Scientific Risk Assessment of Genetic Weapon Systems

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Contents

Executive Summary

For any emerging technology, defense and homeland security analysts strive to understand (1) its dual-use potential, meaning whether the same research and technology applied for peaceful purposes may be diverted to illicit ends, for example to develop a weapon; (2) the State and sub-State actors with access to that dual-use potential, whether peacefully or illicitly directed; and (3) motivational factors and indicators of intent that might suggest these actors would divert the emerging technology to illicit ends. Precision medicine represents one such emerging technical space. Precision medicine is defined as medical care designed to optimize benefit for particular groups, especially based on genetic (or molecular) profiling. A long-speculated but incompletely understood dual-use consideration of precision medicine is the possible development of a genetic weapon system, defined as a weapon system designed to optimize effect on particular groups based on genetic profiling.

On July 1, 2020, the James Martin Center for Nonproliferation Studies (CNS) undertook a one-year project to assess whether precision medicine could be diverted to develop a population-specific genetic weapon system, on what timeline, with what resources, and with what advantages and limitations. The project specifically focused on State actors China and Russia targeting US populations. The ultimate goal was to determine whether controls are warranted, ensuring that controls do not infringe upon the highly beneficial applications of the technology.

The project comprised two phases. In the first phase, we conducted multi-source/language data mining and analysis to develop a baseline technical report at the 6-month project timepoint. In the second phase, we convened a Technical Focus Group of industry and academic experts to review the report, answer a series of structured and open questions, and debate key points. We incorporated all expert findings into this updated final report, with key findings as follows:

- Genomic datasets enable the identification and characterization of vulnerable populations and are therefore exploitable. The implications of collecting and sharing genomic datasets extend from improving human health to safeguarding the US bioeconomy. While there is tremendous value to be generated by peaceful applications of these data, allowing any organization unrestricted data access equates to

sharing exploitable information, whether that information is exploited to develop tailored pharmaceuticals or for nefarious purposes such as extortion. Security considerations are therefore integral to any discussion of genomic data-sharing whether or not a genetic weapon system is viable; i.e., regardless of the downstream applications or threat vectors, once genomic information is shared, it cannot be unshared. To date, the US has openly shared its genomic data; by comparison, China has been increasingly protective of its own data, including through the introduction of new legislation in 2019 restricting foreign access to Chinese genetic material and information.

- Genetically targeting a population to the exclusion of other populations presents a significant technical challenge. In general terms, there is an inverse relationship between the frequency and specificity of genetic markers: the more frequent a marker is in a given population, the less likely it is to be specific to that population; conversely, the more specific a marker, the less likely that it will be of desirable frequency to characterize a population. Currently available data, while incomplete, indicate that markers of high frequency in one population will also be present in nearby populations due to migration and interbreeding. The implication for a genetic weapon system is that while targeting the majority of a certain population may be possible, some collateral damage would be expected in other populations. The simultaneous targeting of multiple markers ("multiplexing") in a population may increase specificity but would be expected to reduce the proportion of the target population that is affected, given the relative frequencies of different markers in different subsets of the population. Ultimately, the ethnic diversity of the US population provides a protective effect that largely undermines the potential strategic payoff of a genetic weapon system.

- The technical requirements for designing and writing genetic code exceed those for reading genetic code. While reading genetic code may provide targetable information for a genetic weapon system, designing and writing the genetic code that enables such targeting may be technically challenging for some actors. China's biotechnology sector offers considerable dual-use capability to this end, whereas Russia appears suitably but less technically capable and has openly expressed interest in genetic weapon systems since 2012.

- Delivery at scale is an unwarranted technical capability for precision medicine and thus should be monitored for security purposes. Introducing a genetic editing construct requires physical contact with a patient or his/her tissues and can be notably inefficient. While corresponding advancements in efficient gene delivery hold the potential for considerable human health gains and thus receive significant investment, there is limited benefit to delivery at scale, at a distance, or in an otherwise undirected way, such that investment in the development of any broad dissemination capability is not warranted. From a threat characterization perspective, this considerably diminishes the current threat potential of a genetic weapon system, and provides an important target for security monitoring activities.

- The uncertain outcome of a genetic weapon system and availability of viable alternative forms of attack limit its potential utility to specific Use Cases. Utility of a genetic weapon system would be uncertain under most scenarios given the inability to conduct testing and evaluation (T&E) against representative target populations, making investment in their development high risk in the face of alternative kinetic and non-kinetic options that could target geolocated or otherwise well-defined populations. From a threat characterization perspective, this further diminishes the current threat potential of a genetic weapon system such that corresponding T&E activities provide another important target for security monitoring activities. If predictability limitations can be overcome, a specific Use Case that may be uniquely suited for a genetic weapon is covert assassination where lack of attribution is paramount, for example assassination of a leadership or opposition target.

- Alternative approaches to biologically target populations may prove more attainable than targeting specific DNA sequences. Notable alternatives to targeting specific DNA sequences include targeting epigenetic markers and targeting the skin or gut microbiome. Both epigenetic markers and the microbiome change over time to reflect different environmental exposures, and may therefore be inducible in an individual or population to provide a temporary target for exploitation. In theory, both approaches enable a perpetrator to identify a genetic signature and deliver a payload; both therefore meet our definition of a genetic weapon system, i.e., a weapon system designed to optimize effect on particular groups based on genetic profiling.

- Eroding technical barriers and enabling technologies may alter the outlook of genetic weapon systems in the long-term (5-15 years and beyond). While the targeting approaches described in this report are technically challenging and data hungry, because of ongoing research these technical barriers are likely to erode over time. We must anticipate a world where genome sequencing is ubiquitous: where even a routine visit to a doctor's office will involve genetic sequencing and analysis. Furthermore, enabling technologies are being increasingly applied to improve and accelerate our understanding. To date, the majority of work to link genetic variants to medical outcomes, pharmacogenomic outcomes, and biogeographic ancestry has employed traditional statistical techniques such as logistical regression. However, DNA sequencing and bioinformatics advances may be increasingly leveraged to collect and analyze more robust genetic information at faster speeds and lower cost; artificial intelligence (AI) and machine learning (ML) advances may be increasingly leveraged to more readily identify associations between these genetic data and other massive data sets (e.g., chemical structures for prospective pharmaceuticals); and high performance computing (HPC) and cloud computing advances may be increasingly leveraged to generate the necessary computational power for corresponding data analysis and storage. Together, these advances may enable identification of increasingly precise targets for a genetic weapon system.

Our corresponding recommendations for the US policymaking community are as follows:

- Differentiate between human and non-human genomic information when determining protection requirements. Both human and non-human genetic information contribute to growing the US bioeconomy, creating jobs, and building a technological advantage. Differentiating between human and non-human data may aid the US in establishing the necessary balance between open information-sharing and security. With one notable exception, creating a culture around openly sharing non-human data would enable the US to retain its position of scientific transparency while protecting its populace against the range of vulnerabilities that sharing human data may present. The notable exception is genomic sequencing data of monoculture plots of staple cultivars that provide much of the food in the US, the genomic homogeneity of which makes them particularly vulnerable to targeting by a genetic weapon.

- Explore applicability of national-level export controls on human genomic information. Securing exploitable human genomic information provides a balanced option for near-term (< 5 years) mitigation of corresponding vulnerabilities. Strengthening national level export controls, particularly measures restricting transfers to specified end-users of concern, to mitigate the security implications of intangible data transfer – in this case, US genomic data – offers a reasonable, minimally-intrusive step to safeguard this information from foreign entities.

- Secure protected data from remote exploitation. Because a successful cyberattack involving surreptitious network intrusion and exfiltration of data would effectively circumvent export controls relevant to human genomic information, corresponding security measures are in the national interest, particularly as exploitable data are increasingly analyzed and stored on the cloud.

- Establish norms and actively monitor for specific capabilities and activities that have limited funding incentive for peaceful purposes. Two key activities that are critical to developing a genetic weapon system but otherwise have limited peaceful application are (1) the development of capabilities for delivering DNA at scale, at a distance, or in an otherwise undirected way; and (2) T&E activities against representative target populations to ensure predictability of effect. The US should actively monitor for these activities while building international consensus against their pursuit.

- Leverage technology to establish deterrence by denial. Technological change that increases the feasibility of a genetic weapon system also improves our ability to reduce the threat such a weapon would pose. Building defensive capabilities that deter a potential adversary from pursuing a genetic weapon system, i.e., "deterrence by denial," therefore represents a foundational counterstrategy that is being actively pursued by the US. Legislative reform focused on deterrent and defensive measures captured under the US National Security Strategy, combined with sustained research and development (R&D) investment to maintain technical superiority and advance technologies to counter genetic weapon systems, would further reduce the confidence of potential adversaries in the effectiveness of such weapons and disincentivize corresponding investment.

- Continue the conversation. The dual-use R&D described in this report holds the potential for tremendous benefit to the US bioeconomy and the health and well-being of US and global populations. China clearly recognizes this transformative power, meriting significant State-level investment. Such sustained investment may enable China to surpass the US as the de facto centralizing power for biotechnology, providing a level of influence over corresponding norms that could prove detrimental to US interests in the long-term. It is therefore incumbent upon US scientists and policymakers to continue to seek forward-leaning approaches that preserve peaceful R&D while limiting the potential for data misuse over time. By continuing the conversation, US science and policy stakeholders will be better positioned both to make informed risk-benefit decisions in this rapidly evolving and complex technical space and to build corresponding consensus at the international level.

Introduction

In 2020, the Office of the Director of National Intelligence (ODNI) commissioned a National Academy of Sciences (NAS) report on Safeguarding the Bioeconomy of the United States.[1] Among other topics, the report considered national security risks posed by access to genetic databases, including the possibility of "Genetic Targeting of Populations."[2] The report concluded that while developing a genetic weapon that would preferentially target select populations poses numerous technical challenges, the accelerated pace of information about the human genome and resulting erosion of technical barriers suggests that this possibility should be monitored. In short, the leading US technical body is concerned about the possibility of genetic weapons.

An underlying basis of this concern is the dual-use potential of the advancing field of precision medicine. Precision medicine is defined as "medical care designed to optimize efficiency or therapeutic benefit for particular groups of patients, especially by using genetic or molecular profiling."[3] Dual-use means that the same research and technology applied for peaceful purposes may be diverted to illicit ends.

From a defense and homeland security perspective, for any emerging technology we strive to understand (1) its dual-use potential; (2) the state and sub-state actors with access to that dual-use potential, whether peacefully or illicitly directed; and (3) motivational factors and indicators of intent that might suggest these actors would divert the emerging technology to illicit ends.

With respect to precision medicine, a long-speculated but incompletely understood dual-use consideration is the possible development of a genetic weapon system, defined as a "weapon designed to optimize effect on particular groups based on genetic profiling." This is a direct adaptation of the above-provided definition of precision medicine, given that the two represent opposite outcomes of the same research and development pathway. In both cases, core capabilities include the reading and writing of genetic material. Relevant technical disciplines for both include genomics and bioinformatics, genetic engineering, synthetic biology, biosecurity, population and forensic genetics, anthropology, data science, and intersecting technologies including artificial intelligence (AI) and machine learning (ML), high performance computing (HPC), and cloud computing.

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[1]National Academies of Sciences, Engineering, and Medicine 2020. Safeguarding the Bioeconomy. Washington, DC: The National Academies Press. https://doi.org/10.17226/25525

[2] Ibid., pp.298-299.

[3] https://www.lexico.com/en/definition/precision_medicine

On July 1, 2020, the James Martin Center for Nonproliferation Studies (CNS), Middlebury Institute of International Studies at Monterey (MIIS), launched a one-year project to explore this dual-use consideration, with a specific focus on the People's Republic of China (PRC) and Russian Federation. Specifically, we sought to determine:

> Is it technically feasible for precision medicine advances to lead to the development by China and/or Russia of a genetic weapon system targeting US populations, on what timeline, with what resources, with what advantages and limitations, and what are our options for control?

The project comprised two phases. In the first phase, we conducted multi-source/language data mining and analysis to develop a baseline technical report at the 6-month project timepoint. In the second phase, we convened a Technical Focus Group of industry and academic experts to review the report, answer a series of structured and open questions, and debate key points. We incorporated all expert findings into this updated final report.

The report includes three parts, each of which addresses a core component of our problem statement. Part I, Technical Feasibility of Genetic Weapon Systems, assesses the technical feasibility, advantages, and limitations of genetic weapon systems. Part II, State Actor Technical Capabilities and Motivations, assesses the technical capabilities and motivations of China and Russia to develop such weapons. Part III, Action Plan, evaluates options for near-term (within the next 5 years) and long-term (in the next 5-15 years) control and provides recommendations for the US policy community to address the potential threat of genetic weapon systems while preserving peaceful applications of precision medicine and related technologies.

While we aspired toward a definitive assessment of genetic weapon systems, the project was limited by a number of factors. First, fluid definitions of key terms such as "genetic" and "population" required us to bound our research, such that some relevant topics may be only peripherally addressed (e.g., epigenetics; the microbiome) or omitted altogether (e.g., predictive modeling and simulation of genetic sequences; deriving targetable protein signatures). Second, because the underpinning science described in this report is rapidly advancing, predicting future applications and innovations on any defined timeline is challenging. Illustrating this point, much of our research focuses on the application of CRISPR, which was only first used for gene editing in 2012.[4] Furthermore, scientific forecasting itself is notably

[4] Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E. A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. *Science.* 2012 Aug 17;337(6096):816-21. doi: 10.1126/science.1225829. Epub 2012 Jun 28. PMID: 22745249; PMCID: PMC6286148.

imprecise, including when conducted via the focus group approach as in this study.[5] Finally, we have taken special care to ensure that our findings do not enable illicit application of corresponding technologies; as such, we have conducted a thorough review of this report's contents and redacted certain aspects as indicated prior to publication.

[5] As other studies have noted, "Scientific forecasting is highly problematic. The difficulties are accentuated when trying to envisage the products, processes, or other applications that a rapidly evolving and growing scientific field will generate. The forecasting method selected for this project is the focus group approach. In general, a focus group consists of a number of persons who are brought together and asked to consider a series of issues related to the subject of concern. Thus, the discussion is focused on a particular subject and group dynamics assist in generating information on that subject. The focus group technique or approach is useful for identifying areas of consensus or disagreement on the presented issues. It often provides valuable information on what people know, and the opinions they have, about a subject and how their knowledge and opinions change in response to being exposed to the views and experiences of others." Zilinskas RA. Possible Terrorist Use of Modern Biotechnology Techniques. 2002.

Part I. Technical Feasibility of Genetic Weapon Systems

Evolutionary Basis of Population-Specific Genetic Differences

Over 150 years ago, Charles Darwin proposed that all life stems from a universal common ancestor.[6] Only in recent years has science been able to boost confidence in Darwin's original proposition by employing quantitative modeling of universally conserved proteins to compare common ancestry versus both independent ancestry (e.g., two ancestors, one giving rise to bacteria and another giving rise to Archaea and eukaryotes) and creationism, with results overwhelmingly supporting common ancestry.[7,8] Today, evolution from a common ancestor is the most widely accepted hypothesis for why the average human shares 90% genetic similarity with a cat,[9] 96% similarity with a chimpanzee,[10] and 99.9% with a fellow human.[11]

The 99.9% genetic similarity among humans raises a similar origin question – did all *Homo sapiens* arise from a single human ancestor? Just as all life is widely believed to stem from a universal common ancestor, all human life is widely believed to have evolved from a single point on the evolutionary timeline. This is called the "out of Africa" hypothesis.[12]

Both across species and among humans, the underlying driver of evolution is genetic change. In simplified terms, the first ancestor

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[6] Darwin, C. & Kebler, L. (1859) On the origin of species by means of natural selection, or, The preservation of favoured races in the struggle for life. London: J. Murray. [PDF] Retrieved from the Library of Congress, https://www.loc.gov/item/06017473/.

[7] Theobald DL. A formal test of the theory of universal common ancestry. *Nature.* 2010 May 13;465(7295):219-22. doi: 10.1038/nature09014. PMID: 20463738.

[8] Theobald DL. On universal common ancestry, sequence similarity, and phylogenetic structure: the sins of P-values and the virtues of Bayesian evidence. Biol Direct. 2011;6(1):60. Published 2011 Nov 24. doi:10.1186/1745-6150-6-60.

[9] Pontius JU, Mullikin JC, Smith DR, et al. Initial sequence and comparative analysis of the cat genome. Genome Res. 2007;17(11):1675-1689.doi:10.1101/gr.6380007

[10] Chimpanzee Sequencing and Analysis Consortium. Initial sequence of the chimpanzee genome and comparison with the human genome. *Nature.* 2005 Sep 1;437(7055):69-87. doi: 10.1038/nature04072. PMID: 16136131.

[11] Shastry BS. SNP alleles in human disease and evolution. J Hum Genet 2002;47(11):0561–6.

[12] Oppenheimer S, 2012. Out-of-Africa, the peopling of continents and islands: tracing uniparental gene trees across the map. Phil. Trans. R. Soc. B367770–784. The central competing hypothesis is one of multiple, geographically disparate emergences, called the "multi-regional" model.

introduced a set of genetic material that has been changing ever since, from early single-celled organisms to modern day *Homo sapiens*. Changes with the potential to be passed from parent to offspring ("heritable") and thus enable evolution across and within species primarily result from uncorrected errors during replication – or copying – of genetic material. In sexually-reproducing organisms such as humans, in order for such an uncorrected error to be heritable, it must occur in the genetic material of germline (i.e., egg or sperm) cells. [Changes in somatic cells, for example DNA damage caused by environmental stressors such as UV exposure, are important to understand for the prevention and management of a range of acquired diseases including cancer, but these changes are not heritable and therefore do not influence dual-use precision medicine approaches.]

There are multiple types of replication errors, including incorrect copying of a single nucleotide ("single nucleotide variant"); the insertion or deletion of a small sequence of nucleotide/s during copying ("indel"); and larger sequence insertions, deletions, or copy number variations during copying ("structural variants"). During human DNA replication, such errors occur due to the massive number of nucleotides being copied, but the error rate is extremely low (approximately one error per 10^8 to 10^{10} nucleotides).[13] The vast majority of these errors are corrected either immediately ("proofreading") or after replication ("mismatch repair"). Those that slip through may alter the observable characteristics ("phenotype") of the organism, depending on where they occur.

Replication errors may occur in (a) protein-coding regions, which determine which proteins are actually made; or (b) non-protein-coding regions, which represent the bulk of human DNA and contain key regulatory sequences that govern protein expression.[14] Uncorrected errors in protein-coding regions may cause no change at all ("synonymous" mutations), may result in an amino acid substitution that alters protein function ("nonsynonymous" or "missense" mutations), or may result in a stop codon that prematurely truncates the protein ("nonsense" mutations). Missense and nonsense mutations have been found to contribute to genetic ("genotypic") and corresponding phenotypic differences *between species,*[15,16]

[13] Bębenek A, Ziuzia-Graczyk I. Fidelity of DNA replication-a matter of proofreading. Curr Genet. 2018;64(5):985-996. doi:10.1007/s00294-018-0820-1

[14] Franchini LF, Pollard KS. Human evolution: the non-coding revolution. BMC Biol. 2017 Oct 2;15(1):89. doi: 10.1186/s12915-017-0428-9. PMID: 28969617; PMCID: PMC5625771.

[15] Chimpanzee Sequencing and Analysis Consortium. Initial sequence of the chimpanzee genome and comparison with the human genome. *Nature.* 2005 Sep 1;437(7055):69-87. doi: 10.1038/nature04072. PMID: 16136131.

[16] Sudmant PH, Huddleston J, Catacchio CR, et al. Evolution and diversity of copy number

and in humans have been implicated in a range of hereditary diseases and risk factors/predisposing factors for disease,[17] but do not appear to meaningfully contribute to genotypic differences between human subpopulations. Uncorrected errors in non-protein-coding regions most often cause no change at all; however, those that alter gene expression appear to contribute the majority of genotypic and corresponding phenotypic differences *between human subpopulations.*[18,19] Non-protein-coding regions where errors may exert such effects include transcription factor binding sites on promoters, miRNA binding sites at 3' un-translated regions (3'UTR), or exon/intron splicing regulatory sites.

