Opportunities and challenges of using epigenetic technologies in defence and security contexts

A scientific report for the Mobilizing Insights in Defence and Security (MINDS) program of the Canadian Department of National Defence

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Preamble:
"Opportunities and challenges of using epigenetic technologies in defence and security contexts" was funded by a Targeted Engagement Grant from the Mobilizing Insights in Defence and Security (MINDS) program of the Canadian Department of National Defence. The project aims to identify opportunities and challenges in using epigenetic technologies in the context of defence and security, with a focus on four applications: (a) exposure to nuclear, chemical or biological weapons; (b) epigenetic age); (c) mental health monitoring; (d) enhancement of bodily functions.

The research team recruited a panel of 19 participants for the workshop. In order to provide a multidisciplinary perspective, their specialties and fields were diverse, and included health law, sociology, philosophy, bioethics, neuroepigenetics, genomics and epigenetics. Furthermore, in order to identify the key challenges and topics to be addressed during the workshop, and to inform the creation of the pre-workshop survey, the team conducted a literature review. Participants were sent the survey prior to the workshop in order to further identify broad themes and key issues at the intersection of epigenetics and defence. This survey aided in the creation and structuring of the workshop and helped guide and foster discussion. Furthermore, the team designed two case studies using participants' responses in the pre-workshop survey on the opportunities and challenges of epigenetics with regard to security and defence.

Although originally intended to be held in-person, due to the COVID-19 pandemic the workshop was held online via Zoom in order to adhere to public safety regulations. Emanating from the workshop, a perspective paper will be published in collaboration with the workshop participants on the various issues, challenges, opportunities and key questions identified by the group.

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Meeting Minutes of the MINDS Workshop:
"Opportunities and challenges of using epigenetic technologies in defence and security contexts"

Virtual Workshop held on January 28, 2022, 9 AM to 1 PM

Attendees:

1. Yann Joly, McGill University, Canada
2. Gratien Dalpé, McGill University, Canada
3. Katherine Cheung, McGill University, Canada
4. Guest 1, Bioethics, Canada
5. Guest 2, Biotechnology, Germany
6. Guest 3, Neuroepigenetics, Switzerland
7. Guest 4, Bioethics, United States
8. Guest 5, Philosophy, Switzerland
9. Guest 6, Bioethics, United Kingdom
10. Guest 7, Bioethics, Switzerland
11. Guest 8, Philosophy, Germany
12. Guest 9, Medical Ethics, Netherlands
13. Guest 10, Bioethics, Germany
14. Guest 11, Genomics, United Kingdom
15. Guest 12, Healthcare law, United States
16. Guest 13, Molecular epigenetics, Netherlands
17. Guest 14, Data science, United Kingdom
18. Guest 15, Epigenomics, United States
19. Guest 16, Epigenomics, Canada
20. Guest 17, Law and bioethics, United States
21. Guest 18, Sociology, United Kingdom
22. Guest 19, Health law, Bioethics, United States

Workshop Agenda:

1. Introduction of participants and the workshop (30 minutes)
2. Presentation on Epigenetic Inheritance, *Guest 3* (45 minutes)
3. Case Study: "Predictive Epigenetics and Epigenetic Age- Potential Applications in the Military" (60 minutes)
4. Presentation on Epigenetic Editing, *Guest 13* (45 minutes)
5. Case Study: "The Possibility of Soldiers' Enhancement Through Epigenetic Editing" (50 minutes)
6. Discussion of Future Outcomes, Meeting Proceedings (15 minutes)

Summary of the Presentation on Epigenetic Inheritance by Guest 3

Guest 3 begins her presentation, "The Power of the Environment on our Genome", by providing a brief description of epigenetic inheritance and its mechanism. She explains that histone methylation and histone demethylation are epigenetic modifications that can reduce or bolster gene expression, especially as a result of altering chromatin structure. She elaborates that epigenetics changes through histone modifications can regulate many normal and disease-related processes, and that DNA in germ cells, e.g. sperm cells, can also be subject to epigenetic modifications.

Guest 3 further explains that there are several approaches to regulate epigenetics and epigenetic inheritance- in essence, different factors such as food, pollution, lifestyle, stress and trauma can influence epigenetics and different cells within our body (e.g. germ cells). However, she explains that not all exposures will have an effect. Environmental factors can have transgenerational effects: in men, they can affect the father's somatic and sperm cells; in women, it can affect the mother, the foetus, and future gametes and oocytes. She notes that the mechanism for this transmission is not well understood. She provides examples of epigenetic transmission by giving evidence of transgenerational transmission of acquired traits across species (e.g. in *C.elegans*, starvation has been associated with developmental arrest in the 3rd generation). In humans, Guest 3 provides examples of how events and factors such as the Rwandan genocide, poor nutrition and parental separation have been studied to have a transgenerational epigenetic effect. Regarding psychiatry, Guest 3 explains that traumatic events such as violence, abuse, abandonment, and neglect have been associated with psychiatric disorders such as depression, schizophrenia, borderline personality disorder, addiction and suicide. Guest 3 concludes that we need to understand better epigenetic innate and acquired mechanisms converging environmental influence on cells and organisms. She also emphasizes that future research should identify diagnostic and therapeutic biological markers of diseases resulting from environmental exposures.

Discussions About the Presentation on Epigenetic Inheritance

Guest 10 asks if there is a proven correlation between epigenetic biotypes and PTSD. For example, a correlation that would tell us whether individuals in the 3rd or 4th generation would be stressed (an epigenetic experience that runs in families). She asks as to how far we are from having causal connections between biotypes and PTSD exposures.

- Guest 3 replies that in humans, we are far from having a direct signature for current or future signs of PTSD. She adds that from the perspective of animal research, as with mice, we are close to having signatures- there is a list of microRNAs that are found in the sperm and blood of the exposed animals, and in the sperm and blood of the progeny. However, translating this to humans will be difficult. Guest 3 concludes by saying that

molecular factors that are robust need to be identified in animal models. Mice are also isogenic – there is thus a large gap in translating this to humans.

Guest 6 asks about the difference between transient and chronic exposures. For example, in the context of the COVID-19 pandemic, would this be a transient or a chronic exposure?

- Guest 3 replies that this is difficult to answer. She explains that everyone will have different reactions to COVID-19, for example, depending on where you live, the size of your living space, whether you are stressed, etc. From the perspective of animal research, all of this can be dosed precisely in mice to allow us to observe the effect on the epigenome – this is not possible in humans. Guest 3 concludes by saying that there is not enough knowledge to see the difference between a transient and long exposure, and that in the context of COVID-19, there are too many factors.

Guest 9 asks of the state of knowledge of the predictive value of epigenetic markers in a human individual. She inquires if there are any epigenetic markers that can be assessed that could say something about recent exposure in humans.

- Guest 3 replies that we are not very far from this stage.

Guest 5 acknowledges that there is tension between the reversibility and the stability of epigenetic marks. A mouse, with its stable phenotype and biotype, can have its epigenetic marks reversed. He asks to what extent should we keep this in mind when researching humans. In addition, Guest 5 says that it could be difficult to disentangle in humans the multitude of factors that contribute, e.g., acute stress, genetics. He asks if we will ever be able to reach a stage of fine-grained analysis.

- Guest 3 concurs and says that there are many factors to consider in humans, for example, when the trauma occurred, what was the trauma, current lifestyle, and what happened during the time elapsed - all these elements require data and rigorous statistical analysis. Guest 3 suggests that it would be better to talk to people more informed about how the data is collected. She explains that in animals, there is a possibility for the reversal of epigenetic marks through the provision of environmental enrichment- however, the longer the time elapsed between the trauma and the provision, the more difficult it is to reverse.

Guest 18 asks why, when we know and have known for a long time about the psychological harms or early-life trauma and adversity, should we focus on the biological mechanisms underpinning this? Does this focus imply that we are collectively more ignorant than we actually are about harms, which disincentivizes policymakers from investing in supportive social policy and public mental health? *(in chatbox)*

- Guest 19 replies that the answer to that may depend largely upon who has the political power to make policy changes. In a very divisive time, this is incredibly difficult.
- Guest 11 replies in the chat that while he can't speak directly to trauma, the case of a toxicant exposure can be considered - when considering safety of exposure for regulation, currently the potential of inter/ transgenerational effects is not considered by regulators, perhaps leading to flawed decision-making *(in chatbox).*
- Guest 11 adds that another example would be in health economic analysis of the cost of exposures - if we do not consider the potential costs of future generations health, then the true cost will be underestimated and decisions balancing health cost versus intervention cost will not be correct. He concludes that there is also the issue of timing, as with smoking. The health effects of paternal smoking on offspring respiratory health have been clearly shown, particularly if future fathers start smoking as adolescents. So, if fixed resources are available, should one invest in a smoking cessation program for pregnant women or invest in a program aimed at adolescents (male and female) to improve their health but also future children's health *(in chatbox)?*

Guest 3 notes that many people have difficulty accepting epigenetic inheritance. The argument that they make is this mechanism does not exist for plants, therefore it's difficult to accept that it does for humans. It is also very difficult to demonstrate in humans.

- In response to Guest 3, Guest 11 adds it is more difficult to study epigenetics in humans- for example, you cannot ask them to breed at a certain time, and generation time for epigenetic marks is much longer. Furthermore, Guest 11 asks why would we expect humans to differ from other mammals - i.e., why would we not expect epigenetic marks to occur?
- In response to Guest 3, Guest 16 explains that advances in embryo research will demonstrate that epigenetics occur in humans. Changes in the sperm's epigenome can be tracked. In extending this to toxin exposures, BMI and diet, Guest 16's lab has shown that there are consistent changes to the epigenome that hold between two very different populations.

Guest 4 notes that something to be kept in mind about epigenetics and special operations personnel, at least in the US, is that they are likely to be drawn from populations that have been more exposed to various stressors including violence and abuse, less stable homes, financial insecurity, etc. *(in chatbox).*

Guest 10 asks if whether epigenetic changes simply reflect on a biological level what is happening on a psychological level or in behavior. She asks if epigenetic intervention could cure PTSD or if it is just a by-product of what trauma does *(in chatbox).*

- Guest 9 replies by "curing" or targeting the epigenome, the psychological/medical problem itself might not at all be addressed *(in chatbox).*

Case Study: "Predictive Epigenetics and Epigenetic Age: Potential Applications in the Military"

1) Should we use the same reliability threshold for military use as we would for clinical or commercial use?

Y.J begins the discussion by saying that the questions from the case study can be answered from many different angles e.g., the scientific, sociological, legal. He asks what the laws and regulations are saying about this at this time.

Guest 19 notes that her first thought is to the framing – is the question about negligence? She says that the important question is whether we should be offering testing for the G2[1] biotype at all, or whether it would cause more discrimination to individuals who have the biotype. She adds that there is too much reliance on biological evidence and not enough on the resilience of individuals themselves. She concludes by saying that individuals might also be denied the opportunity to be part of Claw[2] if they have the G2 biotype, adding to the discrimination component.

Guest 14 says that the G2 biotype association to 34 clinical features sounds a lot like a publication (Yang et al. 2020) - the discovery cohort is what we would call a pilot, the recall and validation even smaller. The sample was males only and the ancestry had to be controlled. There are not many such studies, and the evidence is skimpy about replication and generalization, as well as controlling for confounders. In short, the biological evidence is not at present strong enough to generalize to move away from academic debate, let alone move into the clinic, or even to military applications *(in chatbox).*

Guest 16 adds to the discussion by asking what the criteria for an epigenetic biotype are to be used reliably as a predictor for PTSD. She explains that DNA methylation can be quantitative, e.g., with a 5%, 10% or a 20% change. However, she asks if this is biologically relevant, and if so, at what level is it biologically relevant? She continues by noting that a marker for PTSD will need to be tested over an ethnically diverse population, as well as tested over the span of an individual's life, to see if these markers are permanent or responsive to different settings.

[1] The G2 biotype is a fictive epi-signature for PTSD adapted for the case study from Yang et al.'s paper "Epigenetic biotypes of post-traumatic stress disorder in war-zone exposed veteran and active duty males" (https://doi.org/10.1038/s41380-020-00966-2)
[2] In the case study, "Claw" refers to the name of a fictitious combat unit at a high risk for PTSD.

