Bioethical Inquiry
https://doi.org/10.1007/s11673-018-9865-6

CRITICAL PERSPECTIVES

Ethical Issues of Using CRISPR Technologies for Research on Military Enhancement

Marsha Greene · Zubin Master

Received: 23 August 2017 / Accepted: 7 May 2018

Abstract This paper presents an overview of the key ethical questions of performing gene editing research on military service members. The recent technological advance in gene editing capabilities provided by CRISPR/Cas9 and their path towards first-in-human trials has reinvigorated the debate on human enhancement for non-medical purposes. Human performance optimization has long been a priority of military research in order to close the gap between the advancement of warfare and the limitations of human actors. In spite of this focus on temporary performance improvement, biomedical enhancement is an extension of these endeavours and the ethical issues of such research should be considered. In this paper, we explore possible applications of CRISPR to military human gene editing research and how it could be specifically applied towards protection of service members against biological or chemical weapons. We analyse three normative areas including risk–benefit analysis, informed consent, and inequality of access as it relates to CRISPR applications for military research to help inform and provide considerations for military institutional review boards and policymakers.

Keywords CRISPR/Cas 9 · Enhancement · Military · Ethics of research involving humans · Informed consent · Risk–benefit analysis

M. Greene
Senior Policy Analyst, Peraton, Contracted to the Office of the Under Secretary of Defense for Research and Engineering, 4800 Mark Center Drive, Suite 17E08, Alexandria, VA 22350-3600, USA
e-mail: Marsha.l.greene.ctr@mail.mil

Z. Master (✉)
Biomedical Ethics Research Program, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA
e-mail: master.zubin@mayo.edu

Introduction

The development of the CRISPR/Cas 9 system has revived the debate over gene editing applications in many areas including biological research, human health, and agriculture and food production among others. What is discussed less in the literature is the use of CRISPR/Cas and other gene editing technologies to enhance humans specifically for military purposes. The President's Council on Bioethics under former President George W. Bush acknowledged that when performance is a matter of life and death, such as with soldiers on the battlefield, human enhancement may be more acceptable and indeed allowable (President's Council for Bioethics 2003). Yet the Council cautioned that it may be unwise to allow the warfighter to become indistinguishable from his weapon. Nevertheless, as evidenced by the Defense Advanced Research Projects Agency (DARPA) Broad Agency Announcement (BAA) in 2014, human performance optimization continues to be a major area of research focus (DARPA-BAA-14-38). In this call, DARPA solicited proposals to improve warfighter performance, improve bioengineering safety, and create a biological based manufacturing

Published online: 02 July 2018

platform. The announcement underscores the Department's current focus on temporary optimization measures to include the development of short acting drugs and biologics designed to enhance everything from wound healing to improvement of a broad range of cognitive abilities. With the emergence of CRISPR/Cas technology and the possibility for permanent gene enhancements of service members, the debate over where the ethical line should be drawn in military human performance optimization requires further consideration.

In this paper, we focus on the ethics of research using CRISPR on adult military service members, specifically as it relates to potential exposure to biological agents. This focus is deliberate because warfare is increasingly becoming asymmetrical with the emergence of guerrilla and insurgent forces. Military operations have shifted to counterinsurgency with specific attention regarding how to combat the threat of non-lethal weapons (e.g., bioagents). We discuss the governance of research involving humans in the military and follow with a discussion of how CRISPR can be used to protect warfighters against biological agents. Finally, we perform an ethical analysis of research involving military personnel specifically on issues of risks–benefit analysis, informed consent, and equality of access and outline several considerations for institutional review boards (IRBs) and policymakers.

Military Applications of CRISPR

CRISPR/Cas9 is a major technological feat with tremendous potential to impact the agriculture and health industries. These tools are currently being used to expedite crop and livestock breeding, engineer new antimicrobials, and control populations of disease-carrying insects (Gao 2018; Nunez and Lu 2017; Hammond et al. 2016). For human health, CRISPR can be used to treat diseases for which gene editing has previously been considered a therapeutic strategy, including Parkinson's disease, Alzheimer's disease, muscular dystrophy, cystic fibrosis, sickle cell disease, hemophilia, autism, HIV, and various cancers among other applications (NASEM 2017). Two first-in-human safety trials have been initiated to study whether CRISPR edited immune cells are more efficient at killing tumour cells in people with terminal cancer (Cyranoski 2016; Reardon 2016). CRISPR technology has reportedly been used to correct gene defects in human embryos (Ma et al. 2017) and is considered important in improving assisted reproductive technologies (Simón 2013; Ishii 2017). Research involving human embryo manipulation, however, is largely being conducted outside the United States due to regulatory restrictions. Several of these applications have relevance to Department of Defense (DoD) initiatives.

