Ethical Frameworks for Deployment of Synthetic Biology in the Indo-Pacific

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Executive Summary

Synthetic Biology (SynBio) encompasses exciting technologies that can revolutionise our way of living through unlocking new energy sources, developing new materials, transforming healthcare and reconditioning local or global ecosystems. As a rising field that holds the potential of changing the way the world functions, its potential misuse and ethical concerns create a daunting task for its appropriate governance.

At the moment, SynBio ethics are governed by a patchwork of international agreements, laws and regulations that are not completely fit for purpose and in some cases are poorly monitored and enforced. In particular, perspectives from the Indo-Pacific countries, which host at least 50% of humanity, are underrepresented in global discussions of SynBio ethics.

Our aim is to initiate the efforts and dialogues that are necessary to fill this gap. Informed by hundreds of discussions with interlocutors from across the region, we devised three frameworks to aid in decision-making and actions. It is our intention to make the frameworks concise and accessible to a wide range of stakeholders and practitioners. Each framework has accompanying matrixes, which we hope can mitigate some of the enforcement and capacity issues pertinent to countries across the region.

The first framework proposes an ethical risk matrix for Synbio applications. It suggests that SynBio ethical risk calculation be governed on the basis of the phenotypic divergence of the application from what already exists in nature and on the reproducibility of the application in nature.

The second framework recognises genetic data as a public good, with informed consent and anonymity as the guiding principles for its use. The proposed decision matrix identifies separate governing factors for human and non-human genomic data to promote responsible cross-border circulation of genetic data. The framework further proposes a tiered structure for countries to grant access to identified genetic data.

The third framework focuses on public and stakeholder engagement. It emphasises two principles of trustworthiness in communication and comprehensiveness in assessing views. Public concerns regarding SynBio can be charted on a matrix with two key dimensions: agency and safety. The framework proposes that public engagement on SynBio focus on feature-based concerns of individual SynBio applications rather than overarching concerns about the field of SynBio.

1

Introduction

Synthetic Biology (SynBio) comprises a suite of critical and emerging technologies that hold great promise for countries in the Indo-Pacific. Applications in key sectors such as nutrition, health, climate action, and bioenergy will have a huge impact on the standard of living across all Indo-Pacific countries. Yet the development and adoption of SynBio applications remain mired in controversies and ethical debates.

1.1. What are Synbio Ethics?

Though there is no consensus on the definition of SynBio, genetic technologies and the principles of engineering are considered its core components. The US and the UK are shifting from "synthetic biology" to "engineering biology" to adapt to the field's expansion. Australia's Commonwealth Scientific and Industrial Research Organisation (CSIRO) defines SynBio as follows:

"Synthetic biology is the rapid development of functional DNA-encoded biological components and systems through the application of engineering principles and genetic technologies. Common characteristics of synthetic biology platforms include laboratory automation, computational design, biological parts standardisation, and high-throughput prototyping and screening."

It is not uncommon to have a broad definition for a rapidly evolving field. The key point we highlight is that it is possible to treat biology as an engineering object and that SynBio enables the development of novel biological systems not found in nature.

It is now possible to read (sequence) and edit the DNA of living organisms cheaply and quickly. It is also possible to write (synthesise) the DNA of organisms, albeit there remain financial and technical constraints to do this at scale.[2] Recently, researchers synthesised whole chromosomes for yeast and inserted them into a DNA-free cell, enabling its

[2] Alex Hoose, Richard Vellacott, Marko Storch, Paul S. Freemont & Maxim G. Ryadnov, "DNA synthesis technologies to close the gene writing gap," Nature Reviews Chemistry, volume 7, Page 144–161 (2023)

reproduction.[3] The development of entirely lab-synthesised organisms may become commercially available. Additionally, research automation and the application of AI to biotechnology have fundamentally accelerated the field.

Humans have consistently shaped the environment through various means, ranging from agriculture and medicine to the breeding of pets. SynBio brings the ability to quickly and accurately engineer biological systems instead of traditional reliance on selecting changes that occurred through iterative and less precise interventions.

SynBio ethics refers to ethical discussions that aim to establish morally acceptable uses of these technological breakthroughs. The ability to 'play God' by writing genetic code and manipulating the fortunes of species or individuals can be unsettling to many. Of course, human impact on the fortunes of species and individual organisms is not new. Climate change is potentially the most powerful example of this. Yet, many would argue that directly altering the genetic attributes of organisms is qualitatively different.[4]

There are many benefits to be accrued from engineering biology. For example, the potential to eliminate devastating genetic diseases such as sickle cell anaemia. In some cases, gene editing appears to be the only solution to save people from unnecessary suffering. But how far should we take human genome editing? Should we try to give humans genetic resistance to cancers or Alzheimer's disease? Should we strive to prevent or remedy biological traits considered 'disadvantaged' or 'diseased'? Who should make these decisions, and what principles should they follow? What further complicates the question is that, in practice, human gene editors will deal with a complex polygenic matrix of trade-offs between certain genes. A boost in one area may create weakness in another.

Human health impact aside, SynBio may also provide solutions to many of the hard-to-abate areas related to climate change. Lab-grown meats, cleaner chemical production using genetically engineered microorganisms, synthetic fuels for aviation and shipping, bioplastics, and biomaterials are all contributors to reducing the impact of the climate crisis. Yet, societal willingness to accept these is not guaranteed, and deployment of Synbio needs to be managed in alignment with the public's ethical and moral judgements.

These are just small snippets of the potential applications, each of which will need to be addressed by a diverse group of stakeholders. What are the pressing issues that arise

[3] Mitch Leslie, "Synthetic yeast project unveils cells with 50% artificial DNA," Science, 8 November 2023, https://www.science.org/content/article/synthetic-yeast-project-unveils-cells-50-artificial-dna.
[4] Daniele Fulvi & Josh Wodak, Planetary Scale Climactic Change Through Bioengineering the Microbial World: A Technofix Imaginary, Under Review, https://doi.org/10.2139/ssrn.4866892

regardless of the specifics of the individual application? How can we create a framework that is helpful to a wide range of stakeholders working across a broad suite of SynBio applications? A few key questions we have identified are:

1. **How should genetic editing of organisms be governed?** What are the foundational principles or practices we should adhere to so that this field can advance sustainably and responsibly transnationally?
2. **How should access to the vast volumes of genetic data collected in gene sequencing be regulated?** The understanding of complex biological systems depends on huge amounts of data. That data could be commercially valuable and, as such, companies are unwilling to share. Another layer of complexity is the privacy and security concerns for human genetic data.
3. **How should the public be consulted, and the benefits to certain groups be weighed against reticence in other groups?** Public views are essential for the sustainable social uptake and support of SynBio technologies.
4. **How should the benefits and costs of these technologies be shared?** Early-stage SynBio products are often out of reach for most people. Countries with environments containing highly diverse plants, animals, or microbes will want to ensure they receive fair economic value for products developed from genetic data contained in their environments. There is a need to derive a delicate balance between benefit-sharing and technological progress.