Guest 17 responds to the question by saying that based on historical precedent, if the biotype were something affecting the safety of the warfighters, the threshold for adopting it would typically be lower than it would be for the civilian population. He asks whether it should be up to the discretion of the individual warfighter to take this risk. He concludes by saying that the cost of caring for people, e.g. veterans with PTSD, is something to take into consideration.

In continuing with Guest 17's comment, Guest 12 says that the threshold used in the military tends to be lower. In addition, there is an emergency authorization law for the military, to allow for lower reliability thresholds. He explains that during this time as an attorney, he would use a legal defence saying that animal studies do not explain what happens in humans. He asks if we are getting better at correlating exposures to certain consumer products or chemicals in animal models, which can then be externalized to human disease.

- In response to Guest 12, Guest 16 replies that animal models are robust, and that the studies can be trusted to reflect human health impacts. She explains that they are highly similar at the level of the genome and epigenome. She draws upon the example of drug development – as every drug used to treat human disease is developed in an animal model. How can you argue that animals are not similar enough if the drugs are working?
- Guest 12 replies that he agrees with Guest 16. He further explains that he believes the argument used by the chemical industry (which he briefly represented as an attorney), which isthat using animal studies as a proxy for human disease causation is "junk science", is a cynical shield to avoid accountability for the human harms caused by their products.

Guest 16 comments that something to consider beyond the immediate impact on the individual is the potential impact on future generations. She further adds that regardless of the epigenetic inheritance factor, it is known that parental stress and poor mental health have negative impacts on the child.

Guest 2 responds to the question by saying that the decision on the threshold would depend upon the decisions one would make due to the pattern of epigenetic modification. He adds that the key thing would be whether the methylation pattern was present before they experienced the trauma, or whether it would only appear post-exposure.

Guest 8 asks if it can be assumed that the epigenetic biotype G2 is stable during one's lifetime and that it is established early in life and cannot occur de novo at any point in life. She says that in this case, since a clear "yes and yes" cannot be answered to these questions, our answer to the questions 1) and 2) of this case study might change *(in chatbox).*

Guest 14 notes that there are many confounders - other comorbidities, depression, alcohol use. He states that we are yet to disentangle a clear PTSD signature in a scaled-up replicable way that

accounts for ancestry and can be generalizable to populations – he suggests that we should be striving for stratification, and precision-medicine solutions (*in chatbox).*

- In response to Guest 14, Guest 16 replies that robust validation across diverse populations and stressors is essential to develop a reliable diagnostic. She adds that for stress and mental health, this will be particularly challenging in comparison to the epigenetic markers of diseases such as cancer *(in chatbox).*

In response to the question, Guest 7 replies that the answer will often depend on the specific empirical details to be inserted into the scenario. He agrees that it should be up to the individual soldier to decide based on the information provided.

Guest 10 states that who should decide seems crucial: informed consent by the soldier is okay. However, exclusion based on a test that is not quite robust and seems ethically difficult. She agrees that the individual and public health perspectives differ *(in chatbox).*

Guest 9 asks how reliable is the epigenetic test in distinguishing those who are at-risk from those who are not at-risk? And secondly, at what level of risk do we consider it unacceptable to expose individuals to potentially traumatic situations? (should the risk threshold be lower for military personnel than for others?) *(in chatbox).*

Guest 18 notes that in the case study, a lot seems to hinge on the statistical significance of the association. He asks how significant is significant? *(in chatbox).*

- Guest 16 replies to Guest 18 that the probability of prediction has to be extremely high. She explains that this would also require blind retrospective trials with individuals that have PTSD and also prospective studies *(in chatbox)*.
- Guest 3 replies to Guest 18 that molecular evidence that psychological harms or trauma do alter cells persistently and cause damage to tissues and the body could rather reinforce the recognition that harms/trauma are responsible for mental health issues, thus leading to an even higher need for social support and mental health care *(in chatbox)*.
- Guest18 replies to Guest 3 that he agrees, although he is also mindful of the evidence that shows biologisation of mental health can counter-intuitively increase stigma *(in chatbox)*.
- Guest 3 replies to Guest 18 that she agrees; however, she adds that stigma may be decreased when one is able to consider that mental diseases are due to dysfunctions of some cellular processes in the brain, just like in other tissues such as heart or liver for other diseases. She notes that seeing psychiatric diseases from a molecular perspective can help move away from a mind/mental view *(in chatbox)*.

- Guest 18 replies that for people, it can, and from a policy perspective, biological evidence stubbornly remains more epistemically attractive in terms of stimulating action in certain contexts *(in chatbox)*.

Guest 15 asks if the case study was based on an actual study, and how this could be studied in a non-military population. He says that he believes PTSD seems rare in civilian populations, in addition to it being difficult to perform before and after studies.

- Guest 14 disagrees: he states that PTSD is not rare in the civilian population, taking the example of sexual assault. He adds that an example of a study looking at PTSD in civilians and veterans simultaneously is the Cohen Veterans Centre study - in a cohort of more than 1,000 people *(in chatbox)*.

Guest 5 supposes for the sake of argument that G2 is specific and significant enough to predict a fair portion of people with PTSD. He suggests that a consideration of equity should be added – what does the army do today to test soldiers for other risk factors for PTSD (e.g., lack of social support in childhood)? He concludes by saying that if G2 is applied routinely, then there is fair reason to think that tests should also be run for other parameters that can predict G2 e.g., childhood trauma.

- Guest 16 agrees and asks if such a test for the G2 biotype would be better at predicting PTSD than ACE scores[3].
- Guest 8 also agrees with Guest 5. She adds that if we rely heavily on the G2 epigenetic biotype, and offer preventive measures for PTSD (e.g., not sending individuals for deployment), then other soldiers might be at a disadvantage by not having this biotype.

Guest 11 notes that the appropriate statistical methodologies for methylation risk scores are still being debated. He agrees with others who have said that the sensitivity or specificity of risk scores would be important factors in decision-making *(in chatbox)*.

- In response to Guest 11, Guest 14 says Cohen Veterans Biosciences[4] focusses on both diagnostic biomarkers of PTSD as well as prognostic biomarkers and stratifying biomarkers. He adds that to clearly understand how these are related to each other and comorbidities and confounders is very challenging *(in chatbox)*.

[3] ACE (Adverse Childhood Experience) scores are a tally of the common traumatic experiences that occur in early life, with a higher score correlating to a higher risk for health problems later in life. (https://developingchild.harvard.edu/media-coverage/take-the-ace-quiz-and-learn-what-it-does-and-doesnt-mean/)

[4] Cohen Veterans Biosciences a non-profit biomedical research and technology organization dedicated to advancing brain health by fast-tracking precision diagnostics and tailored therapeutics (https://www.cohenveteransbioscience.org/mission-overview/)

Guest 9 notes that the level of test performance may need to be the same in the military as with clinical use, in comparison with commercial use, where standards may be lower *(in chatbox)*.

Guest 11 poses the question as to what is more important- identifying the biotype as a marker of PTSD risk or understanding the exposures that lead to the biotype signature and tackling these? *(in chatbox)*

2) Should information from individuals' epigenetic tests be kept on a database or registry on a long-term basis by military authorities?

Guest 19 begins the discussion by noting that the question recalls the experience of Iceland and their genetic database. She explains the case of a daughter who asked the government to remove her father's DNA from the database as it reflected badly on her[5] . Guest 19 notes that keeping information on a long-term basis has the potential to affect future generations by stigmatizing them - she concludes by saying that long-term should be defined.

Guest 6 asks the question of whether the database would be an information database, or one solely with samples. She asks what the purpose of the database is. She explains that depending on the purpose of the database, there might be different ethical attitudes toward it. For example, would it be for research purposes, or for people deployed in future arenas? She adds that this also raises the question of who can have access to it e.g., relatives, children.

Guest 16 notes that an important consideration is that the epigenome is flexible and can change. She asks if a positive test will mean that a person will always test positive. *(in chatbox)*

- Guest 11 agrees with Guest 16, and asks how many people should be prevented from deploying in order to prevent one case of PTSD? *(in chatbox)*
- Guest 14 responds that there are already many people with PTSD before deployment. As an example, early trauma may be linked to PTSD. Early trauma may be due to disaster events, sexual abuse, physical and psychological abuse, witnessing violence. In contrast, traumatic brain injury (TBI) is distinct- as it is an added burden but separate from PTSD. There are individuals diagnosed with PTSD, or PTSD with TBI, or TBI on its own. He adds that there are many ways to diagnose PTSD, and that Guest 16's question is difficult to answer *(in chatbox)*.

Guest 10 notes that the purpose of the storage needs to be clarified in advance. She suggests that soldiers should consent and be informed, and that governance should be such that data cannot be used in discriminatory ways.

[5] https://www.bionews.org.uk/page_89221

Guest 4 contributes by saying that in the United States, the political system will insist that the data be maintained for the protection of veterans e.g., to reconstruct exposure levels.

Guest 11 replies to the question by saying that an important question pertains to the stability of the epigenetic biomarker in the individual. He explains that most studies are done with a single cross-sectional measurement. He asks if the signature will be stable over time, and how this will affect whether or not it is kept on the registry.

- Guest 16 replies to Guest 11 that repeat testing is needed in these studies in animals and humans. She explains that ongoing studies on epimutation stability and preliminary data indicate they are reversible as well as the associated phenotype. She concludes that if this holds there is lots of potential for treating humans by epigenome manipulation.
- Guest 11 replies to Guest 16 that if the markers are reversible then what is the value of retaining the data when you should test again each time a decision needs to be made.

Guest 12 adds to the discussion by saying that keeping it on a registry is legitimate for medical monitoring. He explains as an example, in communities exposed to a spill, the disease might not manifest for another 20 years. If there is a purpose, it might make it more legitimate. He draws upon the real case of the University of Arizona, where the University of Arizona decided to take a sample and use it for purposes it wasn't originally intended. In this situation, it wasn't until a graduate student noticed then it became an issue[6].

Guest 15 asks what the rules for informed consent in solders are. He notes that prisoners cannot be used for studies without their consent but asks whether soldiers need to provide their consent. He adds that with the military, it is very difficult to renegotiate the terms of what the sample was used for *(in chatbox)*.

- Guest 4 replies that consent is needed, as well as there being no pressure from superiors *(in chatbox)*.

Guest 5 asks the question of when intervention should be done. He asks if "resilience training" should be made on soldiers or whether the army should rather invest in social support of the children that may likely develop these predispositions and possibly move into a military career *(in chatbox)*.

Guest 14 notes that a lot of soldiers are reluctant to admit to the specifics and may not be truthful in many self-reporting diagnostic tests *(in chatbox)*.

[6] https://journalofethics.ama-assn.org/article/genetic-research-among-havasupai-cautionary-tale/2011-02)

3) Are there factors that could interfere with the age estimated from epigenetic clock tests?

Guest 1 contributes to the discussion by noting that these epigenetic clock tests have not been validated in varying populations and should be if they are to be used.

Guest 16 begins the discussion by noting that the epigenetic clock of Steve Horvath[7] is highly reliable. She asks if in terms of predicting an impact, if it is reliable, and is it stable? She adds that if someone tests five years beyond their epigenetic age while smoking, and then stops smoking, will the epigenetic age still hold? The epigenome is flexible.

- Guest 14 comments that there is a difference between chronological and biological clocks- the Horvath clock is trying to establish the actionable age of a person, while a biological clock is giving you the epigenetic age. He explains that all the models are done with simple statistical approaches- they do their best to account for a number of confounders/co-variates, but there is not such great confidence so far, because of the sheer complexity of epigenetics. He adds that there is population complexity as well. He concludes that as with the G2 biotype, he is reluctant to move away from the academic debate.

Guest 12 poses the question as to whether children in conflict zones "age" faster *(in chatbox)*.

Guest 8 states that as the epigenetic age test appears to be a mere indicator, with no clear proof, we might still rather rely on the "in dubio pro reo" principle than on the age test *(in chatbox)*.

Guest 14 notes that there are many cases in history where science is brought to the general public well before scientists have agreed. He states that just because one can do something doesn't mean one should.

Guest 11 contributes by saying that clocks are highly correlated with age, but they do vary. He further notes that clocks have been developed with DNA samples from adults and may be less accurate when used with adolescents. He states that studies need to be done to validate it in more populations.

Guest 9 asks the question of whether, in a "decent society" [8], we going to have people undergo biological testing to verify their age (instead of asking them). She says that this is a rather intrusive 'scrutiny' *(in chatbox)*.