Other military applications of CRISPR could involve directly enhancing human soldiers. Humans remain the rate-limiting factor in the conduct of war. While weapons have become increasingly more sophisticated, provisions must be made in modern wargame exercises to allow the warfighter to sleep, receive nutrition, and heal after trauma or injury. Science fiction has conjured images of warfighters with super strength, enhanced vision, and limited psychosomatic reactions to the horrors of war. CRISPR research in the private sector is also trending towards enhancements that could be desirable for military applications. For example, a study with CRISPR-mediated gene editing of beagle embryos produced pups with twice the muscle mass having direct implications for human research (Zou et al. 2015). Scientists have also isolated genes from other species that could theoretically be genetically engineered to enhance humans such as a thermal imaging gene in reptiles which may confer the ability to see in low light conditions (Gracheva et al. 2010). Even a potential candidate gene for Post-Traumatic Stress Disorder has been described indicating that it may be possible to one day eliminate emotional detachment that warfighters sometimes encounter in the aftermath of war (Cornelis et al. 2010). Such experimental endeavours are likely to face major regulatory hurdles if they are ever seriously considered for development.

More practically, the availability of CRISPR gene editing is likely to impact both policy and practice in warfighter health and performance research. CRISPR itself could be used to weaponize biological agents and the military will need to consider how the warfighter could be optimized for performance during a hypothetical attack (Hoehn et al. 2017). Historically, service members are often subject to mandatory vaccination programs to protect against biological agents while deployed. However, it may prove difficult to develop effective vaccines for some of these new and emerging biological threats. Initial work aimed at identifying candidate genes that confers sensitivity to anthrax could lay the ground work for these types of studies (Martchenko

et al. 2012). Reduced expression of one such gene, capillary morphogenesis gene 2 (CMG 2), correlates strongly with lower susceptibility to anthrax. Interestingly, individuals who are closely related express CMG2 at similar levels which could indicate that sensitivity to these types of bioagents may be heritable traits. If genes such as CMG2 can be validated, the CRISPR system could be exploited in a variety of ways, some of which may not involve gene editing at all. In 2012, a team of researchers engineered a Cas9 enzyme that was unable to cut DNA (Qi et al. 2013). Essentially, the CRISPR/Cas9 machinery could be directed to a specific locus in the genome and used as either a gene promoter or suppressor, a sort of on/off switch for certain genes. More importantly, the effects could be reversible. One study did report targeted silencing of CMG receptors protected against anthrax toxin (Arévalo et al. 2014). Potential advantages are a shorter time frame between warfighter inoculation and deployment to a hostile zone and the ability to naturally reverse effects over time. More research is needed to determine the precise timing required for such inoculations and how long the expected response would be sustained.

Governance of the Ethics of Research Involving Humans in the Military

The public exposure to several unethical experiments conducted in the United States and abroad led to the development of the Belmont Report (Smith and Master 2014). The Belmont Report underscores three fundamental tenets of research ethics: respect for persons, beneficence, and justice. Heavily influenced by the Belmont Report, the Common Rule (45 CFR 46) is an overarching set of regulations that aims to protect human subjects participating in research. Fifteen Federal agencies, including the DoD, have signed on to the Common Rule in 1991 with the purpose of promoting uniformity in how research involving humans is governed. The Common Rule has several subparts providing additional protections for vulnerable populations such as pregnant women, human fetuses and neonates, prisoners, and children (Smith and Master 2014). Provisions within the Common Rule include the composition and processes of institutional review boards and informed consent among others. The Common Rule was revised in January 2017 with an effective date for July 19, 2018.