1.2. The Challenge for Existing Synbio Ethics in The Indo-Pacific

Existing efforts to manage SynBio ethics are spread across a patchwork of different frameworks, conventions, rules and norms. These do not specifically target SynBio but rather deal with different elements of genetic resource management that are related to SynBio. This patchwork of existing activities faces three fundamental challenges:

1. **Suspension over managing the future of gene editing.**

Gene editing is a key technology in the development of SynBio. A global consensus over the specifics of what is acceptable under which condition may be unlikely. But, given known consequences of gene flow and gene drive, and yet-to-be-known impacts of heritable human genome editing, few would disagree that the impact of gene editing transcends geographic or national borders, as well as generational boundaries. Thus, we need to work toward broad principles so as to achieve global coordination if not resolution on critical ethical concerns.

Leading CRISPR scientists jointly called for a moratorium on heritable human genome editing in 2023 as “governance frameworks and ethical principles for the responsible use

of heritable human genome editing are not in place." This is not to say that there have not been efforts to provide global guidelines for human gene editing. UNESCO published a Universal Declaration on the Human Genome and Human Rights in 1997, which was updated after the development of CRISPR.[5] Furthermore, the World Health Organisation (WHO) constituted an advisory committee to develop global standards for Human Genome Editing, which published a framework and a position paper on this topic in 2021.[6] There is also the Oviedo Convention for the Protection of Human Rights and Dignity of the Human Being concerning the Application of Biology and Medicine, which has 29 ratifying countries and currently prohibits heritable human genome editing.[7] It is the only international legally binding instrument on the protection of human rights in the biomedical field.[8] Only European countries ratified the Convention, and most major SynBio powers are not included, so its broader impact is limited.

Most leading SynBio research nations have regulations that explicitly prohibit human genome research for reproduction.[9] However, the ongoing moratorium on the heritable human genome is unlikely to persist indefinitely, particularly in light of the growing public anticipation and (legal and illegal) experimental use of gene editing to tackle urgent health issues.[10] This underlines the urgency of developing a long-term ethical vision for responsible human genome editing.

For other organisms, too, there is a lack of universally agreed-upon gene editing frameworks. For example, there is no universal framework that governs the editing of plants or animals. The International Treaty on Plant Genetic Resources for Food and

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[5] "Universal Declaration on the Human Genome and Human Rights," UNESCO.org, 1997

[6] 'Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing'. Accessed 29 November 2023. https://www.who.int/groups/expert-advisory-committee-on-developing-global-standards-for-governance-and-oversight-of-human-genome-editing.

[7] "Oviedo Convention and its Protocols," The Council of Europe website, last accessed 29 November 2023, https://www.coe.int/en/web/bioethics/oviedo-convention; "Genome editing technologies: final conclusions of the re-examination of Article 13 of the Oviedo Convention," The Council of Europe website, 11 October 2022, https://www.coe.int/en/web/bioethics/-/genome-editing-technologies-final-conclusions-of-the-re-examination-of-article-13-of-the-oviedo-convention.

[8] "Oviedo Convention and its Protocols," The Council of Europe website, last accessed 29 November 2023, https://www.coe.int/en/web/bioethics/oviedo-convention.

[9] Baylis, Françoise, Marcy Darnovsky, Katie Hasson, and Timothy M. Krahn, "Human Germline and Heritable Genome Editing: The Global Policy Landscape", 2020

[10] Owen G Schaefer, "A Case against a Moratorium on Germline Gene Editing," The Conversation, January 9, 2023, https://theconversation.com/a-case-against-a-moratorium-on-germline-gene-editing-113827; Zhang, J. Y. (2023) 'Commoning genomic solidarity to improve global health equality'. *Cell Genomics*, 3(10), 100405. https://doi.org/10.1016/j.xgen.2023.100405.

Agriculture governs the access and sharing of plant resources.[11] However, it does not make fundamental judgments about what is ethically acceptable when editing plant and animal genomes. Furthermore, rules on plant and animal gene editing vary by jurisdiction. Some countries and subnational governments have bans on genetically modified organisms (GMOs).

Most governments have some rules around genetic editing, but they struggle to keep pace with the technology. For example, since 2001, Australia's Office of the Gene Technology Regulator (OGTR) has published three reviews in 2006, 2011 and 2017 of Australia's National Gene Technology Scheme.[12] The last review, which had 27 recommendations for legislative, policy and communication changes, has been in the process of implementation for seven years.[13] However, the technology has changed so much that the 2017 review is out of date.

Because of the confusion and rapid rate of development, many practitioners and governments use the precautionary principle, which focuses on forestalling any potential damage. This is understandable, but as we demonstrate in the first framework in this report, in some cases, this principle may hinder real development opportunities where the risks from SynBio are quite low.

2. **Concerns over benefit-sharing are limiting genetic data sharing, with no clear understanding of what level of data access should be provided under different circumstances.**

Genetic data is a key resource for developing commercially viable SynBio products. However, the circumstances of transferring that data across borders are unclear and often poorly enforced.

Many nations have large-scale human genome data collection for their populations. In terms of broad societal benefit, widespread sharing of this data would allow researchers worldwide to work toward new SynBio products to help improve human health and correct historical health modelling biases. The UK, for example, has its biobank to share UK data with over 30,000 researchers globally as a critical strategy to boost the UK's status in global science as well as in the global bioeconomy. Yet a number of countries,

[11] Charles Lawson and Kamalesh Adhikari, *Biodiversity, Genetic Resources and Intellectual Property*, 2018, 2, https://doi.org/10.4324/9781315098517-1; "International Treaty on Plant Genetic Resources for Food and Agriculture," Food and Agriculture Organization of the United Nations, accessed 28 November 2023, https://www.fao.org/plant-treaty/en/.

[12] Office of the Gene and Technology Regulator, "Legislative reviews," last accessed 5 June 2024, https://www.ogtr.gov.au/about-ogtr/legislative-reviews.

[13] "The Third Review of the National Technology Scheme," Australian Department of Health, October 2018, https://www.genetechnology.gov.au/sites/default/files/2022-02/2017-review-final-report.pdf.

especially those in the Global South, are hesitant to share their data with foreign researchers, not only due to historical and contemporary concerns over biopiracy but also due to a lack of infrastructure and capacity for safe and equitable data-sharing.

Similar concerns over sharing non-human genetic data also exist. Some Southeast Asian countries limit the transfer of such data to protect the unique genetic resources of those countries. Yet, in practice, the laws are not always well enforced. This reinforces the exploitation concerns and further stalls the discussions on institutionalised and supervised data-sharing schemes. This speaks to a lack of enforcement capacity, a general government uneasiness with sharing genetic data, and a government desire (however unsuccessful) to directly protect certain data.

3. **Many Indo-Pacific countries find current conventions for (non-human) genetic resource management and benefit-sharing more harmful than helpful in navigating SynBio ethics.**

The Convention for Biological Diversity (CBD) and its subsequent Nagoya Protocol are designed to ensure the protection of global diversity and appropriate benefit-sharing of genetic resources. Concurrent conventions exist for plants, animals and marine organisms. The CBD has not stopped or slowed down global biodiversity loss.[14] Furthermore, numerous signatory countries in the Indo-Pacific find the CBD to be harmful in certain ways within their domestic contexts.