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[7] Horvath's epigenetic clock uses 82 Illumina DNA methylation array data sets involving 51 healthy tissues and cell types in a multi-tissue predictor of age which allows one to estimate the DNA methylation (DNAm) age of most tissues and cell types (https://horvath.genetics.ucla.edu/html/dnamage/)

[8] Avishai Margalit, "The Decent Society", 1996. (https://www.hup.harvard.edu/catalog.php?isbn=9780674194373)

Guest 18 says that nothing can be considered without the politics of it all. The use of these clocks is not for progressive, egalitarian ends: it is more for restricting and excluding. Therefore, the onus for the tests to be accurate is gigantic, and it needs to be far more perfect than it is. It needs to be more perfect than it would have to be for more inclusive purposes, as it is for exclusive purposes.

Guest 15 states that epigenetic clocks measure your biological age, whereas your chronological age is your actual age. He asks if there are other ways to tell chronological age e.g., by looking at teeth. He explains that one would not want to look at epigenetic age to determine the age of a child, but more so other markers of chronological age. He poses the question as to whether we should try to find other biomarkers of age, before using epigenetic clocks.

- Guest 3 replies that it is possible to profile blood proteins in order to evaluate age[9]

Summary of the Presentation on Epigenetic Editing by Guest 13

Guest 13. begins her presentation, "Repurposing genome editing for (sustained) transcription modulation without damaging the host genome: Epigenetic Editing", by stating that one is born with a certain set of genes - however, through epigenetics, we have some modicum of control over what is expressed and what is not. She notes that the definition of epigenetics is still unclear- it can vary from epigenetic memory (stable/sustained effects in absence of the trigger-changes in gene expression that are mitotically/meiotically stable) to epigenetic marks (DNA methylation, histone modification, histone variants). Guest13. explains that epigenetic reprogramming looks at longer-term changes: it can occur through diet and lifestyle, or through epi-drugs (some are now approved from hematological malignancies, many are in clinical development). Elaborating upon this, she explains that epigenetic drugs can change the epigenetic profile of the individual. Guest 13. continues her presentation by describing how some pathophysiology may be due to dysregulated epigenetics. Epigenome-wide association studies have led to the identification of diagnostic markers, and epigenetic enzyme inhibitors can provide epigenetic therapies. Guest 13. explains some of the disadvantages of epigenetic drugs, which include genome-wide effects, genome instability and the potential of non-chromatin targets. She explains that the solution to this is to localize epigenetic enzymes to the gene(s) of interest (however this is very difficult!). Guest 13. suggests that epigenome engineering is potentially less invasive, reversible, equally effective, and may have fewer biosafety concerns. Expanding upon this, she explains that in epigenetic editing, there are "writers" and "erasers": a writer fused to a DNA-binding domain will lead to more epi-marks, while an eraser fused to a DNA-binding domain will result in fewer epi-marks. She explains that this has the potential to achieve sustained cell reprogramming. She concludes her presentation by saying that gene

[9] https://www.nature.com/articles/s41591-019-0673-2

expression can be induced (which closely mimics nature), or gene expression can be silenced (in a "one and done" approach).

Discussions About the Presentation on Epigenetic Editing

Guest 15 asks of the ethics of treating diseases in a permanent/semi-permanent manner. He asks what would happen if epigenetic editing had counter effects. He suggests that a better approach might be Crispr used to target RNAs, which would be less permanent.

- Guest 13 replies that if one targets at the level of the RNA, the treatment would need to be done repeatedly. She counters that for many diseases, one might want to see a more sustained change than treatments typically done in the clinic.

Guest 9 asks of the mode of administration of epigenetic editing, and whether there are potential side effects.

- Guest 13 replies that delivery is a significant problem, and that it makes epigenetic editing very ineffective. She explains that it is difficult to hit all the cells and produce an effect biologically. For genome editing, one only needs to have one successful event, and then it will work. In clinical trials, people are using viral methods – lentivirus (which does integrate, gives an additional genetic change, but not predictable where it will integrate), adenovirus (does not integrate, does so sporadically, but episomally[10]– but is a very small virus, and thus is hampered as to what it can carry as cargo). People are looking into non-viral modes of delivery as well. There is a lot of development, driven by Crispr as a genome editor.

Guest 8 asks whether targeting RNA is also called epigenetic editing.

- Guest 13 replies that microRNAs are often seen as epigenetics. She explains that some microRNAs are seen to interfere with chromatin, but this is an exception.

Guest 18 notes that with regard to genome editing, a significant critique has been made as to public engagement, which came in too late. He asks whether epigenetic editing is at the stage where public engagement would be useful, and how the public can shape the focus of research. He asks how Guest 13 would envision this looking like.

[10] Episomes are non-integrated extrachromosomal closed circular DNA molecule that may be replicated in the nucleus, See Colosimo A, Goncz KK, Holmes AR, Kunzelmann K, Novelli G, Malone RW, Bennett MJ and Gruenert DC. Transfer and expression of foreign genes in mammalian cells. Biotechniques. 2000; 29(2):314-+.

- Guest 13 replies that one should definitely engage with any interested group beyond biology and clinical researchers. She adds that in collaborating with people who really know about this field, just presenting the promise of epigenetic editing is not enough. She explains that we also need to frame epigenetic editing carefully and that we should not bring too many promises. Individuals should be made aware of the limitations of epigenetic editing.

Guest 3 states that she believes it is a waste of time to debate terminology, and that the term "epigenetics" should be kept as broad as possible. She proposes her definition of epigenetics, which is that epigenetic factors are any factors that are present that can modulate genome activity. She asks how important it is to solve this debate.

- Guest 18 agrees and says that definitional debates often reduce down to turf wars, which are generally more wearying than useful *(in chatbox)*.
- Guest 9 replies to Guest 3 that scientists oftentimes underestimate the importance of semantics, perspective, and public engagement. what we call things influences how we think about them:the language is important to the way we think as well as the way we might want to regulate things ethically *(in chatbox)*.
- Guest 5 replies to Guest 3's comment with a paper: Historian Ute Deichmann and Tatjana Buklijas on the shifts in terminology and boundaries of epigenetics over the 20th century[11]: *(in chatbox)*
- Guest 8 responds that she was asking about the terminology (see earlier question), due to epigenetic editing still being relatively unknown outside biology. She suggests that when we start to discuss epigenetic editing more broadly, in ethics, society, law, … we should try to agree on what we are talking about when we talk about epigenome/epigenetic editing, e.g., to refer to the effectiveness, risks, etc. as accurately as we can in (non-scientific) discourse *(in chatbox)*.
- Guest 14 replies that how we refer to epigenetics in the non-scientific discourse would affect perception and policy, and thus would be in the interest of scientists to take into consideration *(in chatbox)*.

Guest 12 inquires as to folic acid, and whether it might be considered epigenetic editing.

- Guest 13 replies that if folic acid has an effect on DNA methylation, it might be considered epigenetic editing.

[11] https://pubmed.ncbi.nlm.nih.gov/27291929/, https://link.springeGuest 6om/chapter/10.1057/978-1-137-52879-7_8

- Guest 16 replies to Guest 12 that her laboratory uses folic acid to manipulate the sperm epigenome very effectively, and that it leads to defects in offspring.

Case Study: "The Possibility of Soldiers' Enhancement Through Epigenetic Editing"

1) What are the advantages and obstacles to the epigenetic enhancement of soldiers for combat and resilience?

Guest 17 begins the discussion by saying that enhancement is a loaded term in bioethics and military bioethics. He states that he would not regard the case study example as an enhancement, but more as a protectant, a preventive measure.

Y.J replies by saying that the border between enhancement and therapeutic is fairly controversial, and that everybody might not agree.

Guest 6 agrees that there are problems with the term enhancement. She continues by saying that we are assuming certain things. One ethical worry is that it might lead to a situation where the military authorities would feel more inclined to send people into riskier situations than they would if they didn't have these enhancements. We would be relying on the soldiers to be enhanced rather than taking other precautions. Just because one has been enhanced against tear gas, doesn't mean they are resistant to other threats. She asks the question of who is benefiting here? She suggests that this may be a way of cost saving in terms of protective equipment. It is important to see who is benefiting from this change.

Guest 4 agrees with Guest 17's earlier comment, and says that from a regulatory standpoint, it comes down to risks and benefits. He says that in the example of the case study, it would be treated like a vaccine. If the soldier didn't take the vaccine which has been clinically validated, then their military career would have ended. He provides the relevant example of giving people pyridostigmin[12] bromide against the possibility of nerve gas exposure *(in chatbox)*.

Guest 19 agrees that enhancement is a loaded term, and states that we should be watching how we communicate what we offer to soldiers. She adds that assuming the science of epigenetic editing is feasible, we may have a concurrent obligation to gamete preservation prior to giving these treatments, to allow these soldiers to feel comfortable using these without endangering potential future children.

[12] The Food and Drug Administration (FDA) approved pyridostigmine bromide to increase survival after exposure to Soman "nerve gas" poisoning. The product is approved for combat use by United States military personnel. See https://www.fda.gov/drugs/bioterrorism-and-drug-preparedness/fda-approves-pyridostigmine-bromide-pretreatment-against-nerve-gas

Guest 7 poses the question of whether or not epigenetic enhancements would come with the advantage of not passing it down to children.

Guest 8 responds to the question by saying that there are some risks associated with epigenetic editing that might not go away, such as off-target effects. She adds that if we discuss enhancements, and if we have issues with enhancements as such, with enhancements being used in the military and sports, this could be an obstacle to further development of the clinical applications. She draws upon the parallel example of the genome discourse, where slippery slope arguments are always discussed. She says that because of this risk, clinical use is not even attempted. She concludes by saying that dual use is another problem.

Guest 9 asks if there are no alternative modes of protecting soldiers from toxic gas. She states that these enhancements are always comparative goods: e.g., from the perspective of military effectiveness, it is always an advantage if you have something, and the opponent does not. She adds that there is a risk of an epigenetic race to the top. She asks if by epigenetically editing, we are crossing a line, and states that if we do, we should have good reasons to edit.

- Guest 5 agrees with Guest 9, in that the race into the soldiers' body is the risky aspect of the approach. He concludes by saying that it would not be the first time in history this has been done, and that we should draw upon previous lessons *(in chatbox)*.

Guest 3 contributes by saying that alternative means seem to be available e.g., using robots or drones to capture information. She suggests that using these means might be more efficient than damaging a human's body. She adds that many diseases are monogenic- however, this is different for epigenetic editing (there are multiple epigenetic factors that contribute to a symptom).

- Guest 14 agrees with Guest 3 and adds that epigenetic factors may affect multiple regulatory processes, some of which we may not know of, even if we hit the right target.
- Guest 13 replies to Guest 3's comment, by saying that 1) many loci can be targeted simultaneously using CRISPR; 2) many preclinical epigenetic editing studies demonstrate therapeutic effects by gene expression modulation of 1 gene (fibrosis, diabetes)

Guest 12 adds that collateral damage on non-enhanced civilians is to be considered *(in chatbox)*.

Guest 6 asks: 1) What is the difference between 'enhancing' individuals by biology as opposed to rigorous training?; 2) What about Rob Sparrow's point that such changes may quickly become obsolete as better techniques come along and then the people with the original 'enhancements' will not be valued[13]? *(in chatbox)*

[13] https://doi.org/10.1080/15265161.2021.1907480

- Guest 5 replies to Guest 6's first question by saying that the structure of the argument against an arms race applies equally to biology and technical gear *(in chatbox)*.
- Guest 9 replies to Guest 6's first question by saying that there is not a categorical difference between enhancement by biological means and enhancement by training, just a general preference for low risk / accessible / easily reversible means *(in chatbox)*.

Guest 2 asks the question of if there is a side effect, would it be considered as an enhancement? How would this affect the liability of the army?

2) Would it raise ethical or health concerns for some soldiers to be epigenetically enhanced in B's unit if others are not?

Guest 17 begins the discussion by saying that in the United States, if the enhancement is deemed necessary, and if B refuses, then he would be delisted from the unit or potentially reassigned. He suggests that B's refusal could impose risks onto others.

Y.J replies by drawing a parallel with vaccination and the army, with individuals who do not want to be vaccinated against COVID-19.

- Guest 17 contributes by saying that on December 17, 2021, the US Air Force and Marines have begun discharging individuals who refused to get vaccinated *(in chatbox)*.

Guest 6 contributes that there might be pressure from the physician to have the enhancement. She suggests that there might be a threat or worry that if B doesn't have the intervention, he might be denied good medical care down the line. She states that this is a very coercive situation.