There are multiple mechanisms for how these effects may propagate, including random genetic drift, founder effect,[20] and natural selection.[21,22] If there is limited subsequent mixing between the altered subpopulation and other subpopulations, for example due

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variation in the great ape lineage. Genome Res. 2013;23(9):1373-1382. doi:10.1101/gr.158543.113

[17] For example, in sickle-cell anemia, the substitution of a single nucleotide (A to T) alters the amino acid structure of an individual's beta hemoglobin chain (glutamic acid to valine), causing the individual's red blood cells to sickle such that they cannot carry oxygen well … However, this same mutation in unaffected carriers ("sickle-cell trait") is protective against malaria, which may explain why it has been evolutionary conserved, i.e., through positive natural selection. See for example https://www.nature.com/scitable/topicpage/sickle-cell-anemia-a-look-at-global-8756219/

[18] Bachtiar M, Jin Y, Wang J, Tan TW, Chong SS, Ban KHK, et al. (2019) Architecture of population-differentiated polymorphisms in the human genome. PLoS ONE 14(10): e0224089.

[19] Changes in non-coding regions also account for considerable genomic differences between humans and chimpanzees (our closest primate relatives), indicating that regulatory changes may be key drivers for human evolution from a shared human-chimpanzee ancestor. Many of these species-specific differences occur in short, evolutionarily conserved regions of the human genome called human accelerated regions (HARs), where a statistically significant increase in single nucleotide substitutions have been acquired and retained by humans since divergence from chimpanzees compared to other areas of the genome. However, from a whole genome perspective, indels and structural variants contribute far more nucleotide differences between humans and chimpanzees than single nucleotide variants in HARs and elsewhere. Franchini LF, Pollard KS. Human evolution: the non-coding revolution. BMC Biol. 2017 Oct 2;15(1):89. doi: 10.1186/s12915-017-0428-9. PMID: 28969617; PMCID: PMC5625771.

[20] Founder effect is defined as "the reduction in genetic variation that results when a small subset of a large population is used to establish a new colony. The new population may be very different from the original population, both in terms of its genotypes and phenotypes. In some cases, the founder effect plays a role in the emergence of new species." https://www.genome.gov/genetics-glossary/Founder-Effect.

[21] Natural selection is defined as "the process that results in the adaptation of an organism to its environment by means of selectively reproducing changes in its genotype, or genetic constitution." https://www.britannica.com/science/natural-selection.

[22] See, for example, Lenski RE. *What is adaptation by natural selection? Perspectives of an experimental microbiologist.* PLoS Genet. 2017;13(4):e1006668. Published 2017 Apr 20. doi:10.1371/journal.pgen.1006668. Vasseur E, Quintana-Murci L. The impact of natural selection on health and disease: uses of the population genetics approach in humans. Evol Appl. 2013;6(4):596-607. doi:10.1111/eva.12045. Dimijian GG. Darwinian natural selection: its enduring explanatory power. Proc (Bayl Univ Med Cent). 2012;25(2):139-147. doi:10.1080/08998280.2012.11928811.

to geographical barriers such as mountain ranges, an ancestry-informative lineage can result that is genetically identifiable by the unique, conserved genotypic difference/s underlying the phenotype.[23] In general, the more homogenous a subpopulation is phenotypically, the more genetically similar it is – with key implications for dual-use precision medicine.

Single Nucleotide Polymorphisms (SNPs), Ancestry Informative SNPs (AISNPs), and Microhaplotypes

As described above, humans share 99.9% of the nucleotides in their genomes.[24] The remaining 0.1% is what makes individual humans unique. This 0.1% is largely made up of single nucleotide polymorphisms (SNPs),[25] defined as single nucleotide variants that exist in at least 1% of the population.[26] SNPs are present at a frequency of approximately 1 in 1000 base pairs throughout the genome, including protein-coding and non-protein-coding regions.[27] Each SNP is traceable to a specific location in the genome called a "locus."

The majority of SNPs are common across human subpopulations; those that are not may enable some level of probabilistic population differentiation.[28] These include Phenotype Informative SNPs (PISNPs), defined as "SNPs that provide a high probability that an individual has particular phenotypes such as a particular skin color, hair color, or eye color, etc.," and ancestry informative SNPs (AISNPs), defined as "SNPs that collectively give a high probability of an individual's ancestry being

[23] See, for example, Wu DD, Zhang YP. *Different level of population differentiation among human genes.* BMC Evol Biol. 2011 Jan 14;11:16. doi: 10.1186/1471-2148-11-16. PMID: 21235767; PMCID: PMC3032687. Park L. *Evidence of Recent Intricate Adaptation in Human Populations.* PLoS One. 2016 Dec 19;11(12):e0165870. doi: 10.1371/journal.pone.0165870. PMID: 27992444; PMCID: PMC5167553. Sabeti PC, Schaffner SF, Fry B, et al. Positive natural selection in the human lineage. *Science.* 2006;312(5780):1614-1620. doi:10.1126/science.1124309. Bamshad M, Wooding SP. *Signatures of natural selection in the human genome.* Nat Rev Genet. 2003 Feb;4(2):99-111. doi: 10.1038/nrg999. PMID: 12560807. For a brief overview of positive selection in humans, see Schaffner S, Sabeti P. Evolutionary adaptation in the human lineage. *Nature Education.* 2008; 1(1):14. https://www.nature.com/scitable/topicpage/evolutionary-adaptation-in-the-human-lineage-12397/

[24] See, for example, Collins FS, Mansoura MK. The human genome project. Cancer. 2001;91(S1):221–5.

[25] Collins FS, Brooks LD, Chakravarti A. A DNA Polymorphism Discovery Resource for Research on Human Genetic Variation. Genome Res. 1998;8(12):1229–31.

[26] https://www.ncbi.nlm.nih.gov/projects/SNP/snp_summary.cgi?view+summary=view+summary&build_id=138; https://www.ncbi.nlm.nih.gov/snp/; ftp://ftp.ncbi.nlm.nih.gov/snp/

[27] Brookes AJ (1999) The essence of SNPs. Gene 234:177–186.

[28] Barbujani G, Magagni A, Minch E, Cavalli-Sforza LL. An apportionment of human DNA diversity. Proc Natl Acad Sci. 1997;94(9):4516–9.

from one part of the world or being derived from two or more areas of the world."[29] AISNPs vary in frequency across populations, requiring sufficiently large datasets on both the target population and reference populations. When assembled in a panel, AISNPs can differentiate between five "continental" clusters of global populations: Africa, Europe, East Asia, South Asia, and the Americas.[30]

Microhaplotypes,[31] defined as "small genomic regions of less than 250 to 300 base pairs with two or more SNPs defining at least three common haplotypes,"[32] provide an intermediate level of precision between AISNP analysis and resource-intensive whole genome sequencing (WGS). Combining AISNP and microhaplotype markers in a single panel may enable ancestral differentiation not only between regions but, to a lesser degree, within regions as well.[33]

Genetic Basis of Precision Medicine: Pharmacogenomics

The goal of precision medicine is to identify subpopulations of patients with unique disease susceptibilities, prognoses, and therapeutic responses in order to optimize their medical management, from basic preventive measures such as preemptive lifestyle modifications to advanced treatments.[34] In clinical practice, precision medicine considers genetic, lifestyle, and environmental factors, but from a pharmaceutical industry perspective the focus is on identifying common genetic factors that can be "precisely" targeted by medical countermeasures. Scientific research has long indicated that such common genetic

[29] Butler, J. M., Budowle, B., Gill, P., Kidd, K. K., Phillips, C., Schneider, P. M., Vallone, P. M., & Morling, N. (2008). Report on ISFG SNP Panel Discussion. Forensic Science International: Genetics Supplement Series, 1(1), 471-472. https://doi.org/10.1016/j.fsigss.2007.10.159.
[30] See, for example, Kidd KK. Thoughts on Estimating ancestry. In Amorim A and Budowle B., eds., Handbook of Forensic Genetics: Biodiversity and Heredity in civil and Criminal Investigation (World Scientific: London, 2017).
[31] See, for example, Oldoni F, Kidd KK, Podini D. Microhaplotypes in forensic genetics. Forensic Sci. Int. Genet. 2019; 38: 54-69.
[32] A haplotype is a "set of DNA variations, or polymorphisms, that tend to be inherited together. A haplotype can refer to a combination of alleles or to a set of single nucleotide polymorphisms (SNPs) found on the same chromosome." https://www.genome.gov/genetics-glossary/haplotype.
[33] Kidd KK Forensic Sci. Int. Genet 2021, in press; see https://doi.org/10.5281/zenodo.4658892
[34] Note that the terms precision medicine and personalized medicine are often used interchangeably; however, "personalized medicine" is a largely outdated term that has fallen out of favor because it implies the development of unique countermeasures for individuals. See National Academy of Sciences. Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease. Washington, DC: National Academies Press; 2011.

factors can lead to different drug responses across regional, ethnic, and racial subpopulations.[35]

SNPs inform precision medicine approaches employing a technique called "pharmacogenomics." Pharmocogenomics is the study of how genomic differences affect pharmaceutical responses across different subpopulations, in terms of both effectiveness and adverse effects.[36] If a SNP alters gene expression in a given drug's absorption, distribution, metabolism and excretion (ADME) pathway, then that drug may be more or less effective – or dangerous – in populations with the SNP. Such relationships can be validated using real-world data – do populations containing a SNP or SNPs that map to a given drug's ADME pathway exhibit different responses (efficacy or adverse effects) to that drug?

Various pharmacogenomic methodologies for identifying SNPs, determining which SNPs are drug-related, and predicting corresponding drug effects in different regional, ethnic, and racial subpopulations (termed "pharmacoethnicity") have been described in the open source domain.[37,38] The resulting SNP-drug effect relationships are curated in a number of openly accessible databases,[39] which will continue to grow as efforts to map an increasing number of human genomes come to fruition.[40]

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[35] See, for example, Abou Auda HS, Najjar TA, Al-Fawzan NF, Gilzai NM. Ethnic differences in nifedipine pharmacokinetics and pharmacodynamics. Comparison of middle eastern Arabs with other population. Saudi Pharm. J. 1998; 6:217-227. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci U S A. 2004 Sep 7;101(36):13306-11. doi: 10.1073/pnas.0405220101. Epub 2004 Aug 25. PMID: 15329413; PMCID: PMC516528. Wilson JF, Weale ME, Smith AC, et al. Population genetic structure of variable drug response. Nat Genet. 2001 Nov;29(3):265-9. doi: 10.1038/ng761. PMID: 11685208.

[36] Ramos E, Doumatey A, Elkahloun AG, Shriner D, Huang H, Chen G, Zhou J, McLeod H, Adeyemo A, Rotimi CN. Pharmacogenomics, ancestry and clinical decision making for global populations. Pharmacogenomics J. 2014 Jun;14(3):217-22. doi: 10.1038/tpj.2013.24. Epub 2013 Jul 9. PMID: 23835662.

[37] Ahn E, Park T. Analysis of population-specific pharmacogenomic variants using next-generation sequencing data. Sci Rep. 2017;7(1):8416. Published 2017 Sep 4. doi:10.1038/s41598-017-08468-y.

[38] Bachtiar M et al. Towards precision medicine: interrogating the human genome to identify drug pathways associated with potentially functional, population-differentiated polymorphisms. *The Pharmacogenomics Journal* (2019) 19:516–527, https://doi.org/10.1038/s41397-019-0096-y

[39] See, for example, https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling; https://www.pharmgkb.org/

[40] See, for example, Carrasco-Ramiro F, Peiró-Pastor R, and Aguado B. Human genomics projects and precision medicine. Gene Therapy (2017) 24, 551–561; doi:10.1038/gt.2017.77. Table 1 of this article lists numerous human genome-related projects, for example the Human Genome Project-Write (Boeke JD, Church G, Hessel A, Kelley NJ, Arkin A, Cai Y et al. Genome Engineering. The Genome Project-Write. *Science* 2016; 353: 126–127) and the 100,000 Genomes Project (https://www.genomicsengland.co.uk/about-genomics-england/

Contribution of Genome Mapping Projects

Genome mapping projects may specifically look for genetic differences among subpopulations. For example, Genome Asia 100K is seeking to stratify genomes into different ethnic groups using genome-wide association studies.[41] This work builds on a foundation of research to identify genetic differences between various ethnic groups.[42] For example, a 2015 Chinese study[43] identified a subset of 299 SNPs that accurately predicted all ethnic subpopulations in the now retired HapMap database;[44] functional analysis of these SNPs demonstrated a role in skin and eye color differences across populations. Importantly, Chinese forensic scientists have invested heavily in SNP as well as short tandem repeat (STR)[45] analysis to distinguish between internal ethnic minorities.[46] More broadly,

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the-100000-genomes-project/).

[41] GenomeAsia100K Consortium. The GenomeAsia 100K Project enables genetic discoveries across Asia. *Nature*. 2019 Dec;576(7785):106-111. doi: 10.1038/s41586-019-1793-z. Epub 2019 Dec 4. PMID: 31802016; PMCID: PMC7054211.

[42] See, for example, Wu DD, Zhang YP. Different level of population differentiation among human genes. BMC Evol Biol. 2011 Jan 14;11:16. doi: 10.1186/1471-2148-11-16. PMID: 21235767; PMCID: PMC3032687. Haque S. Frequency of XRCC1 Exon 9 G>A gene polymorphism in Saudi Arabian population: A comparative study with worldwide ethnic groups. J BUON. 2018;23(4):1195-1199. Yew CW, Hoque MZ, Pugh-Kitingan J, et al. Genetic relatedness of indigenous ethnic groups in northern Borneo to neighboring populations from Southeast Asia, as inferred from genome-wide SNP data. Ann Hum Genet. 2018;82(4):216-226. doi:10.1111/ahg.12246.

[43] See, for example, Huang T, Shu Y, Cai YD. Genetic differences among ethnic groups. BMC Genomics. 2015 Dec 21;16:1093. doi: 10.1186/s12864-015-2328-0. PMID: 26690364; PMCID: PMC4687076.

[44] https://www.ncbi.nlm.nih.gov/variation/news/NCBI_retiring_HapMap/. On June 16, 2016, the following was posted on the HapMap site: "A recent computer security audit has revealed security flaws in the legacy HapMap site that require NCBI to take it down immediately… NCBI was planning to decommission this site in the near future anyway (although not quite so suddenly), as the 1,000 genomes (1KG) project has established itself as a research standard for population genetics and genomics…Please visit the 1000 Genomes Project resources for access to current and best data (genotypes, sequences and genome mapping) at http://www.1000genomes.org/. The archived HapMap data will continue to be available via FTP from ftp://ftp.ncbi.nlm.nih.gov/hapmap/."

[45] STRs are structural variants that have been used for individual identification such as in paternity testing or forensic analysis; by analyzing multiple STR regions in a given genetic sample, investigators can uniquely match the sample's STR "profile" (or "DNA fingerprint") to a specific individual with a high degree of confidence. In general, STRs are conserved over shorter periods of time (hundreds of years) versus SNPs, making them of limited utility for population differentiation and thus precision medicine. STRs can be alternatively referred to as "microsatellites." See, for example, Norrgard K. Forensics, DNA fingerprinting, and CODIS. Nature Education. 2008; 1(1):35.

[46] Such analysis may focus on autosomal DNA (atDNA), which provides information on both maternal and paternal ancestry; mitochondrial DNA (mtDNA), which provides information on maternal ancestry only; or Y-DNA, which provides information on paternal ancestry only, and can only be tested in males because only males possess the Y chromosome. See, for example, Song M, Wang Z, Zhang Y, et al. Forensic characteristics and phylogenetic analysis of both Y-STR and Y-SNP in the Li and Han ethnic groups from Hainan Island of China. Forensic Sci Int Genet. 2019 Mar;39:e14-e20. doi: 10.1016/j.fsigen.2018.11.016.

numerous studies have associated SNPs with skin (as well as eye and hair) pigmentation differences.[47]

Contribution of Enabling Technologies

To date, the majority of work to link genetic variants to medical outcomes, pharmacogenomic outcomes, and biogeographic ancestry has employed traditional statistical techniques such as logistical regression. Enabling technologies may be increasingly leveraged to improve and accelerate such understanding, including:

- DNA sequencing and bioinformatics to collect and analyze more robust genetic information at faster speeds and lower cost;
- AI and ML[48] to more readily identify associations between these genetic data and other massive data sets (e.g., chemical structures for prospective pharmaceuticals);[49] and

Epub 2018 Nov 29. PMID: 30522950. Zhang J, Zhang J, Tao R, et al. Mass spectrometry-based SNP genotyping as a potential tool for ancestry inference and human identification in Chinese Han and Uygur populations. Sci Justice. 2019 May;59(3):228-233. doi: 10.1016/j.scijus.2019.01.006. Epub 2019 Jan 29. PMID: 31054813. Lang M, Liu H, Song F, et al. Forensic characteristics and genetic analysis of both 27 Y-STRs and 143 Y-SNPs in Eastern Han Chinese population. Forensic Sci Int Genet. 2019 Sep;42:e13-e20. doi: 10.1016/j.fsigen.2019.07.011. Epub 2019 Jul 23. PMID: 31353318. Gao Z, Chen X, Zhao Y, et al. Forensic genetic informativeness of an SNP panel consisting of 19 multi-allelic SNPs. Forensic Sci Int Genet. 2018 May;34:49-56. doi: 10.1016/j.fsigen.2018.01.006. Epub 2018 Jan 31. PMID: 29413635. Shen CM, Hu L, Yang CH, et al. Genetic polymorphisms of 54 mitochondrial DNA SNP loci in Chinese Xibe ethnic minority group. Sci Rep. 2017 Mar 22;7:44407. doi: 10.1038/srep44407. PMID: 28327596; PMCID: PMC5361124.

[47] See, for example, Crawford NG, Kelly DE, Hansen MEB, et al.. Loci associated with skin pigmentation identified in African populations. Science. 2017 Nov 17;358(6365):eaan8433. doi: 10.1126/science.aan8433. Epub 2017 Oct 12. Erratum in: Science. 2020 Jan 17;367(6475): PMID: 29025994; PMCID: PMC5759959. Hart KL, Kimura SL, Mushailov V, et al. Improved eye- and skin-color prediction based on 8 SNPs. Croat Med J. 2013;54(3):248–56. Stokowski RP, Pant PV, Dadd T, et al. A genomewide association study of skin pigmentation in a South Asian population. Am J Hum Genet. 2007;81(6):1119–32. Valverde P, Healy E, Jackson I, Rees JL, Thody AJ.

[48] For example, Chinese researchers used Weka (https://www.cs.waikato.ac.nz/ml/weka/), an open-source ML platform, to search for SNPs that might serve as ethnic biomarkers given their unique, conserved nature across different human subpopulations. Huang T, Shu Y, Cai YD. Genetic differences among ethnic groups. BMC Genomics. 2015 Dec 21;16:1093. doi: 10.1186/s12864-015-2328-0. PMID: 26690364; PMCID: PMC4687076.

