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Genome Editing for Soldier Enhancement – trends and implications

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Summary

This memo explores the emerging field of genome editing technology for soldier enhancement and maps out some possible applications of the technology and implications for military operations.

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Preface

This memo is largely the result of two industrious graduate students conducting a summer project at FFI before resuming their university studies. Their assignment was to take a closer look at emerging human enhancement technology, and provide an assessment of the possible future applications and consequences from a military perspective.

The field of human enhancement is exceptionally broad. We therefore decided to apply a more narrow scope and focus exclusively on genome editing. This subject is particularly interesting from an interdisciplinary perspective, as neither the biologist nor the social scientist alone can fully grasp the full range of the technology's future applications and consequences. Consistent with this approach, the memo provides both a thorough explanation of the technology and a preliminary attempt at identifying some of its future implications.

Much of the success of this memo is a result of the curiosity, dedication and "out-of-the-box" thinking applied by the students responsible. Best of luck in your future studies, Ingunn and Susanne!

Mats Rjaanes

Kjeller, 21 October 2020

1 Introduction

New and emerging technologies have on numerous occasions had profound impact on society and the outcome of military operations and conflict. Air travel, information technology, nuclear energy, and modern medicine are a few examples (1). Understanding the possible impact emerging technology will have on future military operations is important in order to assess whether a given technology should be acquired and adapted, or if defensive measures must be altered or developed. This memo examines one such technology; *human enhancement*. More specifically, we look at the potential use of *genome editing* and its potential applications for military purposes and soldier enhancement. The aim of the memo is to provide the reader with a brief overview of the technology, identify some areas in which genome editing can be used, point attention to some limiting factors, and discuss the possible consequences the technology might have on the armed forces.

We start by examining the importance of emerging and disruptive technologies, before mapping out the general structure of human enhancement. We then look at genome editing, a specific part of human enhancement, before turning to possible applications. Finally, we discuss consequences for military operations and some ethical considerations. Our research finds that genome editing is a technological field with numerous applications in a military setting, but mainly so in a long-term perspective. At some point, human enhancement and genome editing will undoubtedly play a central role in the future operating environment and armed conflict. Several of the more extreme applications presented by the technology will, due to ethical and political considerations, likely not be viable for certain states as the risks are deemed too high. Despite this, human enhancement and genome editing has the potential to cause disruptive effects and should therefore not be ignored.

2 Methodology and definitions

This memo is the result of a collaboration between two research projects at FFI. It thus draws on technological expertise from subject matter experts within biotechnology and human enhancement, as well as trend insight and forecasting expertise from the FFI-project "Technological trends and consequences for military operations (TEKNO)" (2). Our work builds on studies of secondary literature as well as some primary sources looking at specific applications of genome editing (3–6). The research is also supported by several studies of the European Defense Agency (EDA) as well as NATO's Sciences and Technology Organization (NATO STO) (7,8).

Our work is examining future developments and is therefore making assumptions and assessments based on uncertainty, with the risk of falling victim to cognitive limitations and biases (1,9). These caveats limit the validity of our specific findings and assessment. However, attempting to understand how a technology develops and what it might mean for the future of warfare does offer valuable insights, which are critical for the defense sector. The aim is not to accurately predict future outcomes, but to examine the *potential* implications of emerging technologies. Acquiring new technology and adapting strategies, doctrine and changes to force structure is often a slow moving and costly process for militaries. Understanding new technology and its possible consequences must therefore be done at an early stage if required changes are to be implemented. It is with this as a backdrop that we attempt to understand the possible future applications of genome editing and human enhancement. Before discussing genome editing, we will define and explain the terns *emerging and disruptive technologies* as well as *human enhancement*.

2.1 Emerging and disruptive technologies

Technologies rarely evolve linearly, but rather in a cyclic fashion. The *Gartner hype cycle* has been proposed as a graphical representation of maturity, adoption and application of technologies (10). However, most technologies do not progress through the entirety of such a cycle because they most often fail somewhere in the process. Even though the cycle is interesting in demonstrating the non-linear development of technology, it has been criticized for containing methodological flaws and procedural inconsistencies (11).

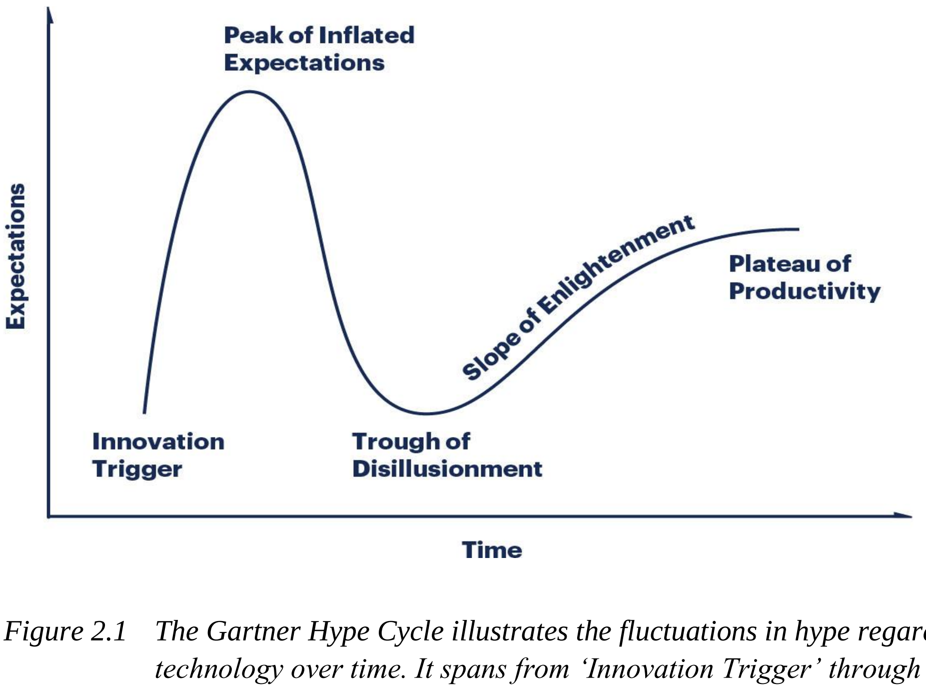

Figure 2.1 The Gartner Hype Cycle illustrates the fluctuations in hype regarding new technology over time. It spans from 'Innovation Trigger' through 'peak of inflated expectation' then through 'trough of disillusionment' before moving over the 'slope of enlightenment' onto the 'plateau of productivity' (10).