First, the burden of protecting biodiversity falls on 17 "megadiverse" countries, which are mostly developing countries. These countries comprise only 10% of the earth's surface, but together, they account for more than 70% of its biodiversity.[15] This was recognised at the 2023 CBD Conference of Parties (COP) in which the Kunming-Montreal Global Diversity Framework (GDF) was signed with the goal of aiming to close "the biodiversity finance gap of $700 billion per year."[16]

Second, the implementation of regulations is constrained by the need for economic development and limited regulatory capability. Megadiverse countries have mostly

[14] "Biodiversity loss: what is causing it and why is it a concern?" European Parliament, last updated, 9 June 2021, https://www.europarl.europa.eu/topics/en/article/20200109STO69929/biodiversity-loss-what-is-causing-it-and-why-is-it-a-concern The Living Planet Index (LPI) measures the average decline in monitored wildlife populations. The index value measures the change in abundance in 31,821 populations across 5,230 species relative to the year 1970 (i.e.1970 = 100%). See "Living Planet Index, World," Our World in Data, last accessed 29 November 2023, https://ourworldindata.org/grapher/global-living-planet-index

[15] "Protecting Biodiversity," DCCEEW, October 10, 2021, https://www.dcceew.gov.au/environment/land/nrs/about-nrs/protecting-biodiversity.

[16] "COP15: Final Text of Kunming-Montreal Global Biodiversity Framework,", 2022

supported the CBD. Indonesia, for example, has been an active participant and a key stakeholder in the inception and sustenance of the CBD. However, "Indonesia continues to face challenges in the implementation of regulations based on the CBD, which include the unbearable costs of programs, industry pressure, weak governance, and the rapid loss of forest areas."[17]

In India, there are several national and state laws for implementing the CBD requirements. They have not achieved their goals and instead have become a complex maze of poorly enforced laws. One example is the required Biodiversity Registers, which are meant to be basic records of each region's biological resources. Local levels of government, for the most part, have failed to create and update these registers.[18] Interlocutors in India told the project team that there is limited regulatory and enforcement capacity to monitor compliance across all CBD mandates. This is tying up government resources but not achieving the goals of the CBD.

Third, the benefits of genetic diversity are not perceived to be equally shared. A fundamental North-South technical disparity with SynBio, for example, makes benefit-sharing difficult to achieve. The technological capacities for utilising genetic resources are concentrated in industrialised countries. The highest levels of biodiversity, and thus of potentially valuable genetic resources, are mostly found in developing countries, which have limited negotiating power or socio-political leverage over their Northern partners.

In response, numerous developing countries are limiting the cross-border sharing of genetic resources (including human resources, which have additional privacy and security concerns that are not covered by CBD). This is a defensive approach against being exploited by external companies, who develop valuable SynBio products with limited intention to benefit the local communities.

1.3 How Do Our Proposed Frameworks Respond to These Challenges?

We have divided the document into three frameworks to give stakeholders key areas to prioritise. The first framework focuses on creating a guidance matrix to govern different

[17] Safendrri Komara Ragamustari and Endang Sukara, "Strengthening the genetic diversity conservation narrative in Indonesia: challenges and prospects," Biodiversity and Conservation (2019) 28:1647–1665 https://doi.org/10.1007/s10531-019-01749-0

[18] V Sundararaju, "Implement the Biological Diversity Act in its true spirit," Down to Earth, 21 February 2019, https://www.downtoearth.org.in/blog/wildlife-biodiversity/implement-the-biological-diversity-act-in-its-true-spirit-63322

applications of gene editing. The second framework focuses on responsible cross-border genetic data collection and its circulation. The final framework focuses on public engagement, with particular emphasis on maintaining public literacy and ensuring meaningful public deliberation keeps pace with scientific development.

Each framework has two main components. The first is a set of principles that should guide the ethical decisions in that area. The second component is a matrix or decision tree to guide decisions on specific technologies. The matrix and decision tree are designed to be general enough to be applicable to a wide range of ethical decisions, but also have a level of modularity, so that practitioners can adapt the framework to their specific context.

The frameworks are intentionally short for they are not designed to provide a specific course of action for every possible eventuality, but rather serve as procedural guides and underlying principles that can be translated into actions by the readers.

1.4. What's Unique and Important About the Indo-Pacific?

This framework is designed to be particularly useful for countries in the Indo-Pacific. We chose this area because of the disconnect between power and population. Most of the existing global discourses on SynBio ethics are led by institutions in the US and in Europe. Yet, much of the world's population lives in the Indo-Pacific.

Geographical delineations of the 'Indo-Pacific' region vary. For this report, it refers to the area that is bounded on the west by Pakistan, on the south by Australia, in the east by the Pacific islands and in the north by China. This region hosts approximately 50% of humanity, which is under-represented in global discussions.

We highlight the following features of this region that is most pertinent to our discussion: First, there is a high degree of biological diversity in a number of the countries (notably, Indonesia, Australia, China, Papua New Guinea, India and many of the Pacific Islands). Thus, these countries will want to protect, and prosper from that diversity. It makes countries extra sensitive to data sharing and to benefit sharing agreements.

Second, many countries in the region are net technology adopters, with the exceptions of China, Japan, South Korea and eventually India. Countries in this region have the capacity for significant breakthroughs or technological improvements in some disciplines while also being net technology adopters. Importantly, in terms of genetic engineering, most countries in this region will largely rely on importing products developed by other countries.

Third, there is a huge disparity in governance and scientific capacity within the region. This is, of course, true in all regions but is particularly notable in the Indo-Pacific. Vanuatu's and

China's capabilities, for example, could not be more different. Many countries have limited enforcement and monitoring capabilities.

Finally, the cultural and religious norms of the region vary greatly. This means the public acceptance of different genetic technology applications will also vary significantly in the region. This makes public deliberation simultaneously more important and challenging.

2

Framework One: SynBio Governance

2.1 Introduction

Ethics is an important factor in the application of SynBio. This framework posits that individual countries should determine their own ethical considerations based on their cultures and history. This framework should be applied to the governance of applications after ethical approval.

Current frameworks governing SynBio incorporate aspects of the precautionary principle as a prior to approaching synthetic biology applications. These include the CBD, OECD Synthetic Biology Risk Assessment Framework, and several national frameworks. In certain applications,the precautionary principle[19] prioritises environmental impact and necessitates the presence of mitigation capacity to forestall any potential damage. For example, the European Union Commission's communication[20] on the precautionary principle notes that

"(it) applies where scientific evidence is insufficient, inconclusive or uncertain and preliminary scientific evaluation indicates that there are reasonable grounds for concern that the potentially dangerous effects on the environment, human, animal or plant health may be inconsistent with the high level of protection chosen by the EU."

Taken alone, the precautionary principle could potentially impede the development and deployment of emerging applications of SynBio in low-resource settings, particularly when local infrastructure or processes may be deemed insufficient to mitigate potential, albeit unlikely, risks. Thus, the precautionary principle needs to be applied with attentiveness of two important contextual factors.

[19] The precautionary principle states that serious environmental threats and health hazards should be anticipated and that they ought to be forestalled before the realisation of damage even if scientific understanding of the risks is inadequate.
[20] EU (2000), Communication from the commission on the precautionary principle COM 1. Brussels: Commission of the European Communities

Firstly, there needs to be a recognition that developing economies in the Indo-Pacific possess inadequate social support structures and lower social resilience against catastrophic events such as climate change, pandemics or energy crises. Consequently, these countries may exhibit a heightened sense of urgency in seeking technical solutions derived from SynBio. Therefore, governance should consider the contextualised potential benefits of SynBio, and policy should inform on actions for risk management, instead of becoming risk averse.