Prior to the Common Rule era, military research involving human subjects was largely accelerated due to the use of poison gas during World War I and the subsequent development of a chemical warfare defence programme. During the time between the two world wars, it is estimated that approximately 60,000 U.S. service members were experimentally exposed to Mustard gas and Lewistite (Brown 2009). Although the programme ramped down significantly following the end of World War II, military scientists continued research and development to seek out more effective compounds that could act as nerve agents, incapacitating compounds, and psychoactive agents. An additional 6,720 service members are estimated to have participated in experiments to test these agents from 1955 to 1979 (Brown 2009). Experiments were conducted under a shroud of secrecy but were still based on Nuremberg and Helsinki guidance and emphasized that participation was voluntary (Brown 2009). Since that time, military research involving service members has involved everything from human performance, feeding and nutrition, military medicine, and social behavioural interactions. Department of Defense human protections oversight has evolved to ensure more transparency, accountability, and greater protection for service members and civilians participating in DoD sponsored research.

Each Federal agency has also adopted protections in their instance of the rule to protect specific populations known to participate in research they sponsor. The DoD makes additional provisions for research involving service members. Due to the superior-subordinate relationship that exists in the military, DoD research policy provides additional protections to minimize command influence, to ensure that each individual gives informed consent in advance, and to limit waivers of informed consent (Amoroso and Wenger 2003). Furthermore, 10 United States Code 980 (10 USC 980) requires that all human participants of DoD sponsored research be able to give consent in advance of the research unless such research is intended to directly benefit the participant, in which case consent may be obtained from a legal representative (Sec 980 2005). The DoD has developed instructions that delineate the implementation of the Common Rule and considerations regarding special protections for service members (DoDI 3216.02, 2002). The DoD has also agreed to comply with all civilian Food and Drug Administration (FDA) regulations regarding the development and use of new pharmaceuticals, including the requirement to obtain

informed consent from human subjects participating in experimental drug and biologics trials.

Several provisions had previously been enacted to allow DoD to request a waiver of the requirement to obtain informed consent if the investigational agent is to be used in military contingency settings for the protection of service members from biological or chemical agents. This exception is known as the Interim Rule and was authorized by the FDA during the first Gulf War (21 CFR 50.23(d) 1990). The Interim Rule raised several ethical issues and a failed legal challenge prompted Congress to update the rule mandating that requests for waivers be approved by the President and strengthened requirements for IRB review of protocols utilizing investigational agents without appropriate informed consent (*Doe v Sullivan* [1991] and 10 USC 1107 2011). Food and Drug Administration rule 23(d) and 10 USC 1107 were further unified by Presidential executive order and added the interests of national security as a parameter upon which a waiver of informed consent decision could be based (Executive Order 13139 1999). In November 2017, the U.S. Congress passed legislation to allow the FDA to authorize emergency use and expedite the development of DoD medical products that have significant potential to affect national security (Public Law No: 115-92). Laws such as these will most certainly benefit service members by allowing more expedient access to DoD science and technology innovations. Nevertheless, it presents a significant challenge in managing the ethical considerations of potential products driven by technologies such as CRISPR/Cas.

Currently, there is no specific regulation barring the enhancement of service members for military purposes although the Department's current emphasis on optimization as opposed to enhancement suggests general weariness regarding permanent gene editing for service members. Nevertheless, research into human performance optimization and by extension biomedical enhancements is very active within the DoD (Land 2010; Jonas et al. 2010). As discussed, using CRISPR, it is possible to create semi-permanent gene enhancements. As public acceptability of gene editing for somatic versus germline therapies shifts (Scheufele et al. 2017), so may acceptance of somatic enhancements. It is thus conceivable that in the future, enhancements could become fully in compliance with the Department's policies.

Ethics of Military Gene Enhancement in Research

CRISPR has revitalized the debate over human gene enhancement. In contemporary bioethics debates, a distinction between gene editing to treat or prevent disease and enhancement for non-health purposes is sometimes made with the latter being more strongly discouraged (Scheufele et al. 2017; Annas and Annas 2009; Ashcroft 2008; Amoroso and Wenger 2003). The distinction is meant to draw a line between practices that are considered morally permissible (gene editing for therapeutic purposes) versus those that are prohibitory (gene editing for enhancement) (Buchanan et al. 2000). Therapy is considered medically necessary in order to achieve normal function. But what is considered "normal" function and what is "pathological" is susceptible to change. Yet in some cases, the moral difference between the therapy versus enhancement distinction becomes blurry. The classic example of two young boys both of whom are born with very short stature helps illustrate this point. Boy A is born short due to a deficiency in the human growth hormone (HGH) gene whereas Boy B is born short because both his parents are very short. Using CRISPR to correct the mutation in Boy A would be considered therapy because of a known gene defect whereas performing gene editing for Boy B would be considered enhancement because there is no clearly identifiable clinical pathology. Yet both Boy A and Boy B would suffer the social prejudice known as heightism, both desire to be taller, and both have very short statures due to a genetic lottery and to no fault of their own. In this situation, it would be ethically permissible to help both boys (Buchanan et al. 2000). Additionally, what may be considered an enhancement now might be considered treatment or routine care in the future (Frankel and Chapman 2000; Buchanan et al. 2000). In the above example, if we knew the specific set of genes making Boy B very short, this may be labelled as a pathology and thus could benefit from CRISPR therapy.