A more widely used estimate of technological maturity is known as the *technology readiness level* (TRL) scale. It was originally developed by NASA and is now widely used within industry, academia and government when assessing technology readiness (12). It is a qualitative measure represented on a scale from one to nine, with nine being the highest level of maturity (13). Figure 2.2 shows the nine levels of technological maturity as currently defined by NASA (13). Several factors influence a technology's developmental path from basic principles to an operational system, such as funding, ethics and political considerations. Other maturity scales have been defined to try to incorporate these considerations into assessment, but TRL is the most widely used scale and therefore the one that is referred to throughout this memo.

The TRL scale does not provide information about the timeframe for when a technology might reach maturity and be ready for utilization. Quantum technology is a good example of this as it has stayed in the lower half of the TRL scale for decades. The timeframe for reaching a high TRL level (meaning above six) provided in this memo can therefore be understood as being estimates drawn from the different trend literature on which the memo relies.

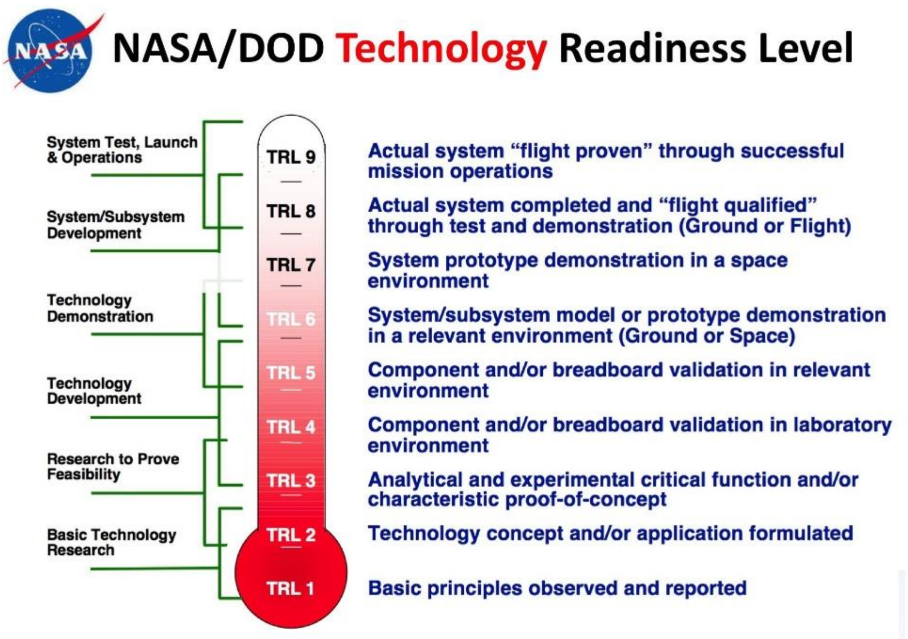

Figure 2.2 Overview of the technology readiness level scale as defined by the National Aeronautics and Space Administration (NASA)(13).

One important term when discussing emerging science and technology trends are *Emerging Disruptive Technologies* (EDT). *Emerging* technologies are technologies that are currently in development, but have not moved beyond low maturity levels (usually TRL one to five). *Disruptive* technologies are technologies with the potential of having major or revolutionary impacts on the nature of conflict. *Convergence* is another useful term, which means that a combination of existing technologies merge together in new ways to allow for disruptive effects. Technologies may also converge with other factors and cause disruptive effects, such as societal developments or military doctrines. It is in the overlap between EDTs that significant disruptions will occur (12). One example of a specific EDT with apparent synergies to other EDTs is *artificial intelligence* (AI) and *novel materials & manufacturing*, as well as *biotechnology* & *human enhancement*. These combinations of technologies have gained major attention and interest both within NATO as an EDT as well as for the members of EDA as a prioritized research area (7,8,12).

2.2 Human enhancement

Human enhancement (HE) refers to *human performance enhancement* (HPE) which encompasses all aspects of modifying the cognitive, physiological and social capabilities of humans. This includes everything from biological interventions to mechanical augmentation, through the convergence of technologies such as biotechnology, neuroscience, engineering and computing. An EU funded project known as the *Sienna Project*, which is exploring the ethical concerns of emerging technologies, defines human enhancement as; the process of positively augmenting human capabilities (box 2.1) (14). NATO has their own working definition of human enhancement technologies (box 2.2) (7). The two definitions differ slightly in what they include as 'enhancing' interventions.

Box 2.1: The Sienna Project definition of Human Enhancement
Human enhancement is the process of positively augmenting our abilities, permanently or temporarily. It includes any technology that expands or positively alters our capabilities or appearance: drugs, hormones, implants, genetic engineering or some surgeries.

Box 2.2: The NATO definition of Human Enhancement Technologies
Human Enhancement Technologies (HET) are biomedical interventions that are used to improve human form or to function beyond what is necessary to restore or sustain health. HET may enhance physiological, cognitive or social functions.

One can distinguish between different variations of the 'normal[1]' level of human potential. For example human performance *modifications* can be understood as any change to an individual's level of performance (15). This can be seen as the broadest understanding of the term, which includes *optimization*, *enhancement*, *degradation* and *restoration* of performance. Human

[1] We acknowledge that 'normality' is a relative notion that is hard to define.

performance *optimization* and *enhancement* is the process of applying existing and emerging science and technology to individuals, allowing them to reach or exceed their biological potential. However, if technology is misused or not ideally integrated, it can lead to unintended *degradation* of human performance. An example would be attempting to surgically enhance eyesight with the unintended consequence of blinding the patient. Performance degradation can also happen naturally as a response to prolonged stress, or other factors influencing the human physical or psychological status. *Restoration* methods and technologies for bringing the individual back to baseline is also part of human performance modification. Additionally, the potential for the use of technologies to purposefully degrade human capabilities in enemy troops should not be dismissed. The memo will generally use *enhancement* to cover all these nuances, as is customary in the literature.