Secondly, factors such as local implementation and monitoring capacity, public engagement mechanisms, and agility of governance systems to respond to changes in technologies are key determinants of the successful adoption of emerging technologies, particularly in low-resource countries. The vastness of the SynBio field demands innovative governance frameworks to maximise its public benefits while safeguarding against risks. For low-resource countries, strategic mobilisation and effective utilization of societal governing resources is particularly important.

2.2 Guiding Principles for the Governance of SynBio

1. **A technology and its applications should be viewed separately**

A distinction should be drawn between the pursuit of knowledge and the ways in which such newfound knowledge can be used. Fundamental research within acceptable safety and ethical standards should be promoted. This is particularly so in the context of SynBio, which is a technology still in its nascent stages, with vast potential to provide benefits in the future.

2. **Context-based management is better than a universal ban**

There have been calls for a complete moratorium on certain applications of SynBio. Such blanket prohibitions will be difficult to enforce and will likely drive the industry underground or to nations with relaxed oversight. For example, despite a ban on growing GMO food crops, they have been found planted in various parts of India. Similarly, the global scientific community imposed a normative ban on germline gene editing, which was broken by a Chinese scientist, He Jiankui in 2018. Therefore, it is more prudent to have a framework of regulations with appropriate checks and balances that permits research and development of SynBio than one that bans it outright.

3. **Domestic governance capacity must be built to use SynBio applications effectively**

The benefits and risks of SynBio are uncertain and will require specialised capacity to effectively govern. This includes domestic infrastructure for longterm monitoring and/or

creating accessible public records of environmental and health impacts, mechanisms for sustained public engagement and diplomatic capacity to participate and negotiate in the global fora. This is particularly relevant to less resourceful countries which stand to make significant benefits from the deployment of SynBio, but are also most vulnerable to irresponsible applications.

4. **The application of SynBio should be equitable**

One of the concerns around SynBio applications relates to a fair and reasonable distribution of the benefits. This reflects an enduring public concern. Decreasing costs of various tools and the sharing of scientific data may help to reduce the siloing of knowledge, genetic resources and potentially make innovative products more accessible. Beyond this, a more equitable application of SynBio means respecting diverse cultural, religious and ethical perspectives, including ingenious rights and alternative ways of living. More importantly, risks are unlikely to be evenly distributed, with some populations and contexts more vulnerable than others.

5. **Deliberations on SynBio applications should be informed by the best available science**[21]

There are concerns about whether SynBio products are natural or should be considered as unnatural. This is also reflected in debates over genetic pollution of global "natural" biodiversity. Such discussions often rely on an arbitrary line between natural and the non-natural, and often distract the public and policy attention from more pertinent issues on safety, public benefit, and evidence-based assessment of environmental impact. It must also be reminded that SynBio can also used in environmental remediation

2.3 Ethical Risk Matrix for Synbio Applications

Ethical questions are complicated by SynBio's power to create organisms that would not have been naturally possible, as well as the unknown, unintended consequences of their creation. Hence, not all SynBio applications can be governed using a single regulatory approach. There has been much debate on the use of gene editing in humans and global frameworks have been created to guide and monitor the application of gene editing - both in vivo and ex-vivo - for medical and non-medical interventions in humans. However, there are several applications of gene editing in non-human organisms including animals, plants, and microorganisms that will likely be the first to be developed and deployed at scale.

[21] The Ethics of Synthetic Biology: Suggestions for a Comprehensive Approach. Allen Buchanan and Russell Powell.
https://bioethicsarchive.georgetown.edu/pcsbi/sites/default/files/The-Ethics-of-Synthetic-Biology-Suggestions-for-a-Comprehensive-Approach.pdf

Ethical considerations such as consent or anonymity do not apply for such applications, but the impact on environment and biodiversity become more important concerns. Thus, policymakers have to prepare governance measures to optimally employ these applications in their national contexts. Two key characteristics of a genetically altered non-human organism have a disproportionate role in determining its ethical risk.

1. **Degree of Divergence** - this is the extent of divergence of a SynBio product from its naturally occurring source or relative. There are two types of divergence:

    a) Genetic Divergence: This indicates the extent of genetic changes in the target organism.
    b) Phenotypic Divergence: This indicates the extent of change in the expressed (visible) physical and behavioural characteristics of the target organism.

Genetic engineering causes genetic changes that result in phenotypic changes. Few genetic changes may alter a phenotype significantly; for example, the rectification of disease-causing genetic mutations such as those seen in thalassemia, sickle cell anaemia etc., will cause disease alleviation in those patients. On the other hand, a large number of genetic changes may not result in any significant divergence from the naturally occurring variant. It is important to recognise that genetic changes are not controlled in natural breeding processes and a change in phenotype to the desired trait is the main indicator of success. Additionally, the interaction of the genetically engineered organism on the environment is mediated through its phenotype.

Some genetic changes may be silent changes with no influence on any phenotypic trait. Thus, while governing genetically modified organisms, the degree of divergence should be based on the phenotype. The use of degrees of divergence in the governance of emerging technologies is not novel and has been previously applied to genetically edited plants. However, given the scope of SynBio applications, divergence alone is not a sufficient parameter to manage ethical concerns. The impact of SynBio applications on the environment is also going to be an important source of unintended consequences and ethical considerations.

2. **Reproducibility in the ambient environment** - this will determine the continuing influence a synthetic organism will have on its environment.

While environmental risk assessments are a common governance tool, they might not be sufficient for the purpose of evaluating SynBio applications. This is because quantifying the potential risk of novel organisms is difficult. Further, the organism itself may evolve during its interaction with the environment, leading to unintended consequences. In addition, evaluating risk depends on the environment, which may change as the organism

moves across different habitats. Hence, instead of a traditional environmental risk assessment, we propose the use of the organism's reproducibility to determine governance.

The differentiated impact of synthetically engineered organisms as compared with naturally evolved organisms lies in their degree of divergence and their interaction with an uncontrolled environment. Thus, a highly divergent organism under controlled laboratory conditions is unlikely to cause any impact on the environment. However, the same organism in an uncontrolled environment may have a far greater impact. If the organism cannot reproduce, its impact will be short-lived; however, if it can reproduce, not only would its impact perpetuate, but there may also be unintended consequences that arise because of its further evolution.