But there are valid reasons for maintaining the therapy/enhancement distinction including concerns that enhancement may be a form of a new, albeit softer, eugenics which likely furthers inequality among those who cannot afford to create children with enhanced traits (Frankel and Chapman 2000; Kiuru and Crystal 2008; Comfort 2015). The disability community finds the topic of gene modification particularly concerning. Many are concerned that the medical model

characterizes disabilities as a medical problem that must be mitigated or eliminated (Generations Ahead 2010). Disability is a social construct with a socially dominant view that disabled people are unhappy and discounts the pride which people have in their disabilities and how it brings diverse and new perspectives to the world (Shakespeare 1995, 1998). Several in the disability community view genetic modification to rid disabilities in the world as highly discriminatory and argue that efforts towards such goals may increase social intolerance and further prejudice disabled persons.

There are, however, dissenting opinions as some argue enhancements are good for society and consider human enhancement a moral obligation (Savulescu 2005; Harris 2007). Based on the principle of procreative beneficence, Julian Savulescu argues that short of having competing interests, such as harm to a pregnant mother, parent(s) are obligated to have the most advantaged child, including by genetic enhancement (Savulescu 2001; Savulescu and Kahane 2009). Not all enhancements might be permissible, such as aesthetic ones like eye colour, but those that improve human flourishing, such as intelligence, would be allowed (Chan and Harris 2007).

For the purposes of our discussion here, we will not focus on the permissibility of enhancements in general or even for military purposes. Instead, we begin from the premise that CRISPR for military enhancement may be permitted and focus on outlining ethical issues surrounding risks and benefits to subjects, informed consent, and inequalities of access.

Risk and Benefits to Soldiers as Research Participants

Considering that military service members already take significant risks simply by enlisting in the armed services, the risk/benefit analysis for research may be more favourable towards gene enhancement as the enhancement itself could improve the chances of survival during armed conflict (Annas and Annas 2009). Nevertheless, the risks of research must be addressed in a systematic manner to ensure that service members are not being exposed to unnecessary harm. Most concerning with gene editing research using CRISPR is the potential for off-target effects. If the CRISPR machinery accidentally docks at an unintended location in the genome it could cause mutations and disrupt or accelerate non-targeted biological processes thereby resulting in any number of illnesses, some of which may be life threatening. Nevertheless, the possibility of significant off target effects remains hypothetical. A recent report indicating that CRISPR gene editing had caused over one thousand single nucleotide mutations and over one hundred deletions was later retracted after heavy criticism of the scientific methods used and the validity of the paper's conclusions (Schaefer et al. 2017; Wilson et al. 2017; Nature Methods, 2018). Nevertheless, our knowledge of biological processes and potential CRISPR effects remains limited. The risk–benefit calculus would require military IRBs to balance risks of off-target effects against the potential benefits of improved survival. The risks would be difficult to predict because more research on the frequency of off-target effects needs to be done in order to determine whether the benefits outweigh the risks. Risks may be minimized through preclinical experiments using robust animal models, reliable measures of off-target effects, and from an adequate understanding of how gene changes affect biological function. Risks may also be minimized if a reversible system was used.

Informed Consent

One of the factors of military life that impacts informed consent for research is the command structure. The military adheres to a single chain of command structure as outlined in the Joint Publication 1-02 (Gade 2015). The Uniform Code of Military Justice makes it a crime for a service member to disobey a lawful order from a superior commissioned officer, as such disobedience could jeopardize operational security and directly compromise the President's directives (Katz 2000). It can be challenging for service members to break from the mould of this strict command structure even in the research setting. Thus, DoD Instruction 3216.02 requires that any research involving military personnel specifically excludes senior officers in the participant's chain of command from solicitation, recruitment, or administering of informed consent. The responsibility of obtaining consent falls with the research team to ensure that this exclusion is enforced and that the autonomy and voluntariness of the research subject is protected at all times.