Human enhancement has applications in many different aspects of society, ranging from medicine to sports to the military. These areas are all interconnected, which means that advances in one field is likely to cross over to others. Human enhancement technologies have often been associated with secrecy, but some research has been developed in the civilian sphere before being implemented into the military. For example, recovery from injuries has mostly been a result of research within sports medicine, but has clear potential for military force maintenance (15). Other examples include the use of gene therapy for disease treatment and the use of bionic limbs to restore mobility (16). Gene doping, a sub-discipline of gene therapy, has been used by athletes for generations to increase their physical performance. One common example of gene doping is the use of erythropoietin (EPO) as a drug to increase oxygen transport in the blood, which can lead to improved endurance (17). Many technologies developed in medicine for human therapy could also be used to enhance some aspects of soldier condition and performance. Some medical technologies began as inventions for military use before seeping into the civilian sphere thereafter. There are several examples that illustrate this, such as the principles of chemotherapy, conservation of donated blood for blood transfusions, and some types of anesthesia (18).

When it comes to the military domain of performance development, the goal is to enhance soldier's abilities to gain an advantage over their adversaries, from now on referred to as *soldier enhancement* (19). Key areas for potential soldier enhancement include strength, attention-span and situational awareness, cognitive and learning capacity as well increasing soldier resistance to stress and exhaustion. Performance-enhancing drugs (PEDs) have the possibility to improve many of these aspects of an individual soldier's capabilities. Over-the-counter stimulants such as caffeine and nicotine, demonstrated to be cognitive enhancers and fatigue countermeasures, are widely used by military personnel (20). More restricted drugs such as *dextroamphetamine* and *modafinil* have shown potential for improving wakefulness and concentration, but are as of now only available for some parts of the US military (20).

Exoskeletons and prostheses are examples of mechanical enhancers that have gained importance during the past decades due to their potential for increasing soldier strength, resistance, endurance and carrying-capacity (21). The TALOS exoskeleton is an example of such a device (22). However, most of the developments are in the early phases of research (low TRL). Some prototypes have been developed by private companies, but have limitations for military use. For the time being, the extensions generally add too much extra weight to the already heavy load of the individual soldier, which therefore reduces mobility and mission performance, and increases fatigue (23). However developments within robotics and new lighter materials are rapidly progressing, and exoskeletons are therefore expected to play a more central part in a military setting at one point, especially for logistical tasks. (2) There is also being conducted a lot of research in order to enhance the individual soldiers cognitive abilities, often referred to as the *hyper-enabled operator* (2). Other technologies currently being researched are brain stimulation techniques, human-machine interfaces and extended reality (XR) equipment for better education and training. The TRL-level of these technologies are currently estimated to be around level five and the time horizon for maturity is expected to be around 10-15 years (7).

The list of human enhancement technologies with relevance for the military is long and worth exploring. Within the sub-group of biological enhancement technologies there is research conducted on areas such as 3D-printing human tissue, and on developing new materials and living camouflage, albeit with a medium- to long time-frame (7,24). As a first step, we will focus on *genome editing* which is believed to have particular relevance for developments in the long-term. Many of the potential applications of this technology, and implications of said applications, will have far-reaching impacts. Advances in molecular biology and bioinformatics have made this an emerging technology worth paying attention to, and therefore a priority area for the military (12). It may only be a few decades before the tools will be available to bring the idea of an enhanced super-soldiers from science fiction into reality. *If* and *how* this technology should be utilized is another question, which will be discussed further below.

3 Genome editing for soldier enhancement

This chapter explores and explains the concept of genome editing, as well as briefly discussing CRISPR/Cas9-technology. The chapter further examines some technical and biological challenges which needs to be considered before genome editing can be applied, as well as identifying three important bottlenecks for further progress. The chapter ends by exploring some possible future applications of the technology in a military setting.

3.1 What is genome editing?

Genome editing is the practice of manipulating specific parts of a genome in order to deliberately change characteristics of living organisms – whether it be bacteria, plants, or humans (25). As genome editing is based on universal DNA-repair mechanisms, it can be used in any cell type or organism that employ these mechanisms (16). Although most of today’s genome editing is used for basic research in bacteria, yeast, plants and mice, the potential use in humans is at the forefront of political and ethical debates (22).

A genome is the complete set of DNA[2] (or RNA[3] in some viruses) in an organism, including all genes (coding sequences) and non-coding regions. Coding sequences are the stretches of DNA (genes) that carry the instructions to make proteins[4] or other functional products. Even though DNA often get the most attention, they only account for about 2% of the human genome. The rest is non-coding, meaning that it does not carry code to make functional products. The non-coding stretches of the DNA does, nevertheless, have important roles in transcriptional and translational regulation, determining when and where genes are turned on or off and to what extent. Another important factor of regulation is the epigenome; all chemical modifications of the genome not affecting the actual sequence, but the structure of DNA and surrounding proteins (26). The epigenome can create changes in the genome that may be passed down to the offspring.

The central dogma of molecular biology is that information flows downstream from DNA to RNA to proteins (Figure 3.1). Simply put; DNA *stores* all genetic information, RNA *carries* and *translates* the information to make proteins, which then *perform* a wide range of different functions in the body. These functions include catalyzing metabolic reactions (proteins called enzymes), transporting essential molecules such as oxygen (i.e. hemoglobin in the blood), providing cell structure and participating in cell signaling (responding to stimuli). The process of going from DNA to a functional product is called gene expression. All living organisms share similar mechanisms of gene expression, which means that basic research on genome editing in microorganisms such as bacteria and animals such as mice can provide biological insights and applications for humans as well. When scientists perform genome editing, they tinker with this process, often to find out more about the function of specific genes or the regulation of their expression. Gene editing is another term commonly in use, but since the concept is not limited to genes (but also includes changes to non-coding regions and to epigenomes) we will continue referring to 'genome editing' as it is more inclusive (25).

[2] Deoxyribonucleic acid
[3] Ribonucleic acid. RNA is an acid molecule that carries genetic codes, and differs from DNA in having ribose in place of deoxyribose and having uracil in place of thymine. Some organisms, such as bacteria, carry their genetic code in RNA molecules, not in DNA-structures, such as humans.
[4] More accurately; polypeptides – chains of amino acids. Proteins can consist of single or multiple polypeptides.