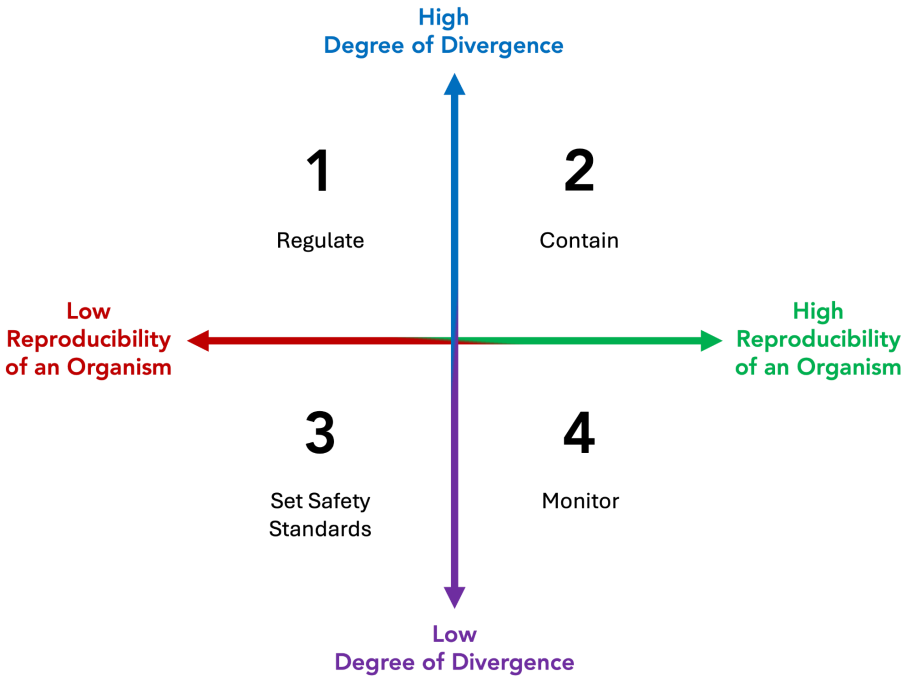

Figure 1: 2X2 Matrix for SynBio Applications

The differentiation of SynBio applications on this 2X2 framework would lead to 4 types of categories:

1. **High Degree of Divergence; Lower Reproducibility - Regulate**

   Organisms that are significantly different from naturally occurring counterparts and cannot reproduce in natural environments. These applications would need application-specific regulation to understand the impact of new traits on safety, interaction with the environment, and monitoring post-release. One example of

operationalising this is to design synthetic organisms with a crucial auxotrophy, that is, the inability to synthesise some organic compound necessary for its life cycle.

2. **High Degree of Divergence; Higher Reproducibility - Contain**

   Organisms that are significantly different from naturally occurring counterparts and can reproduce in natural environments. Such applications should be first deployed under controlled conditions and only in case of sufficient safety evidence and if the benefits accrued by their deployment outweigh the projected risks, should such applications be environmentally released.

3. **Low Degree of Divergence; Lower Reproducibility - Set Safety Standards**

   Organisms that are phenotypically similar to their naturally occurring counterpart and cannot reproduce in uncontrolled environments. For example, higher yielding genetically edited crops which produce sterile seeds. Such applications can be governed by setting safety standards so that their products do not harm the environment or human health, in case they are consumed.

4. **Low Degree of Divergence; Higher Reproducibility - Monitor**

   Organisms that are phenotypically similar to the naturally occurring counterpart but can reproduce in uncontrolled environments. Such applications can be overseen through monitoring mechanisms post-market release. However, since the organism is similar to its natural variant and could have been hypothetically achieved through natural breeding, stringent regulation is not necessary for this category.

2.4 Action Points for Stakeholders Based on Above Categorisation

Based on the outcome of the 2X2 Matrix for SynBio Applications, different stakeholders may opt for specific action points to operationalise the framework.

A. <u>Regulate</u>

   i. **Government**
      a. Set up expert committees to evaluate applications on a case-by-case manner
      b. Applications can be judged by advantage of the product over existing solutions and a cost-benefit analysis.

ii. **Academia**
    a. Research methods to keep divergent synthetic organisms from reproducing in the environment.
    b. Create a code of conduct for working on such applications and the public release of such data.

iii. **Private Companies**
    a. Manufacture products with kill-switches or a crucial auxotrophy to reduce possibility of reproduction in nature
    b. Monitor for any evolution of deployed organisms.

iv. **Funding Agencies**
    a. Evaluate necessity of the product prior to funding. Prefer projects where synthetic organisms are unable to reproduce in nature.

B. Contain

i. **Government**
    a. Set up expert committees to evaluate applications and prescribe containment standards for the application. Set up monitoring agency to ensure compliance.

ii. **Academia**
    a. Adhere to standards for containment.
    b. Evaluate need for such applications
    c. Inform the government in case of any discrepancies
    d. Set up mechanisms to identify and report incidents.

iii. **Private Companies**
    a. Adhere to standards for containment
    b. Set up mechanisms to identify and report incidents
    c. Put in kill-switches

iv. **Funding Agencies**
    a. Evaluate need for the product and fund such projects judiciously.

C. Set Safety Standards

i. **Government**
    a. Agree to minimum standards for approval of applications
    b. Set standards for research, commercialisation, infrastructure, supply chains and product safety

c. Encourage fundamental research

ii. **Academia**
   a. Update national agencies about the science, utility and potential risks of such applications
   b. Create code of conduct for peers
   c. Ensure standards are followed in their peer groups.

iii. **Private Companies**
   a. Carry out risk assessment for applications
   b. Adhere to standards set out by government
   c. Make safety studies data transparent
   d. Propose code of conduct for private networks

iv. **Funding Agencies**
   a. Check implementing institutions are meeting prescribed standards before allocating funding to projects

D. Monitor

i. **Government**
   a. Set up regulatory pathway for approval of such applications
   b. Set up monitoring mechanisms to understand the interaction of the organism in the environment and the sterility of the organism in the outside world.

ii. **Academia**
   a. Research impact of novel traits on an organism and its interaction with the environment
   b. Research novel ways of restricting the horizontal propagation of novel traits and novel organisms
   c. Perform exhaustive studies to demonstrate the safety and utility of novel traits.

iii. **Private Companies**
   a. Aid government with monitoring
   b. Report any anomalies immediately and transparently
   c. Ensure quality control studies and safety studies are at government-prescribed standards

iv. **Funding Agencies**
   a. Prefer funding projects with an inbuilt monitoring component.

3

Framework Two: Cross-Border Genetic Data Sharing

3.1 Introduction

Data sharing is crucial in research and innovation and it facilitates collaboration, transparency, and efficiency across the scientific community. It also allows for independent validation of results and encourages rigorous scrutiny, which are essential for maintaining the integrity of the scientific process. Furthermore, data sharing can lead to unexpected insights and discoveries when datasets from different sources are combined and analysed. By sharing diverse datasets, researchers can uncover patterns, correlations, and relationships that may not be apparent within individual datasets alone, leading to new discoveries and innovations.

Research using genetic data is not restricted to universities and research hospitals. Other entities, including private companies and startups, actively collect and research using genetic data. Due to the proliferation of direct-to-consumer genetic testing companies, which have collected large amounts of genetic data, there is an ever-increasing collaboration between academia and industry, especially startups. Furthermore, the emergence of artificial intelligence and big data analytics has made scientific and academic collaboration significantly easier and more extensive. This has led to increased demand for larger and more diverse datasets.

3.2 The Need for a Cross-Border Genetic Data-Sharing Framework

The complexity attached to data-sharing frameworks is not new. There have been several guidelines formulated for different types of data sharing over the last few decades, ranging from the Bermuda Agreement in 1996[22], to the Fort Lauderdale Agreement in

[22] The Bermuda Principles. dukespace.lib.duke.edu, https://dukespace.lib.duke.edu/communities/9bf2e54b-6912-407e-90a7-22213ff0c90a. Accessed 8 May 2024.

2003[23] and finally to a comprehensive Nagoya Protocol in 2011.[24] Multilateral organisations like the European Union and WHO have also released relevant guidelines such as the General Data Protection Regulation (GDPR), 2016 and WHO guiding principles for pathogen genome data sharing, 2022[25] respectively. However, two major concerns have acted as a constraint to comprehensive genetic data sharing between countries.