[49] See, for example, Schneider N, Lowe DM, Sayle RA, et al. Big Data from Pharmaceutical Patents: A Computational Analysis of Medicinal Chemists' Bread and Butter. *Journal of Medicinal Chemistry* 2016 59 (9), 4385-4402. DOI: 10.1021/acs.jmedchem.6b00153

- HPC[50] and cloud computing[51] to generate the necessary computational power for corresponding data analysis and storage,[52] underscoring the need for robust cybersecurity to protect personally identifiable information for reasons of both privacy and security (a challenge that may be compounded by storage in the cloud).[53]

Summary Findings – Dual-Use Aspects of Precision Medicine and Related Technologies

From the above discussion, we can distill the following key points that suggest the dual-use potential of precision medicine and related technologies to develop a genetic weapon system:

Summary Findings – Dual-Use Aspects of Precision Medicine and Related Technologies

- There are unique, conserved genetic signatures that can differentiate individuals based on their biogeographic ancestry
- These signatures are currently being investigated for precision medicine and forensic applications
- A growing body of pharmacogenomic literature describes how some such signatures can be mapped to drug pathways to establish subpopulation profiles for drug efficacy and adverse effects

[50] See, for example, https://www.hpcwire.com/2019/09/30/accelerating-high-performance-computing-hpc-for-population-level-genomics/; https://www.genengnews.com/magazine/286/supercomputing-is-the-future-of-genomics-research/

[51] See, for example, Google Genomics (https://cloud.google.com/genomics/); Microsoft Genomics (https://enterprise.microsoft.com/en-us/industries/health/genomics/); Amazon Genomics in the Cloud (https://aws.amazon.com/health/genomics/)

[52] Public repositories for corresponding genomic and phenotypic data include the Sequence Read Archive (SRA, https://www.ncbi.nlm.nih.gov/sra) and database of Genotypes and Phenotypes (dbGaP, https://www.ncbi.nlm.nih.gov/gap/) at the National Center for Biotechnology Information (NCBI); the European Genome-phenome Archive (EGA, https://www.ebi.ac.uk/ega/home) at the European Bioinformatics Institute (EBI); and the Japanese Genotype-phenotype Archive (JGA, https://www.ddbj.nig.ac.jp/jga/index-e.html) at the DNA Data Bank of Japan (DDBJ). NCBI, EBI, and DDBJ comprise the International Nucleotide Sequence Database Collaboration: http://www.insdc.org/

[53] See, for example, Tang H, Jiang X, Wang X, et al. Protecting genomic data analytics in the cloud: state of the art and opportunities. BMC Med Genomics. 2016 Oct 13;9(1):63. doi: 10.1186/s12920-016-0224-3. PMID: 27733153; PMCID: PMC5062944.

- The rate of technological advance is increasing our ability to identify and understand these signatures while reducing both technical barriers and cost

Genetic Weapons System Attributes

What might such a weapon look like? Preliminarily, we identified the following core characteristics of an effective genetic weapon system for assessment by subject matter experts:

Key Attributes of a Genetic Weapons System (Postulated)

1. Targets unique, conserved signatures in target population
2. Targeted signatures are "absent" in other populations
3. Ability to effect a desired change upon successful targeting
4. System (1-3 above) can be reliably introduced into cells
5. System (1-3 above) can be packaged for dissemination as a weapon ("weaponized")

Technical Focus Group Analysis

In February 2021, we convened a Technical Focus Group of academic and industry experts to assess the technical feasibility, advantages, and limitations of developing such a genetic weapon system.[54] The Technical Focus Group debated the system as a whole as well as each individual attribute, with results as follows.

Overarching Considerations. The Technical Focus Group identified the following foundational concepts as central to assessing technical feasibility, advantages, and limitations of genetic weapon systems.

Security of Genomic Datasets. Genomic datasets enable us to characterize vulnerable populations. The implications of collecting and sharing these datasets extend from improving human health to safeguarding the US bioeconomy. While there is tremendous value to be generated by peaceful applications of these data, allowing any organization unrestricted data access equates to sharing exploitable information, whether that information is exploited to develop tailored pharmaceuticals or for nefarious purposes such as extortion. Those with interest in either positive or negative aspects of finding functional variants are therefore incentivized to collect as much data as possible. Corresponding security risks are compounded by challenges with

[54] Technical Focus Group members and their affiliations are provided in Appendix I.

bounding and monitoring the technical space, which compared to other industries is not as geospatially contained or definable, with readily accessible information, widely available raw materials, and a range of technical, safety, and ethical standards that suggest a range of applications and potential. Security considerations are therefore integral to any discussion of genomic data-sharing whether or not a genetic weapon system is viable, i.e., regardless of the downstream applications or threat vectors, once genomic information is shared, it cannot be unshared. To date, the US has openly shared its genomic data whereas China has been more restrictive,[55] including through the introduction of new legislation in 2019 that specifically limits foreign access to Chinese genetic material and information.[56]

Differentiating between Human and Non-Human Genetic Information. Both human and non-human genetic information contribute to growing the US bioeconomy, creating jobs, and building a technological advantage. Differentiating between human and non-human data may aid the US in establishing the necessary balance between open information-sharing and security. By openly sharing non-human data, the US can retain its position of scientific transparency while protecting its populace against the range of vulnerabilities that sharing human data may present.

Differentiating between Reading and Designing/Writing Genetic Code. Bioengineering involves both reading and designing/writing genetic code. Reading human genetic code, i.e., DNA sequencing, is less technically challenging than designing and writing corresponding genetic constructs. Thus, while the comparatively widespread capability to read genetic code may provide targetable information for a genetic weapon system, designing and writing the genetic code that enables such targeting presents a technical challenge that may limit the pool of potential perpetrators.

Differentiating between Writing and Delivering Genetic Constructs. Once code is written, it must be successfully delivered to desired target cells in order to exert an effect. Introducing a genetic editing construct currently requires physical contact with a patient or his/her tissues and can be nota bly inefficient.[57] Corresponding advancements

[55] Chen Y, Song L. China: concurring regulation of cross-border genomic data sharing for statist control and individual protection. Hum Genet. 2018 Aug;137(8):605-615. doi: 10.1007/s00439-018-1903-2. Epub 2018 Jul 16.

[56] http://www.gov.cn/zhengce/content/2019-06/10/content_5398829.htm

[57] To demonstrate the complexity of this delivery challenge, the expert panel discussed the example of CRISPR therapeutics for sickle cell anemia. These therapeutics require that affected blood cells be removed from the body; ablative chemotherapy be administered to diminish the current population of cells to be replaced; ex vivo editing be conducted,

in efficient gene delivery hold the potential for considerable human health gains and thus receive significant investment.

Differentiating between Delivering DNA Individually versus at Scale. While advancements in efficient gene delivery align with highly positive advancements in medicine and synthetic biology and thus receive significant investment, there is limited benefit to delivery at scale, at a distance, or in an otherwise undirected way, such that investment in the development of any broad dissemination capability is not warranted.[58] From a threat characterization perspective, this considerably diminishes the current threat potential of a genetic weapon system, and provides an important target for security monitoring activities.[59]

Predictability of Effect upon Delivery. Even if successfully written and delivered, predicting a DNA construct's effect is challenging without dedicated testing and evaluation (T&E) against representative target populations, i.e., a construct that is effective in a laboratory setting may not be effective in vivo against a given target population. This makes such investment high risk in the face of alternative kinetic and non-kinetic options that could target geolocated or otherwise well-defined populations. Precision medicine continues to demonstrate the complexity of going from a genomic sequence to a living organism with layers of regulatory networks, where the predictive power is low even in large subject populations. From a threat characterization perspective, this further diminishes the current threat potential of a genetic weapons system. T&E activities therefore provide another important target for security monitoring activities.

Use Cases. Conceptually, identifying a target population, computationally deriving a weapon based on a genetic signature,

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which carries an observed efficiency of 20-30%; and successfully edited cells be grown and reinserted into the body. This is the process for a single gene modification in a sickle cell patient. Compared to blood cells, other tissues such as solid tissues are increasingly complex due to the presence of barrier tissues, mucous layers, and other factors that further diminish editing efficiency.

[58] It should be noted that some members of the panel had differing opinions regarding the potential utility versus social viability of mass vaccination by aerosol, and how the COVID-19 pandemic might positively or negatively alter perceptions and investments to this end.

[59] Consider, for example, potential dual-use applications of transmissible vaccines as described in: Nuismer SL, Bull JJ. Self-disseminating vaccines to suppress zoonoses. Nat Ecol Evol. 2020 Sep;4(9):1168-1173. doi: 10.1038/s41559-020-1254-y. Epub 2020 Jul 27. PMID: 32719452. Bull JJ, Smithson MW, Nuismer SL. Transmissible Viral Vaccines. Trends Microbiol. 2018 Jan;26(1):6-15. doi: 10.1016/j.tim.2017.09.007. Epub 2017 Oct 13. PMID: 29033339; PMCID: PMC5777272. Murphy AA, Redwood AJ, Jarvis MA. Self-disseminating vaccines for emerging infectious diseases. Expert Rev Vaccines. 2016;15(1):31-9. doi: 10.1586/14760584.2016.1106942. Epub 2015 Nov 2. PMID: 26524478; PMCID: PMC4732410.

accessing the target population, and delivering the weapon with confidence that it will have the intended effect pose multiple challenges for a perpetrator. The corresponding technical hurdles and uncertainty of outcomes versus simpler methods of attack that could have the same discriminatory effect suggest that genetic weapon systems may be poor choices in the majority of Use Cases. However, "mirror imaging" was acknowledged as a potential pitfall to such assessment;[60] i.e., perpetrators may not be restricted to the same set of technical, safety, and/or ethical standards as the panel members, or the US more broadly.[61]

If predictability limitations can be overcome, a specific Use Case that may be uniquely suited for a genetic weapon system is covert assassination where lack of attribution is a key consideration, for example assassination of a leadership or opposition target. Alternatively, a perpetrator might select a genetic weapon system for assassination purposes as a "calling card" that has some level of plausible deniability while demonstrating an intimidating capability once characterized. The sharing of DNA ancestry information by family members may increase an individual's vulnerability in these Use Cases, and such an attack need not have immediate effect to be successful; causing physical or mental deterioration over time for example due to cancer may in fact be a perpetrator's preferred scenario, in particular if deniability is paramount.

Additional potential Use Cases of a genetic weapon system include to generate disproportionate economic or social disruption, whether covertly in a way that is not attributable or overtly as an act of terrorism such that specificity becomes less critical. A perpetrator may also seek to simply possess such a weapon in order to achieve deterrence without any specific plan for use.

Alternative Approaches to Discriminately Target Populations. The security implications of any emerging technology depend in large part on comparative value versus alternative approaches to achieve the same effect. A genetic weapon system's desired effect is the discriminate targeting of a specific population or individual. Alternative approaches to achieve this same effect include a range of kinetic and non-kinetic options that are less costly and technically

[60] See, for example, Witlin L. Of Note: Mirror-Imaging and Its Dangers. SAIS Review of International Affairs, vol. 28 no. 1, 2008, p. 89-90. Project MUSE; https://muse.jhu.edu/article/233105

[61] In the context of "mirror imaging," the expert panel debated but did not come to agreement on whether a rational actor must be assumed, given limitations on analysis of irrational actors (i.e., systematic thinking cannot be expected to apply) and the complexity of a genetic weapon system.

complex and may have a more assured effect, calling into question of why a country might invest in developing a genetic weapon system in contravention to international law when better alternatives are available. For example, distinct foodways may segregate populations based on culture or ethnicity (e.g., a certain type of American beer that is generally not consumed by non-American populations such as adherent Muslims), such that introduction of a contaminant might reach a target population with greater predictability, frequency, and specificity, all at lower cost and with less research and development required. In addition, alternative approaches exist to biologically target a specific population, including the following:

Epigenetic Markers. Epigenetics governs gene activation and deactivation without altering the underlying sequence[62] and is an active area of study for defensive purposes.[63] Epigenetic markers change over time to reflect different environmental exposures and corresponding locations, and may therefore be inducible in an individual or population to provide a temporary target for exploitation. Inducing a targetable epigenetic change may be more achievable than identifying a traditional nucleotide or set of nucleotide markers.

Microbiomes. Like epigenetic markers, human gut and skin microorganisms (i.e., "microbiomes") may reflect different environmental exposures and corresponding locations,[64] and may therefore be inducible in an individual or population to provide a temporary target for peaceful[65] or illicit exploitation.

Alternative Misapplications of Genomic Data and Technologies. An alternative misapplication of genomic data is to gain leverage over specific individuals. For example, a perpetrator might target individuals for extortion based on predilections for chronic disease, mental health issues, addictions, etc., aided by the increasingly widespread sharing of attributable genomic data via direct-to-consumer genetic testing and other avenues.[66]

[62] https://www.genome.gov/genetics-glossary/Epigenetics
[63] See, for example, https://www.darpa.mil/program/epigenetic-characterization-and-observation; https://www.darpa.mil/program/preemptive-expression-of-protective-alleles-and-response-elements
[64] Tu P, Chi L, Bodnar W, et al. Gut Microbiome Toxicity: Connecting the Environment and Gut Microbiome-Associated Diseases. Toxics. 2020 Mar 12;8(1):19. doi: 10.3390/toxics8010019. PMID: 32178396; PMCID: PMC7151736
[65] See, for example, https://www.darpa.mil/program/revector
[66] See, for example, Gryphon Scientific. China's Biotechnology Development: The Role of US and Other Foreign Engagement. US-China Economic and Security Review Commission, 2019.

An alternative misapplication of genomic technologies is as an anti-plant agent. In the field of plant genomics, scientists routinely collect and apply genetic information to modify plants and develop new plants, sometimes with unintentional, adverse outcomes. A genetic weapon designed to target monoculture plots of staple cultivars could cause considerable economic and social disruption, potentially destabilizing a selected region.

Eroding Technical Barriers. While the targeting approaches described in this report are technically challenging and data hungry, the pace of ongoing research suggests that these limitations are likely to erode over time. The global movement toward pan-genomics[67] and describing genetic diversity is accelerating data generation and discovery potential considerably,[68] a trend that is likely to continue as genome sequencing becomes ubiquitous: where even a routine visit to a doctor's office will involve genetic sequencing and analysis. Leveraging Enabling Technologies. To date, the majority of work to link genetic variants to medical outcomes, pharmacogenomic outcomes, and biogeographic ancestry has employed traditional statistical techniques such as logistical regression. However, enabling technologies are being increasingly applied to improve and accelerate such understanding.

DNA Sequencing and Bioinformatics. DNA sequencing and bioinformatics advances may be leveraged to collect and analyze more robust genetic information at faster speeds and lower cost. Sequencing costs are diminishing faster than Moore's law (the principle that the speed and capability of computers can be expected to double every two years, as a result of increases in the number of transistors a microchip can contain), while sequencing technology is being developed that can plug into a laptop to enable rapid sequencing of virtually anything, anywhere.

Artificial Intelligence. Machine Learning, and Deep Learning. Artificial Intelligence (AI), machine learning (ML), and deep learning advances may be leveraged to more readily identify associations between these genetic data and other massive data sets, for example chemical structures for prospective pharmaceuticals. Such deep learning models require many millions of training sequences, incentivizing collection of as much genomic data as possible. Those groups that have a critical mass of datasets and are best able to aggregate those

[67] See, for example, Sherman RM, Salzberg SL. Pan-genomics in the human genome era. Nat Rev Genet. 2020 Apr;21(4):243-254. doi: 10.1038/s41576-020-0210-7. Epub 2020 Feb 7. PMID: 32034321; PMCID: PMC7752153.
[68] See, for example, https://humanpangenome.org/year-1-sequencing-data-release/

data will have the best training sets and thus the highest likelihood of success in identifying meaningful sequences, whether for precision medicine or other ends.[69]

Other Enabling Technologies. Other enabling technologies include high performance computing (HPC) and cloud computing, the advances of which may be leveraged to generate the necessary computational power for corresponding data analysis and storage.

Attribute 1. Targets unique, conserved signatures in target population. Human population genetics involves identifying DNA-based polymorphisms in populations. There are some 7,000 distinct populations based on language, which is a good surrogate for defining a population that is reasonably endogamous, i.e., that marries within the population. Only a fraction of these have been studied (e.g., 144 populations by one leading researcher), meaning that existing data represent only a fraction of human diversity. Our current understanding is therefore based on limited available data, though extrapolation suggests that additional population datasets are likely to be consistent.

Identifying ancestry-informative markers across defined populations requires good variation in gene frequency. In general terms, there is an inverse relationship between frequency and specificity: the more frequent a marker is in a given population, the less likely it is to be specific to that population (conversely, the more specific a marker, the less likely that it will be of desirable frequency to characterize a population). Currently available data, while incomplete, indicate that markers of high frequency in one population will also be present in nearby populations due to human migration and interbreeding.[70] For example, a set of markers might collectively distinguish Uyghurs from Han Chinese but not uniquely so, and those markers would be less likely to distinguish Uyghurs from neighboring Mongolian populations. The ability to infer ancestral origin is therefore probabilistic, i.e., it is not a matter of kind but degree.

The implication for a genetic weapon system is that while targeting the majority of a certain population with such a weapon may be possible,

[69] In the case of long read sequences, datasets would include epigenetic data that might be leveraged as well.

[70] The expert panel discussed two notable outliers: (1) CCR5 delta 32 (https://pubmed.ncbi.nlm.nih.gov/16216086/), which prohibits HIV virus entry into cell and is found in up to 15% of Northern Europeans but is less common in southern Europe and virtually absent in other parts of the world, and (2) the Duffy blood group system (https://www.ncbi.nlm.nih.gov/books/NBK2271/), which lacks the receptor malaria-causing Plasmodium vivax and is present nearly at fixation (i.e., Duffy null) in Central Africa but virtually absent outside of Africa.

doing so to the exclusion of other populations presents a considerable challenge. The use of multiple markers increases specificity but would be expected to reduce the proportion of the target population that is affected given the relative frequencies of different markers in different subsets of the population. Ultimately, the ethnic diversity of the US population provides a protective effect that largely undermines the potential strategic payoff of a genetic weapon system.

It is important to note that perpetrators may not define populations by genetic markers but by self-identification into a group. Targeting based on self-identification compounds precision challenges related to both frequency and specificity of genetic markers, making it increasingly difficult to identify a set of markers of desirable frequency in the target population that would not have some off-target effects. Limiting such off-target effects may in fact pose the greater technical challenge to a potential perpetrator, such that the perpetrator's tolerance of collateral damage might ultimately determine the perceived utility of a genetic weapon system.

Attribute 2. Targeted signatures are "absent" in other populations. There is a large gap in our knowledge of global genetic variation, but what we do know argues that targeting population-specific variants to the exclusion of others (i.e., something that is high frequency in only one population and very low frequency/absent elsewhere) poses a significant challenge unless the perpetrator is willing to accept that only a portion of the target population is affected. Genetic markers are probabilistic. According to the product rule of probabilities, targeting multiple markers in combination ("multiplexing") boosts specificity. The more markers used, the more specific the weapon, but with a tradeoff: the more markers that are used, the less inclusive the weapon would be on the target population given various marker frequencies.

The use of multiple markers to increase specificity would require enough data to define their relative frequencies in the target population and reference populations. The use of multiple markers to increase specificity also increases the technical complexity of the targeting approach. Because such multiplexing is a heavily invested area due to its potential therapeutic and diagnostic benefits, however, technical barriers and corresponding costs are likely to ease over time.

Rather than targeting DNA sequences, a perpetrator may achieve greater specificity by targeting epigenetic markers or the microbiome. Both epigenetic markers and the microbiome change over time to reflect different environmental exposures, and may therefore be

inducible in an individual or population to provide a temporary, highly specific target for exploitation.

Attribute 3. Ability to effect a desired change upon successful targeting. Translating a sequence difference into a differential biological effect carries all of the above-described challenges related to frequency in the target population, specificity to the target population, access to the target population, and predictability of effect.

The most straightforward approach to effect change is to leverage a genetic editing system such as CRISPR to target a desired sequence and exert an effect. CRISPR systems enable scientists to alter a specific site in a given genome – human or otherwise – by (1) targeting the site using a complementary strand of nucleic acid called guide RNA; (2) making a precise cut at the site using an enzyme such as the Cas9 protein; and (3) either rendering the cut gene nonfunctional ("knockout") or replacing it with a different gene ("knock-in"). An undergraduate education can provide the necessary knowledge to apply CRISPR in its most basic form, for example by writing out a nucleotide sequence on a computer, ordering a custom-made DNA fragment for that sequence, and using the fragment to target a CRISPR system to that sequence with high specificity.[71]

A rudimentary weapon system might simply seek to use CRISPR to disrupt DNA containing the target sequence, i.e., targets the sequence via complementary guide RNA and makes a cut via Cas, which – because of the imperfection of the body's DNA repair system – may knock out the gene possessing the sequence, with functional impact based on the impaired gene (up to a targeted shutdown of critical molecular pathways that might prove fatal). Corresponding impact may be increased by multiplex targeting for multiple SNPs, causing an increased number of double-stranded DNA breaks and thus reducing the likelihood of complete repair.

Because genetic editing systems such as CRISPR enable not only the introduction of dsDNA breaks but also alternation or insertion of genetic material at defined loci, targeted genetic changes might be attempted to insert harmful sequences or trigger diseases with identified genetic links based on data gleaned from an increasing number of genome-wide association studies (GWAS). Other functionally exploitable sequences might include SNPs that affect drug ADME pathways and could be leveraged in a weapons context.