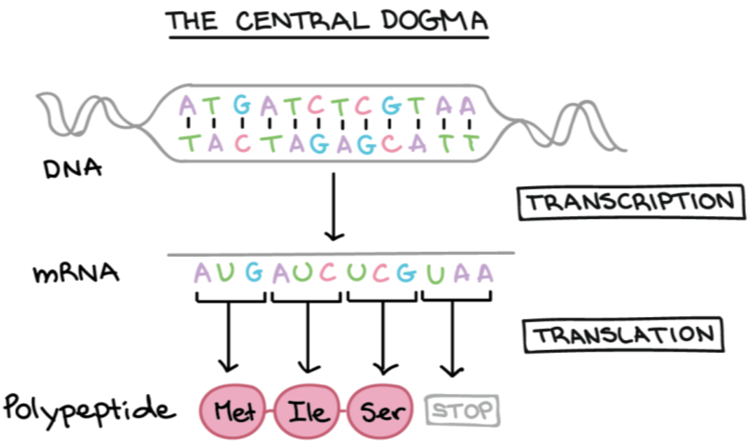

Figure 3.3.1 The central dogma of molecular biology; genetic information flows from DNA to mRNA (transcription) and from mRNA to polypeptides (translation). From (27).

3.2 Types of genome editing

Several techniques of genome editing have been developed over the last decades, all based on the same principle: making targeted cleavages in the DNA and then using the cell's own built-in mechanisms to repair the damaged DNA. These techniques are widely applied today in basic laboratory research on cells and in agriculture to improve crops. Applications of the technology in human health is mainly done at the concept level, but increasingly in clinical trials, for example for cancer treatment (28).

CRISPR/Cas9[5] is a new and improved genome editing technique which was established in 2012 (29). Since then, it has revolutionized the field of molecular biology and it is regarded as having disruptive impacts on many areas – including the possibility of enhancing certain human traits. The CRISPR/Cas9[6] system is more efficient, easier to use and cheaper compared to earlier methods, such as Zinc-finger nucleases (ZNFs) and Transcription activator-like effector nucleases (TALEN)[7] (30). Prime editing is a newly discovered technique which builds on CRISPR/Cas9 and may prove even more precise than its predecessor, although it is still in its early stages of development (31,32). CRISPR/Cas9 is based on a natural adaptive immune system found in bacteria and archaea to defend against invading viral DNA (4). Figure 3.2 briefly illustrates how the process goes. The Cas9 protein can also be designed to fit the purpose

[5] CRISPR stands for *Clustered Regularly Interspaced Short Palindromic Repeats*, and Cas9 stands for *CRISPR-Associated Protein 9.*

[6] Several other Cas-proteins, which can be used in this editing process, have been identified. We will continue to refer to the Cas9-protein, as it is the most well known and most widely used.

[7] These are prominent tools of genome editing mostly in use for basic research but also for applied purposes such as in gene therapy. There are for example ongoing clinical trials for the use of ZFNs and TALEN in attempts to eliminate HIV from AIDS patients by deleting the CCR5 co-receptor (3).

of the editing, for example to make changes in the proteins of the epigenome, thus changing the *regulation* of the gene rather than the gene itself (25,33,34).

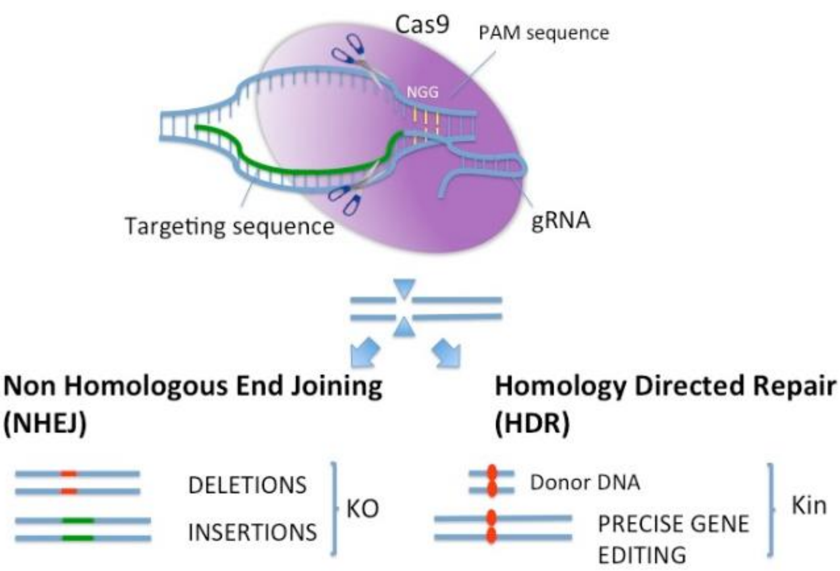

Figure 3.2 *Demonstration of CRISPR/Cas9 system cutting the genome and endogenous pathways repairing the DNA. Guide RNA (gRNA) will form complementary base pairing with the strand opposite to the targeting sequence (green). The targeting sequence is immediately upstream of a 5'-NGG PAM sequence, and the Cas9 nuclease (purple) makes a double stranded break further 3 bp (base pairs) upstream. Non-homologous end joining (NHEJ) introduces random deletions or insertions, while homology directed repair (HDR) inserts a provided donor DNA. KO: knock-out. Kin: knock-in. Image from (35).*

There are two types of genome editing techniques that can be used in humans, which is known as somatic and *germline* editing. The difference is in the type of cell where changes are introduced. Changing the DNA of somatic cells – all non-reproductive cells – will only affect the person treated. Transfer of genes into these cells in order to treat diseases (gene therapy) is a promising procedure, and is less controversial than germline editing. In germline editing, the changes are performed on the DNA of embryos, eggs, or sperm. This means that changes – whether beneficial or harmful – are passed down to all future generations (36). In November 2018, Chinese researcher He Jiankui reported that he had created the first gene-edited baby. He had performed germline editing on twin girls at embryo stage by mutating the *CCR5*-gene with CRISPR/Cas9 to make them HIV-resistant (36). This case, and germline editing in general, raises several important ethical questions.