Another closely related factor of military training that presents a challenge to informed consent in the military setting is that service members are trained to act as a unit. This is based on several studies which positively tie unit cohesion to military performance (National Defense

Research Institute 2010). Sometimes, recruitment efforts may target an entire unit and in such cases researchers may conduct group briefings. It can be especially challenging for an individual to not go along with an activity especially if a majority of the unit has decided to participate. This presents some difficulty in the informed consent process, especially in terms of undue pressure of group conformity. It may be that group recruitment activities within units or group briefings should be avoided for first-in-human CRISPR research for military enhancement. A focus on providing information to individuals in both written form i.e., education packets, in addition to discussing the research and answering questions through a gradual process may be important to help ensure potential subjects are adequately informed of the procedures, risks and benefits, ability to withdraw, and alternatives to study enrolment.

Attitudes regarding CRISPR gene editing and expectations among service members may also impact the informed consent process. Service members may be drawn to participate if they believe that the procedure could give them an advantage over the enemy or protect them from a terrorist attack. Further complicating the issue is that some research participants may have trouble grasping the basic concepts of genetics and gene therapy trials (Rose, Russo, and Wykes 2013). Often misconceptions exist regarding the intent of these types of trials. Deaths that have occurred during other human gene therapy trials highlight the disparity that often exists between goals of the research and participant expectations (Dresser 2009). Although personal benefit may be possible in early clinical trials, the main objective of first-in-human studies is to address safety. As such, a type of "therapeutic misconception" is likely to exist among military research subjects where CRISPR may protect them against harm from combat. Military IRBs will need to consider whether the benefits of improved performance are being overstated during informed consent to service members.

A final point to consider surrounding informed consent is the impact of the FDA's newly adopted stance on expedited development of DoD medical products. During the first Gulf War, the FDA allowed the DoD to administer two experimental treatments to deploying service members to protect them against potential biochemical attacks (Boyce 2009). Practically speaking, no one can predict when war may break out. If a CRISPR-based experimental treatment were developed enough for testing on service members but had not yet been approved for use, it would be impractical to obtain informed consent from every service member prior to deployment. Under the current regulations the product could be used under emergency situations or, depending on the stage of development, could be expedited. If some service members refused, then they could place themselves at risk of personal harm and jeopardize the success of a mission. Administering CRISPR gene editing prematurely could threaten service members' safety, autonomy, ability to consent and whether they could opt out of these types of enhancements. This precedent could be important in genetics research as service members can conceivably be given orders, even against their wishes, if they are being sent to a war zone where biological weapons are being used. A cautionary approach to gene enhancement research using CRISPR may be prudent such that smaller scale testing can be done in controlled research settings prior to large-scale use and application during combat missions. Military leadership, IRBs, and the FDA must carefully evaluate unknown risks to soldiers and the risk of an unsuccessful mission if adequate human subjects research using the technology has not yet been performed.

Inequality of Access

Inequality of access has been raised as a potential negative consequence of gene editing (Rabino 2003). The inequality of access argument against human gene enhancement could also apply in military settings (Amoroso and Wenger 2003). Uniformity is one mechanism the armed forces use to instil discipline and foster willingness to follow directions and is intimately tied to the chain of command structure. Due to the risks associated with gene enhancement research, first-in-human studies may be restricted to Special Forces personnel or those slated to participate in risky missions. If some deployed service members had enhancements and others did not, this could lead to dissent. Under the dissent rules, service members may refuse deployment claiming they have not been provided with the same level of protection as others. This could greatly hamper the success of missions. Even if a particular enhancement is given to an entire unit, temporary duty assignments or permanent change of stations could also create inequality within the forces and could disrupt the overall chain of command structure.

Another DoD regulation that may impact inequality of access to CRISPR research is whether the service

member is on active duty. Military human subjects' regulations prohibit active duty service members from being compensated for participating in research trials (DoDI 2002). Essentially if a service member is being paid by the DoD, they cannot simultaneously be compensated with additional funds through other DoD funding mechanisms for research purposes. A CRISPR trial designed to offer compensation may be viewed as an unfair incentive to service members who are on leave. Researchers may want to consider not offering compensation at all. If participation is limited to only service members on leave in order to offer fair compensation to all participants, military IRBs may need to consider whether this violates principles of fairness for all military research subjects.