[71] See, for example, https://research.cornell.edu/news-features/crispr-creating-genetic-circuits-cells

Databases like the Encyclopedia of DNA Elements (ENCODE)[72] and University of California Santa Cruz (UCSC) Genome Browser[73] map SNP locations to regulatory regions or coding sequences where they may or may not be exploitable, for example to alter an amino acid; while there are hundreds of thousands of SNPs that are identified as *possibly* altering function, to date such functional analysis is largely lacking.

Targeted sequences need not be functional, however. Virtually any sequence could conceivably be targeted, for example by the guide RNA of a CRISPR system, to deliver a payload. For example, CRISPR-Cas13 systems have been developed that allow detection and targeting of specific sequences that can differ by just a single nucleic acid; these systems use a guide RNA to target a sequence and release a payload, in this case a reporter, via collateral RNA cleavage by a Cas13 enzyme.[74] Alternative payloads might include cytotoxic molecules that kill cells containing the target sequence. The implication for genetic weapon system development is a far wider range of potential targets.

Molecular computing could similarly enable the targeting of specific sequences to deliver a range of payloads.[75] Molecular computing uses DNA, biochemistry, and molecular biology hardware to perform computation using a series of logic gates.[76] Such logic gates are programmable; for example, a molecular machine might be programmed to release a therapeutic – or weapon payload – if and only if certain markers are present and others are absent. As complexity of the molecular compute increases, however, the test and evaluation burden to assure predictability rises. This is currently an

[72] https://www.encodeproject.org/. The ENCODE project is funded by the National Human Genome Research Institute (NHGRI) to "build a comprehensive parts list of functional elements in the human genome, including elements that act at the protein and RNA levels, and regulatory elements that control cells and circumstances in which a gene is active."
[73] https://genome.ucsc.edu/.
[74] Gootenberg JS, Abudayyeh OO, Kellner MJ, et al. Multiplexed and portable nucleic acid detection platform with Cas13, Cas12a, and Csm6. Science. 2018 Apr 27;360(6387):439-444. doi: 10.1126/science.aaq0179. Epub 2018 Feb 15. PMID: 29449508; PMCID: PMC5961727.
[75] While terminology differs in the literature, we utilize the term molecular computing to represent a range of biologically-based computing systems, perhaps the most widely referenced of which are "genetic circuits." See, for example: Grozinger L, Amos M, Gorochowski TE et al. Pathways to cellular supremacy in biocomputing. Nat Commun. 2019 Nov 20;10(1):5250. doi: 10.1038/s41467-019-13232-z. PMID: 31748511; PMCID: PMC6868219. Xiang Y, Dalchau N, Wang B. Scaling up genetic circuit design for cellular computing: advances and prospects. Nat Comput. 2018;17(4):833-853. doi: 10.1007/s11047-018-9715-9. Epub 2018 Oct 5. PMID: 30524216; PMCID: PMC6244767.
[76] Liang X, Zhu W, Lv Z, Zou Q. Molecular Computing and Bioinformatics. Molecules. 2019 Jun 26;24(13):2358. doi: 10.3390/molecules24132358. PMID: 31247973; PMCID: PMC6651761

area of considerable investment and dual-use technological advance, for example to develop cancer therapies where dose administration is dependent upon the presence of certain makers.

Attribute 4. System (1-3 above) can be reliably introduced into cells.
A range of cellular delivery techniques are used for gene therapy, other nucleic acid-based therapeutics, and CRISPR delivery. These include physical methods such as microinjection, electroporation, and hydrodynamic delivery; viral vectors such as adeno-associated virus (AAV), adenovirus, and lentivirus; and non-viral vectors such as liposomes and nanoparticles.

Current CRISPR delivery techniques generally require physical access to the patient or removal and return of cells. When physical access is achieved – for example via intramuscular injection – the delivered item may not reach desired cell types to achieve the intended result. Improving delivery and in vivo editing is considered central to lowering current costs of gene editing therapies, which extend to costly hospital stays, parallel treatments, and so on. The trend in precision medicine thus favors development of in vivo genetic editing tools with more predictable access to target DNA, such that current limitations are expected to improve over time.

In vivo delivery of AAV-vectored CRISPR therapies are an area of rapid advance to this end, despite persisting hurdles related to efficiency, unintended effects, and preexisting immunity.[77] Despite similar hurdles, non-viral delivery vectors such as virus-like particles (VLPs) and ribonucleoproteins (RNPs) hold the potential to overcome size and corresponding tissue penetration limitations of nanoparticle delivery.[78] Also important are new Cas developments such as CasX[79] and Cas(phi)[80] that are dramatically smaller and thus offer advantages for cellular delivery. Finally, different chemistries can be used to

[77] See, for example, He X, Urip BA, Zhang Z, Ngan CC, Feng B. Evolving AAV-delivered therapeutics towards ultimate cures. J Mol Med (Berl). 2021 May;99(5):593-617. doi: 10.1007/s00109-020-02034-2. Epub 2021 Feb 16. PMID: 33594520; PMCID: PMC7885987. Wang D, Zhang F, Gao G. CRISPR-Based Therapeutic Genome Editing: Strategies and In Vivo Delivery by AAV Vectors. Cell. 2020 Apr 2;181(1):136-150. doi: 10.1016/j.cell.2020.03.023. PMID: 32243786; PMCID: PMC7236621.
[78] See, for example, Rui Y, Wilson DR, Green JJ. Non-Viral Delivery To Enable Genome Editing. Trends Biotechnol. 2019 Mar;37(3):281-293. doi: 10.1016/j.tibtech.2018.08.010. Epub 2018 Sep 29. PMID: 30278987; PMCID: PMC6378131.
[79] Liu JJ, Orlova N, Oakes BL, Ma E,et al. CasX enzymes comprise a distinct family of RNA-guided genome editors. Nature. 2019 Feb;566(7743):218-223. doi: 10.1038/s41586-019-0908-x. Epub 2019 Feb 4. Erratum in: Nature. 2019 Apr;568(7752):E8-E10. PMID: 30718774; PMCID: PMC6662743.
[80] Pausch P, Al-Shayeb B, Bisom-Rapp E, Tsuchida CA, Li Z, Cress BF, Knott GJ, Jacobsen SE, Banfield JF, Doudna JA. CRISPR-CasΦ from huge phages is a hypercompact genome editor. Science. 2020 Jul 17;369(6501):333-337. doi: 10.1126/science.abb1400. PMID: 32675376.

increase efficiency by targeting specific delivery challenges or barriers of interest.[81]

The skill level required to apply such advances generally exceeds that of a "do-it-yourself" (DIY) genetic editing enthusiast, though bacterial targets may be more achievable than human targets. A State-level program, on the other end, could conceivably coordinate multidisciplinary efforts of molecular biologists, cell biologists, chemists, and nanoscientists to this end. Corresponding technical barriers are likely to erode as delivery efficiency and other limitations improve over time.

Attribute 5. System (1-3 above) can be packaged for dissemination as a weapon ("weaponized"). While improving genetic editing tools to predictably target DNA *in vivo* is a heavily invested area of research and development, there is little incentive to improve delivery at scale, at a distance, or in an otherwise undirected way. Because such delivery at scale is a key limiting factor to weapon system applications, a key counterstrategy involves security monitoring for technology that enables such delivery at scale, for example employing the framework outlined in the NAS report Biodefense in the Age of Synthetic Biology.[82] Testing to validate predictability of effect is another key limiting factor and potential target for security monitoring.

In general terms, a genetic weapon system could be delivered by adapting traditional approaches to drug administration, in particular injection or inhalation. Intramuscular or intravenous injection is more likely to enable targeting of individuals versus specific populations, though the latter might be attempted for example via mosquito vector. Inhalation as a liquid or dry powder might enable more widespread dissemination, though at present even local administration of CRISPR-based therapeutics remains limited.[83]

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[81] See, for example, Da Silva Sanchez A, Paunovska K, Cristian A, Dahlman JE. Treating Cystic Fibrosis with mRNA and CRISPR. Hum Gene Ther. 2020 Sep;31(17-18):940-955. doi: 10.1089/hum.2020.137. Epub 2020 Sep 8. PMID: 32799680; PMCID: PMC7495921.

[82] National Academies of Sciences, Engineering, and Medicine. 2018. Biodefense in the Age of Synthetic Biology. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/24890. Figure 3-1, pg. 24. https://www.nap.edu/catalog/24890/biodefense-in-the-age-of-synthetic-biology

[83] See, for example, Chow MYT, Chang RYK, Chan HK. Inhalation delivery technology for genome-editing of respiratory diseases. Adv Drug Deliv Rev. 2021 Jan;168:217-228. doi: 10.1016/j.addr.2020.06.001. Epub 2020 Jun 5. PMID: 32512029; PMCID: PMC7274121. Zhang H, Bahamondez-Canas TF, Zhang Y, et al. PEGylated Chitosan for Nonviral Aerosol and Mucosal Delivery of the CRISPR/Cas9 System in Vitro. Mol Pharm. 2018 Nov 5;15(11):4814-4826. doi: 10.1021/acs.molpharmaceut.8b00434. Epub 2018 Oct 1. PMID: 30222933; PMCID: PMC6453125.

Part II. State Actor Technical Capabilities and Motivations

State and sub-state threat assessment methodologies typically assess threats as a function of technical capabilities (i.e., whether a potential actor has the technical ability to pursue or enact the threat) and motivations (i.e., whether a potential actor has the motivation to pursue or enact the threat). Adopting this approach to genetic weapon systems, we have mined the open source domain in both English and native languages to compile relevant information on each component of the threat, including:

Technical Capabilities. Operationally, precision medicine initiatives comprise two key elements: (1) collection of large amounts of genomic data, and (2) robust analysis of the collected data. As noted above, corresponding dual-use technical capabilities are advancing at the intersection of three foundational technical areas:

- Genomic sequencing and bioinformatics capabilities that enable a deep understanding of the genetics and biological make-up of people
- AI, ML, and related cutting-edge data mining and analysis tools that enable ingest and analysis of massive data sets
- HPC and cloud computing capabilities that provide the necessary computational power to conduct such analysis as well as store data, etc.

Genomic sequencing provides massive amounts of data that must be mined to identify and exploit specific genetic identifiers. Bioinformatics extracts useful information from such data. AI and ML render computationally-intensive data mining – for example genomic comparisons down to the SNP level and correlation with patient longitudinal data – achievable at a fraction of the time and cost of prior approaches. HPC and cloud computing platforms further enable such computationally-intensive data mining. As with any emerging technology, common constraints include lack of tacit knowledge and the potential for funding/resource limitations.

Motivations. While motivations are challenging to discern in the context of dual-use capabilities in general and dual-use biotechnology capabilities in particular, indicators of a State actor's interest in or pursuit of genetic weapons may be found in official statements, State and independent media sources, state websites, social media, and scientific publications. These indicators are factored

against the strategic intent of genetic weapon systems to assess adversary investment strategies and corresponding deterrence measures.

In the following subsections, we describe corresponding technical capabilities and motivations of China and Russia, respectively, to this end, with the goal of determining each country's near- (<5 years) and long-term (5-15 years) outlook.[84] We conclude Part II of this report with an assessment of implications for strategic stability.

Capabilities and Motivations of the People's Republic of China (PRC)

PRC Technical Capabilities

China's precision medicine-related activities, investments, and governance span the following categories, each of which is described in turn:

- General Overview
- Government Policy Directives
- CAS Capabilities and Assets
- Commercial Sector
- Relevant Conferences and Trade Shows
- Academic Institutes and Universities
- Military-Civil Fusion

General Overview. In 2016, China launched a $9.2B Precision Medicine Initiative under the Chinese Academy of Sciences (CAS),[85,86] the nation's

[84] While this project is specifically focused on State actors China and Russia, we are documenting any incidental findings related to other States or sub-state actors such as terrorist organizations. In general, while considerable capability barriers would have to be overcome, such potential interest on the part of other States, terrorist and extremist organizations, or even individuals should not be discounted. See, for example, https://www.foreignaffairs.com/articles/world/2017-06-01/cyberterrorism-and-biotechnology

[85] It is important to note that while $9.2B is the widely cited value of the Chinese Precision Medicine Initiative, calculating the exact value of the initiative is more complex. The Chinese Ministry of Finance is to provide 20B Yuan (roughly $3B), while local governments are expected to provide an addition 40B Yuan (roughly $6B). The widely cited $9.2B budget has thus been described as "unestablished fact" by a prominent government official. See: https://cn.weforum.org/agenda/2018/07/3e03d63e-a9da-4f26-928f-cfadfafa3a2b/; https://zhuanlan.zhihu.com/p/33322529; https://pdf.hanspub.org//QR20151000000_91989559.pdf; http://www.jjckb.cn/2018-03/13/c_137034828.htm; https://m.askci.com/news/chanye/20180119/152007116397.shtml; http://www.yutainews.com/jjfy/2020/0617/12222.html

[86] China's $9.2B Precision Medicine Initiative is buttressed by larger government investments in supporting big data and cloud computing infrastructure. See, for example, https://www.reuters.com/article/us-china-economy-technology/china-to-invest-15-billion-in-big-data-cloud-computing-over-next-five-years-idUSKCN1LZ17S.

leading academic research and development institution.[87,88] CAS is directly subordinate to the central government ("State Council"[89]), but receives funding from a range of sources including the Ministry of Science and Technology (MOST)[90] and National Natural Science Foundation (NNSF)[91] under the coordination of the State Council Steering Group for Science, Technology, and Education.[92] The CAS's medical research and development component operates similarly to the US National Institutes of Health (NIH), comprising both intramural and extramural research programs that extend government funding to a broad base of internal and external researchers. For the sake of comparison, in 2016 – the same year that China launched its $9.2B Precision Medicine Initiative – the US launched its own Precision Medicine Initiative under the NIH, with an initial investment of $215M.[93]

The Chinese Precision Medicine Initiative is set to span 15 years (2016-2030), with stated aims as follows:[94]

- Research on precision prevention techniques and models, with a focus on cohorts of healthy populations, cohorts of particular disease sufferers, and cohorts of high-risk populations
- Identify and utilize molecular markers, with a focus on early diagnosis and treatment, as well as their application in the treatment and prognosis of diseases
- Develop diagnostic tools such as molecular imaging and new methods of molecular pathology
- Facilitate the clinical application of precision medicine

[87] http://www.cas.cn/; http://english.cas.cn/

[88] In conjunction with the 2016 launch of the Chinese Precision Medicine Initiative, Science – widely recognized as one of two leading technical journals (the other being Nature) – released a sponsored supplement entitled Precision medicine in China. The supplement was sponsored by Bioyong Technology Company (http://www.bioyong.com/), a for-profit precision medicine platform development company based in Beijing that is otherwise largely absent from our data mining results. The Science supplement is accessible at: https://www.sciencemag.org/sites/default/files/custom-publishing/documents/Bioyong-Precision-Medicine-supplement_Final.pdf

[89] For more information on the State Council organizational structure, see: https://npcobserver.com/bilingual-state-council-organizational-chart/

[90] http://www.most.gov.cn/

[91] http://www.nsfc.gov.cn/

[92] For a brief overview of the Chinese science and technology complex, see: https://www.swissnexchina.org/wp-content/uploads/sites/4/2014/08/A-quick-overview-of-Chinese-S-T-system_2011.pdf

[93] See, for example, https://obamawhitehouse.archives.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative; https://medlineplus.gov/genetics/understanding/precisionmedicine/initiative/

[94] Unofficial translation of primary source documentation: http://www.sps.tsinghua.edu.cn/uploadfile/2018/1211/PrecisionMedicinePolicySummitReport.PDF

The central government has identified corresponding policy priorities for the initiative that effectively seek to bridge government, academia, and industry stakeholders, including "a cross-functional coordination mechanism…to facilitate cooperation between different government agencies" and "innovation…combined with industry."[95] The initiative was launched with over 60 subprograms,[96] including a core program to conduct whole genome sequencing and develop sequence-specific health profiles for an initial cohort of Chinese citizens.[97] This core program is being led by the CAS's Beijing Institute of Genomics,[98] involves multiple academic laboratories, and is supported by cloud infrastructure developed by industry partners Wuxi NextCODE and Huawei Technologies.[99]

The above-described program highlights the two foundational elements of China's Precision Medicine Initiative as well as those of the US and other nations around the world: (1) collection of genomic data; and (2) technology development to enable robust analysis of collected data.

Genomic Data Collection. China has invested heavily in the collection of genomic data both from select Chinese subpopulations and international populations, including the US.

In addition to Chinese DNA data collection and analysis conducted under the Precision Medicine Initiative, the Chinese government has collected genomic data under its "Physicals for All" program in the northwest province of Xinjiang (formally, the Xinjiang Uyghur Autonomous Region), home to multiple ethnic groups including the native Uyghur (alternatively spelled Uigher) population.[100] The Uyghurs are a Muslim minority that has come under increasing scrutiny by the Chinese government, which cites concerns of separatist violence based on sporadic attacks including a 2013 incident in Beijing's Tiananmen Square when a car was driven into a crowd, and a 2017 incident in Xinjiang when eight people were killed in a knife attack.[101] China has reportedly established hundreds of "re-education," detention, and prison facilities largely targeting the Uyghur population in the region.[102] According to the Physicals for All program guidelines, collected DNA is to be "sent to the county police bureaus for profiling" (unofficial Human Rights Watch translation).[103] Reportedly, the

[95] Ibid.
[96] Ibid.
[97] Genetic information is being collected from 4,000 volunteers, with 2,000 receiving whole genome sequencing and profiling. See, for example, http://www.china.org.cn/china/Off_the_Wire/2016-01/09/content_37537726.htm
[98] http://english.big.cas.cn/
[99] https://www.bio-itworld.com/news/2016/05/24/wuxi-nextcode-huawei-launch-precision-medicine-cloud-for-china
[100] https://www.nytimes.com/2019/02/21/business/china-xinjiang-uighur-dna-thermo-fisher.html#:~:text=In%20Xinjiang%2C%20in%20northwestern%20China,Uighurs%20and%20human%20rights%20groups.
[101] See, for example, https://www.bbc.com/news/world-asia-china-22278037.
[102] https://xjdp.aspi.org.au/explainers/exploring-xinjiangs-detention-facilities/
[103] https://www.hrw.org/news/2017/12/13/china-minority-region-collects-dna-millions

resulting sequences are retained in a national DNA database called the "Forensic Science DNA Database System," also known as the "National Public Security Agencies DNA Database Application System."[104] The sequencing equipment used to conduct this profiling was originally supplied at least in part by US company Thermo Fischer Scientific, which discontinued such sales in 2019.[105] In addition, Thermo Fischer Scientific has provided DNA test kits for the purpose of establishing a "male ancestry inspection system,"[106] including a DNA test that can differentiate Chinese ethnic groups including Uyghurs.[107] China has since expanded its DNA collection activities to Tibet and, more recently, the rest of the country, with a focus on males of all ages.[108] China's reported goal for its forensic DNA database was 100 million records by the end of 2020,[109] a target analysts believe the country may have exceeded by as many as 40 million.[110]

Internationally,[111] China has taken a multi-pronged approach to DNA data collection, including direct-to-consumer (DTC) genetic testing;[112] research relationships;[113] low-cost outsourcing of genetic testing to Chinese firms; and acquisition by China of foreign genetic testing companies. The latter two efforts have borne particular fruit in the US, where China has gained steady access to large amounts of American DNA via both low-cost outsourcing of US genetic testing to China and Chinese acquisition of US-based genetic testing companies (Table 1). [114,115]

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[104] https://www.hrw.org/news/2017/05/15/china-police-dna-database-threatens-privacy
[105] https://www.wsj.com/articles/thermo-fisher-to-stop-sales-of-genetic-sequencers-to-chinas-xinjiang-region-11550694620
[106] https://www.nytimes.com/2020/06/17/world/asia/China-DNA-surveillance.html
[107] https://www.thermofisher.com/order/catalog/product/4472117#/4472117. "Offers high discrimination for Chinese populations."
[108] https://www.aspi.org.au/report/genomic-surveillance
[109] https://www.wsj.com/articles/china-snares-innocent-and-guilty-alike-to-build-worlds-biggest-dna-database-1514310353
[110] https://www.aspi.org.au/report/genomic-surveillance
[111] It should be noted that the World Economic Forum's (WEF) new Centre for the Fourth Industrial Revolution in China will focus on advancing precision medicine in addition to other initiatives. Representative efforts described in WEF's 2018-2019 Annual Report (pg. 36) include the Leapfrogging with Precision Medicine project and the Breaking Barriers to Health Data project, the latter of which is focused on enabling cross-border access to genomic data. The WEF has maintained a Beijing Representative Office since 2006. See: https://www.weforum.org/agenda/archive/fourth-industrial-revolution; https://www.weforum.org/search?query=china; http://www3.weforum.org/docs/WEF_Annual_Report_18-19.pdf
[112] Du L, Wang M. Genetic Privacy and Data Protection: A Review of Chinese Direct-to-Consumer Genetic Test Services. Front Genet. 2020 Apr 28;11:416. doi: 10.3389/fgene.2020.00416. PMID: 32425986; PMCID: PMC7205185.
[113] See, for example, https://www.reuters.com/article/us-health-coronavirus-bgi-specialreport-idUSKCN2511CE
[114] Gryphon Scientific. China's Biotechnology Development: The Role of US and Other Foreign Engagement. US-China Economic and Security Review Commission, 2019. Recommendations include: "[I]t is important for the US to analyze the potential long-term risks from…nonmarket interventions and formulate appropriate policies to respond."
[115] Safeguarding the Bioeconomy: Applications and Implications of Emerging Science (NAS Workshop Report, 2019). Key findings include: "With the growth of the US bioeconomy comes increasing security risks and threats to physical proprietary materials and informatics. The consequences and ramifications of these threats are currently not well understood, nor have

Table 1. China's Exposure to the US Genetic Testing Market

Company	Client/Hospital/ Institution	Contracts to Receive US Genetic Data	Landed US Holdings to Process Data
Novogene	Multiple/Open	X[116]	X[117]
BGI	Johns Hopkins University[118]	X	X
	Mount Sinai Hospital[119]	X	
	Children's Hospital of Philadelphia[120]	X[121]	
	Fred Hutchinson Cancer Research Center[122]	X[123]	
	Complete Genomics[124]		X
GENEWIZ	Multiple/Open	X[125]	X[126]
WuXi NextCODE[127]	Multiple/Open	X[128]	X[129]
WuXi Healthcare	23andMe[130]		X
Tencent	GRAIL[131]		X[132]
iCarbonX	SomaLogic[133]		X

they been assessed."