3.3 Genome editing challenges

Despite the advancement of a variety of genome editing tools, there are limitations and challenges of technical or biological characters to consider (37). Some consider these challenges to be of such gravity that genetically enhancing humans will be impossible (38). Even though CRISPR is viewed as an improved technique compared to older genome editing technologies, it is still far from perfect. Some have stated that CRISPR/Cas9 has lower specificity than other genome editing techniques, but recent improvements have reduced the incidence of off-target effects (31,39). Reasonably priced commercial CRISPR/Cas9 kits are available today along with guidelines and protocols (40). Such techniques are not free from risks, and one should carefully reflect on the design of the components of the system before use.

Another limiting factor is how efficiently the substance altering the genome can be when introduced into the cells. Some common methods include microinjection, electroporation, lipofection and viral transfection.[8] A common complicating factor of delivery is that the insertion of DNA may occur at a later developmental stage than intended, which results in *mosaicism*. This means that not all cells of an individual will carry the altered gene; several mutations co-exist and is transmissible to the next generation. This has been a common observation when testing in mice with an incidence up to 50 %. Nevertheless, strategies to reduce mosaicism are currently in development (5,25).

The most significant limitation to the practical exploitation of genome editing is the level of knowledge of gene function. Although biological functions have been annotated for many human genes, there is still much we do not know. Editing techniques cannot be used until we know which regions of the genome to edit in order to introduce or eliminate certain traits. Overcoming this obstacle requires considerable research (25).

It is important to make a distinction based on the complexity of a trait. A few decades ago, it was believed that one gene accounts for only one specific function in the body, but we now know that this 'one gene - one trait' hypothesis is often not true. The fact that *one* gene can influence *several* traits, a concept known as pleiotropy, provides an important challenge of genome editing. Deleting one gene could have unexpected effects, potentially harmful ones. It is important to consider the complexity of biological systems and how genes are connected to different pathways. A related concept to pleiotropy is *polygenic inheritance,* the controlling of a single trait by the additive effect of multiple genes (41). For example, behavioral traits such as intelligence, aggression and fear, with valuable enhancement potential for military purposes, are influenced by many genes. Such complex, polygenic traits are also known to be highly affected by environmental factors. This means that it is more challenging to change these characteristics by genome editing than it is to alter "easy" traits controlled by a small number of genes. Predicting the outcome of genome editing therefore needs to consider the whole network of pathways connected to the gene being modified.

Two major issues that must be considered for genome editing to have a purpose is: genetic *reification* and *determinism* (38). First, one must be able to define *exactly* which trait one wants to modify. It needs to be a concrete entity that can be quantified, in order to find the gene(s) responsible for producing the desired effect. The second premise is that gene expression is

[8] See Synthego's CRISPR transfection protocols (40) for more on this.

deterministic; it is essential that what we change *causes* the specific phenotype[9] of interest in a fundamental way. Figuring out the correlation between genotype and phenotype is a prerequisite of successful genome editing. This is a challenging endeavor, especially for complex traits controlled by multiple genes, as mentioned. Further complications include both the epigenome's and the human microbiome's effects on the phenotype (42). Montgomery et al. further points to the difficult task of evolving from basic research:

> *"If genome editing is to prove practically valuable in the way that crop breeding, livestock domestication and biomedicine have done to date, it will be equally important, and arguably much more difficult, to demonstrate that the phenotypic modifications that may be achieved in the laboratory can be achieved in the field, the barn, and the clinic, and, equally importantly, to ensure that they can be introduced safely, ethically and acceptably in these contexts" (25).*

3.4 Possible applications

Genome editing has a range of potential applications which can augment and enhance the overall performance of the individual soldier. Which traits should be enhanced will differ according to the operation in question and the needs of the military. For example, cold weather operations are a priority in Norway and a great deal of research goes into finding ways to make soldiers more tolerant and adaptable to extreme cold temperatures (44). Genome editing might contribute in this field, although more research is needed. It is also important to note that there are other less invasive methods available than genome editing that can provide similar results and offer a good alternative in the short term.

Genomics and bioinformatics are two fields that both work as facilitators for genome editing, and present beneficial opportunities in combination with genome editing in a military setting. Sequencing the DNA of an individual soldier, and understanding how to interpret it through the use of bioinformatics tools can aid in personnel selection. People carrying genetic vulnerabilities for disorders such as osteoporosis, psychosis, post-traumatic stress disorder (PTSD) or other vulnerabilities not considered ideal for military service, could be filtered out at an early stage. Simultaneously, new recruits with a genetic pre-disposition for physical strength, robustness against stress and extreme pressures could be identified and recruited. PTSD is a major concern for the military and a disorder that affect many people in service. The US Department of Veterans' Affairs estimates that up to 30% of soldiers who served in operation Iraqi Freedom and Enduring Freedom suffer from PTSD (45).[10] Much research is conducted in identifying the markers in a human's genome for vulnerability to PTSD (47). As well as the human cost of this disorder, there are significant societal costs (48). Receptors associated with higher resistance to cold, and others tied to resistance to traumatic brain injury (TBI) have been revealed (49,50). This information could be applied in the selection of soldiers less at risk for frostbite and more tolerant to shock waves, respectively. Such procedures could reduce costs

[9] Observable characteristics determined by the genotype (set of genes) and environmental influences.
[10] See (46) for a comparison of several studies on PTSD-prevalence in US veterans from different wars.

and increase effectiveness, but would also be a way to make sure that soldiers are less at risk for serious psychological or physical injury. In the long term, when genome editing technology has matured enough to safely correct such vulnerabilities, new recruits could be given the choice to correct their vulnerabilities with genome editing and be accepted into service.

Knowledge of the genome can in due time allow for more personalized medicine; tailoring medical treatment to the individual soldier's needs based on their genetic profile. Personal genomics, through the collection of genotype and phenotype data from individual soldiers, are already showing rapid progress and gaining interest, especially in the US (42). According to a 2010 JASON[11] report, the technique could be utilized when assessing the health and performance of military personnel (42). In the meantime, it is necessary to investigate the connection between phenotypes with special relevance to military performance and their possible genetic component (42).