Conclusions

We conclude with two points. First is to encourage public and stakeholder engagement on the ethics of using CRISPR in military enhancement technology. Currently, public debate on the use of CRISPR for germline and enhancement purposes indicates that many in the public display concern about somatic and germline enhancements (McCaughey et al. 2016; Pew Research Center 2016; STAT-Harvard T.H. Chan School of Public Health 2016; Gaskell et al. 2017; Scheufele et al. 2017). These studies capture the views of different populations and vary in how questions are worded thereby accounting for some of the differences in opinions. But no study has yet to investigate the views of stakeholders on the use of CRISPR for enhancement for the purpose of protecting soldiers. Public and stakeholder views may differ when considering the use of CRISPR technology for military enhancement. Engagement within DoD and the public will help DoD research ethicists and leadership understand public and stakeholder concerns and be able to manage ethical issues of research involving military personnel as the research is translated into human applications. To promote discourse, several deliberative strategies and research methods could be employed including town hall meetings, citizen juries, consensus conferences, polling, and focus groups among others (Abelson et al. 2003). Deliberation can focus on a range of ethical questions such as how to translate CRISPR gene technology for military applications, how best to handle research ethics issues including informed consent and risk analysis for first-in-human studies, and when and how to best inform the public to ensure transparency of gene editing research.

The second point is that DoD should consider several research ethics issues as this technology moves forward. Gene editing is clearly advancing and as gene modification becomes accepted in military research, several considerations need to be made to minimize risks and ensure service members are appropriately informed should they become research participants. This will include taking steps to reduce the group pressure that could be a by-product of military cohesiveness training and making improvements in the consent process such that service members understand the risks and purpose of these interventions. The military will likely be watching the first-in-human trials very closely while simultaneously exhausting all preclinical options in order to fully evaluate the risks of off-target effects. There will need to be some certainty from further validated studies prior to initiating any wide-scale use for military applications. Additionally, researchers and military leadership alike will need to be cognizant of the potential for CRISPR applications to be deployed in the military setting prior to approval of these interventions by the FDA. Prior to invoking the Interim Rule due to a bioterrorist threat, several considerations need to be weighed to ensure appropriate protections to front line military personnel. From the DoD perspective, ensuring that service members have the best available protection in a war zone is paramount. However, this creates many ethical issues regarding breach of individual rights and autonomy. At the same time, a consideration could be that these risks are built into enlisting and recruiting discussions so that service members understand clearly that this is a possibility under certain scenarios. While the President's Council in 2003 felt that the risks of using gene editing for military enhancement were too high, it remains unclear given scientific advancements in gene editing whether similar conclusions would be made.

Acknowledgements We would like to thank the anonymous reviewer for helpful feedback of the manuscript. This project was initiated while ZM was at the Alden March Bioethics Institute of Albany Medical College. The views expressed in this article are those of the authors and do not necessarily reflect the views or official policy of Peraton, the Department of Defense, or the United States Federal Government

References

Abelson, J., P-G. Forrest, J. Eyles, P. Smith, E. Martin, and F-P. Gauvin. 2003. Deliberation about deliberative methods: Issues in the design and evaluation of public participation processes. *Social Science & Medicine* 57(2): 239–251.

Amoroso, P.J., and L. Wenger. 2003. The human volunteer in military biomedical research, Vol 2. In *Military medical ethics*, edited by T. Beam and L.R. Sparacino. Office of The Surgeon General. Washington, DC: TMM Publications.

Annas, C.L., and G.J. Annas. 2009. Enhancing the fighting force: Medical research on American soldiers. *Journal of Contemporary Health, Law and Policy* 25(2): 283–308.

Arévalo, M.T., A. Navarro, C.D. Arico, et al. 2014. Targeted silencing of anthrax toxin receptors protects against anthrax toxins. *The Journal of Biological Chemistry* 289(22): 15730–15738.

Ashcroft, R.E. 2008. Regulating biomedical enhancements in the military. *American Journal of Bioethics* 8(2): 47–49.

Boyce, R.M. 2009. Waiver of consent: The use of pyridostigmine bromide during the Persian Gulf War. *Journal of Military Ethics* 8(1): 1–18.

Brown, M. 2009. Military chemical warfare agent human subjects testing: Part 1—History of six-decades of military experiments with chemical warfare agents. *Military Medicine* 174(10): 1041–1048.