[116] https://www.genomeweb.com/molecular-diagnostics/novogene-gets-clia-certification-us-lab#.XiorZFNKiPR

[117] https://www.prnewswire.com/news-releases/novogene-establishes-first-us-genomic-sequencing-center-located-at-uc-davis-acquires-second-illumina-hi-seq-x-ten-system-300251077.html

[118] https://www.genomeweb.com/sequencing/bgi-partners-johns-hopkins-mount-sinai-hospital-plans-place-first-bgiseq-north-america#.XioY61NKiPS

[119] https://www.genomeweb.com/sequencing/bgi-partners-johns-hopkins-mount-sinai-hospital-plans-place-first-bgiseq-north-america#.XioY61NKiPS

[120] https://www.bgi.com/us/company/careers/childrens-brain-tumor-tissue-consortium-announces-addition-two-new-satellite-member-institutions-china/

[121] https://www.bgi.com/us/company/news/bgi-announces-new-partnerships-8th-anniversary-milestone-us/

[122] https://www.genomeweb.com/sequencing/bgi-fred-hutchinson-sign-collaboration-mou#.Xiol6lNKiPR

[123] https://www.clinicalomics.com/topics/precision-medicine-topic/cancer/bgi-fred-hutch-to-partner-on-cancer-genomics-infectious-disease-research/

[124] https://www.uscc.gov/sites/default/files/Research/US-China%20Biotech%20Report.pdf

[125] https://www.genewiz.com/en/Public/Services

[126] https://www.genewiz.com/en/Public/Company/News-and-Events/Press-Releases/GENEWIZ-Acquires-the-Genomic-Services-Business-of-Beckman-Coulter

[127] https://www.nist.gov/system/files/documents/2018/10/19/who_will_own_the_secrets_in_our_genes_woodrow_wilson_center.pdf

[128] https://www.prnewswire.com/news-releases/wuxi-nextcode-launches-new-state-of-the-art-genetic-analysis-laboratory-in-us-with-illuminas-new-trusight-500-assay-300821439.html

[129] https://www.uscc.gov/sites/default/files/Research/US-China%20Biotech%20Report.pdf

[130] https://www.biospace.com/article/releases/-b-wuxi-healthcare-b-invests-in-us-genomics-testmaker-23andme-/

[131] https://www.uscc.gov/sites/default/files/Research/US-China%20Biotech%20Report.pdf

[132] https://grail.com/about/

[133] https://www.uscc.gov/sites/default/files/Research/US-China%20Biotech%20Report.pdf

Access to these genomic data and corresponding longitudinal data[134] – data that the US is unable to aggregate due to privacy restrictions including the Health Insurance Portability and Accountability Act (HIPAA) – provides a considerable competitive advantage in future Intellectual Property (IP) across the corresponding market space, most notably pharmaceuticals.[135] Chinese licensing, privacy, and cybersecurity regulations prohibit reciprocal access to Chinese data by US firms,[136] and China has recently taken additional steps to limit the sharing of Chinese genomic information via scientific collaborations, sample and data transfers, and publications in international scientific journals.[137] New legislation introduced in 2019 expands upon these protective measures and enables the PRC to levy heavier financial penalties on transgressors.[138] Resulting strategic advantages may include weakened US security posture,[139] economic imbalance versus China, US dependency on foreign pharmaceuticals, or – conceivably – development of genetically-targeted weapons applying precision medicine techniques.

Technology Development. China has similarly invested heavily in corresponding technology development efforts to enable robust analysis of collected data, yielding considerable progress in the three foundational technical areas of genetic sequencing and bioinformatics capabilities; AI, ML, and related data mining and analysis tools; and HPC and cloud computing capabilities. PRC investments and initiatives in AI appear to be particularly robust: the stated goal of its formal Artificial Intelligence Development Plan released in 2017 is to make the country and its industries world leaders in AI technologies by 2030,[140] though corresponding investments may[141] or may not[142] be positioning it to surpass US capabilities in the next decade. Examples of concrete investments include a $2B commitment by the city of

[134] See for example https://www.ckbiobank.org/site/Data+Access/Data+Overview
[135] See for example https://globalbiodefense.com/2020/02/11/the-silent-threat-of-covid-19-americas-dependence-on-chinese-pharmaceuticals/; https://www.ft.com/content/245a7c60-6880-11e7-9a66-93fb352ba1fe
[136] Chen Y, Song L. China: concurring regulation of cross-border genomic data sharing for statist control and individual protection. Hum Genet. 2018 Aug;137(8):605-615. doi: 10.1007/s00439-018-1903-2. Epub 2018 Jul 16. Erratum in: Hum Genet. 2018 Aug 17;: PMID: 30014187; PMCID: PMC6132628.
[137] See, for example, https://www.nature.com/articles/d41586-018-07222-2
[138] http://www.gov.cn/zhengce/content/2019-06/10/content_5398829.htm
[139] For example, analysts have noted that access to the sensitive genetic information of certain US persons may enable blackmail or expose health-related vulnerabilities that might be otherwise targeted. See, for example, Gryphon Scientific. China's Biotechnology Development: The Role of US and Other Foreign Engagement. US-China Economic and Security Review Commission, 2019.
[140] Pg. 6, https://flia.org/wp-content/uploads/2017/07/A-New-Generation-of-Artificial-Intelligence-Development-Plan-1.pdf (unofficial translation of http://www.gov.cn/zhengce/content/2017-07/20/content_5211996.htm).
[141] See, for example, https://www.marketwatch.com/story/china-is-overtaking-the-us-as-the-leader-in-artificial-intelligence-2019-02-27; https://www.forbes.com/sites/cognitiveworld/2020/01/14/china-artificial-intelligence-superpower/?sh=20e14efd2f05
[142] https://cset.georgetown.edu/wp-content/uploads/Chinese-Public-AI-RD-Spending-Provisional-Findings-1.pdf

Beijing to establish an AI-focused industrial park,[143] and plans by the northern port city of Tianjin to invest $16B in support of its AI industry.[144] Additional examples of relevant technology development and corresponding investment are provided where applicable throughout this document.

Related Capabilities. China is a recognized world leader in synthetic biology and gene editing, yielding over 800 citations upon PubMed search of the terms "Chinese Academy of Sciences" and "CRISPR." Key dual-use institutes with relevant publications in the open source include the Academy of Military Medical Sciences, Changchun, which for example used CRISPR-Cas9 to genetically modify pigs in order to confer protection against classical swine fever virus;[145] Institute of Microbiology, Beijing, which has over 50 publications exploring targeted mutagenesis and genome editing using the CRISPR-Cas9 system; and Wuhan Institute of Virology, which for example has explored the utility of CRISPR and related technologies in the treatment of cancer and genetic diseases.[146] Chinese scientists have been actively investigating CRISPR-Cas9 as a tool for correcting genetic mutations in non-viable human embryos since at least 2015.[147]

Future Outlook. China's estimated 2019 precision medicine market value of $12.2B is projected to more than double in the next five years to $29.5B.[148]

Government Policy Directives. China outlines its economic and social development strategy in sequential Five-Year Plans, the most recent of which ("The 13th Five-Year Plan") was issued in 2016 for the period of 2016-2020.[149] Its 23rd Chapter, Strategic Emerging Initiatives, calls out both next generation biotechnologies and precision medicine initiatives as emerging industries that will bolster the Chinese economy. Specifically, the Plan commits to the following (official translation):

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[143] https://www.reuters.com/article/us-china-artificial-intelligence/beijing-to-build-2-billion-ai-research-park-xinhua-idUSKBN1ES0B8

[144] https://www.reuters.com/article/us-china-ai-tianjin/chinas-city-of-tianjin-to-set-up-16-billion-artificial-intelligence-fund-idUSKCN1II0DD

[145] Xie Z et al. Genetically modified pigs are protected from classical swine fever virus. PLOS Pathog. 2018 Dec 13;14(12):e1007193.

[146] Khan FA et al. CRISPR/Cas9 therapeutics: a cure for cancer and other genetic diseases. Oncotarget. 2016 Aug 9;7(32):52541-52552.

[147] See, for example, Liang P, Xu Y, Zhang X, et al. CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes. Protein Cell. 2015 May;6(5):363-372. doi: 10.1007/s13238-015-0153-5. Epub 2015 Apr 18. PMID: 25894090; PMCID: PMC4417674. Tang L, Zeng Y, Du Het al. CRISPR/Cas9-mediated gene editing in human zygotes using Cas9 protein. Mol Genet Genomics. 2017 Jun;292(3):525-533. doi: 10.1007/s00438-017-1299-z. Epub 2017 Mar 1. PMID: 28251317.

[148] See https://www.askci.com/news/chanye/20200423/1721011159604_3.shtml. Per this source, market size was expected to reach USD $14.7B at the end of 2020, $17.6B at the end of 2021, $21.0B at the end of 2022, and $25M at the end of 2023.

[149] https://en.ndrc.gov.cn/policyrelease_8233/201612/P020191101482242850325.pdf. http://www.gov.cn/zhengce/content/2016-08/08/content_5098072.htm

- Move faster to facilitate the wide application of genomics and other biotechnologies
- Create demonstrations of network-based biotech applications
- Stimulate the large-scale development of personalized medical treatment, new drugs, bio-breeding, and other next generation biotech products and services
- Promote the creation of basic platforms such as gene and cell banks

Coinciding with the 13th Five-Year Plan, China released the "2016 Guidelines for (Participation in) the Precision Medicine Initiative," [150,151] which detailed the significance of, goals, and plan of action for accelerating the development of Chinese precision medicine capabilities spanning genomics, proteomics, bioinformatics, and big data.[152] The 2016 Plan and Guidelines represent key milestones on an accelerating timeline of Chinese policy development related to precision medicine, with recent highlights presented in ***Table 2***.[153,154]

[150] https://service.most.gov.cn/kjjh_tztg_all/20160307/894.html
[151] https://service.most.gov.cn/u/cms/static/201603/08185201pc3d.doc
[152] http://html.rhhz.net/ZGWSZY/html/2020-1-14.htm
[153] https://www.qianzhan.com/analyst/detail/220/191202-274e764e.html
[154] https://zhuanlan.zhihu.com/p/33322529

Table 2.
National policies and regulations concerning precision medicine in China (2014 – 2019)

Year	Month	Event/Policy/Regulation	Additional Highlights
2014	July	The National Medical Products Administration authorizes the marketing of certain types of next-generation sequencing instruments[155]	Noninvasive prenatal testing (NIPT) products from BGI and Da An Gene are approved to be introduced into the Chinese market; BGI, Berry Genomics, and other companies' sales jump by over 100%
2015	March	First "strategic expert meeting" on precision medicine, held by the MOST[156]	The central government officially launches its precision medicine initiative
2016	March	MOST issues Guidelines for 2016 National Research and Development (R&D) Programs Focused on Precision Medicine and Other Key Projects	Precision medicine is designated as one of the prioritized key R&D projects for 2016
	March	2016 Guidelines for (Participation in) the Precision Medicine Initiative	Details the significance of, goals, and plan of action for accelerating the development of precision medicine in China, including genomics, proteomics, bioinformatics, big data, etc.
	March	13th Five-Year Plan for Economic and Social Development	Rigorously promote technical innovation and industrialization of precision medicine and other emerging industries to foster new growth
	July	Executive Meeting of the State Council	Based on the National Plan for Scientific and Technological Innovation During the Period of the Thirteenth Five-year Plan, transform China into an innovative country and carry out a variety of precision medicine projects
	October	"Healthy China 2030" Planning Outline	Promote technological advancement in chronic diseases prevention, precision medicine, and smart healthcare; achieve standardized management and usage of population health data in support of personalized healthcare by 2030
	November	National 13th Five-Year Plan for the Development of Strategic Emerging Industries	Support the advancement of life sciences, encourage the development, applications of, and innovation in biotechnology, and leverage genetic engineering techniques to quickly move precision medicine forward
	December	National 13th Five-Year Plan for the Development of Bioindustry	Accelerate new drug development, improve drug quality, and broaden the applications of DNA sequencing and other emerging technologies

[155] https://www.360zhyx.com/home-research-index-rid-70817.shtml
[156] https://www.seqchina.cn/7655.html

2017	February	Strategic Emerging Industries Key Products and Services Catalogue	Create an ecosystem for clinical diagnosis and treatment via genetic testing services needed for personalized medical care
	April	National 13th Five-Year Special Planning on Biotechnology	Achieve breakthroughs in such techniques as genetic testing and genetic manipulation
	June	National 13th Five-Year Special Planning on Technological Innovation in Healthcare	Develop a knowledge base in the field of precision medicine and a national platform for sharing biomedical big data; concentrate on advancing technologies that are key to precision medicine like next-generation sequencing, -omics techniques, and big data integration and analytics; introduce precision medical solutions and technologies such as early detection for significant diseases, molecular typing, personalized and targeted therapies, targeted surgical approaches, and prediction and monitoring of treatment effects
	December	Guidelines on Molecular Diagnostics for Infectious Disease Related Personalized Medicine	Regulate diagnostic testing and laboratory practice of healthcare facilities providing molecular diagnostic tests
	December	Technical Specification for DNA Microarrays Genechip for Personalized Medicine	Regulate healthcare facilities operating personalized microarrays gene chip diagnostics services
2018	September	Measures for Managing the Standardization, Security, and Services of Big Data in Healthcare and Medicine (For Trial Implementation)[157,158]	National Healthcare Data Standards are introduced
2019	February	Outline Development Plan for the Guangdong- Hong Kong-Macao Greater Bay Area[159]	"[S]upport the establishment of the 'Belt and Road' Life Science and Technology Advancement Alliance by relying on the China National GeneBank in Shenzhen." In this document, biotechnology is categorized as one of the "new pillar industries" for the Greater Bay Area, and genetic testing as a "key sector."
	June	Regulations of the People's Republic of China on the Management of Human Genetic Resources	National security focus includes special limitations on foreign access (Article 7): "Foreign organizations, individuals and their institutions established or actually controlled shall not collect or preserve human genetic resources in China within the territory of our country, and may not provide human genetic resources of our country abroad."[160]

[157] https://m.ofweek.com/medical/2020-07/ART-11106-8420-30447805.html
[158] http://www.nhc.gov.cn/mohwsbwstjxxzx/s8553/201809/f346909ef17e41499ab766890a34bff7.shtml
[159] https://www.bgi.com/wp-content/uploads/2020/04/ 华大基因 2019年年度报告.PDF
[160] http://www.gov.cn/zhengce/content/2019-06/10/content_5398829.htm

CAS Capabilities and Assets. The CAS is a Cabinet-level organization directly under the State Council comprising some 100 research institutes and 50,000 researchers. It is the "[H]ighest academic institution for comprehensive R&D in the natural and applied sciences in China and reports directly to the State Council in an advisory capacity, with much of its work contributing to products for military use."[161] Key CAS institutes conducting research and development related to precision medicine include the Beijing Institute of Genomics (BIG),[162] Tianjin Institute of Industrial Biotechnology,[163] and Institute of Genetics and Developmental Biology in Beijing,[164] with BIG at the forefront.

BIG's story began in 1998 with the founding of the CAS Human Genome Research Center of the Institute of Genetics,[165] renamed the Human Genome Research Center of the Institute of Genetics and Developmental Biology (HGRCIGDB) after merging with two other institutes in 2001.[166] Beginning in 1999, the Institute led China's participation in the International Human Genome Project in collaboration with researchers from the US and other nations. It subsequently gave rise to two key entities supporting China's Precision Medicine Initiative: (a) the Beijing Genomics Institute (BGI), a "non-governmental independent research institute" that operates like an industry partner and is described further in the *Commercial Sector* discussion below, and (b) BIG under the CAS (***Figure 1***). To reiterate for the sake of clarity, BGI – which has since been renamed BGI Group – and BIG are different entities despite their similar names, and there is no evidence in the open source domain of any formal affiliation between the two organizations despite numerous press reports that appear to conflate their assets and accomplishments. HGRCIGDB continues to function as a national asset at the nexus of genomics and agricultural modernization – namely plant genomics, for which it maintains multiple National Key Laboratories – but does not appear to play a role in China's Precision Medicine Initiative.

Today, BIG houses a number of key assets related to China's Precision Medicine Initiative, including the CAS Key Laboratory of Genomic and Precision Medicine;[167] CAS Key Laboratory of Genome Sciences and Information;[168] National Genomic Data Center of China;[169] and Core Genomic

[161] Threats to the U.S. Research Enterprise: China's Talent Recruitment Plans, US Senate Permanent Subcommittee on Investigations, 11/18/2019, p. 90.
[162] http://english.big.cas.cn/
[163] http://english.tib.cas.cn/
[164] http://english.genetics.cas.cn/
[165] http://www.big.cas.cn/gkjj/lsyg/
[166] http://english.genetics.cas.cn/au/
[167] http://english.big.cas.cn/rh/rd/201510/t20151016_153543.html
[168] http://english.big.cas.cn/rh/rd/200907/t20090720_24135.html
[169] https://bigd.big.ac.cn/

Facility.[170] BIG participated in the International HapMap Project[171] established on the heels of the Human Genome Project to uncover patterns in human genome variation,[172] resulting in the development of a positive selection database named "SNP@Evolution" that mapped millions of SNPs to different geographical population groups.[173] BIG scientists have averaged roughly 180 peer-reviewed publications per year in international scientific journals over the past five years, including 364 publications that cross-reference with the term "precision medicine."