Guest 12 adds that during the Gulf War, some soldiers who refused the anthrax vaccine were court-martialled. He continues by saying that reversibility has to be part of our analysis, and we must consider the consequences for individuals and future generations. If it is not reversible, then it raises much more serious ethical issues.

Guest 8 contributes by saying that if not all are enhanced, the dual use problem can potentially be less severe. The unit with some, but not all, enhanced soldiers might not use strategies that require more stamina than the opposing forces might have, or they might not use e.g., chemical weapons that some, but not all of the unit's own soldiers are resistant to *(in chatbox)*.

Guest 5 expresses some unease with the trait chosen (stamina). He says that everything is still in need of development, and that stamina is a complex trait to think about. He believes it goes a bit too far to think about stamina.

Guest 10 says that the vaccination analogy changes the picture of how we evaluate the situation ethically. In the context of vaccination, it could be plausible that there is peer pressure from the group to have everyone vaccinated. In the context of stamina, it is an advantage for the whole group. If one is not enhanced, the others would have to care for him, with this potentially hindering them. She concludes by saying that we then would have to scrutinize if the vaccination analogy really holds: if it does, then we can do anything.

- Guest 8 responds to Guest 10 that if everybody is enhanced to be resistant to some chemical, then the troop might use these weapons. This would be more similar to vaccination. She agrees that with enhancing stamina it seems more complicated to bring everybody to the same level.

Guest 15 states that with RNA editing, there would be less off-target effects, and would thus be less deleterious. However, it would require continuous treatment.

- Guest 18 replies by saying that if we are talking about modification that involves repeated inputs, it would bring us back into the territory of pharmaceutical enhancement and the ongoing taking of pills.

Guest 12 adds that there is a long history of using pharmacological agents (such as amphetamines, stimulants) in the military. He suggests that if there is a less permanent alternative, why would we not use that instead of epigenetics?

Guest 5 contributes by saying that stamina is a complex matter. It's not just biology. It's training together, it's collegial ways of knowing the world surrounding soldiers, knowing how much you can push it into the field along with your teammates (to make a sports analogy). He is not sure the protective benefits have the same meaning of vaccination, or a small intervention *(in chatbox)*.

3) Is it possible to reverse epigenetic modifications?

Guest 17 replies to question three by mentioning that the risks of requiring alteration should not be the sole item considered. He explains that certain benefits obtained in military life could be deemed unfair in civilian life e.g., stamina enhancement if the person decided to become an athlete. Depending on what the enhancement was, there might be other situations where they could have a disadvantage. He suggests that it could also be thought of as a recruiting tool.

In addressing reversibility, Guest 11 says that if we can turn off as well as turn on genes using epigenetic editors, theoretically reversal might be possible. However, we would then be potentially dealing with two (non-overlapping) sets of off-target effects - one when putting the modification in and the second when taking it out, thus doubling the risk of deleterious effects *(in chatbox)*.

Discussion of Future Outcomes and Meeting Proceedings

Y.J suggests developing a joint publication. This proposed publication could be formulated to raise important questions rather than to provide answers. He suggests that it is too early to provide a statement or guideline.

Guest 17 agrees that a publication would be a good idea, and that it should point out the relevant differences between genomic and epigenomic modification. He contributes that an interesting question is how epigenetic modification differs in the military, and what questions would this raise.

Guest 7 agrees that a joint publication of this nature would be good. He adds that by asking questions, instead of answering, a wide variety of intellectual diversity and perspectives could be addressed.

Guest 3 agrees that a publication should be written, as epigenetics is a field that evolves so quickly. She notes that a publication based on the workshop would help capture the current status of knowledge, key questions, and potential applications of the field, and thus will allow us to see how the field evolves in coming years. She recommends contacting Bart Rutten, who researches epigenetics in soldiers and has an intergenerational perspective in mind.

Guest 18 adds that the publication could perhaps address the framing of epigenetic editing, and how different framings of the topic open up different questions to be addressed.

Guest 10 suggests that the publication can also hint at approaches to address these questions. For example, having a general mandate that ethical debates about scientific fields or technologies should have the scientific background and details explained prior to the debate. She adds that an important message is that ethical debates need to keep up with science, and science is required to explain the pitfalls and current status of technology.

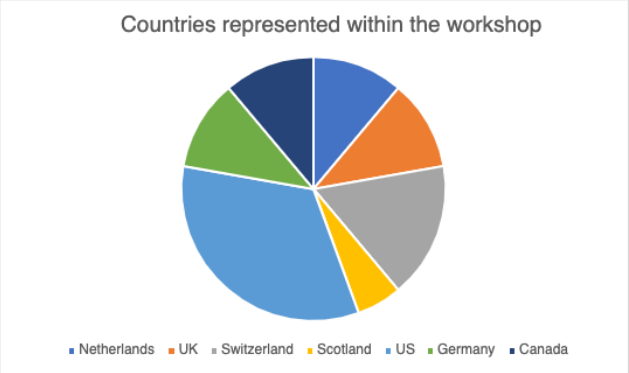
Guest 2 adds that the publication could also address the role of public deliberation and engagement, and what would be the role of public engagement for military applications.

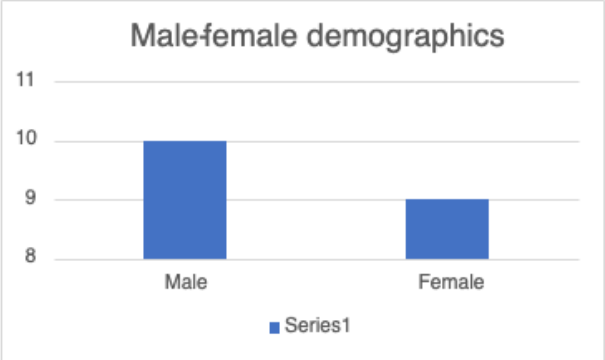
Guest 8 suggests that it would be helpful for a potential publication to review potential therapeutic and potential enhancement applications of epigenetic editing and to ask whether applying these concepts as a filter for ethical analysis is warranted.

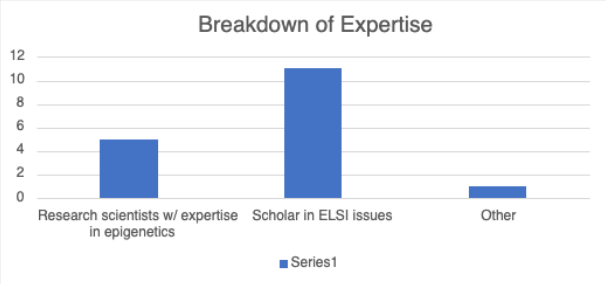
Y.J closes the workshop by acknowledging the MINDS funding and thanking the participants for contributing their expertise to this most informational workshop. He stated that a draft manuscript of the planned joint publication would be circulated to all workshop participants to build upon and edit. He noted that if a participant would like to contribute a paragraph on a particular topic, they should email G.D. or him. Similarly, if a participant would not like to participate in the publication, they can inform the same people.

Appendix I: Pre-Workshop Survey Results

Demographic data



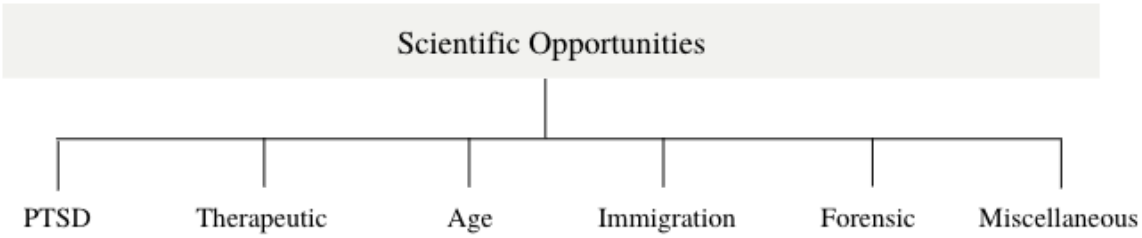




Vignette 1: Epigenetic tests to assess chronological age

DNA methylation patterns vary with age and can be used to estimate "epigenetic age, " an indicator of biological age. Studies have shown that targeted DNA methylation analysis at a few age-associated CpGs by pyrosequencing, BBA-seq, and particularly ddPCR enables high precision of epigenetic age-predictions. These estimators, also known as "epigenetic clocks,' 'could be valuable tools to assess migrant and displaced children's age in an immigration context. For instance, in Europe, police in Hildesheim, Germany, turned to DNAge™*, an epigenetic clock, to determine whether an asylum seeker was under the age of 18, as he claimed to be. Other future uses can be imagined, such as for child labour and trafficking surveillance or even identifying child combatants in armed conflicts. Epigenetic clocks provide an opportunity to investigate the relationship between posttraumatic stress disorder (PTSD) and epigenetic aging acceleration. However, while some studies have shown that PTSD is associated with advanced epigenetic age, others have found significantly lower epigenetic age in veterans with PTSD.

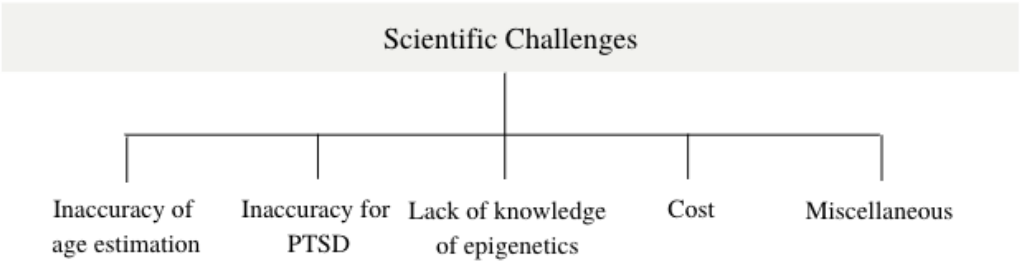
What are the most significant scientific opportunities inherent to this epigenetic application in defence and security contexts?



Category	Response
Confirmation of age	• Forensic age estimation from unknown individuals • Determining combatant age • Confirmation of claims of age • Identifying child combatants in armed conflicts • Verifying age
Forensic	• Identification of malfeasance • Identification of individuals • Identity issues
PTSD	• Reducing PTSD risk to war fighters and families • Prophylactic steps to mitigate PTSD • Epigenetic signatures of stressful events/trauma • Discovering correlations with PTSD
Therapeutic	• Drugs to treat solders with epigenetic age acceleration • Epigenetic age acceleration potential for early identification of long-term health effects of toxicological exposure • Predicting health/disease • Epigenetic treatment for service-related injuries

Immigration	• Border control • Asylum seeker under 18 • Determining age of illegal immigrants
Miscellaneous	• Epigenetic surveillance and screening • Epigenetic testing for enlistment/assignment • Verification of factual claims • Personalization of military retirement based on epigenetic age (leading to a shorter duration of service for some, and longer duration of service for others (if so desired))

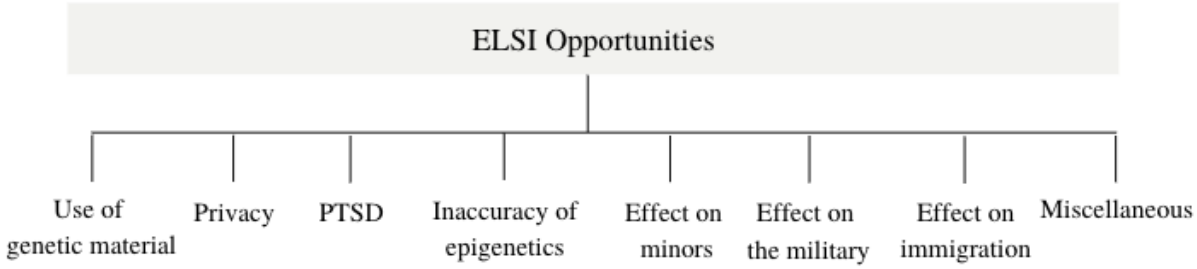
What scientific or technological limitations make this application of epigenetics in defence and security contexts challenging?