Buchanan, A., D.W. Brock, N. Daniels, and D. Wikler. 2000. *From chance to choice. Genetics and justice.* New York: Cambridge University Press.

Chan, S., and J. Harris. 2007. In support of human enhancement. *Studies in Ethics, Law, and Technology* 1(1): Article 10.

Comfort, N. 2015. Can we cure genetic diseases without slipping into eugenics? *The Nation* https://www.thenation.com/article/can-we-cure-genetic-diseases-without-slipping-into-eugenics/. Accessed March 22, 2018.

Cornelis, M.C., N.R. Nugent, A.B. Amstadter, and K.C. Koenen. 2010. Genetics of post-traumatic stress disorder: Review and recommendations for genome-wide association studies. *Current Psychiatry Reports* 12(4): 313–326.

Cyranoski, D. 2016. CRISPR gene-editing tested in a person. *Nature* 539(7630): 479.

Defense Advanced Research Projects Agency (DARPA) Broad Agency Announcement 14-38. 2008. https://www.fbo.gov/index?s=opportunity&mode=form&id=4d817774c8221b0487a8318d41b8034e&tab=core&_cview=1. Accessed May 18, 2018.

Department of Defense Instruction (DoDI) 3216.02. 2002—*Protection of human subjects and adherence to ethical standards in DoD-supported research.*

Dresser, R. 2009. First-in-Human trial participants: Not a vulnerable population, but vulnerable nonetheless. *Journal of Law, Medicine and Ethics* 37(1): 38–50.

Frankel, M.S., and A.R. Chapman. 2000. Human inheritable genetic modifications: Assessing scientific, ethical, religious, and policy issues. *American Association for the Advancement of Science Working Group.* https://nationalethicscenter.org/resources/185/download/genetic_mod.pdf. Accessed July 17, 2017.

Gao, C. 2018. The future of CRISPR technologies in agriculture. *Nature Reviews Molecular Cell Biology* 19(5): 275.

Gade, R. 2015. The U.S. Judge Advocate in contemporary military operations. In *U.S. military operations: Law, policy, and practice*, edited by G.S. Corn, R.E. VanLandingham, and S.R. Reeves. New York: Oxford University Press.

Gaskell, G., I. Bard, A. Allansdottir et al. 2017. Public views on gene editing and its uses. *Nature Biotechnology* 35(11): 1021–1023.

Generations Ahead. 2010. A disability rights analysis of genetic technologies. Report on a national convening of disability rights leaders. http://www.generations-ahead.org/files-for-download/articles/GenerationsAhead_DisabilityRightsConveningReport.pdf. Accessed March 22, 2018.

Gracheva, E.O., N.T. Ingolia, Y.M. Kelly et al. 2010. Molecular basis of infrared detection by snakes. *Nature* 464(7291): 1006–1011.

Hammond, A., R. Galizi, K. Kyrou, et al. 2016. A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector *Anopheles gambiae*. *Nature Biotechnology* 34(1): 78–83.

Harris, J. 2007. *Enhancing evolution: The ethical case for making better people.* Princeton: Princeton University Press.

Hoehn, A.R., R.H. Solomon, S. Efron, et al. 2017. *Strategic choices for a turbulent world: In pursuit of secuirty and opportunity.* Santa Monica:Rand Corportation.

Ishii, T. 2017. Germ line genome editing in clinics: The approaches, objectives and global society. *Briefings in Functional Genomics* 16(1): 45–56.

Jonas, W.B., F.G. O'Connor, P. Deuster, J. Peck, C. Shake, and S.S. Frost. 2010. Why total force fitness? *Military Medicine* 175(8): 6–13.

Katz, R.D. 2000. Friendly fire: The mandatory military anthrax vaccination program. *Duke Law Journal* 50: 1835–1865.

Kiuru, M., and R.G. Crystal. 2008. Progress and prospects: Gene therapy for performance and appearance enhancement. *Gene Therapy* 15(5): 329–337.

Land, B.C. 2010. Current Department of Defense guidance for total force fitness. *Military Medicine* 175(8): 3–5.

Ma, H., N. Marti-Gutierrez, S. Park, et. al. 2017. Correcting a Pathogenic gene mutation in human embryos. *Nature* 548: 413–419.

Martchenko, M., S.I. Candille, H. Tang, and S.N. Cohen. 2012. Human genetic variation altering anthrax toxin sensitivity. *Proceedings of the National Academy of Sciences* 109(8): 2972–2977.