As mentioned, genome editing has major potential for diagnosing and treating diseases, and it is expected to be used directly in the human body in order to remove or turn off the function of disease-causing genes, or add genes that are absent from normal functioning (52). For some diseases, gene therapy has already demonstrated great potential, but it is important to acknowledge that many diseases have complex causes and cannot be easily treated by this kind of procedure. Genome editing could also be used to go beyond restoration in order to optimize certain physiological functions, such as sleep, energy metabolism and stress resistance. Sleep deprivation can be a major problem in military operations, and reducing the time needed to sleep or enhancing wakefulness would therefore be beneficial. Much research is devoted to understanding sleep and ways to minimize humans' need for it by editing the human's genome, among other techniques (53). Malnutrition and lack of food is another challenge for soldiers in the field, a solution to which may be creating self-sustaining soldiers with limited need to eat. DARPA has a research and technology projects looking at this, where they plan to engineer human cells to start working as nutrient-factories (52). Genome editing may in the future be used to alter soldiers need for food or their ability to digest uncommon substances, for example grass, in order to stay alert and operational.

Much genome editing research is being done in order to mitigate stress responses in extreme situations and military operations. Stress is a natural response that is evolutionary important for us to recognize dangerous situations, but prolonged stress could degrade a soldier's performance and potentially lead to post-traumatic stress disorder. Genome editing could in the future be used to prevent such disorders by taking advantage of personal genomics. For example, some people might be more susceptible to such disorders, and genome-editing treatments can be personally tailored so that they are less at risk. However, the use of pharmaceuticals to mitigate stress responses might be a more near-term strategy.

Increasing and enhancing the physical performance of the individual soldier, such as improved strength and endurance, is an achievable effect with genome editing which can add value in a military operation. Former NASA employee Josiah Zayner injected himself with his own

[11] An advisory panel consulting for the U.S. government in defense matters. See (51) for a collection of their work.

company's $20 CRISPR myostatin inhibitor in order to boost muscle mass during a livestreamed conference (54). This kind of do-it-yourself biohacking is generally not recommended, as few know the risks of such a procedure. In the future it might be possible to take genome editing even further and insert synthetic genes or genes transferred from other organisms to gain characteristics that are new to humans (25). However, other technologies such as XR and tissue engineering might have the same effect, but with lower invasiveness and less controversy associated with them.

Rather than directly targeting the human genome, one can engineer other organisms to work in symbiosis with the soldier. This can be considered less invasive and therefore more applicable near-term than genome editing. Basic research on the human gut microbiota and how microbes inside our bodies interact with our own cells is ongoing. Genome editing might be used to engineer these microbes in order to influence the host's metabolism or immune system in the future. There is also a lot of focus on the use of microbes for protection against pathogens and other CBRNE-threats. Performing a direct knockout of critical genes in bacteria or viruses already invading the body could serve as a new form of antibiotic treatment (55). Engineered microbes could produce protective biological polymers, such as spider silk, for incorporation into body armor and helmets.[12] The silk also has potential for medical applications working as a scaffold in tissue regeneration or for wound treatment.[13] Genetically engineered microbes could function as sensors, monitoring soldier's health and automatically administering the correct treatment in real-time (2).[14] Other defense strategies include using engineered organisms such as the marine microorganism *Marinobacter* to detect when enemy ships pass, proposed by the U.S military (57). However, releasing synthetic life forms into the environment presents some ethical considerations.

3.5 Technological maturity and expected developments

The technological maturity level of genome editing is often difficult to determine. This is because it depends on the application and on the organism on which it is performed, but in general it is reasonable to say that it currently is in the lower part of the TRL-scale.[15] The time horizon for the technology to reach maturity is expected to be between 10 to 20 years (7), but before genome editing can be properly used for enhancing the abilities of soldiers, three bottlenecks or hurdles must be solved.

The first hurdle which must be solved is the need for minimizing or eliminating the risks of error stemming from genome editing techniques. As explained above, the techniques of genome editing function rather well when tapping into a cell's natural mechanisms for DNA repair and editing. There are, nevertheless, some undesirable consequences of the techniques, such as

[12] Source: Biotechnology and Human Enhancement Technologies Workshop, NATO, June 16th 2020.
[13] Source: Biotechnology and Human Enhancement Technologies Workshop, NATO, June 16th 2020.
[14] Research in this area is already advanced, and modifying microbes in order to produce products such as malaria medication and synthetic opiates is widely applied. See (56) for more on this.
[15] See (43) for an overview of the history of gene editing in mammals.

mosaicism and off-target cuts, which need to be addressed before it is considered safe to begin testing on humans.

The second hurdle which must be solved is the need for an adequate understanding of the pathways of gene expression. The knowledge of how gene expression is regulated and influenced is far from complete. More research is needed to understand how the epigenome and non-coding sequences of DNA play into the process in order to ensure that the changes introduced into the genome have the desired effect. The field of systems biology is already contributing in this process, but much work remains. It is considerably more difficult and risk-filled to edit complex traits expressed through a web of interconnected genes and potential environmental factors, rather than 'simpler' traits regulated by fewer genes and variables. This makes it reasonable to assume that genome editing of complex traits are further into the future than editing of less complex ones.

The third hurdle one must overcome is related to human testing. Experimental genome editing is currently only conducted on simple organisms like mice or bacteria, whereas gene therapy on humans is exclusively available in clinical trials. The level of uncertainty associated with unintended and long-term effects of genome editing makes testing on human subjects challenging. Any change introduced into the genome will be risky, or maybe even impossible to reverse, forcing the test subject to live with the alteration. A better understanding of the genome and pathways for expression is crucial before one attempts to alter either simple or complex traits in humans. There are emerging technologies that may converge with genome editing and speed up this process, such as quantum computing for processing power and artificial intelligence (AI) for modelling capacity. Advances in these technologies could help with mapping and modelling of possible effects of genome editing changes, thus lowering the risk related to human testing.

4 Consequences for military operations

This chapter examines and identifies some implications and consequences that might materialize when utilizing genome editing to enhance soldiers. The specific consequences discussed in this chapter are possible future developments one should be aware of when considering implementing this technology. There will undoubtedly be high levels of uncertainty associated with speculations about possible futures, but this chapter provides a first glimpse at some relevant topics and questions one should be aware of.

4.1 Human factors

New and emerging technologies will undoubtedly have enormous impact on how warfare and military operations will be conducted in the coming decades. The general prediction by futurists is that many tasks that are performed by humans today, at some point will become obsolete due to developments within technology. Autonomous vessels and robots could in the long-term end up doing much of the actual fighting, creating more space between individual soldiers on the battlefield. Meanwhile, advances in technologies such as big data, AI and quantum computing are making it easier to process and analyze the amounts of sensor information and data collected. The technological goal is that much of the analysis needed for this data at some point will be more or less fully automated, thus reducing the need for a man-in-the-loop to the bare minimum.