Category	**Response**
Inaccuracy of age estimation	• Ethnic and tissue specificities of clocks • Epigenetic age acceleration can occur in stressed children • Data derived from groups of people, individual variations occur • Likely that age estimates are probabilistic and uncertain • Accuracy of age prediction should be established • Link between epigenetic age and biological age/performance/functional condition/subjective sense of fitness should be established
Inaccuracy for PTSD	• Wide variation in interpretation of test results (PTSD patients)

	• The proportion of PTSD that epigenetic clocks explain in a population is likely to be very low
Lack of knowledge of epigenetics	• Uncertainty of findings • Limits to current epigenetic knowledge and understanding • Epigenetic age in a new field with unknown limitations • Scientific validity of test results among diverse populations
Cost	• Studies are needed to develop cost-effective approaches of assessment, verified targets • High throughput automated approaches are needed
Miscellaneous	• Field detection methods • Rapid development of new military technologies • Over reliance on seemingly objective evidence

What are the most important ethical, legal and social opportunities inherent to this epigenetic application in defence and security contexts?

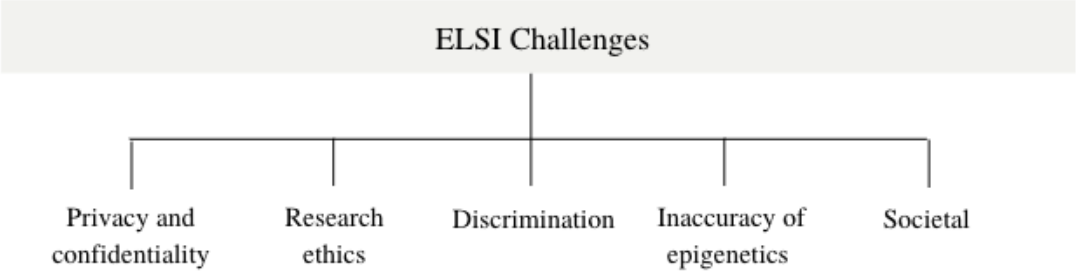


Category	**Response**
Use of genetic material	• Epigenetic data includes genetic data and as such the same legal, ethical, and social restrictions for its use, establishment and application • Genetic material is required to determine epigenetic age
Privacy	• Privacy and use

	• While some scientists insist the epigenetics is not identifiable information, in the future it will probably be identifiable e.g. unique mC pattern • Protection of verifiable personal information, with limits
Inaccuracy of epigenetics	• False sense that the test will be unfailingly accurate • Raise awareness of technological limitations • Epigenetic biomarkers need to be shown to work equally well in all races/ethnicities
Effect on minors	• Combatting exploitation of minors • Deciding if someone is under or 18 years of age based on an epigenetic ageing block test is a misapplication of technology with major human consequences • Better ability to protect children's rights
Effect of war / military	• Monitoring/validating the success of interventions counteracting bioweapons • Identifying groups at risk for a given bioweapon attack • Possibly helping to estimate collateral damage • Justice with respect to accountability of combatants and governments • Allowing officers to remain active and valuable if they so wish; greater military effectiveness
Effect on immigration	• Evidence based policy at borders • Prevention of misuse of immigration policies
PTSD	• Reducing PTSD risk to war fighters and families • Identification of the care needs of sub-populations of PTSD patients • Understanding the medical bases for PTSD

Miscellaneous	• Differentiation of social support and care based on age differences • Legitimizes a politics of suspicion

In your opinion, what are the most important ethical, legal and social issues related to this use of epigenetic technologies in defence and security contexts?

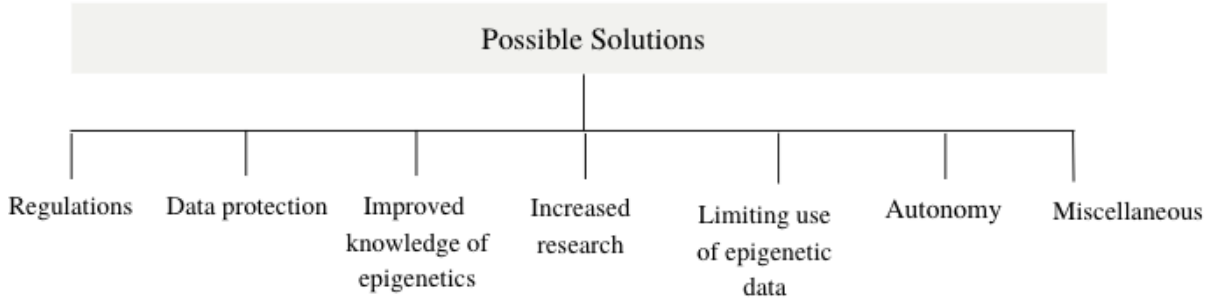


Category	**Response**
Privacy and confidentiality	• Privacy and use • Identifiable information from epigenome data • War fighter privacy and autonomy • Loss of confidentiality • Data security (especially in field applications), privacy • Protection and ownership of subjects' epigenetic data • Use of samples collected for these analyses for other surveillance purposes
Ethical	• Consent • Ethical conduct of military epigenetic research • Autonomy in epigenetic testing
Discrimination	• Discrimination based on race • Potential for unfair discrimination against warfighters with certain epigenetic profiles

	• Risk of unfair discrimination in enlistment, assignment, promotion • Epigenetic discrimination: Epigenetic tests might be used to predict age. Prediction might generate false results. If such tests are used in defence and security, this is ethically as well as legally problematic if the use of epigenetic tests for age prediction is to the disadvantage of already disadvantaged groups like child asylum seekers, very young but not underaged workers in detrimental working conditions, young military conscientious objectors (who might be required to serve upon reaching the age of majority), and others.
Inaccuracy of epigenetics / epigenetic determinism	• Accuracy of clock sufficient to tell 17 from 18-year-old? • Dual use, epigenetic discrimination, "hype", false hope: If these tests are further developed for defence and security purposes, their general range of applications in other areas might increase. From a societal perspective, the use of epigenetic tests to predict age might reinforce notions of epigenetic determinism. This might result in discrimination through insurance agencies, but it might also contribute to a general "hype" which might be associated with potentially harmful false hopes regarding epigenetics' immediate societal benefits (such as its informative potential regarding health-related information and its therapeutic potential) • False sense that the test will be unfailingly accurate with implications for rights (e.g. housing, health, financial assistance, etc) • Misattribution of findings • Technology needs to be substantially improved before defence/security decisions can be made based on their results • Risk of basing decisions on misleading test results
Societal effects	• Social justice with reference to already traumatized populations • Exclusions from care/support of people in need on the basis of a probabilistic estimation of their age

	• Due process of law • In various countries, military personnel is allowed to retire with benefits based on a certain number of years of service, regardless of their biological/epigenetic age. Prolongation could not be acceptable to some / perceived as a loss

What are some possible avenues or solutions towards responsible use of this epigenetic application in defence and security contexts?



Category	Response
Regulations	• Establishment of laws and guidelines in consultation with scientific experts, ethicists and legal experts • Clear international triage guidelines • Guidelines needed that avoid making situation even worse for those already disadvantaged • Strict regulation of use and disposal of samples • Application and oversight by international institutions • Yearly evaluations • Requiring informed consent before any testing
Data protection	• Regulation for the protection of epigenetic data • Epigenetic information should be blinded, as is genetic information
Improved knowledge of epigenetics	• Better understanding of epigenetics and its ELSI issues • Understanding of error profiles in epigenetic tests

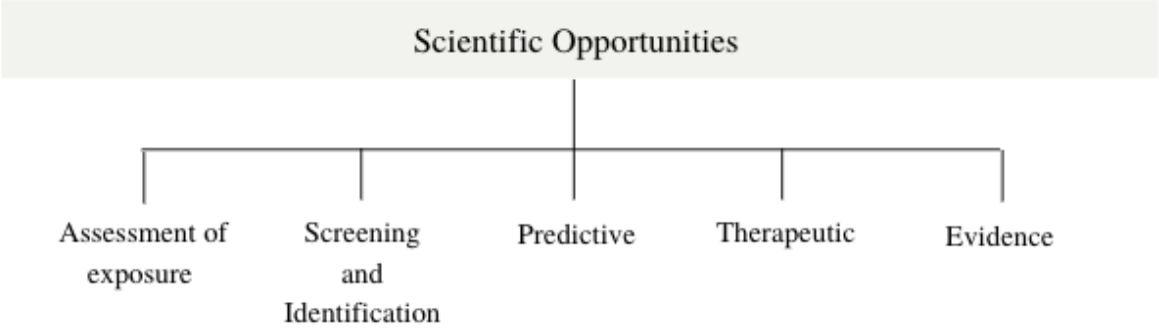
	• Reproduce findings and establish error rates of testing
More research	• Interdisciplinary explorations such as this • Increased scientific research • Improved study of diverse populations • Wide consultation with epigenomic and genomic experts on what can be learned from specific epigenetic data
Limiting use of epigenetic data	• Do not overinterpret epigenetic data • Use of these technologies only for inclusion purposes (e.g. assignment into legal age or underage care) and not for exclusion (e.g. eligibility of asylum) • Mere indicators, no prove: Even if some advantages of the use of epigenetic tests for age prediction in defence and security should become apparent, it is necessary to merely use the results of these tests as indicators, but not as prove of the tested person's age in order to avoid epigenetic discrimination. • Agreements about / oversight of appropriate use (e.g. use epigenetic clock technology only when there are indications that someone may not be truthful)
Military specific	• Military personnel should be able to choose whether to make use of epigenetic block (no mandatory applications)
Miscellaneous	• Self-imposed ethical duties • Seeking consensus on appliable bioethical principles • Greater confidence in what the science actually shows

Vignette 2: Epigenetic tests to assess exposure

Human exposure to high concentrations of nuclear, chemical, or biological weapons can significantly alter military personnel's epigenome and future offspring. For example, following the Persian Gulf War, research showed that military personnel experienced genome-wide epigenetic changes (differential methylation at CpG sites and promoter regions) that were likely attributable to toxic chemical exposure, including insecticides containing organophosphates and low levels of sarin/cyclosarin. Epigenetic profiles can reveal biological vulnerabilities and

trauma and identify individuals that are less susceptible to severe impairments. This suggests that epigenetic technologies can be used on military personnel and future generations to provide evidence of harm with or without the presence of mental illness.

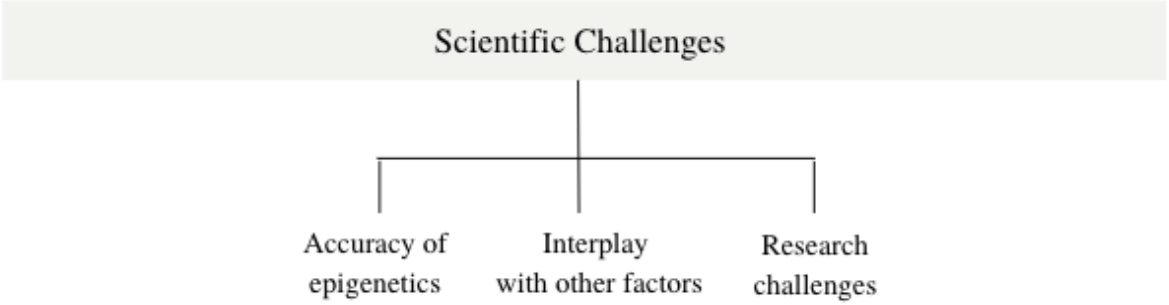
What are the most significant scientific opportunities inherent to this epigenetic application in defence and security contexts?



Category	Response
Assessment of exposure	• Assessing dose of toxicant/chemical exposure • Identifying exposure based on epigenetic changes • Biological traces of risky exposures • Advances understanding of biological and psychological effects of exposures • Establishing harmful exposures with epigenetic biomarkers
Screening and identification	• Screening soldiers before being exposed to chemicals to select against sensitive soldiers • Assessing vulnerability in harmful exposures before they occur • Reducing risk to war fighters due to their epigenetic profiles • Identifying elusive epigenetic harms to warfighters • Identification of individuals that are less susceptible to severe impairments. These individuals may then be recruited for special assignments
Prediction	• Predicting health and disease in next generation

Therapeutic	• Epigenetic editing might be developed to prevent (protect) or reverse (treat/cure) such epigenetic changes • Help in discovering new kinds of epigenetic treatment/prevention • Understanding generational effects of trauma • Developing better treatments • For a differential diagnosis, to find the cause of an officer's medical problems
Evidence	• Proof in litigation/compensation claims for occupational hazard • Provide evidence of harm with or without the presence of mental illness

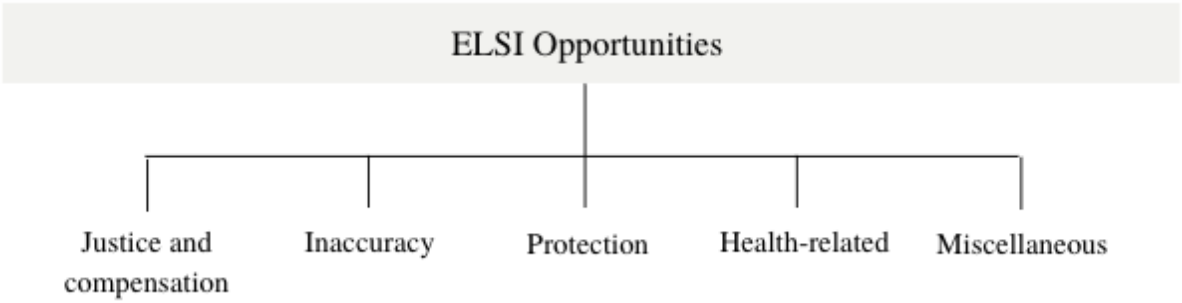
What scientific or technological limitations make this application of epigenetics in defence and security contexts challenging?