[It should be noted that while "National Key Laboratory" (a.k.a. "State Key Laboratory") is a special designation that indicates funding and administration support from the central government as a national asset in the research area,[174] a "CAS Key Laboratory" is an institute-level designation considered secondary to its national level counterparts.[175] National Key Laboratories are affiliated with Chinese universities and research institutions, administered by central and local administrative departments, and overseen by the MOST; according to the 2016 MOST Report on National Key Laboratories, there are 254 recognized National Key laboratories and seven Pilot National Key laboratories. [176]]

[170] http://english.big.cas.cn/rh/rd/201510/t20151022_153742.html
[171] https://www.genome.gov/10001688/international-hapmap-project; https://www.nature.com/articles/nature02168
[172] http://english.big.cas.cn/rh/rps/200908/t20090828_34606.html
[173] Cheng F, Chen W, Richards E, Deng L, Zeng C. SNP@Evolution: a hierarchical database of positive selection on the human genome. BMC Evol Biol. 2009 Sep 5;9:221. doi: 10.1186/1471-2148-9-221. PMID: 19732458; PMCID: PMC2755008.
[174] See, for example, http://www.chinadaily.com.cn/a/201806/26/WS5b323775a3103349141deebf.html; https://www.datenna.com/chinese-state-key-laboratories/
[175] A list of CAS Key Laboratories is available at: https://www.cas.cn/kxyj/cx/201311/t20131119_3980864.shtml
[176] https://www.sciping.com/13188.html

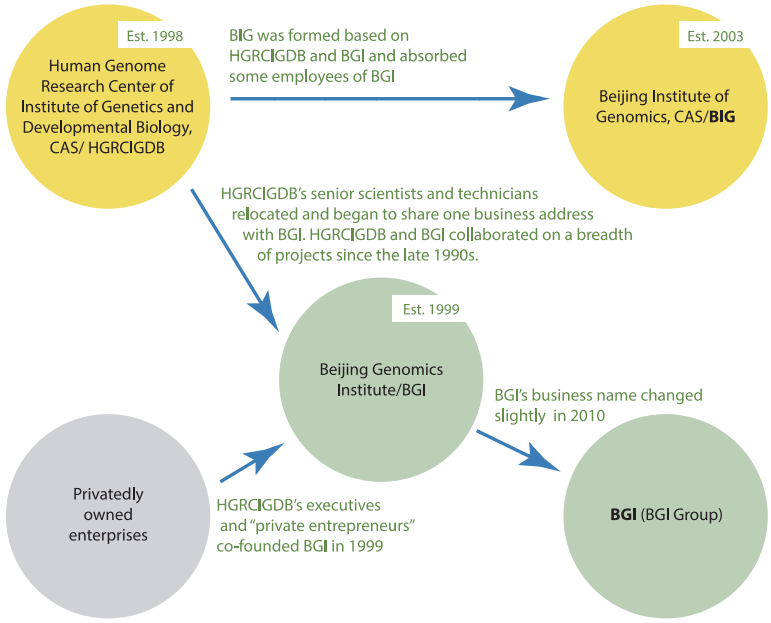

Figure 1. Historical relationship between key entities supporting China's precision medicine initiative[177]

Commercial Sector Capabilities and Assets. China's burgeoning biotechnology sector comprises dozens of companies directly and indirectly involved in China's Precision Medicine Initiative, but the clear leader is BGI Group.

As described above, BGI Group (a.k.a. BGI, Beijing Genomics Institute) was founded in 1999 as an offshoot of the CAS Institute of Genetics.[178] It is headquartered in Shenzhen, southern Guangdong Province, where it houses key precision medicine capabilities including subsidiary BGI Genomics, one of the world's largest genomics testing and research service providers,[179] and the China (a.k.a. Shenzhen) National GeneBank.[180] From 2008 to 2015, BGI Group was a core member of the 1000 Genomes Project Consortium, which employed whole genome sequencing to explore genetic variation among geographic subpopulations (2,504 genomes from 26 population subgroups).[181] The 1000 Genomes Project effectively supplanted the HapMap Project as the research standard for population genomics; it is worth noting that while BIG led China's involvement in the HapMap Project, BGI assumed

[177] http://www.big.cas.cn/gkjj/lsyg/, http://blog.sciencenet.cn/home.php?mod=space&uid=611951&do=blog&id=1162188.
[178] https://en.genomics.cn/en-about.html
[179] https://www.bgi.com/global/company/about-bgi/
[180] https://www.cngb.org/index.html?i18nlang=en_US; https://en.genomics.cn/en-gene.html
[181] See: https://www.nature.com/articles/nature15393; https://www.nature.com/articles/526052a#ref-CR1; https://www.internationalgenome.org/about; https://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/

that role for the 1000 Genomes Project. We have sought but have to date been unable to uncover an explanation for this shift.

BGI Group acquired US sequencing technology developer Complete Genomics[182] in 2013,[183] launched its own sequencing technology in 2015,[184] and established subsidiary MGI as its de facto technology manufacturing arm in 2016.[185] MGI now manufactures multiple sequencers[186] and corresponding sample/library preparation kits and analysis capabilities (e.g., the MegaBOLT bioinformatics analysis accelerator[187]) designed for forensic[188] and population genomics[189] applications.

Since the onset of the COVID-19 pandemic, BGI Group established the Global Initiative on Open-source Genomics for SARS-CoV-2 (GIOG-S) to facilitate the analysis and sharing of SARS-CoV-2 genomic data[190] and has aggressively promoted its whole genome sequencing services[191] and laboratory diagnostic solutions[192] to meet clinical testing needs around the world.[193] In addition, BGI Group researchers have contributed to COVID-19 genomic surveillance[194] and disease understanding, including identification of genetic contributors to COVID-19 susceptibility and severity.[195]

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[182] https://www.completegenomics.com/
[183] https://www.prnewswire.com/news-releases/bgi-shenzhen-completes-acquisition-of-complete-genomics-198820331.html
[184] Huang J, Liang X, Xuan Y, et al. A reference human genome dataset of the BGISEQ-500 sequencer. Gigascience. 2017 May 1;6(5):1-9. doi: 10.1093/gigascience/gix024. Erratum in: Gigascience. 2018 Dec 1;7(12): PMID: 28379488; PMCID: PMC5467036.
[185] https://en.mgi-tech.com/about/
[186] https://en.mgi-tech.com/products/
[187] https://en.mgi-tech.com/products/software_info/2/
[188] https://en.mgi-tech.com/applications/2/; https://en.mgi-tech.com/applications/info/7/
[189] https://en.mgi-tech.com/applications/info/10/
[190] https://giogs.genomics.cn/
[191] https://www.bgi.com/global/sequencing-services/customised-solutions/covid-19-solutions/; https://services.bgi.com/en/bgi-wgs-promotion-for-sars-cov-2-research-1; https://cdn2.hubspot.net/hubfs/7024340/SARS-CoV-2%20WGS%20Promo%20Overview..pdf?__hssc=87901191.1.1607627972895&__hstc=87901191.b320db127d7d2715a654110a05227e55.1607625378466.1607625378466.1607627972895.2&__hsfp=1832413912&hsCtaTracking=910ab5db-cf98-4a06-ba39-8b77bcb9b477%7Cb771e45b-d18e-4ba9-8398-781013177e41
[192] https://www.prnewswire.com/news-releases/bgi-group-helping-over-80-countries-for-timely-covid-19-detection-and-intervention-301043895.html; https://www.bignewsnetwork.com/news/266069402/spotlight-a-glimpse-into-hong-kongs-inflatable-covid-19-testing-lab; https://www.globaltimes.cn/content/1186853.shtml; https://www.globaltimes.cn/content/1187086.shtml; https://www.bgi.com/global/covid-19-local-laboratory-solution/; https://www.genengnews.com/insights/bgis-coronavirus-response-build-a-lab-in-wuhan-in-a-week/; http://www.xinhuanet.com/english/2020-06/22/c_139158662.htm
[193] https://www.reuters.com/article/us-health-coronavirus-bgi-specialreport-idUSKCN2511CE
[194] Du P, Ding N, Li J, et al. Genomic surveillance of COVID-19 cases in Beijing. Nat Commun. 2020 Oct 30;11(1):5503. doi: 10.1038/s41467-020-19345-0. PMID: 33127911; PMCID: PMC7603498.
[195] Wang F, Huang S, Gao R, et al. Initial whole-genome sequencing and analysis of the host genetic contribution to COVID-19 severity and susceptibility. Cell Discov. 2020 Nov 10;6(1):83. doi: 10.1038/s41421-020-00231-4. PMID: 33298875

In a 2020 genomics market analysis, BGI ranked third, after Korean firm Macrogen and US giant Thermo Fischer Scientific (and above US sequencing solution architect Illumini at number four).[196]

Beyond BGI and its subsidiaries, other key Chinese firms in the precision medicine space include the following:

- *WuXi NextCODE (Shanghai).* As described elsewhere,[197] WuXi NextCODE was founded in 2015 when Chinese firm WuXi PharmaTech acquired US genomics company NextCODE Health.[198] It is a wholly-owned subsidiary of Chinese pharmaceutical, biotech, and medical services giant WuXi AppTec.[199] WuXi NextCODE combines capabilities in next generation sequencing, genomic sequence analysis, and database architecture to deliver, mine, and expand one of the world's largest troves of genomics information.[200] WuXi NextCODE's Shanghai sequencing facility was the first of its kind in China to receive Clinical Laboratory Improvement Amendments (CLIA) certification from the US Centers for Medicare and Medicaid Services and accreditation from College of American Pathologists (CAP), enabling the company to provide gold standard testing services to US entities.[201] In 2019, it opened a similarly CLIA-certified and CAP-accredited laboratory in the US.[202] WuXi NextCODE has also partnered with both Chinese firm Huawei[203] under China's Precision Medicine Initiative and US firm Google Cloud[204] to establish the necessary cloud computing infrastructure for its services. In 2020, WuXi NextCODE spun out Genuity Science, which will continue to deliver WuXi NextCODE's services from US-based headquarters and supporting operations in Iceland and Ireland;[205] as of this writing, it is unclear how the company's

[196] https://trybiotech.com/top-10-genome-sequencing-companies-in-2020/
[197] Gryphon Scientific. China's Biotechnology Development: The Role of US and Other Foreign Engagement. US-China Economic and Security Review Commission, 2019.
[198] https://www.genengnews.com/topics/omics/wuxi-snaps-up-nextcode-health-for-65m/; https://www.prnewswire.com/news-releases/wuxi-pharmatech-acquires-nextcode-health-to-create-global-leader-in-genomic-medicine-300018311.html
[199] https://www.wuxiapptec.com/about/
[200] https://techcrunch.com/2017/09/07/wuxi-nextcode-aims-for-the-genomics-database-gold-standard-with-new-240-million/
[201] https://www.prnewswire.com/news-releases/wuxi-nextcode-becomes-the-first-and-only-cap-clia-and-california-accredited-sequencing-laboratory-in-china-300224420.html
[202] https://www.prnewswire.com/news-releases/wuxi-nextcode-launches-new-state-of-the-art-genetic-analysis-laboratory-in-us-with-illuminas-new-trusight-500-assay-300821439.html
[203] https://wxpress.wuxiapptec.com/huawei-wuxi-apptec-join-forces-create-china-precision-medicine-cloud-platform/
[204] http://www.pharmajournalist.com/wuxi-nextcode-reveals-genomics-partnership-google-cloud/
[205] https://genuitysci.com/news/wuxi-nextcode-genomics-medicine-ireland-are-now-genuity-science/; https://www.prnewswire.com/news-releases/wuxi-nextcode-restructures-and-

Shanghai-based assets will be divested or otherwise restructured. The term "WuXi" means "without tin;" it is also the name of a city in eastern China.

- *iCarbonX (Shenzhen).* iCarbonX[206] has been called the "Google of biotech."[207] The company was founded by BGI co-founder Jun Wang and BGI chief scientist Yingrui Li. Its primary interest lies in the application of AI and big data analytics to genomic and corresponding longitudinal data to identify targeted treatment regimens. iCarbonX recently invested $400 million in multiple US companies under its iCarbonX Digital Life Alliance,[208] including proteomics firm SomaLogic, microbiome therapeutics firm AOBiome, immune system diagnostics firm HealthTell, consumer health data-sharing platform PatientsLikeMe, microbiome diagnostics firm General Automation Lab Technologies (GALT), and recombinant enzyme and cosmetics firm Robustinique. iCarbonX has also established a subsidiary in Israel (iCarbonX-Israel) as well as acquired Israeli firm Imagu, which is building AI-driven digital models of human health.[209] iCarbonX received a $1B valuation within its first six months of operation.[210]

- *Novogene (Beijing).* Novogene[211] is a leading next generation sequencing service provider with branches in Europe and the US, including a genomic sequencing laboratory at the University of California, Davis.[212]

becomes-genuity-science-301081462.html; https://endpts.com/meet-the-latest-genomic-data-company-aka-wuxi-nextcode-without-the-china-operations/

[206] https://www.icarbonx.com/en/

[207] https://innovator.news/china-leaps-ahead-in-precision-medicine-72cfc469df3d; https://www.cbinsights.com/research/icarbonx-teardown-genomics-ai-expert-research/

[208] https://www.icarbonx.com/en/news/387.html; https://www.genomeweb.com/informatics/chinas-icarbonx-invests-somalogic-grows-medical-data-alliance#.X9KgvOWSmUm

[209] https://www.icarbonx.com/en/news/385.html

[210] https://www.fiercebiotech.com/it/ex-bgi-ceo-s-startup-hits-1b-valuation-6-months; https://www.icarbonx.com/en/news/383.html#:~:text=iCarbonX%20has%20finished%20its%20Series,%241%20billion%20post%2Dmoney%20valuation.&text=iCarbonX%20will%20now%20devote%20itself,precision%20health%20and%20precision%20medicine.

[211] https://en.novogene.com/about/about-novogene/

[212] https://www.prnewswire.com/news-releases/novogene-establishes-first-us-genomic-sequencing-center-located-at-uc-davis-acquires-second-illumina-hi-seq-x-ten-system-300251077.html

Relevant Conferences and Trade Shows. Key conferences and trade shows include the following:

- 5th World Precision Medicine (China) Summit 2020 (WPMCS2020).[213] This event was held in November 2020 despite the COVID-19 pandemic.
- 2020 Guangzhou Precision Medicine Expo.[214] Like WPMCS2020, this event was held in November 2020 despite the COVID-19 pandemic.
- 2020 Precision Medicine Conference.[215] This conference was scheduled to coincide with the above Guangzhou Precision Medicine Expo and was held accordingly.
- China Precision Medicine Conference & China International Precision Medicine Industry EXPO 2020.[216] This annual event occurs the last week of each December.
- China-US Precision Medicine Summit.[217] In 2018, the CAS, Peking Union Medical College, and Thermo Fisher Scientific met in Beijing to advance cooperation on precision medicine between the two countries.

Academic Institutes and Universities. Numerous academic institutes are directly or peripherally involved in China's Precision Medicine Initiative, led by Peking Union Medical College, which together with its sister institution the Chinese Academy of Medical Sciences operates 18 institutes, 7 schools, and 6 hospitals.[218] Its State Key Laboratory of Molecular Oncology and hospital network have partnered with WuXi NextCODE to identify cancer-specific biomarkers via genomic profiling.[219]

Other relevant academic institutes include:

- Fudan University Shanghai Medical College[220] (note: numerous news articles state that Fudan University collaborates with BGI Group, but we were unable to corroborate this relationship using primary/native language sources)

[213] http://www.wpmcs.com.cn
[214] http://pmex.gdpmaa.com/list.php?pid=1
[215] http://pmex.gdpmaa.com/list.php?pid=1
[216] http://www.ebiotrade.com/newsf/2020-6/2020630100527616.htm
[217] http://meeting.sciencenet.cn/index.php?s=/Category/news_display&rid=3232
[218] http://english.cams.cn/about.html
[219] See, for example, Cui Y, Chen H, Xi R, et al. Whole-genome sequencing of 508 patients identifies key molecular features associated with poor prognosis in esophageal squamous cell carcinoma. Cell Res. 2020 Oct;30(10):902-913. doi: 10.1038/s41422-020-0333-6. Epub 2020 May 12. PMID: 32398863; PMCID: PMC7608103.
[220] See, for example, Qian M, Li Q, Zhang M, et al. Multidisciplinary therapy strategy of precision medicine in clinical practice. Clin Transl Med. 2020 Jan;10(1):116-124. doi: 10.1002/ctm2.15. Epub 2020 Mar 31. PMID: 32508051; PMCID: PMC7240867.

- Sichuan University West China Hospital[221]
- Peking University
- Jianghun University
- Tsinghua University
- Guangzhou Medical University
- Huazhong University of Science and Technology
- Wuhan University of Technology

Civil-Military Fusion. "Dual-use…biology" is a focus of China's military-civil fusion strategy formally adopted in 2016 (i.e., in parallel with the China Precision Medicine Initiative), enabling research conducted under civilian authority to advance China's military modernization drive.[222] Key military-civil fusion stakeholders include the Central Military Commission's (CMC) Steering Committee on Military Scientific Research and Science and Technology Commission (S&TC), which together set the strategy and priorities for military innovation, and the People's Liberation Army's (PLA) Academy of Military Science (AMS), which leads corresponding military research and development efforts.[223] AMS Vice President Major General He Fuchu,[224] a recognized genomics expert and former President of the Academy of Military Medical Sciences, has commented extensively on future military applications of biotechnology, for example:

- "As the weaponization of biological bodies will become a reality in the future, non-traditional combat styles will take the stage, 'biological frontier' will become a new high frontier of national defense."[225]

- "Biotechnology will make biological weaponization a reality, new non-traditional forms of confrontation such as biological attack, biological destruction and ecological control will become possible, and "biological frontier" will break through the traditional national security and national defense boundaries and become a new national defense frontier after land, sea, air, sky, electricity and network…Mankind will face a more powerful wave of new military revolutions. Modern biotechnology and its cross-integration with information, nanotechnology, cognition and other fields will have a

[221] See, for example, Wang M, Zhou Y, Zong Zet al. A precision medicine approach to managing 2019 novel coronavirus pneumonia. Precis Clin Med. 2020 Feb 4;3(1):14-21. doi: 10.1093/pcmedi/pbaa002. PMID: 32330209; PMCID: PMC7107203.
[222] Thirteenth Five-Year Science and Technology Military-Civil Fusion Development Special Plan, September 26, 2017, available at: http://www.aisixiang.com/data/106161.html
[223] See, for example, "China's National Defense in a New Era," Xinhua, July 24, 2019.
[224] https://www.chinavitae.com/biography/He_Fuchu/bio
[225] Lu Peipei and He Fuchu, "Biotechnology will become a new strategic commanding point for the future military revolution." PLA Daily, October 6, 2015, available at: http://www.81.cn/jwgz/2015-10/06/content_6709533.htm

> revolutionary impact on weapons and equipment, combat space, war form, military theory, etc. The biological military revolution will be the first military revolution since mankind entered the new millennium, and the first military revolution started by biotechnology in nearly 5000 years."[226]

While the selection of He Fuchu as AMS Vice President suggests the importance of genomics and related biotechnologies to the PLA's civil-military fusion strategy, we did not identify any direct ties with China's Precision Medicine Initiative or related civilian entities.

PRC Motivations

China has consistently denied any interest in or pursuit of biological weapons in formal statements, declarations, and disclosures by its State leaders and media.[227] China acceded to the international Biological Weapons Convention (BWC) abolishing biological weapons in 1984,[228] and has submitted annual Confidence Building Measure (CBM) reports – which aim to improve cooperation of States Parties under the Convention, including CBM F on "Declaration of past activities in offensive and/or defensive biological research and development programmes" – since 1989.[229] China has restricted access to its submissions to States Parties only, such that their contents are not publicly available;[230] however, it is reasonable to assume that the submissions reiterate China's unwavering formal opposition to biological weapons.