Despite the reduced need for human cognitive processing, there will still remain tasks which can only be solved with the use of human capital. Furthermore, other technological developments are speeding up the intensity of warfare and could end up reducing the time available for human decision-making. In such instances genome editing for cognitive enhancement could become a useful tool in military operations. Enhancers that increase the individual soldier's situational awareness and help them concentrate for longer periods of time under extreme pressure could perhaps lead to more observant and well-coordinated soldiers and analysts. Enhancement and genome editing could further be used to make soldiers more resistance towards post-traumatic-stress, allow them remain calm when in combat, and overall reduce the stress factors associated with armed conflict. There is a misconception in the debate, often aided by dystopian science fiction entertainment, that a primary target of enhancement technology is to dampen normal human reactions to extreme situations, and in the process eliminate the soldier's humanity. The most feared scenario would be that of a soldier, unchecked by empathy, compassion or regret who becomes uncritical to the violence of combat. This is not the case and the goal would rather be to make sure the soldier is aware of his actions and that their physical and mental health remains intact. Cognitive enhancement could help the soldier comprehend complex situations and assist them with reaching ethical judgements quickly (58). Their heightened cognitive and observational abilities could increase precision and less unintended damage.

4.2 Physical enhancement and operational effectiveness

Incorporating soldier enhancement technologies and genome editing into the armed forces is expected to increase the overall operational effectiveness of military operations (7,58). Depending on the type of technology and the scale of implementation, one can expect soldiers to operate more effectively and over longer periods of time. Being physically enhanced to transport heavier loads would mean that soldiers could carry more ammunition, equipment and supplies, lowering the frequency of replenishment, their logistical needs and time. If soldiers, with the help of genome editing or other types of human enhancement technologies such as exoskeletons, were able to physically outperform other soldiers without such enhancements, their operational capabilities could allow for superior military engagements and the ability to operate more effectively over longer periods of time. These soldiers could operate heavy machinery at a faster pace and make sure that manual labor does not become a limiting factor in military operations. Such heightened physical traits will though perhaps not have the desired effect as future warfare is believed to become more robotized, autonomous and automated with time (59). Despite this, there will always be certain soldiers and units that rely heavily on physical strength. Genome editing and physical enhancement could end up being a force multiplier for these units.

Increasing the operational effectiveness of each individual soldier could eventually affect the overall force structure of the armed forces. Decreasing a unit's size while still being able to perform the physical functions needed affects the requirements in order to engage in specific military operations and engagements. Fewer troops who each have heightened capabilities would make the forces cheaper to maintain and statistically speaking, likely decrease the number of casualties (7,58). The theatre of war could be similarly narrowed, making the material cost of war lower (58). Maintaining the same level of troops and units could also mean heightened operational flexibility as they would be able to out-perform units that have not received such enhancements.

Genome editing which allows for climate or perhaps even CBRN resistant soldiers could expand the operational area of these units. For example, enhanced long-range reconnaissance patrols could operate for longer periods of time, without the need of bringing protection gear if they were able to withstand extreme climate temperatures or CBRN-threats. Genome editing targeting nutrition and digestion could allow troops to survive by eating grass or bark in extreme situations. Genome editing which allows the soldier to have heightened vision, hearing etc. could further assist in military operation. Enhancers such as this would increase the overall survivability and operational flexibility of these troops.

4.3 Enhanced adversaries

Genome editing and human enhancement technology could also directly affect the threat level of an opposing force. This would mean that an approaching enemy soldier may be genetically or pharmaceutically altered to have quicker reflexes, be stronger and thus carry more ammunition and gear than assumed possible. Assessing the enemy's actual capabilities could therefore end up becoming increasingly difficult as the maturity of this technology increases. Combat engagements with more unknown factors could therefore become a reality. Engaging in combat with non-state actors or rouge states not concerned with ethical implications could mean that the opposing force is willing to take higher risks when it comes to applying this technology to their own troops. In some cases this could lead to extreme versions of enhancements if the opposing force considers this a possible competitive advantage.

Several gene-editing tools are already widely available and these could theoretically be used by terrorists, insurgency groups or even private military contractors in the near or distant future. As the technology matures, it will eventually become commercialized and available to non-state actors. These actors may be subject to fewer limitations on their use of soldier enhancement technologies than would state actors, and they may also be incentivized to utilize the technology more quickly to gain competitive advantages. Private military contractors could end up being at the forefront of this trend, given their economic incentives and level of technological sophistication. If states are unable to use enhancement technologies due to regulations or ethical considerations, they may effectively circumvent these concerns by simply hiring enhanced private military personnel for the job of waging war and utilize them as a proxy. Gray-zone conflicts could therefore become even more complicated with the introduction of genome editing and human enhancement technology.

It is safe to assume that early adaptation of this technology will constitute a significant competitive advantage, which may tempt some actors to accept more risk. Certain states may not wish to be the first movers in this field, but may be pushed to follow suit if the technological gap compared with potential adversaries becomes uncomfortably large. Next generation warfare will likely pose different demands to soldiers on the battlefield. A British Army Officer states the following: *"In the past human frailty dictated when and for how long a soldier could fight before resting. This seems a luxury that may not be afforded to the next generation. Without enhancement (…) there is a real prospect that the human will become the weakest link in the Defence system."*(60) Therefore, it is important to engage with these topics before the technology reaches the battlefield.

4.4 Unintended negative consequences of enhancing soldiers

Soldier enhancement technology will in many instances result in the soldier being better protected then without enhancement. A segment of the literature is exploring the psychological effects that increased abilities could have on soldiers (61). Enhancement may cause soldiers to feel empowered to such an extent that they are willing to accept higher risk on the battlefield, potentially beyond the protection offered by the technology. An increase in confidence is a double-edged sword, as it could make soldiers more forward-leaning and creative, but also dangerously risk-seeking. A similar psychological effect may take place among field commanders, leading them to overestimate the abilities of their soldiers and tolerate placing them in higher risk situations. Understanding the (new) limits of enhanced soldiers' capabilities will have to be a process of careful trial and error.