Category	**Response**
Accuracy of epigenetics	• Need to validate markers in larger and diverse populations • Many chemicals such as heavy metals have similar or identical epigenetic signatures • Variations in population to epigenetic changes makes them hard to interpret • Specificity of markers (confounding) • Predictive values of these markers (how much of the condition dot they explain)

	• Latency between exposure and manifestation of harm • Uncertainty that evidence of exposure signifies material harm • Epigenetic association studies with positive findings are neither interpretable nor proven biomarkers • Lack of precision/reliability • Validation of predictions, relevance of epigenetic changes • Genome-wide changes; which loci are causative for the subsequent effects
Interplay with other factors	• Teasing out what is actually epigenetic and what arises from other factors • Parsing whether the epigenetic effect noted is in fact causally related to a specific exposure that happened within a specific temporal window • Disease etiology is often complex. Link between epigenetic change and disease may be unclear
Research challenges	• Challenges of conducting pertinent research • Predictive accuracy should be established. This may require research exposing human subjects to toxins

What are the most important ethical, legal and social opportunities inherent to this epigenetic application in defence and security contexts?



Category	Response
Justice / compensation	• Possibilities for compensation or even just an explanation for victims • Recognition of harm; restorative justice • Rational compensation schemes for service-related harmful exposures • Accountability of employers (including the state in the case of the army) • Legal proof of war crimes and crimes against humanity could be made easier. This is to be welcomed from an ethical perspective (perspective of peace ethics). This might also be desirable from a societal perspective (societal consensus on this application of epigenetics in defence and security might be easier to achieve than on other epigenetic applications in defence/security).
Inaccuracy	• Variation is very high and makes results difficult to interpret • False positive result: implication of harm can be damaging to the individual • False negative result: testing can be an excuse for not providing necessary care
Protection	• Protection of (potentially) vulnerable people

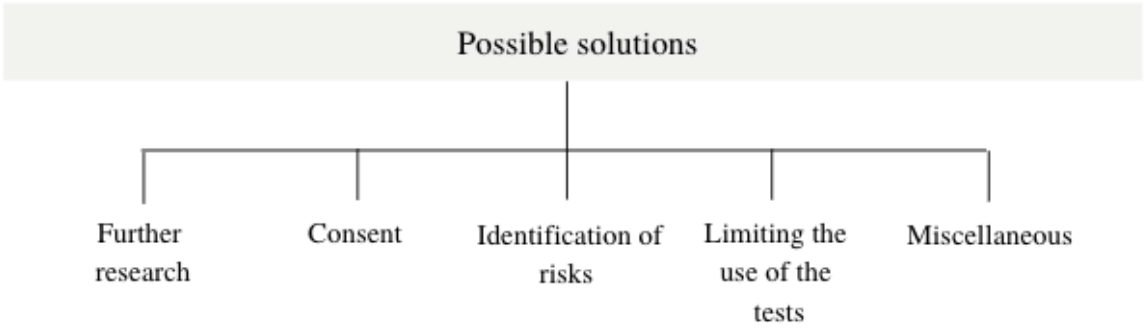
	• Patient wellbeing (important for people to know what the problem is and how it arose), possibility of identifying ways to prevent future harm. • Greater safety for military personnel • Enhancing the determination of proportionality of risks to war fighters • A means to prevent or mitigate harms in susceptible populations • Protection of those who protect us
Health-related	• Better assessment of exposure to, and harm from such weapons • Access to healthcare and benefits • Reducing PTSD risk to warfighters and families • Support in diagnosing traumatic conditions, prevent further harm • Predicting impact on fertility and health of offspring
Miscellaneous	• Bring issues into public discussion • Determining ethical principles for epigenetically-informed decisions on enlistment, specialization, assignment, etc. • epigenetic information should be blinded like genetic information

In your opinion, what are the most important ethical, legal and social issues related to this use of epigenetic technologies in defence and security contexts?

Category	**Response**
Privacy	• Protection of epigenetic data • Use of data in military context (e.g. assignment of military personnel, medical insurance) • Warfighter privacy and autonomy • Loss of confidentiality • Data security
Discrimination	• Unfair discrimination against warfighters
Research issues	• Blind studies to make them unidentifiable • Challenges in the conduct of ethical research • It may be too risky to conduct studies exposing healthy persons (who are believed to be less vulnerable) to toxic or otherwise unhealthy environments.
Inaccuracy / reliability of epigenetics	• High variation in epigenetic responses • Misattributed causation > misattributed blame. Medical problems possibly / probably not caused by the single exposure exclusively. • Overinterpretation of evidence
Trust	• Do we need biological proof of trauma/toxic exposure to grant veterans the care they need?

	• Complete trust in the tests versus the professed experiences of claimants, which might be used to de-validate their claims
Miscellaneous	• Those who seem more resilient, might be sent out in the battlefield more frequently • Difficulty of accountability and responsibility both backward and forward looking • Misuse, "slippery slope" and "dual use" (see also Vignette 4): If departments of defence conduct research in the direction of epigenetic applications to test exposures to substances, dual use is a highly relevant problem. It is considered by the US department of defence to develop "inner strength to survive and recover from potentially lethal health threats" (project entitled PREPARE). This could include research into resistance to substance exposure. As Alta Charo has stated, this comes with the problem of dual use. Such research might result in future use of these substances by countries with armed forces that are resilient to the exposures to the detriment of other human beings that are not resilient. While this is currently a slippery slope argument, misuse is a very important issue and at least an aspect that is relevant for a societal discussion and therefore challenging not only from an ethical perspective, and from a legal perspective (establish appropriate legal safeguards against misuse), but especially challenging from a societal perspective. • Informing exposed individuals of potential health impacts and potential risks to offspring

What are some possible avenues or solutions towards responsible use of this epigenetic application in defence and security contexts?



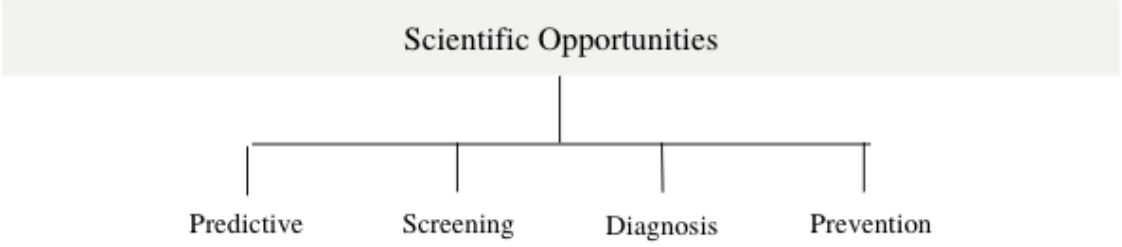
Category	Response
Further research	• Large N studies will make identification more significant • Expand epigenetic studies beyond mC and telomere length • Continued research on epigenetics • Interdisciplinary explorations • Use retrospective data or 'natural experiments' (situations in which military intervention is unavoidable and planned as usual, all normal safety standards are applied (e.g. to avoid exposure), but data can be collected if it does occur) • Much more discussion needed of individual and institutional responsibilities in this area • Societal discourse and thorough philosophical analysis: The challenges and opportunities need to be broadly discussed with society and simultaneously extensively analyzed by philosophy/applied ethics. Societal and ethical consensus needs to be established before application.
Consent / disclosure	• Well informed volunteers • Disclosure and consent requirements

Identification of risks	• If men and women are at risk of damaging exposures that may impact their descendants, they can be advised, and costs covered to preserve sperm and eggs • Service members can be screened to identify vulnerabilities or relative immunity to harmful exposures in advance. • Defence ministries can identify service-related harmful exposures and set up compensation scheme based on evidence of epigenetic markers.
Limiting the use of tests	• Use the tests only as one aspect of assessing exposures • Disconnect liability from this evidence: what employers owe to veterans/employees does not depend solely on biological proof of harm
Miscellaneous	• Maintain broader perspective on military personnel's health • Independent oversight mechanism

Vignette 3: Epigenetic tests to assess vulnerability to exposure

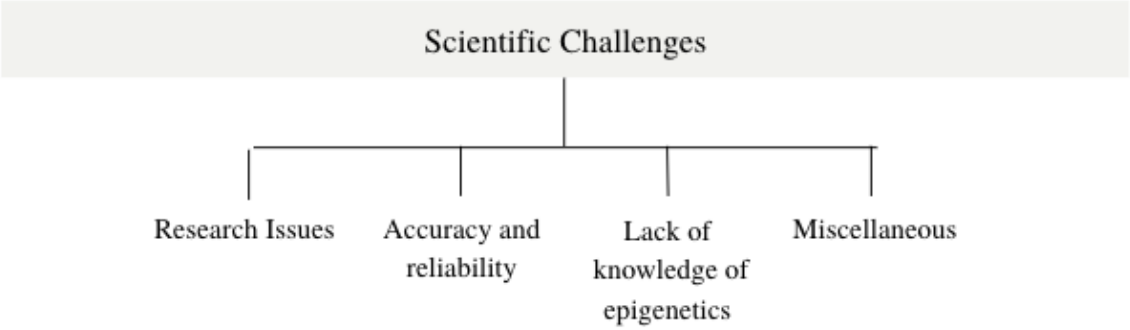
Veterans are commonly affected by posttraumatic stress disorder (PTSD) Research has also shown that the development of combat-related PTSD is linked with distinct methylation patterns in several genomic positions and regions. Pre-trauma DNA states and post-trauma DNAm modifications differ between those who develop PTSD following trauma and those who show resiliency. Furthermore, there is evidence of transgenerational transmission of epigenetic changes of both maternal and paternal PTSD. As such, epigenetics can help identify soldiers who are at the most significant risk of PTSD to implement early-stage prevention and intervention strategies.

What are the most significant scientific opportunities inherent to this epigenetic application in defence and security contexts?



Category	Response
Prediction	• Develop a panel of markers that are predictive of PTSD risk
Screening (e.g. for those at high risk)	• Regular screening to assess the impacts of trauma relative to mental health • Detection of susceptibilities • Screening and surveillance of soldiers to identify different stages of PTSD or resiliency to trauma. • Identifying warfighters at heightened risk of PTSD • Recruitment and selection of trauma-resilient officers
Diagnosis	• Early identification and treatment of PTSD based on epigenetic profiles • Early identification and treatment of chemical exposures • Pathway to recognition and help for people • Relatively easy diagnosis or prognosis tool
Prevention	• PTSD prevention • Prevention of mental illness • Development of preventive and therapeutic treatments to PTSD. • Prevention and care for susceptible / exposed officers • Preventive wellness interventions

What scientific or technological limitations make this application of epigenetics in defence and security contexts challenging?