The US State Department's 2020 report, *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments* (Compliance Report), states that "[d]uring the reporting period, the People's Republic of China (China) engaged in biological activities with potential dual-use applications, some of which raises concerns regarding its compliance with Article I of the BWC."[231] The report further states that "[t]

[226] He Fuchu, "The future direction of the new military revolution in the world." Reference News, August 24, 2017, available at: https://web.archive.org/web/20190823210313/http://www.xinhuanet.com/politics/2017-08/24/c_129687890.htm

[227] This section of the report on PRC motivations draws in part from Pilch R and Pomper M. Asia-Pacific Perspective on Biological Weapons and Nuclear Deterrence in the Pandemic Era. Asia-Pacific Leadership Network for Nuclear Nonproliferation and Disarmament, 2020. Available at: http://www.apln.network/project/project_view/Pandemic-Nuclear_Nexus_Scenarios_Project__Asia-Pacific_Perspective_on_Biological_Weapons_and_Nuclear_Deterrence_in_the_Pandemic_Era

[228] http://disarmament.un.org/treaties/t/bwc

[229] https://www.unog.ch/80256EDD006B8954/(httpAssets)/DE1EE44AFE8B8CF9C1257E36005574E4/$file/cbm-guide-2015.pdf

[230] https://bwc-ecbm.unog.ch/state/china

[231] https://www.state.gov/wp-content/uploads/2020/06/2020-Adherence-to-and-Compliance-with-Arms-Control-Nonproliferation-and-Disarmament-Agreements-and-Commitments-Compliance-Report.pdf, pp. 56-57.

he United States assesses China possessed an offensive biological warfare program from the early 1950s to at least the late 1980s…China's CBM reporting has never disclosed that it ever pursued an offensive BW program, and China has never acknowledged publicly or in diplomatic channels its past offensive program."

As described in the previous section of this report, with respect to precision medicine the US position that China is nominally engaged in "biological activities with potential dual-use applications" is certainly accurate. The question therefore becomes whether China would attempt to divert dual-use precision medicine capabilities toward the development of genetic weapon systems in breach of its BWC obligations.

China's compliance with the BWC is critical not only to the external success of China's Belt and Road Initiative[232] and, more broadly, economic expansion in the Global South – which rely on international perception[233] and relationships with both partner nations as well as key international organizations like the World Health Organization (WHO), World Trade Organization (WTO), and World Bank – but also to China's internal stability. Biological weapons are widely abhorred, perhaps nowhere more so than in China, where the Chinese people suffered biological attacks at the hands of the Japanese during the Second Sino-Japanese War that coincided with World War II.[234] With respect to genetic weapons in particular, China's largely homogenous population[235] suggests that such weapons present a greater threat to the Chinese people than to heterogenous populations such as that of the US. And China has other, more predictable military options for area denial and deterrence, which form the basis of its national military strategy.[236] We discuss the implications of these points in the below *Assessment* section.

Despite China's formal opposition to biological weapons, however, some PLA officers have suggested that China should consider biological weapons, including specifically targeted genetic weapons, as viable and perhaps more humane alternatives to other forms of war. In making their case, such authors

[232] See, for example, https://www.cfr.org/backgrounder/chinas-massive-belt-and-road-initiative

[233] See, for example, https://www.reuters.com/article/us-health-coronavirus-china-sentiment-ex/exclusive-internal-chinese-report-warns-beijing-faces-tiananmen-like-global-backlash-over-virus-idUSKBN22G19C

[234] See, for example, https://www.nytimes.com/1997/02/04/world/germ-war-a-current-world-threat-is-a-remembered-nightmare-in-china.html.

[235] Han Chinese, representing approximately 92% of China's population, have been found by multiple studies to be genetically homogenous, with minor differences between northern and southern regional location. See, for example, Liu S, Huang S, Chen F, et al. Genomic Analyses from Non-invasive Prenatal Testing Reveal Genetic Associations, Patterns of Viral Infections, and Chinese Population History. Cell. 2018 Oct 4;175(2):347-359.e14. doi: 10.1016/j.cell.2018.08.016. PMID: 30290141.

[236] See, for example, https://www.csis.org/analysis/chinas-new-2019-defense-white-paper; https://www.rand.org/content/dam/rand/pubs/conf_proceedings/CF145/CF145.chap7.pdf

commonly cite Sun Tzu's The Art of War, which states that "[T]hose skilled in war subdue the enemy's army without fighting hard. They capture the enemy's cities without a storming attack and overthrow his state without excessive and perpetual damage. Their aim must be to take all under heaven intact through strategic superiority."[237] Specific examples, presented in chronological order, include the following:

- A 1999 *Bulletin of the Atomic Scientists* report entitled "China: War Without Rules"[238] described the central conclusion of the 1999 Chinese language book *Warfare Beyond Rules: Judgment of War and Methods of War in the Era of Globalization*[239] – authored by two prominent PLA officers and published by the PLA Press – as follows: "China should not hesitate–if it should have to defend itself–to use as many means of warfare as possible, including weapons that are not 'permitted' by international law and the rules of war, such as chemical and biological weapons."

- In a 2005 English language paper, Colonel Guo Ji-Wei, Director of the PLA's Department of Medical Affairs, Southwest Hospital, Third Military Medical University, Chongqing, and biotechnologist Xue-sen Yang argued that "[b]iotechnological weapons can cause destruction that is both more powerful and more civilized than that caused by conventional killing methods like gunpowder or nuclear weapons…the increased pace of development of modern biotechnology tells us that the day on which we will begin to make full military use of its advantages is not too far off. We believe that command of military biotechnology is a reasonable scientific presumption, not a scientific illusion. In the near future, when military biotechnology is highly developed, modern biotechnology will have a revolutionary influence on the organization of military power with its more direct effects on the main entity of war—human beings. Modern biotechnology offers an enormous potential military advantage."[240]

[237] Sunzi, active 6th century B.C and Samuel B. Griffith, The Art of War. London: Oxford University Press, 1971.
[238] Zhang M. China: War Without Rules. Bulletin of the Atomic Scientists. 1999;55(6):16-18. doi:10.2968/055006007
[239] Liang Q and Xiangsui W. Warfare Beyond Rules: Judgment of War and Methods of War in the Era of Globalization. Beijing: PLA Literature and Arts Publishing House; February 1999.
[240] Ji-Wei G and Yang X. Ultramicro, Nonlethal, and Reversible: Looking Ahead to Military Biotechnology. Military Review, July-August 2005. https://www.armyupress.army.mil/Portals/7/military-review/Archives/English/Dir-Select/nano-technology.pdf

- In a 2006 English language paper, Colonel Ji-Wei again argued for the application of biotechnology – including genetic weapons – as a "new attacking power," as follows: "[m]odern biotechnology…can be used to bring damages and injuries to individuals in war in a more accurate and effective fashion. Different military biotechnologies can be chosen in accordance with different pathogenic factors to meet different military goals. The attack, therefore, will wound different levels of specific gene, protein, cell, tissue, and organ. It no doubt will be more effective to cause damages than conventional weapons, yet the nonlethal effect will remain to be civilized in terms of postwar reconstruction and hatred control. With ultrastructural damage, targets are chosen directly from a nucleotide sequence or a certain protein structure. Affecting the structure and function of a gene or a protein as a damaging effect can cause human physiological dysfunction. Precision injury and ultramicro damage are two wounding methods of modern biotechnologies based on genomics and proteomics…By means of gene regulation, certain, or a couple of, key physiological functions in a human body—such as learning, memorizing, balancing, fine manipulation, and even the 'bellicose' character—can be injured precisely without a threat of life… Therefore, biotechnology aggressiveness gives rise to relatively merciful conquest as compared to other weapons."[241]

- In 2010, Colonel Ji-Wei expanded on these concepts in the Chinese language book *Right-to-Life War*[242] (a.k.a. *War for Biological Dominance*).[243]

- As noted previously, in 2015 a PLA Daily article co-authored by then-president of the PLA's Academy of Military Medical Sciences He Fuchu[244] (now AMS Vice President overseeing implementation the PLA's civil-military fusion strategy) entitled "Biotechnology will become a new strategic commanding point for the future military revolution" argued that "the weaponization of biological bodies will become a reality in the future, non-traditional combat styles will take the

[241] Ji-Wei G. The Command of Biotechnology and Merciful Conquest in Military Opposition. Military Medicine, Vol. 171, November 2006.
[242] https://baike.baidu.com/item/%E5%88%B6%E7%94%9F%E6%9D%83%E6%88%98%E4%BA%89
[243] See the August 2019 article Weaponizing Biotech: How China's Military is Preparing for a 'New Domain of Warfare,' https://www.defenseone.com/ideas/2019/08/chinas-military-pursuing-biotech/159167/?oref=d-mostread
[244] https://www.chinavitae.com/biography/He_Fuchu/bio

stage, 'biological frontier' will become a new high frontier of national defense."[245]

- Also noted previously, a 2017 article by He Fuchu entitled "The future direction of the new military direction in the world" stated that "[b]iotechnology will make biological weaponization a reality, new non-traditional forms of confrontation such as biological attack, biological destruction and ecological control will become possible, and 'biological frontier' will break through the traditional national security and national defense boundaries and become a new national defense frontier after land, sea, air, sky, electricity and network."[246]

- In 2017, the PLA's National Defence University published a book by retired PLA General Zhang Shibo[247] entitled *New Highland of War* (a.k.a. *War New Heights*), which emphasized the potential offensive applications of biotechnology including "ethnic genetic attacks."[248]

Capabilities and Motivations of the Russian Federation

Russian Federation Technical Capabilities

Like China, Russia has increasingly emphasized the potential for biotechnology to transform the battlefield and has nonspecifically promoted biotechnology to strategically offset 'new foreign weapons," including those "created abroad on the basis of the latest achievements in genomics..."[249,250] However, we failed to uncover any indicators of military development of dual-use biotechnology related to precision medicine, nor have we identified any indicators of military application of civilian precision medicine-related biotechnology, whether for offensive or defensive purposes. What appears clear is that the Russian Federation (and, previously, the Soviet Union) has long recognized the potential for genetic engineering to alter the threat landscape – including

[245] https://web.archive.org/web/20190813042422/http://www.81.cn/jwgz/2015-10/06/content_6709533.htm
[246] https://web.archive.org/web/20190823210313/http://www.xinhuanet.com/politics/2017-08/24/c_129687890.htm
[247] https://www.chinavitae.com/biography/Zhang_Shibo
[248] https://www.amazon.cn/dp/B01MT8VA03
[249] Russian Federation. Principles of State Policy in the Field of Chemical and Biological Safety/Security in the Russian Federation to 2025 and Beyond." Order no. PR-2573, November 1, 2013.
[250] For a full accounting and analysis of official Russian statements in this regard, see Chapter 3, Russian Biosecurity and Military Modernization of Zilinskas RA and Mauger P, 2018. Biosecurity in Putin's Russia. (Boulder, CO: Lynne Rienner Publishers).

with respect to genetic weapons – and that Russia has increasingly prioritized genomics for both precision medicine and forensics applications, supported by considerable investment in supporting technologies such as AI.

The former Soviet Union housed the world's largest and most advanced offensive biological warfare (BW) program, which involved extensive efforts to apply genetic engineering to enhance weaponized pathogens. Since the dissolution of the Soviet Union, former BW institutes have continued to perform related research; for example, scientists at Russia's State Research Center for Virology and Biotechnology "Vector," the civilian virology hub of the former program, have successfully inserted into vaccinia virus (a relative of the smallpox virus) genes coding for Japanese encephalitis virus protein E, Venezuelan equine encephalitis (VEE) virus structural protein, tickborne encephalitis (TBE) virus protein E, Ebola vp24, Marburg virus nucleoprotein, beta endorphin, angiogenin, and myelin basic protein. Scientists at Russia's Gamaleya Institute, another former BW institute which has openly published on CRISPR-Cas9 technologies, maintains research ties with the Russian Ministry of Defense's (MOD) 48th Central Research Institute ("Kirov Institute"), a long-closed lead agency for Russian military research on biology, and specifically its Virology Center in Sergiev Posad (formerly Zagorsk), the primary viral arm of the closed MOD BW apparatus.[251] Both the Kirov Institute and Sergiev Posad, as well as a third closed MOD facility of the 48th Central Research Institute in Yekaterinburg (formerly Sverdlovsk), are restricted under the US Department of Commerce Bureau of Industry and Security's Export Administration Regulations ("Entity List").[252] Of note, the Russian MOD's official website includes a definition of genetic weapons as follows:

> "A type of weapon able to damage the genetic (hereditary) apparatus of people. It is assumed/expected that some viruses can/may serve as the active principle. These viruses are in possession of mutagenic activity (with the capability to cause hereditary changes) and can introduce into a chromosome cells that contain deoxyribonucleic acid (DNA) and even chemical mutations, taken from natural sources by chemical synthesis or biotechnological methods. The primary result of the use of genetic weapons is damage/injury and changes

[251] See, for example, Dolzhikova IV, Zubkova OV, Tukhvatulin AI et al. Safety and immunogenicity of GamEvac-Combi, a heterologous VSV- and Ad5-vectored Ebola vaccine: An open phase I/II trial in healthy adults in Russia. Hum Vaccin Immunother. 2017 Mar 4;13(3):613-620. doi: 10.1080/21645515.2016.1238535. Syromyatnikova, Borisevich, Pantyukhov and numerous others are identified as being from "48 Central Research Institute, Ministry of Defense, Oktjabr'skaja Str. 11, Sergiev Posad-6, Moscow oblast, 141306, Russia."
[252] Federal Register Vol. 85, No. 167; Thursday, August 27, 2020; Rules and Regulations; Department of Commerce Bureau of Industry and Security 15 CFR Part 744 [Docket No. 200824–0225] RIN 0694–AI11, Addition of Entities to the Entity List, and Revision of Entries on the Entity List

> to basic/primary structure of DNA, which can lead to serious diseases and their hereditary transmission."[253]

Beyond legacy BW institutes, Russia has taken direct and indirect steps to enhance relevant dual-use technical capabilities.[254,255] For example, The Genome Russia project at Saint Petersburg State University is developing a database of whole-genome sequences from at least 3,000 men and women originating from different regions of Russia whose ancestors are indigenous to the region for several generations, with the reported goal of understanding genome variations in these groups, detecting features that affect disease incidence and prevalence, and identifying medically-relevant genomic variants that might serve as the basis for future precision medicine initiatives.[256] A number of Russian research institutes are actively exploring genomic indicators of drug response[257] and, more broadly, disease susceptibility and severity.[258] However, there is a paucity of related Russian peer-reviewed publications in international scientific journals, whether due to the historically limited access of search engines such as PubMed to Russian journals, potential publication restrictions on the part of Russian researchers, or a comparably slow pace of research and technological advance compared to China and the US as well as other nations.

From a forensics perspective, in November 2020 Russia introduced a bill to expand the State's legal authority to collect genomic information and empower the Investigative Committee of the Russian Federation to mandate genomic

[253] Ministry of Defense of the Russian Federation, Encyclopedia: Weapons on New Physical Principles [in Russian], available at http://encyclopedia.mil.ru/encyclopedia/dictionary/details.htm?id=13770@morfDictionary

[254] See Zilinskas RA and Mauger P, 2018. Biosecurity in Putin's Russia. (Boulder, CO: Lynne Rienner Publishers).

[255] See for example https://www.nature.com/articles/d41586-020-00753-7; https://www.themoscowtimes.com/2020/03/04/rosneft-joins-russias-gene-editing-tech-program-a69520

[256] http://genomerussia.spbu.ru/?lang=en

[257] See, for example, Sorokin M, Kholodenko R, Suntsova M, et al. Oncobox Bioinformatical Platform for Selecting Potentially Effective Combinations of Target Cancer Drugs Using High-Throughput Gene Expression Data. Cancers (Basel). 2018 Sep 29;10(10):365. doi: 10.3390/cancers10100365. PMID: 30274248; PMCID: PMC6209915. Zolotovskaia MA, Sorokin MI, Petrov IV, et al. Disparity between Inter-Patient Molecular Heterogeneity and Repertoires of Target Drugs Used for Different Types of Cancer in Clinical Oncology. Int J Mol Sci. 2020 Feb 26;21(5):1580. doi: 10.3390/ijms21051580. PMID: 32111026; PMCID: PMC7084891.

[258] See, for example, Levchenko A, Kanapin A, Samsonova A, et al. A genome-wide association study identifies a gene network associated with paranoid schizophrenia and antipsychotics-induced tardive dyskinesia. Prog Neuropsychopharmacol Biol Psychiatry. 2020 Oct 13;105:110134. doi: 10.1016/j.pnpbp.2020.110134. Epub ahead of print. PMID: 33065217. Shadrina AS, Shashkova TI, Torgasheva AA, et al. Prioritization of causal genes for coronary artery disease based on cumulative evidence from experimental and in silico studies. Sci Rep. 2020 Jun 26;10(1):10486. doi: 10.1038/s41598-020-67001-w. PMID: 32591598; PMCID: PMC7320185. Shadrina A, Tsepilov Y, Sokolova E, et al. Genome-wide association study in ethnic Russians suggests an association of the MHC class III genomic region with the risk of primary varicose veins. Gene. 2018 Jun 15;659:93-99. doi: 10.1016/j.gene.2018.03.039. Epub 2018 Mar 15. PMID: 29551506.

registration of its citizens.[259] Russia's Ministry of Internal Affairs subsequently announced its intention the establish a biometric database called the Federal Information System of Biometric Accounting containing genomic as well as fingerprint and facial recognition data from both Russians and foreigners over the next three years.[260] Russian researchers have published in peer-reviewed international scientific journals on genomic relatedness between species[261] as well as human subpopulations,[262] including internal Russian and regional/neighboring country subpopulations,[263] though it should be noted that the number of relevant publications is again far less than those produced by China, the US, and other nations.

Future precision medicine and forensics efforts might benefit from Russia's current expansion in the field of AI. In October 2019, the Office of the President of the Russian Federation released a national AI strategy;[264] the Russian Direct Investment Fund (RDIF) has raised $2 billion from foreign investors to support domestic companies developing AI solutions;[265] and Russia is funding AI research through both the State-owned Russian Venture Company, whose 30 billion ruble fund – roughly $450 million – aims to create a mature venture capital market that will make Russia a leader in the global

[259] №1048800-7 Законопроект :: Система обеспечения законодательной деятельности (duma.gov.ru)
[260] МВД создаст банк биометрических данных россиян и иностранцев - Общество - ТАСС (tass.ru)
[261] See, for example, Suntsova MV, Buzdin AA. Differences between human and chimpanzee genomes and their implications in gene expression, protein functions and biochemical properties of the two species. BMC Genomics. 2020 Sep 10;21(Suppl 7):535. doi: 10.1186/s12864-020-06962-8. PMID: 32912141; PMCID: PMC7488140.
[262] See, for example, Khvorykh GV, Mulyar OA, Fedorova L, et al. Global Picture of Genetic Relatedness and the Evolution of Humankind. Biology (Basel). 2020 Nov 10;9(11):392. doi: 10.3390/biology9110392. PMID: 33182715; PMCID: PMC7696950.
[263] See, for example, Balanovska E, Lukianova E, Kagazezheva J, et al. Optimizing the genetic prediction of the eye and hair color for North Eurasian populations. BMC Genomics. 2020 Sep 10;21(Suppl 7):527. doi: 10.1186/s12864-020-06923-1. PMID: 32912208; PMCID: PMC7488246. Boulygina EA, Borisov OV, Valeeva Evet al. Whole genome sequencing of elite athletes. Biol Sport. 2020 Sep;37(3):295-304. doi: 10.5114/biolsport.2020.96272. Epub 2020 Jun 10. PMID: 32879552; PMCID: PMC7433326. Khrunin AV, Khvorykh GV, Fedorov AN, Limborska SA. Genomic landscape of the signals of positive natural selection in populations of Northern Eurasia: A view from Northern Russia. PLoS One. 2020 Feb 5;15(2):e0228778. doi: 10.1371/journal.pone.0228778. PMID: 32023328; PMCID: PMC7001972. Stepanov VA, Vagaitseva KV, Kharkov VN et al. [Panel of X-linked single-nucleotide polymorphic markers for DNA identification (XSNPid) based on multiplex genotyping by multilocus PCR and MALDI-TOF mass spectrometry]. Mol Biol (Mosk). 2016 May-Jun;50(3):445-56. Russian. doi: 10.7868/S0026898416030150. PMID: 27414782. Stepanov V, Vagaitseva K, Kharkov V, Cherednichenko A, Bocharova A, Berezina G, Svyatova G. Forensic and population genetic characteristics of 62 X chromosome SNPs revealed by multiplex PCR and MALDI-TOF mass spectrometry genotyping in 4 North Eurasian populations. Leg Med (Tokyo). 2016 Jan;18:66-71. doi: 10.1016/j.legalmed.2015.12.008. Epub 2015 Dec 19. PMID: 26832380.
[264] https://tass.com/economy/1082644
[265] https://www.themoscowtimes.com/2019/05/31/russia-raises-2bln-for-investment-in-artificial-intelligence-a65824

technology development,[266] and the Russian Direct Investment Fund,[267] another major effort to support more private sector companies developing AI. The Russian Direct Investment Fund is currently sanctioned by the US Department of the Treasury's Office of Foreign Assets Control (OFAC).[268]

Russian Federation Motivations

Despite its role as an initial signatory State Party to the BWC, it is well-documented that the former Soviet Union maintained the world's largest offensive biological warfare (BW) program from the coincident birth of genetic engineering in the early 1970s through the Soviet Union's collapse in December 1991. It has been widely speculated, both by official US government sources and private analysts, that the same BW program continues in the Russian Federation against international law to this day. Accordingly, the US State Department's 2020 Compliance Report states that "[a]vailable information does not allow the United States to conclude that the Russian Federation (Russia) has fulfilled its Article II obligation to destroy or to divert to peaceful purposes BW items specified under Article I of its past BW program."[269] The report further states that "since 2011, the Russian Federation has revised plans and funding to its national chemical and biological facilities that fall under the Russian Ministry of Defense without providing relevant details in their annual CBM reports."