The first is the concept of genetic sovereignty, which refers to the belief that a country or population has the right to control and protect its genetic resources and data. The central idea is that a country's genetic makeup and resources are a national asset or "public good" that should be controlled and utilised primarily to benefit that country's population. This is based on the notion that populations have unique genetic profiles that are commercially, scientifically, and symbolically valuable[26]. However, there are several conceptual problems and unintended consequences of the concept of genomic sovereignty, especially when discussing human genetic data.

Human genetic variation is largely shared across populations[27], and ethnic and Indigenous groups often span multiple nation-state borders[28]. This makes national-level sovereignty over their genetic resources challenging to enforce. Despite efforts by governments to safeguard the genetic data of their populations, several efforts are underway to address the underrepresentation of genetic data from certain ethnicities and races by tapping into the diaspora communities in countries where genetic data sharing is more permissible[29]. Furthermore, national governments' ownership and control of human genetic samples

[23] Wellcome Trust. (2003, January). Sharing data from large-scale biological research projects: a system of tripartite responsibility. In Report of a meeting organized by the Wellcome Trust and held on 14–15 January 2003 at Fort Lauderdale, USA. London: Wellcome Trust. https://www.sanger.ac.uk/wp-content/uploads/fortlauderdalereport.pdf. Accessed 8 May 2024.
[24] Secretariat of the Convention on Biological Diversity. (2011). Nagoya Protocol on access to genetic resources and the fair and equitable sharing of benefits arising from their utilization to the convention on biological diversity: text and annex. UN.
[25] WHO (2022). Guiding Principles for Pathogen Genome Data Sharing. https://apps.who.int/iris/handle/10665/364222. Accessed 8 May 2024.
[26] Séguin, Béatrice, Billie-Jo Hardy, Peter A. Singer, and Abdallah S. Daar. "Genomic medicine and developing countries: creating a room of their own." Nature Reviews Genetics 9, no. 6 (2008): 487-493. https://doi.org/10.1038/nrg2379
[27] National Institutes of Health (US); Biological Sciences Curriculum Study. NIH Curriculum Supplement Series [Internet]. Bethesda (MD): National Institutes of Health (US); 2007. Understanding Human Genetic Variation. Available from: https://www.ncbi.nlm.nih.gov/books/NBK20363/
[28] The 1000 Genomes Project Consortium. A global reference for human genetic variation. Nature 526, 68–74 (2015). https://doi.org/10.1038/nature15393
[29] Ramsay, Michèle. "African genomic data sharing and the struggle for equitable benefit." Patterns 3.1 (2022).https://doi.org/10.1016/j.patter.2021.100412

raises ethical and philosophical issues[30], as it may not be appropriate for governments to claim ownership over individual genetic information.

Countries usually use genetic sovereignty (especially in the Global South) to address the historical and prevent the future exploitation of genetic resources[31]. As biomedical research increasingly relies on data-driven approaches, excessive restrictions on access to genetic data in the name of genomic sovereignty have unintentionally worsened the underrepresentation of non-white populations in global biomedical research and datasets[32].

Second, is the institutionalisation of Access and Benefit Sharing Agreements (ABSAs), which seek to establish fair and equitable sharing of benefits derived from utilising genetic resources. These agreements can include various benefits, such as monetary benefits like royalties from commercial products developed using genetic resources or non-monetary benefits like the transfer of research skills and knowledge. The Convention on Biological Diversity (CBD) and the Nagoya Protocol provide a legal framework for implementing fair and equitable sharing of benefits arising primarily from non-human genetic resources. However, the experience with ABSAs has been mixed.

Expectation management presents significant challenges. Research and innovation are unpredictable processes. Despite funnelling significant time and resources into a project, there is no guarantee that a commercially viable product will be forthcoming. Therefore, if every single use of every genetic resource that is accessed for a research project needs ABSAs, it will impose significant bureaucratic and procedural constraints, creating further obstruction rather than facilitating R&D. This would also disincentivise scientists from engaging in the high-throughput natural product screening programs.[33] The complexity of ABSA legislation, compliance challenges in provider countries, and issues around the material and temporal scope of the Nagoya Protocol are other major challenges.

While both the concepts of genomic sovereignty and ABSAs emerged as responses to concerns about the exploitation of national genetic resources, they are incomplete and, at times, inadequate in governing the access, use and circulation of genetic data, especially

[30] Roberts, Jessica L. "Theories of Genetic Ownership." Harvard Law Review (2015): 1-64.
[31] De Vries, Jantina, and Michael Pepper. "Genomic sovereignty and the African promise: mining the African genome for the benefit of Africa." Journal of Medical Ethics 38.8 (2012): 474-478. https://doi.org/10.1136/medethics-2011-100448
[32] Zhang, Joy Y. "Commoning genomic solidarity to improve global health equality." Cell Genomics 3.10 (2023). https://doi.org/10.1016/j.xgen.2023.100405
[33] Michiels, F., Feiter, U., Paquin-Jaloux, S., Jungmann, D., Braun, A., Sayoc, M. A. P., ... & David, B. (2021). Facing the harsh reality of access and benefit sharing (ABS) legislation: An industry perspective. Sustainability, 14(1), 277. https://doi.org/10.3390/su14010277

given the global and collaborative nature of genomics research. Consequently, a framework to regulate the cross-border circulation of data is essential.

3.3 Guiding Principles for Cross-Border Genetic Data Sharing

The proposed framework primarily applies to data generated from public funds or held with public institutions such as universities, academic institutions or government research institutions. However, we encourage privately held data or data generated exclusively by private enterprises for commercial purposes to engage with responsible data sharing as well.

1. **Genetic data as a public good**

The cost of genome sequencing technologies has decreased exponentially over the last two decades. The Human Genome Project, which ended in 2003, cost around USD $2.7 billion, and the cost of sequencing a human genome fell to about $10,000 in 2011, a few years ago, that fell further to $1,000, and today, it is about $600[34]. Vast amounts of genetic data are being collected globally, partly because of the reduced cost of genome sequencing technologies and partly because of the realisation that genetic data is useful in healthcare and precision medicine. These datasets can help develop novel proteins, targeted gene therapies, and even a new family of antibiotics. In all these cases, the utility of genetic data is in the fact that it is part of a larger dataset. The more enriched a dataset is with diverse genotypic or phenotypic data, the more effective the outcome will be.[35] Cross-border data sharing can significantly contribute to a certain dataset's genotypic and phenotypic diversity.

2. **Informed consent**

All genetic data must be collected with proper consent. The owners of the primary data should provide consent for sharing the data and should be informed about the level and purpose of their data being shared. For human genetic data, consent must be obtained from those providing the samples. As non-humans cannot provide informed consent, it should be obtained from the relevant data owner, government, or regulatory body as per the specifics of the case. Furthermore, the consent also applies to the data bank from which the data is shared with external entities. If the consent is conditional with restrictions on end-user, purpose or any other factor, it must be respected.