Category	Response
Research issues	• Need for large studies and validated markers
Accuracy / reliability	• Many exposures and stressors can create similar epigenetic changes • High variation in the population • False positives • Again, what portion of PTSD in the veteran population do these markers explain? • Evidence of transgenerational inheritance is contested • Proving predictions/prognoses excluding other relevant factors • Latency of development of PTSD in individuals and future generations
Lack of knowledge	• Transgenerational Epigenetics is still not very well understood: which regions apart from imprinted Genes will escape the Demethylation waves? • Uncertainty in myriad of factors that can lead to PTSD or resiliency post-trauma. • Clarify link epigenetic markers - resilience to future trauma

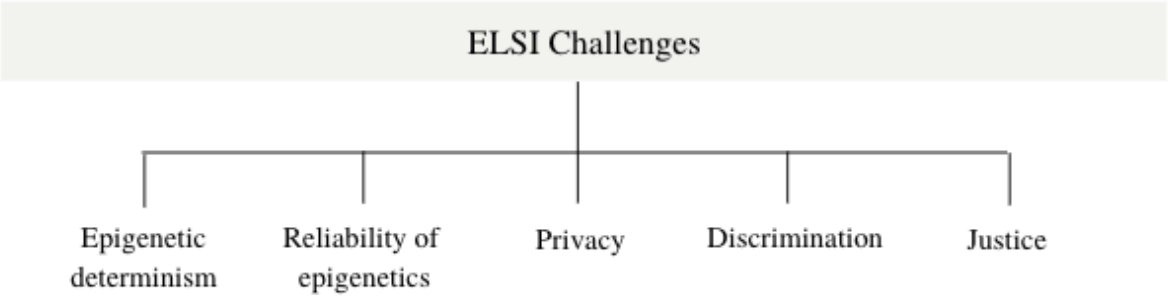
	• The primary data supporting these associations, especially the transgenerational transmission, are extremely weak • Lack of understanding of epigenetics
Miscellaneous	• Political will, or lack of it • The problem of identifying solutions and resources for these solutions

What are the most important ethical, legal and social opportunities inherent to this epigenetic application in defence and security contexts?

Category	**Response**
Privacy	• Non-identifiable studies • Making data available to participants
Compensation	• Compensatory program
Limiting harm and risk	• Help identify soldiers who are at the most significant risk of PTSD • Healthier work force, reduction of social / economic impact of PTST among soldiers, families and society, possibly greater safety in society, greater military effectiveness • Reducing PTSD risk • Potential to limit harms for susceptible individuals and/or identify preventive and therapeutic measures for PTSD. • Identification of personnel's needs and susceptibilities

	• Promotion of personnel's wellbeing • Reduction of suffering from PTSD among veterans • Use of epigenetic data for more judicious assignment of military personnel • Exclusion / inclusion based on pre-trauma states
Ethical issues	• Consent / ethical precautions • Epigenetic "determinism" for individuals and future generations identified as having PTSD markers.

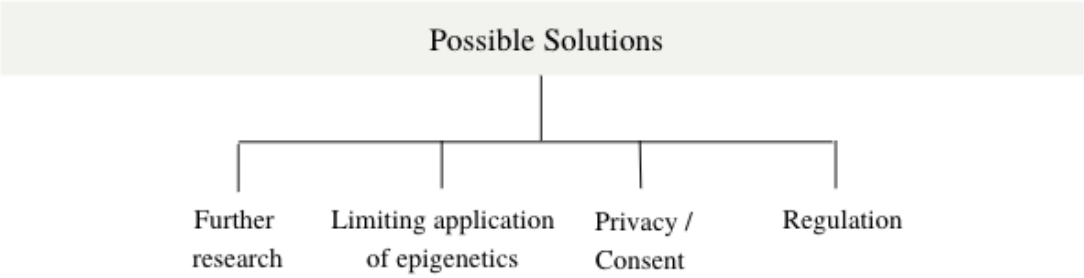
In your opinion, what are the most important ethical, legal and social issues related to this use of epigenetic technologies in defence and security contexts?



Category	**Response**
Epigenetic determinism	• Notions of epigenetic determinism might be reinforced. This might result in a general "hype" which might be associated with potentially harmful false hopes regarding epigenetics' immediate societal benefits and benefits for soldiers, such as its informative potential regarding health-related information and its therapeutic/preventive potential. • Protection & use of epigenetic data (e.g. impact on medical coverage) • Promoting the wrong view that those who are not susceptible on epigenetic grounds are somehow more resilient to PTSD than the others

	• Use retrospectively, fatalism (e.g. (undue) attribution of mental problems (in offspring) to specific trauma(s), (undue) idea in officer and healthcare professionals that there is no way to improve mental health, military may be held responsible for (generations of) mental / behavioral problems
Reliability of epigenetics	• Reliability of markers and their use • Over interpretation of marginal results • Early diagnosis of PTSD false positives • Reliability of predictions based on such data
Privacy	• Protection & use of epigenetic data (e.g. impact on medical coverage) • Epigenetic privacy for current and future generations. • data security, data access, privacy
Discrimination	• Potential for stigma and epigenetic discrimination against those labeled as "vulnerable" or having undesirable epigenetic markings. • Inequalities of treatment and employment within the personnel (deployment on the basis of susceptibilities or lack thereof) • Used prospectively, stigmatization, exclusion of those believed to be less resilient, possibly over-exposure of those believed to be more resilient
Justice	• Epigenetic interference is performed in trauma-related cases (trials): the side effects should balance intended positive outcomes (ethical) • How to identify what is owed as a matter of justice and by whom

What are some possible avenues or solutions towards responsible use of this epigenetic application in defence and security contexts?



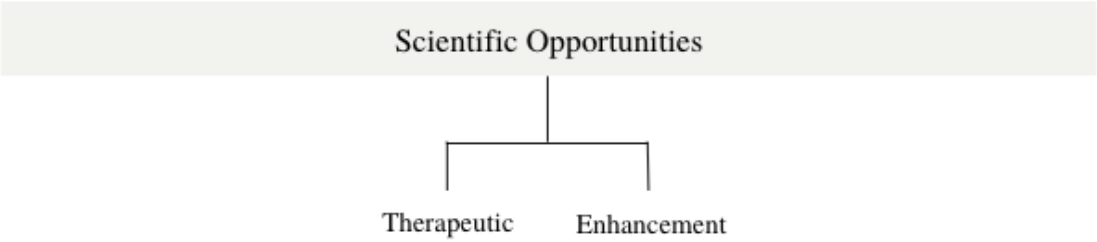
Category	Response
More research / discussion	• Validation and reliability assessment by several research groups in various trauma contexts • Longitudinal studies before and after exposures • Large N studies in population • More scientific research, good (animal) models • More discussion needed of epigenetic justice • Better understanding of epigenetic science
Limiting application of epigenetics	• Unless there is scientific certainty on its effectiveness, this application should not be considered at all. If considered, informed consent is an ethical and legal issue. Furthermore, false hopes associated with epigenetics within society should be addressed.

	• Holistic approach to PTSD prevention (combine epigenetics with memory editing, psychological interventions, etc.) • Avoid conflating the biology of PTSD with epigenetic markers.
Privacy and consent	• Privacy and data protection for individual and familial results. Consent protocols balancing individual privacy rights and legitimate government security interests.
Regulation	• Epigenetic nondiscrimination regulations for employment and educational opportunities, so long as there is not a compelling national security imperative for such discrimination bases on epigenetic profiles. • Independent oversight on storage and use of such data

Vignette 4: Epigenetic Intervention

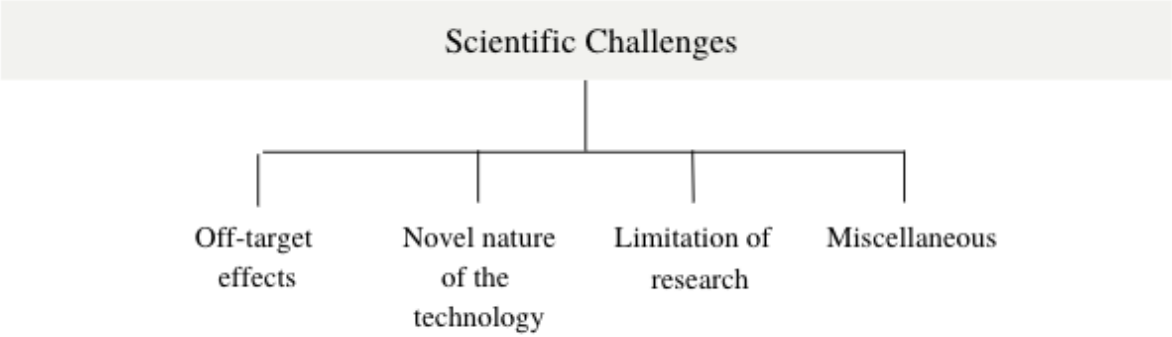
Many human traits, such as strength, intelligence, and even disease states, are influenced by epigenetic signatures. Recent studies demonstrated that epigenetic modifications are reversible, suggesting that diseased gene states can be reprogrammed" to healthy states using the epigenetic editing technologies CRISPR/dCas9. With research rapidly progressing to optimize safety, efficacy, and specificity, these technologies can potentially be used to enhance military personnel who will better resist bodily damage by nuclear, chemical or biological weapons. Epigenome editing technologies can also be used for therapeutic purposes to reverse the effects of exposures on veteran's health.

What are the most significant scientific opportunities inherent to this epigenetic application in defence and security contexts?



Category	Response
Therapeutic	• Drugs that can reverse accelerated epigenetic aging • Reversing post-traumatic effects (mental, somatic) • Improve therapeutic outcomes • Treatment of exposure-related conditions • Reversing harms acquired through service • Preventing epigenetic harms being passed onto future generations • Better treatment for toxic exposures • To improve veteran's health and wellbeing
Enhancement	• Reprogramming to improve (soldiers, bioweapons, …) • Enhanced resilience • Improve effectiveness of combatants • Enhancement of personnel's capacities • Enhanced warfighter performance and resilience • Enhancing warfighter safety and effectiveness • Weaponization

What scientific or technological limitations make this application of epigenetics in defence and security contexts challenging?



Category	Response
Off-target effects	• Off target Cas9 a major issue • There are off target effects that can be damaging • Epigenome editing comes with several risks: e.g., lack of long-term stability, off-target editing, risks associated with vectors, lack of on-target specificity. • Effective delivery of (CRISPR) tools to intended organ(s) • To this day, these applications amount largely to speculation, but: CRISPR-based tools' lack of specificity; off-target effects; unknown long-term consequences of these interventions • Typically, the changes genome-wide are numerous. A CRISPR system would have to be developed to target many sites at once
Novel nature of tech.	• Epigenome editing of traits is highly experimental and has been done by few research groups world-wide in animal models. Many more animal studies are needed to demonstrate efficacy for editing traits • Research on epigenome editing is currently in its very early stages. Initial applications in humans will most likely concentrate on developing a potential preventive measure or therapy for diseases that are currently complicated to treat. Enhancing applications are likely not to be studied clinically immediately.

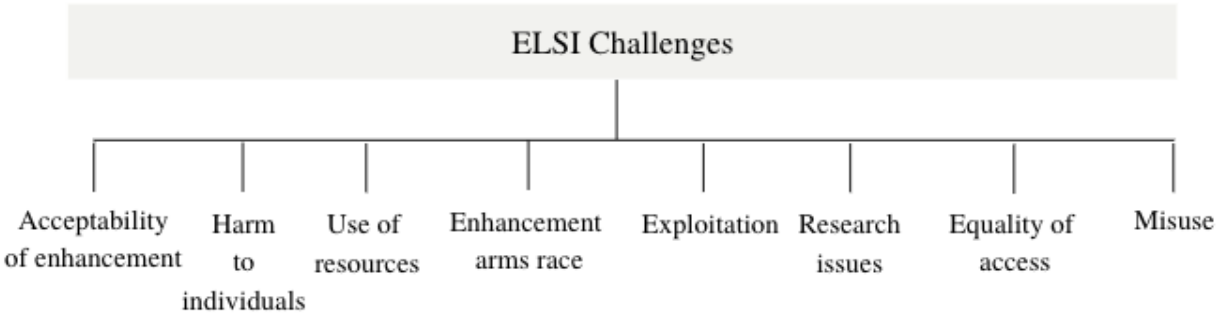
	• The speculation that it is possible to treat PTSD with the reversal of an epigenetic modification is an error of biological scale and complexity • Not yet known whether epigenomic editing can be done safely and effectively
Limitation of research	• Limits on the ability to conduct relevant human subjects research • Lack of long-term data on such interventions in humans. • Challenges of conducting research on human subjects
Miscellaneous	• Drugs would have much broader effects than Cas9 but maybe safer and easier to administer • Inappropriate usage

What are the most important ethical, legal and social opportunities inherent to this epigenetic application in defence and security contexts?