A widely publicized 2012 essay by then-Russian Prime Minister Vladimir Putin accelerated international concerns by apparently calling for his nation's development of genetic weapon systems, as follows:

> "In the more distant future, weapons systems based on new principles…genetic, psychophysical and other technology) will be developed. All this will…provide entirely new instruments for achieving political and strategic goals. *Such high-tech weapons systems will be comparable in effect to nuclear weapons but will be more 'acceptable' in terms of political and military ideology."*[270] [Emphasis added]

It is worth noting that the *acceptability* argument presented by Putin echoes similar genetic weapon justifications voiced by PRC military officials the decade before (see above discussion on PRC motivations). The implication that such weapon systems are "acceptable" suggests that Russian leadership

[266] https://www.rvc.ru/en/
[267] https://rdif.ru/Eng_Index/
[268] https://sanctionssearch.ofac.treas.gov/Details.aspx?id=8641
[269] https://www.state.gov/wp-content/uploads/2020/06/2020-Adherence-to-and-Compliance-with-Arms-Control-Nonproliferation-and-Disarmament-Agreements-and-Commitments-Compliance-Report.pdf, pp. 45-46.
[270] Putin V. Rossiiskaya Gazeta, February 20, 2012.

assesses no or limited moral or legal constraints to pursue genetic weapon systems, despite their apparent prohibition by the BWC.

While Putin's statement was echoed by senior officials at the time,[271] further official statements and media reports have been limited in the years since. Russian BW expert Dr. Raymond Zilinskas, in a seminal 2018 analysis of Russian BW-related indicators, "noted the numerous high-level calls for the development of biotechnology-based weapons in Russia, without further specification."[272] Later that year, the Washington Post reported that Putin's statement had sparked years of significant activity at former BW laboratories in Russia, including procurement of dual-use production equipment, extensive construction at Ministry of Defense (MOD) laboratories, and upgrades to testing facilities.[273]

Concurrently, Russian malign influence campaigns have continued to identify the US as potential perpetrators of ethnic targeting,[274] a strategy dating back to Soviet-era disinformation identifying the US as responsible for Africa's AIDS epidemic.[275] For example, the 2017 article "'Ethnic Bomb' Feared as US Air Force Confirms Collection of Russian DNA" by Venezuela's teleSUR news outlet – which shares content with the Russia Today news outlet and is considered by some US officials to be spreading anti-American propaganda[276] – included the following quote attributed to President Putin:

> "Do you know that biological material is being collected all over the country, from different ethnic groups and people living in different geographical regions of the Russian Federation? The question is – why is it being done? It's being done purposefully and professionally. We are a kind of object of great interest. Let them do what they want, and we must do what we must."[277]

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[271] See, for example: Zilinskas RA. Take Russia to task on bioweapons transparency. Nature Medicine 18:6, June 2012. Hoffman DE. Genetic weapons, you say? Foreign Policy, March 27, 2012. All corresponding Russian language archives, including "Prime Minister Vladimir Putin Holds a Meeting on the Tasks He Set in His Articles as a Presidential Candidate" (March 22, 2012, Archive of the Official Site of the 2008–2012 Prime Minister of the Russian Federation Vladimir Putin), appear to have been removed.

[272] Zilinskas RA and Mauger P, 2018. Biosecurity in Putin's Russia. (Boulder, CO: Lynne Rienner Publishers).

[273] Warrick J. Poisoning of Russian ex-spy puts spotlight on Moscow's secret military labs. Washington Post, March 18, 2018.

[274] See, for example, http://dilyana.bg/the-pentagon-bio-weapons/; http://dilyana.bg/us-diplomats-involved-in-trafficking-of-human-blood-and-pathogens-for-secret-military-program/

[275] See, for example, https://www.nytimes.com/2018/11/12/opinion/russia-meddling-disinformation-fake-news-elections.html; https://aktivnyye.com/f/Soviet_Active_Measures_in_the_Post-Cold_War_Era_1988-1991.pdf; https://www.globalsecurity.org/intell/library/reports/1987/soviet-influence-activities-1987.pdf

[276] See, for example, Torres NG. US Congressman Asks for Investigation of Venezuela's Telesur. Miami Times, April 4, 2018. Available at: https://joewilson.house.gov/media-center/articles/us-congressman-asks-for-investigation-of-venezuela-s-telesur

[277] https://www.telesurenglish.net/news/Ethnic-Bomb-Feared-as-US-Air-Force-Confirms-

While the motivation behind such disinformation – beyond sowing broad mistrust toward the US – is debatable, one hypothesis is that this messaging is internally directed to feed the so-called siege mentality of the Russian population and its strategic and military culture, contributing to internal cohesion and protectionism that might justify research and technology development that would enable, at a minimum, an "in kind" response. The Soviet Union exhibited similar behavior during the Cold War, when allegations about (nonexistent) US biological weapons-related activities served to justify its own BW program.[278] Given the lack of (1) a BWC compliance mechanism, and (2) transparency regarding Russian biological weapons-related activities, particularly within its long-inaccessible MOD laboratories, at a minimum the possibility cannot be excluded.

Assessment

Both China and Russia are actively investing in precision medicine capabilities and have acknowledged their dual-use potential. China's current technical capabilities and long-term outlook appear to exceed those of Russia based on the observed rate of technological progress and corresponding investment, though the results of our data mining activities may be confounded by comparative differences in Chinese and Russian research transparency and reporting practices. China appears to be more open with its activities and investments, likely driven at least in part by economic interdependencies and the potential economic gains that come with marketing Chinese capabilities and technologies to Western clients and funding sources. These economic interdependencies are critical to the stability of the global economy; however, they have enabled China to strategically target critical emerging technologies with the potential to establish innovation and market dominance, whether or not China leverages access to and mastery of these technologies to develop next generation military equipment/weapon systems through its CMI programs. The US has largely allowed this to happen despite increasing internal warnings and external rhetoric regarding underlying intent and implications. [It should be noted that throughout our data mining activities, we observed a number of co-publications between Chinese and US researchers, Russian and US researchers, and Chinese and Russian researchers, indicating a level of collaboration and data-sharing that should serve to benefit all three nations as well as the global community.]

From a strategic stability perspective, the question then becomes whether China or Russia may seek to exploit the dual-use potential of precision

Collection-of-Russian-DNA-20171102-0028.html

[278] See, for example, Zilinskas RA. The Soviet Biological Weapons Program and Its Legacy in Today's Russia. Center for the Study of Weapons of Mass Destruction, Occasional Paper No. 11 (National Defense University Press; Washington, DC: July 2016), pp. 28-29.

medicine, why/to what end, and to what degree of technical competence in the near- (<5 years) and long-term (5-15 years)?

Chinese and Russian doctrine (and leadership commentary) indicate a common concern regarding technological surprise, citing advances in genomics, and biotechnology more broadly, as potential adversary capabilities that must be studied, understood, and monitored. One might assume that the primary adversary in either case is the US; however, great power competition extends to China-Russia competition as well, and there are a number of reasons to consider the complex China-Russia relationship as a potential driver for the exploration of dual-use precision medicine capabilities and the possibility of genetic weapon systems by both parties.

First, China appears to recognize its own vulnerability to genetic targeting given the comparative genomic homogeneity of its dominant Han Chinese population, who make up 92% of China's population.[279,280,281] Second, Russia and China share a border with a large population differential that has witnessed conflict in the past: in fact, in 1969 conflict on the then-Sino-Soviet border escalated to the point that Moscow publicly threatened and privately considered a preemptive nuclear strike on China's fledgling nuclear program.[282]

Third, it has been theorized, including by Russian BW scientists themselves during informal conversations between 2003-2006, that the Soviet BW program was as much driven by China as it was the West. This theory was corroborated by interviews conducted with Russian scientists regarding why the State Research Center of Virology and Biotechnology "Vector," the long-recognized civilian virology arm of the former Soviet offensive BW program,

[279] See, for example, Chiang CWK, Mangul S, Robles C, Sankararaman S. A Comprehensive Map of Genetic Variation in the World's Largest Ethnic Group-Han Chinese. Mol Biol Evol. 2018 Nov 1;35(11):2736-2750. doi: 10.1093/molbev/msy170. PMID: 30169787; PMCID: PMC6693441.

[280] The Han Chinese Genomes Database (PGG.Han), which includes genomic data from 114,783 Han Chinese individuals, is available at: 汉族基因组数据库 (biosino.org); 汉族基因组数据库 (hanchinesegenomes.org).

[281] It should be noted that while Han Chinese are a comparatively homogenous population, deep sequencing has revealed considerable genomic variation, and SNP profiles notably differ between Northern and Southern Han Chinese. See, for example: Lan T, Lin H, Zhu W, et al. Deep whole-genome sequencing of 90 Han Chinese genomes. Gigascience. 2017 Sep 1;6(9):1-7. doi: 10.1093/gigascience/gix067. Chen J, Zheng H, Bei JX, et al. Genetic structure of the Han Chinese population revealed by genome-wide SNP variation. Am J Hum Genet. 2009 Dec;85(6):775-85. doi: 10.1016/j.ajhg.2009.10.016. PMID: 19944401; PMCID: PMC2790583. Xu S, Yin X, Li S, et al. Genomic dissection of population substructure of Han Chinese and its implication in association studies. Am J Hum Genet. 2009 Dec;85(6):762-74. doi: 10.1016/j.ajhg.2009.10.015. PMID: 19944404; PMCID: PMC2790582.

[282] See, for example, Gerson M. The Sino-Soviet Border Conflict. Center for Naval Analyses: November 2010. https://www.cna.org/CNA_files/PDF/D0022974.A2.pdf. See also: https://nsarchive2.gwu.edu/NSAEBB/NSAEBB49/index2.html

was located outside the city of Novosibirsk in southwestern Siberia.[283] Fourth, a genetically-targeted weapon would, like BW more broadly, conceivably serve as both a powerful deterrent and effective depopulation agent. Russia shares the aforementioned border with China, which harbors the largest population in the world. China, having suffered numerous devastating BW attacks at the hands of the Japanese during World War II, also harbors a generational phobia about such weapons. And Russia has proven to be a strategic actor with respect to its BW program, first by accelerating its pace upon signature of the BWC; later by prioritizing smallpox research upon worldwide eradication of the disease; and more recently by selecting agents for development that can be readily disguised by emerging peaceful research, for example the use of vaccinia virus as a transmission vector for gene delivery.

Given this context, we assess that while the genomic heterogeneity of the US population is largely protective, the perceived genomic homogeneity and thus vulnerability of Han Chinese might drive China to investigate dual-use aspects of precision medicine for defensive purposes. In this respect, the greatest threat to China may be Russia, given their shared border and Russia's BW history. From an offensive perspective, if China were so inclined, it could conceivably explore the utility of a genetic weapon system to target an ethnic minority such as the Uyghurs within its borders,[284] but as discussed above the combination of technical challenges and alternative approaches to such a Use Case make such exploration impractical. The PRC certainly is developing the precision medicine capability that would enable them to explore this possibility, is collecting civilian genomic information that might be applied accordingly, and has long-targeted these same minorities via a variety of measures, including detention centers and reeducation programs.

[283] Leitenberg M and Zilinskas RA. The Soviet Biological Weapons Program. Cambridge, Harvard University Press, 2012. Page 207: "Interviewed Biopreparat scientists agree that the [VECTOR] site was chosen for five major reasons: (1) Proximity to China. [VECTOR] scientists said that if the Soviet Union went to war with China, [VECTOR] would be where it needed to be. In other words, China was a possible target for biological attack with viruses, particularly because Soviet relations with China had been strained since the 1969 Damansky Island incidents."

[284] See, for example, Zhang J, Wang H, Niu G, et al. Deciphering DMET genetic data: comprehensive assessment of Northwestern Han, Tibetan, Uyghur populations and their comparison to eleven 1000 genome populations. Artif Cells Nanomed Biotechnol. 2018;46(sup3):S1176-S1185. doi: 10.1080/21691401.2018.1533849. Epub 2019 Jan 28. PMID: 30688101.

Part III. Action Plan

The Technical Focus Group discussed whether the technological landscape warrants the introduction of controls, and considered a range of potential control options for implementation (**Figure 2**). The group emphasized the need to preserve R&D in the public interest while identifying options that are both broadly applicable to preserving the US bioeconomy and highly specific to the threat of genetic weapon systems, and ultimately recommended the following set of controls for consideration by the US policymaking community.

Figure 2. Potential control options (adapted from Tucker JB. Double-Edged Innovations. Defense Threat Reduction Agency Advanced Systems and Concepts Office, July 2010)

Differentiate between human and non-human genomic information when determining protection requirements. Both human and non-human genetic information contribute to growing the US bioeconomy, creating jobs, and building a technological advantage. With one notable exception, differentiating between human and non-human data may aid the US in establishing the necessary balance between open information-sharing and security. By creating a culture around openly sharing non-human data – for example, the open sharing of viral sequences, the benefits of which were demonstrated during the COVID-19 pandemic[285] – the US can retain its position of scientific transparency while protecting its populace against the range of vulnerabilities that sharing human data may present.[286] The notable exception is genomic sequencing data of monoculture plots of staple cultivars that provide much of the food in the US, the genomic homogeneity of which makes them particularly vulnerable to targeting by a genetic weapon.

Explore applicability of national-level export controls on human genomic information. Securing exploitable human genomic information provides a balanced option for near-term (< 5 years) mitigation of corresponding vulnerabilities. Export controls can help mitigate the security implications of intangible data transfer to this end; however, the major mechanisms in place – including international regimes, national legislation, and third party oversight – have had mixed results in stemming the tide of strategic information flow from the US to date, including via export of technical data and technologies by US companies, growing foreign investments in critical sectors in the US, and the increasingly dual-use nature of many technologies. China, in particular, further benefits from residing outside certain multilateral export control regimes [the Australia Group, Missile Technology Control Regime (MTCR), and Wassenaar Arrangement] as well as the jurisdiction of regulatory mechanisms such as HIPAA. Additionally, export controls on data that may be considered simply informational in nature – as opposed to technology (e.g., "know how") – are likely to be resisted by academic, scientific, and industrial communities, especially if already widely distributed and available.

While international initiatives like Multilateral Action on Sensitive Technology (MAST), which focuses on countering China's strategic technology acquisition programs such as foreign direct investment and intangible technology transfer, may provide some level of gap closure, national level export control measures to protect US genomic information and interests by restricting transfers to specified end-users of concern may offer the greatest return on investment

[285] See, for example, Lu R, Zhao X, Li J et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020 Feb 22;395(10224):565-574. doi: 10.1016/S0140-6736(20)30251-8. Epub 2020 Jan 30. PMID: 32007145; PMCID: PMC7159086.

[286] It should be noted that one panel member disagreed with this recommendation due to the medical value of openly sharing human genomic data, and instead called for the development of a system that determines the degree to which these data can be shared.

in the near-term. Such measures – such as placing an end-user of concern on the U.S. Department of Commerce's Entity List – would be defined less by the nature of the data itself and more by the whether the end-user has a track record of abusing similar data or presents a risk of doing so. Strengthening implementation of national policy reform and the corresponding new legislative measures related to the Committee on Foreign Investment in the US (CFIUS) – namely the 2018 Foreign Investment Risk Review Modernization Act (FIRRMA) and the 2018 Export Control Reform Act (ECRA) comprising "CFIUS 2.0" – could supplement these measures, particularly in defining and safeguarding enabling technologies applicable to misuse of human genomic information by foreign entities.

Secure protected data from remote exploitation. Events during the COVID-19 pandemic demonstrated the importance of protecting sensitive biotechnological data from cybersecurity threats around the world, including China and Russia.[287] A successful cyberattack involving surreptitious network intrusion and exfiltration of data would effectively circumvent any export controls relevant to human genomic information, obviating the need for direct access. Corresponding security measures are therefore in the national interest, particularly as exploitable data are increasingly analyzed and stored on the cloud.

Establish norms and actively monitor for specific capabilities and activities that have limited funding incentive for peaceful purposes. The Technical Focus Group sought to identify those dual-use capabilities and activities critical to developing a genetic weapon system that would have limited peaceful application, with the goal of establishing corresponding norms and security monitoring approaches. The Technical Focus Group ultimately identified two key activities to this end: (1) the development of capabilities for delivering DNA at scale, at a distance, or in an otherwise undirected way; and (2) T&E activities against representative target populations to ensure predictability of effect. The US should actively monitor for these activities while building international consensus against their pursuit, including via provisioning for non-Party engagement (e.g., Australia Group); reinforcement and expansion of international ethical standards such as those set forth by the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine ("Convention on Human Rights and Biomedicine");[288] and peer-to-peer engagement within the global scientific community akin to the 1975 International Congress on Recombinant DNA Molecules ("Asilomar Conference").[289]

[287] See, for example, https://www.cisa.gov/news/2020/05/13/fbi-and-cisa-warn-against-chinese-targeting-covid-19-research-organizations; https://www.wsj.com/articles/covid-19-vaccine-makers-face-russian-north-korean-cyberattacks-microsoft-says-11605276003

[288] https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164

[289] See, for example, Berg P. Meetings that changed the world: Asilomar 1975: DNA

Leverage technology to establish deterrence by denial. Technological change that increases the feasibility of a genetic weapon system also improves our ability to reduce the threat such a weapon would pose. Building defensive capabilities that deter a potential adversary from pursuing a genetic weapon system, i.e., "deterrence by denial," therefore represents a foundational counterstrategy that is being actively pursued by the US. For example, the Defense Advanced Research Project Agency's (DARPA) Safe Genes program strives to control, counter, and reverse the effects of nefarious or otherwise undesirable genome editing.[290] Another DARPA example is the Insect Allies program, which strives to address the above-described vulnerability of homogeneous crop systems by enabling rapid, scalable introduction of genetic modifications using insect vectors.[291] Legislative reform focused on deterrent and defensive measures captured under the US National Security Strategy, combined with sustained R&D investment to maintain technical superiority and advance technologies to counter genetic weapon systems, would further reduce the confidence of potential adversaries in the effectiveness of such weapons and disincentivize corresponding investment.

Continue the conversation. The dual-use R&D described in this report holds the potential for tremendous benefit to the US bioeconomy and the health and well-being of US and global populations. China clearly recognizes this transformative power, meriting significant State-level investment. Such sustained investment may enable China to surpass the US as the de facto centralizing power for biotechnology, providing a level of influence over corresponding norms that could prove detrimental to US interests in the long-term. It is therefore incumbent upon US scientists and policymakers to continue to seek forward-leaning approaches that preserve peaceful R&D while limiting the potential for data misuse over time. By continuing the conversation, US science and policy stakeholders will be better positioned both to make informed risk-benefit decisions in this rapidly evolving and complex technical space and to build corresponding consensus at the international level.

modification secured. Nature. 2008 Sep 18;455(7211):290-1. doi: 10.1038/455290a. PMID: 18800118.

[290] https://www.darpa.mil/program/safe-genes

[291] https://www.darpa.mil/program/insect-allies

Appendices

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