Incorporating enhancement technologies into the armed forces may have other unfortunate consequences on military culture. A first main concern is that an enhanced soldier which accepts greater risk, obtains better results more quickly and by extension advances more rapidly in his or her career, may foster friction, jealousy, resentment or distrust with unenhanced colleagues. The successes of enhanced soldiers may also entice soldiers to tolerate greater risks in subjugating themselves to the technologies (61–63). This risk will likely decrease over time when the technology matures. The second main concern is the potential effect it has on core military values. There is a debate in the literature on how human enhancements of soldiers may erode the primacy of courage as a core value. This debate runs parallel to the debate on the courage or heroisms assigned to drone pilots[16] (58,61). Emphasis on physical courage might

[16] Bioethicist and specialist in moral philosophy, Michael J. Selgelid has argued that drone pilots should not be defined as *courageous warriors*, but rather *post-heroic*-soldiers. Since drone pilots are removed from corporal

make the enhanced soldiers be viewed in a similar way as they (might) be better protected, absorb less risk and thus exercise less courage (58).

4.5 Ethical and moral concerns

Ethical and moral issues are of primary concern when it comes to genome editing and soldier enhancement. In fact, these concerns could end up being the factors that determine whether a state decides to acquire and implement the technology or not. If we are comfortable or not utilizing the technology for military purposes will determine if the implications sketched out in this memo will materialize. However, ethical and moral rules and norms reflect their societies and cultures of origin and may thus move corresponding to societal change.

Genome editing interferes profoundly with the life of the individual soldier and represents an invasiveness that crosses societal boundaries. Balancing the considerations for the individual soldier versus military benefit of the technology is a challenging task (58). A rule-of-thumb in soldier enhancement is that it should be *temporary*, meaning all implants and robotic modifications of the human body must be removable and all pharmaceutical and biological alterations must be reversible. However, reversibility is currently a challenge when it comes to genome editing. Theoretically, one could attempt to reverse an introduced change in the genome, but it would be doubly difficult and dangerous. The long-term effects are hard to predict and even harder to counter. This may make it practically impossible to reverse an alteration in the genome, which should be considered when deciding on how to use the technology. This topic is heavily researched, including a DARPA-funded program on 'safe genes' that works to develop reversibility options for genetically altered soldiers (65).

Further, there is a question of ownership of the technology when enhanced soldiers terminate their service. Militaries are required to exercise control over the equipment and knowledge they possess to ensure that it does not fall into the wrong hands. When the technology is part of a person's body, the issue becomes more complicated as the person is entitled to corporal autonomy and privacy after their term of service has ended. If enhancement is not possible to reverse, a veteran will potentially bring the enhancement into his or her next employment, hence bringing military technology into a civilian sphere. Attempting to discourage veterans from specific types of employment may become a question of discrimination. It would pose a particularly large challenge for law enforcement should the veteran enter into illegal activity. The individual rights of the veteran, laws governing the protection of military property, and societal safety is thus a potential significant challenge of soldier enhancement (58,62).

There is an ongoing debate among ethicists on whether enhancements should be mandatory or voluntary for military personnel (61). If it is to be voluntary, the question of freedom of consent within military culture arises. For example, the ethicist Adam Henschke makes the following observation:

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danger, as opposed to soldiers in a theater of war, Selgelid argues that their actions do not hold the same moral value (64).

> *"If military service inculcates a disposition to follow commands, then it must also undermine military personnel's capacity to give consent freely. And, insofar as the research into and the application of enhancement technologies are conducted within a culture of assent, then the conditions around consent are — at the very least — complicated."(66)*

In a military context, however, there is precedence for soldiers waiving a portion of their autonomy to facilitate the effective function of the organization; a pragmatic approach to personal rights and freedoms. A soldier would, by enlisting in the army, consent to some infringements in his or her privacy, autonomy and right to refuse treatment (58,67,68). With this in mind, making some level of enhancement mandatory for soldiers would build on an existing practice, although the invasiveness would still have to undergo debate.

Somatic and germline editing each raises distinct ethical concerns. As mentioned the changes introduced from editing somatic genes only alters a single individual, whereas germline changes are transmissible to the next generation and onward. Any undesired effects of enhancement will follow the bloodline in the same way. Germline editing is the most troublesome ethical field within the whole of genome editing for this very reason. One would be making an active choice on behalf of future generations and potentially influence the course of evolution by 'enhancing' generations to come. In the aftermath of He's revelation of his alteration of the genome of two twin girls at embryo-stage, many prominent biological scientists advocated for a moratorium on the genome editing technology, precisely because the potential ramifications for humanity (69,70). However, germline editing makes it theoretically possible to eliminate diseases with immense human and economic costs. One tends to focus on the negative effects of such enhancements and conclude that this would be unethical, but its usage could also potentially make sure that future generations are immune to viruses i.e. Covid-19, which perhaps affect the equation and ethical assessment.

5 Conclusion

There are several areas of military activity where genome editing technology can affect the future operating environment. When the technology eventually reaches maturity, it could be used to enhance both the physical and cognitive operational capabilities of individual soldiers. This has the potential to create new opportunities as well as new or altered threats. The current technological trend trajectory will ensure that the future operating environment over the next two decades will be fast, data-driven and more precise. These changes will require more agile, adaptable and aware soldiers, lest humans become the weakest link. Enhancing human capabilities can therefore become a necessity in order to stay relevant and operational.

For many countries, ethical considerations will likely play a significant role in how they approach this emerging technology. Many will undoubtedly restrain from testing or utilizing the technology due to its highly invasive nature and uncertainty regarding long-term effects. However, some potential adversaries may not share such concerns. We may therefore at one point run the risk of facing an enemy who is boosting their operative capabilities with the aid of genome editing, regardless of our own ethical assessments.

When discussing this technology in a military context, its negative and unknown side effects often garner the most attention. However, breakthroughs and developments within genome editing could just as likely occur in a civilian sphere. For example germline genome editing which ensures that future generations are immune to covid-19 would likely involve an entirely different set of ethical considerations than when the usage discussed is strictly militarily. Understanding the likely consequences of this technology and following its development will therefore be as important as considering the ethical implications of its use.

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FFIs organisasjon