3. **Respecting anonymity**

[34] Mullin, Emily. 'The Era of Fast, Cheap Genome Sequencing Is Here'. Wired. www.wired.com, https://www.wired.com/story/the-era-of-fast-cheap-genome-sequencing-is-here/. Accessed 8 May 2024.
[35] Gaffney, Jim, et al. "Open access to genetic sequence data maximizes value to scientists, farmers, and society." Global Food Security 26 (2020): 100411. https://doi.org/10.1016/j.gfs.2020.100411

Ensuring that shareable data is adequately anonymised is extremely important when discussing human genetic data. Privacy concerns are one of the most sensitive issues people face when considering sharing their genetic data, especially for medical research.[36] Any lapse in preserving the privacy of individuals whose genetic data is in the database can lead to their identification. Consequently, this identification may expose them to discriminatory behaviour, especially concerning access to services, employment, or differential pricing for services like medical insurance.

3.4 Factors That Influence Cross-Border Genetic Data Circulation

1. **Source organism**

Concerns regarding data sharing may differ substantially depending on the source organism of the genetic data. For example, countries and research institutions may be more sensitive to sharing data involving humans than non-humans. Some countries will also limit genetic data sharing for non-human organisms such as flora, fauna, microorganisms, and insects, among others, especially if those organisms are endemic to the region or country. This increased sensitivity is primarily from the potential economic and strategic gains that outsiders may extract from human genetic data, especially if human genetic data is at risk of being de-anonymised.

2. **Purpose of data usage**

Genetic data can be used by research institutions, academia, government agencies, or the private sector. The custodian of the biobank/dataset may provide differential cross-border access to genetic data. This is because considerations of the greater good often dominate while contributing to scientific or medical research. In contrast, concerns regarding commercialisation and biosecurity dominate when sharing data with private entities and government agencies, respectively. Therefore, the intended purpose of the data request is another major factor. If the purpose is academic research, both countries or people will likely be more amenable to sharing their data than their data serving purely commercial, economic or strategic interests.

3. **Regulatory Infrastructure**

Given the sensitive nature of genetic data, especially human genetic data, a country's privacy framework and regulations are critical when evaluating cross-border sharing of genetic data. For example, even if the source, end user, and purpose components are in

[36] Etchegary, H., Darmonkov, G., Simmonds, C. et al. Public attitudes towards genomic data sharing: results from a provincial online survey in Canada. BMC Med Ethics 24, 81 (2023). https://doi.org/10.1186/s12910-023-00967-0

order, more stringent privacy regulations or enforcement mechanisms may be needed to ensure data sharing. This assumes more significance in light of recent developments where, despite anonymised data being available in the database, it has become easier to de-anonymise the data by triangulate it with other publicly available datasets.[37] Furthermore, the lack of a robust data privacy framework or adequate enforcement may impact any legal or institutional recourse to which the aggrieved party may resort.

4. **Benefits sharing**

Economic and social benefits resulting from data sharing may be important in formulating and enabling regulations to facilitate cross-border genetic data sharing. For instance, suppose the anticipated benefit of cross-border data sharing is large and affects many countries. In that case, the likelihood of sharing increases along with the number of interested parties and the expected economic benefit. On the other hand, if the benefit of data sharing is limited to a certain region or geography, then data sharing may be more challenging. For example, countries may be more amenable to sharing genetic data to help tackle global issues, like the menace of plastic pollution, by sharing relevant microbial data to help research on plastic-eating bacteria. However, suppose genetic data sharing aims to address a disease that is endemic to a specific part of the country or community. In that case, there will be reluctance to share the data due to fear of being exploited for commercial interests, rendering the country dependent on foreign products. This often leads to increased demand to sign ABS agreements beforehand or as a prerequisite for cooperation.

3.5 Determining Factors for Policy Action

To govern the cross-border circulation of genetic data, three factors can form the basis of classifying policy actions that can be taken when dealing with any type of genetic data:

1. **Global Impact**

This factor includes assessing the potential benefits the global community might accrue from sharing the data. For example, in the case of human genetic data, countries might be willing to share data on Type-I diabetes, given that it is a global lifestyle disease whose research can benefit from more diverse genetic data of patients and ethnic/racial groups. Similarly, when discussing non-human data, sharing genetic data relating to antimicrobial resistance might resonate within the global community, given that it is a shared challenge. We saw this principle in action during the COVID-19 pandemic, when genetic samples of

[37] Humbert, M., Huguenin, K., Hugonot, J., Ayday, E., & Hubaux, J. P. (2015). De-anonymizing genomic databases using phenotypic traits. In 15th Privacy Enhancing Technologies Symposium (PETS) (Vol. 2015, No. 2, pp. 99-114). https://doi.org/10.1515/popets-2015-0020.

various variants of SARS-CoV-2 were readily shared, given the spread of the pandemic. The WHO's Global Influenza Surveillance and Response System (GISRS) is one such effort.

2. **Risk of de-anonymization**

This factor includes the possibility of de-identified genetic data being traced back to the person it belongs to. It is one of the major concerns that people and governments have. Given the significant economic, privacy, and medical consequences such a revelation may have, governments are risk averse when sharing their citizens' genetic data. If the risk of genetic data being de-identified is limited, countries should actively share the data for the benefit of researchers and scientists. These countries can further decide on a case-to-case basis when the risk of de-identification is significant.

3. **Degree of endemism**

This includes consideration of the endemic nature of the organism whose data is being shared. This is important because the more endemic an organism is, the higher the chance that the source country can extract economic value from that genetic data; hence, it would try to restrict data sharing. Conversely, a country would not accrue much economic benefit by restricting access to genetic data for organisms that are not unique to that geography. This is because there is a higher likelihood that researchers would get access to similar genetic data from another source, weakening the potential economic benefit argument in this case.

3.6 Proposed Policy Actions

Countries in the Indo-Pacific can approach requests for cross-border genetic data sharing in multiple ways. One way to operationalise this framework is to create a country-level or region-level biobank/database to serve as a repository of genetic data. Once a request has been processed through the framework matrix, several policy actions can be taken regarding data access:

1. **Open access**

This implies that genetic data sharing is not restricted at all, and everyone can access and use relevant data in a publicly accessible database or biobank. The agency maintaining the database/biobank may establish guidelines on data collection format and standards for the privacy and security of the uploaded data.

2. **Controlled access**

This implies that access to genetic data is moderately restricted. To access data in this category, an application needs to be made to access the database/biobank. The regulatory

agency responsible for maintaining the database/biobank will decide on the parameters for granting access. The information obtained through this route is expected not to be shared with anyone else without prior permission.

3. **Restricted access**

This implies that access to genetic data is quite restricted. The designated government agency must approve access to the data in the biobank/dataset. The decision would be made on a case-to-case basis, depending on the facts of the request being made.

3.7 Framework Matrix for Genetic Data Sharing

It is essential to treat data from humans and non-humans differently. This is primarily because the biosafety, dual-use sensitivities, and privacy concerns relating to human data differ from those of non-human genetic data.

A common axis in visualising both frameworks would be the likely global impact of sharing that data with the larger scientific and research community. Since states are broadly reluctant to share data across borders, particularly due to privacy, lost economic potential or biodiversity concerns, it would be prudent to begin sharing data with the most global benefit. While some applications, such as rising antimicrobial resistance or climate action, are easy to classify as applications with global public benefits, others, such as a database of genetic data of all diabetes patients, may be more difficult to assess. A contributing country can determine the research's global nature and public benefits according to its own social, political, cultural and economic understanding. However, a different factor would apply to human and non-human data in conjunction with global impact.