McCaughey, T., P.G. Sanfilippo, G.E. Gooden, et al. 2016. A global social media survey of attitudes to human genome editing. *Cell Stem Cell* 18(5): 569–572.

National Academy of Sciences, Engineering, and Medicine (NASEM). 2017. *Human genome editing: Science, ethics, and governance*. Washington: National Academies Press.

National Defense Research Institute. 2010. *Sexual orientation and U.S. personnel policy.* CA: Rand Corporation. https://www.rand.org/content/dam/rand/pubs/monograph_reports/2009/RAND_MR323.pdf. Accessed March 27, 2018.

Nature Methods. 2018. CRISPR off-targets: A reassessment. *Nature Methods* 15(4): 229–230.

Nunez de la Fuente, C., and T.K. Lu. 2017. CRISPR-Cas9 technology; Applications in genomic engineering, development of sequence-specific antimicrobials and furture prospects. *Integrative Biology* 9(2): 109–122.

Pew Research Center. 2016. U.S. public wary of biomedical technologies to "enhance" human abilities. http://www.pewinternet.org/2016/07/26/u-s-public-wary-of-biomedical-technologies-to-enhance-human-abilities/. Accessed March 3 , 2018.

President's Council on Bioethics. 2003. Beyond therapy: Biotechnology and the pursuit of happiness. Report from the President's Council for Bioethics. https://bioethicsarchive.georgetown.edu/pcbe/reports/beyondtherapy/fulldoc.html. Accessed May 18, 2018.

Qi, L.S., M.H. Larson, L.A. Gilbert, et al. 2013. Repurposing CRISPR as an RNA-guided platform for sequence-specific control of gene expression. *Cell* 152(5): 1173–1183.

Rabino, I. 2003. Gene therapy: Ethical issues. *Theor Med Bioethics 24(1):* 31–58.

Reardon, S. 2016. First CRISPR trial gets green light from US panel. *Nature News*, June 22. https://www.nature.com/news/first-crispr-clinical-trial-gets-green-light-from-us-panel-1.20137. Accessed March 22, 2018.

Rose, D., J. Russo, and T. Wykes. 2013.Taking part in a pharmacogenetic clinical trial: Assessment of trial participants understanding of information disclosed during the informed consent process. *BMC Medical Ethics* 14: 34.

Savulescu, J. 2001. Procreative beneficence: Why we should select the best children. *Bioethics* 15(5/6): 413–426.

———. 2005. New breeds of humans: The moral obligation to enhance. *RBMOnline* 10(Supp 1): 36–39.

Savulescu J., and G. Kahane. 2009. The moral obligation to create children with the best chance of the best life. *Bioethics* 23(5): 274–290.

Schaefer, K.A., W. Wu, D.F. Colgan, et al. 2017. Unexpected mutations after CRISPR–Cas9 editing in vivo. *Nature Methods* 14(6): 547–548.

Scheufele, D.A., M.A. Xenos, E.L. Howell et al. 2017. U.S. attitudes on human genome editing. *Science* 357(6351): 553–554.

Shakespeare, T. 1995. Back to the future? New genetics and disabled people. *Critical Social Policy* 44(5): 22–35.

———. 1998. Choices and rights? Eugenics, genetics and disability equality. *Disability and Society* 13(5): 665–681.

Simón, C. 2013. Personal assisted reproductive technology. *Fertility and Sterility* 100(4): 922–923.

Smith, E., and Z. Master. 2014. *Ethical practice of research involving humans. Reference module in biomedical research*, 3rd Edition. Oxford: Elsevier. 1–11.

STAT-Harvard T.H. Chan School of Public Health. 2016. The public and genetic editing, testing, and therapy. https://www.hsph.harvard.edu/horp/stat-harvard-polls/. Accessed March 23, 2018.

Wilson, C.J., T. Fennel, A. Bothmer, et al. 2017. The experimental design and data interpretation in "Unexpected mutations after CRISPR Cas9 editing in vivo" by Schaefer et al. are insufficient to support the conclusions drawn by the authors. bioRxiv 153338. https://www.biorxiv.org/content/early/2017/06/21/153338. Accessed May 18, 2018.

Zou, Q., X. Wang, Y. Liu, et al. 2015. Generation of gene-target dogs using CRISPR/Cas9 system. *Journal of Molecular Cell Biology* 7(6): 580–583.