes, allows use in a variety of viral vectors	Difficult due to the large size of each TALEN and repetitive nature of DNA encoding TALENs, leading to unwanted recombination events when packaged into lentiviral vectors	Moderate: The commonly used Cas9 from *S. pyogenes* is large and may impose packaging problems for viral vectors such as AAV, but smaller orthologs exist.
Ease of multiplexing	Low	Low	Low	High
Recognition site	Between 14 and 40 bp	Typically 9 to 18 bp per ZFN monomer, 18 to 36 bp per ZFN pair	Typically 14 to 20 bp per TALEN monomer, 28 to 40bp per TALEN pair	22bp (20bp guide sequence + 2bp PAM sequence for *S. pyogenes* Cas9); up to 44 bp for double nicking

Source: Reproduced and rearranged from [245]. Bp = base pair.

Figures

Tables

Abbreviations

AI	artificial intelligence
AGI	artificial general intelligence
BCI/BMI	brain-computer interface; brain-machine interface
Cas	CRISPR-associated system
CRISPR	clustered regularly interspaced short palindromic repeats
DNA	deoxyribonucleic acid
DOD	Department of Defense
DSB	double-strand break
FDA	US Food and Drug Administration
FICINT	fictional intelligence
HDR	homology directed repair
iGEM	International Genetically Engineered Machine
NFC	near-field communication
NHEJ	nonhomologous end joining
PAM	protospacer adjacent motif
RFID	radio-frequency identification
RNA	ribonucleic acid
TALEN	transcription activator-like effector nuclease
UCMJ	Uniform Code of Military Justice
ZFN	zinc finger nuclease

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This report was written by CNA's Operational Warfighting Division (OPS).

OPS focuses on ensuring that US military forces are able to compete and win against the nation's most capable adversaries. The major functional components of OPS work include activities associated with generating and then employing the force. *Force generation* addresses how forces and commands are organized, trained, scheduled, and deployed. *Force employment* encompasses concepts for how capabilities are arrayed, protected, and sustained at the operational level in peacetime and conflict, in all domains, against different types of adversaries, and under varied geographic and environmental conditions.

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