Category	**Response**
Enhancement	• Potentially stronger combat force • I really cannot see any that is worth a collective investment for the enhancement side of it • Enhancement of soldiers using epigenetic "bio-armor" to shield against harms.
Reduction of risk	• Benefits for serving personnel

	• Reducing warfighter risk
Therapeutic possibilities	• If technological developments allow therapeutic intervention, why not for veterans (ethical) • Promotion of veteran's wellbeing • Development of therapies to reverse disease states that currently have no effective treatments. • Much like any other treatment the therapeutic application could improve individual wellbeing • therapeutic opportunities to reverse the effects of exposures on veterans' health
Miscellaneous	• The statement that "Epigenome editing technologies can also be used for therapeutic purposes to reverse the effects of exposures on veterans' health" is unfounded, this question is based on a hypothetical possibility. • Improving mission accomplishment

In your opinion, what are the most important ethical, legal and social issues related to this use of epigenetic technologies in defence and security contexts?

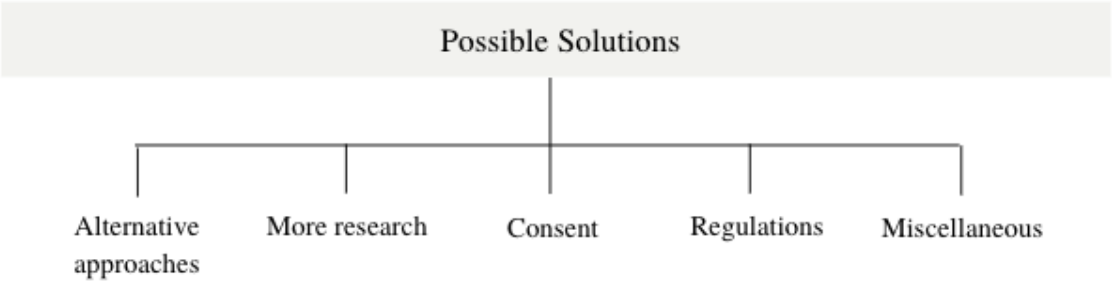


Category	Response
Acceptability of enhancement	• The issues here relate to widely rehearsed problems with so-called 'enhancement'. I'm not sure that the specifically epigenetics aspect introduces strikingly novel concerns over an above the significant existing worries ethicists have over eg pharmaceutical and genetic enhancement

	• Should any of this become a real option: questions of access to this therapeutic option; diversion of public attention from the fundamental causes of these conditions (diseases of the epigenome and lack of accountability for hazardous military policies) • Not to use epigenomic editing for the purposes of enhancement (of non-medical traits) - this is not (ethically) acceptable in many societies
Harm to individuals	• Unintentional harm / maleficence • Risks from unintended effects
Use of resources	• Cost • Best use of limited resources? • Lesser urgency of enhancement as opposed to addressing harm
Enhancement arms race	• Enhancement arms race: is it unavoidable? • I can already imagine a global rush towards the perfect soldier; but without a slippery slope in there, there is a real question about global oversight of use of these tools
Exploitation / coercion	• Exploitation of vulnerable populations to conduct human experimentation, i.e., soldiers, who typically have little ability to refuse orders when on active duty. • Voluntary vs. Compulsory use • Instrumentalization of soldiers using enhancement techniques that might not serve their long-term best interests. • Informed consent & coercion to enhance
Research issues	• Large N studies needed and blinded studies • Feedback to participants
Equality of access	• Justice and equality of access • Fairness in access to epigenetic enhancement
Misuse	• As with the applications described in Vignette 2, there is an ethically and societally highly important risk of misuse: If departments of

	defence conduct research in the direction of epigenetic applications to test exposures to substances (see Vignette 2), dual use is a highly relevant problem. It is considered by the US department of defence to develop "inner strength to survive and recover from potentially lethal health threats" (project entitled PREPARE). This could include research into the application of epigenome editing to generate resistance to substance exposure. As Alta Charo has stated, this comes with the problem of dual use. Such research might result in future use of these substances by countries with armed forces that are resilient to the exposures to the detriment of other human beings that are not resilient. While this is currently a slippery slope argument, misuse is a very important issue and at least an aspect that is relevant for a societal discussion and therefore challenging not only from an ethical perspective, and from a legal perspective (establish appropriate legal safeguards against misuse), but especially challenging from a societal perspective. • Misuse as bioweapons

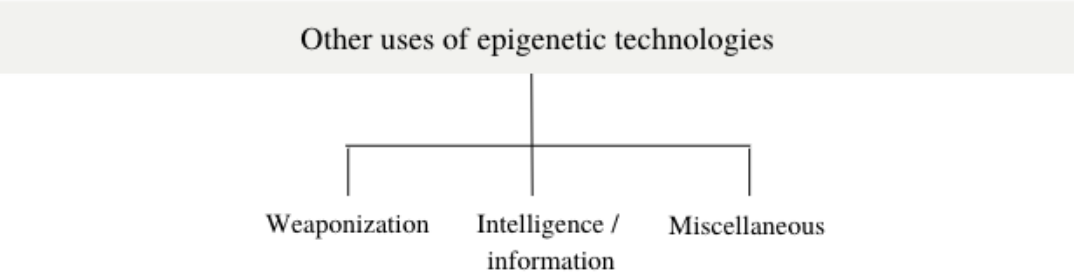
What are some possible avenues or solutions towards responsible use of this epigenetic application in defence and security contexts?



Category	Response
Alternative approaches	• There are non-epigenome editing approaches that can reverse epigenome "damage" these should be explored • Because of the risk of severe misuse with a lack of potential benefits, this application should not be considered at all.
More research	• Drug development and Cas9 epigenomic treatments

	• Large N population studies to understand variation • Clearer understanding of what exactly enhancement means • More research / clinical trials • Regarding epigenome editing in general we need societal discourse and thorough philosophical analysis: The challenges and opportunities of clinical applications of epigenome editing (outside the defence sector) need to be broadly discussed with society and simultaneously extensively analyzed by philosophy/applied ethics, whereby potential risks of misuse within the defence sector must be considered.
Consent	• Regulations protecting informed consent • Strict informed consent protocols that allow any soldier the opportunity to refuse treatment.
Regulations	• Tie uses of CRISPR-based technologies to international conventions, guidelines and limitations • In-depth interdisciplinary exploration • Establish e.g. committee of experts to decide on applications of epigenomic editing, working transparently, taking into account societal opinion (e.g. through regular consultations) • Agreement on appropriate research methods • Oversight on/review of experiments; discussions under bioweapon convention • International dialogue and cooperation to ensure that a new "arms race" based on epigenetically enhanced soldiers does not emerge in the short-term.
Miscellaneous	• Education of the army troops and their families • Systematic monitoring of soldiers who underwent such interventions

What else comes to mind, if anything, when you think of epigenetic technologies utilized in defence and security contexts?



Category	Response
Weaponization	• Use as bioweapons • Potential weaponization • As the sky seems the limit, and given the easy availability of the reagents, it might be very complicated to defend populations against CRISPRed bioweapons… • Unlike other defence technologies (nuclear, ICBM's, etc), epigenetic technologies will likely be easier to replicate by many nations. Without international cooperation on what limits and redlines should be set, countries with lesser protections for individual rights can become testbeds for development of potentially disruptive and dangerous epigenetic enhancements, or treatments (make population more docile) that threaten the rights of populations and individuals.
Intelligence / information	• Samples could be analyzed to gather information on diet, exposures, age, BMI, disease risk • Possible discovery of past behaviours; Privacy issues with regard to employers' capacity of assessing previous smoker status, drug consumption patterns, or even sexual conduct. • This may be far-fetched, but I was thinking of intelligence. Epigenetic analysis of enemy bodies / bodily material may reveal geographic regions, exposures, etc..

Miscellaneous	• Epigenetic variability is inescapably linked to genetic variability, the two need to be studied in parallel. A framing for this discussion is that the response to trauma is more likely to be epigenetic (=non-genetic) than genetic, but predisposition is likely to have a strong genetic component. After accounting for genetics, including related issues of diverse race and ethnicity, then we need better epigenetic association studies that go on to be proven as robust biomarkers. Once those foundations are in place, we can revisit the idea that we can use epigenetic technologies in defence and security, at which stage the main ethical question emerges -- for whose benefit is the testing performed? For the potentially traumatized or exposed member of the military, or for their armed forces employers? Incentives for testing will differ for each. • To what extent can this technological development be regulated through existing laws (e.g. in the U.S. & Canada), rather than calling for new regulations? • While likely safer than genetic treatments, epigenetic treatments such as CRISPR technologies can have dangerous off-target effects that might also affect future generations. • Since epigenetic editing is currently being discussed ethically mainly (or almost exclusively) at this level of enhancement (e.g. enhancement in sports, and military enhancement, although this discussion is still small), and we are currently conducting a research project that has ethically investigated the fundamentals of epigenetic editing, we could contribute to the questions of this dual-use problem from our COMPASS-ELSI project context, especially since the technology is so new that there have been virtually no ethical analyses of it so far (in general, be it medical or (non-therapeutic) enhancement). In addition, it is becoming increasingly clear to me that, from an ethical point of view, it is very difficult to exclude questions of enhancement from the debate about therapeutic/research use if one wants to take a position on the debates that discuss “slippery slopes” or “dual use”.

Appendix II: "Predictive Epigenetics and Epigenetic Age- Potential Applications in the Military" (Workshop case study)

An epigenetic biotype (called G2) is indicative of PTSD risk following warzone exposure. This biotype shows significantly different methylation patterns (principally hypermethylation) in several genes and is associated with 34 clinical features related to PTSD. Post-deployment, individuals with a G2 biotype have a significantly higher score on the PTSD checklist (Diagnostic and Statistical Manual of Mental Disorders) than individuals without the biotype. Furthermore, the G2 biotype is found to be predictive of PTSD risk. An elite combat unit named Claw is frequently deployed in warzones and is therefore at high risk for PTSD. The military is considering testing members of Claw for G2.

1)Should we use the same reliability threshold for military use as we would for clinical or commercial use?

2) Should information from individuals' epigenetic tests be kept on a database or registry on a long-term basis by military authorities?

The members of combat unit Claw were additionally tested with epiGrim, an epigenetic pattern associated with accelerated cellular ageing and premature mortality. Chemical weapon exposure of soldiers with epiGrim is associated with a significantly higher ageing process when compared to control groups.

3) Should active-duty members be offered an early retirement with benefits based on the epiGrim epigenetic test?

Some soldiers from the Claw combat unit have been deployed in Nigeria. During their mission, a small number of militia fighters were captured by the country's military forces. Upon interrogation, some young-looking rebels claim to be children kidnapped from their villages three months ago. The unit commander recalls a conversation he had with a scientific consultant for the military who mentioned that some biotech companies now advertise novel tests that can estimate a person's actual age based on an epigenetic clock. Since none of these captured rebels have a government-issued ID, the commander decides to use these tests to determine whether these individuals are child soldiers.

4) Are there factors that could interfere with the age estimated from these epigenetic clock tests?

Appendix III: "The Possibility of Soldiers' Enhancement Through Epigenetic Editing" (Workshop case study)

The possibility of soldiers' enhancement through epigenetic editing. A 30-year-old man, "B", has recently enlisted into the army. The military is currently developing its capability to provide soldiers with epigenetic modifications for combat and resilience enhancement purposes. Assuming the technology has been validated scientifically, B is offered the opportunity to undergo epigenetic enhancement to resist the effect of tear gas. When discussing this with his physician, he admits that he would feel more secure if he were epigenetically enhanced before engaging in active combat. However, he is worried about the effects of this technology on his future children, as he does not want to pass these genetic enhancements to them.

1) What are the advantages and obstacles to the epigenetic enhancement of soldiers for combat and resilience?

Some years later, the military has discovered an epigenetic modification that confers increased stamina onto individuals. Everyone else in B's cohort has undergone this epigenetic modification. However, B is unsure whether he would like to undergo this procedure. B feels in great shape and believes he does not need this additional improvement. However, there is a lot of peer pressure coming from B's unit to have the enhanced stamina epigenetic enhancement before the next mission overseas, especially from the physician in charge and the commander.

2) What could be the consequences if B refuses this new stamina enhancement?

3)Would it raise ethical or health concerns for some soldiers to be epigenetically enhanced in B's unit if others are not?

Years later, military researchers have found long-term adverse effects associated with the tear gas epigenetic enhancement. B is worried about a risk to his future health and would like to remove the epigenetic enhancement.

4) Will it be possible to reverse his epigenetic modification?