A. Human Genetic Data

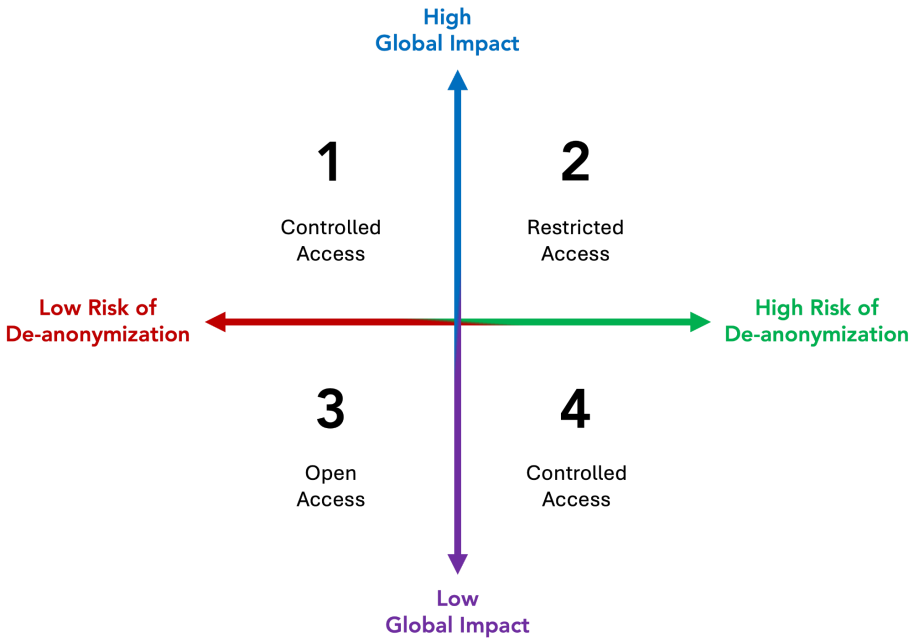

Figure 2: 2X2 Matrix for Human Genetic Data

For human genetic data, the two major factors would be the perceived global impact and the evaluated risk of de-anonymisation. This is because the primary concern with sharing data is the privacy risks associated with potential data misuse. The various policy options available under this framework are depicted in Figure 2. The framework is illustrated through the following hypothetical examples:

1. **High Global Impact; Lower Risk of De-anonymisation - Controlled Access**

   Single nucleotide polymorphisms (SNPs) from patients with thalassemia without associated phenotypic data can be included in this section. This allows the data to be shared for research with the broader community. Controlled access allows the data depository to record who accessed the data and for what purpose.

2. **High Global Impact; Higher Degree Risk of De-anonymization - Restricted Access**

   The sharing of whole genome sequences of individuals is an example of data falling into this category. As it is a full genome sequence, several de-anonymisation methods can be applied to endanger the privacy of individuals whose data is being shared. Therefore, Restricted access to this data should be allowed, and the

country's regulatory agency can evaluate data-sharing requests on a case-to-case basis depending on the purpose of the data request and privacy infrastructure with those requesting access. ABSAs may also be considered as a prerequisite for providing access.

3. **Low Global Impact; Lower Risk of De-anonymisation - Open Access**

   The information extracted from published journals and associated data where germline mutations causing human genetic disease are described falls under this category. As these are descriptions of mutations, there is a lower risk of being identified, and there is limited global utility, while utility for individuals may be significant. Providing Open access to such data would help further the collaborative nature of genetics research.

4. **Low Global Impact; Higher Risk of De-anonymisation - Controlled Access**

   For data requests where the risk of de-anonymisation is high and perceived global impact is low, controlled access is preferred because privacy concerns are significant for human genetic data. To ensure compliance, it is essential to keep track of with whom high-risk data is being shared.

B. Non-Human Genetic Data

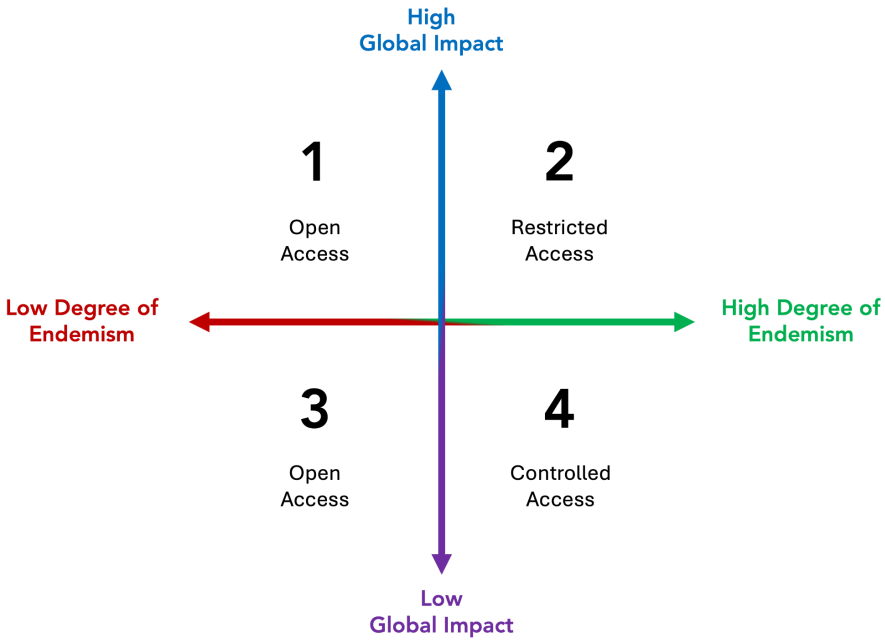

Figure 3: 2X2 Matrix for Non-Human Genetic Data

For non-human genetic data, the two major factors would be the perceived global impact and the degree of endemism of the source organism whose data is being shared. This is because the primary concern with sharing this data is the loss of potential economic benefit from that data. The various policy options available under this framework are depicted in Figure 3. The framework is illustrated through the following hypothetical examples:

1. **High Global Impact; Lower Degree of Endemism - Open Access**

   C. diffilcle is a bacterium that causes life-threatening diarrhoea. It is usually a side effect of taking antibiotics and is one of the most common hospital-acquired infections and a major cause of death for elderly patients. Sharing genetic data of C. difficle from a health facility would likely have a high global impact with positive consequences for researching this bacterium. However, given that this bacterium is found almost all over the world, the degree of endemism is extremely low. Therefore, Open access to this data should be allowed.

2. **High Global Impact; Higher Degree of Endemism - Restricted Access**

   Suppose scientists discover a fern in a remote location in Amazon that is seen as a promising candidate for developing anti-cancer drugs. In that case, the research can potentially have a significant global impact. However, given that the fern is endemic to the region it was found, it would have a higher degree of endemism. Therefore, restricted access to this data should be allowed where the country's regulatory agency can evaluate data-sharing requests on a case-to-case basis depending on the needs and the research infrastructure present in the country. ABSAs may also be considered as a prerequisite.

3. **Low Global Impact; Lower Degree of Endemism - Open Access**

   Any genetic samples that are not known to have an apparent global impact or are not endemic in nature fall in this category. Providing Open access to such data would help further the collaborative nature of genetics research.

4. **Low Global Impact; Higher Degree of Endemism - Controlled Access**

   If a non-infectious disease is discovered in a country and is caused by an endemic species, its genetic data may not really have a high global impact because of its limited geographic spread. However, it may be useful for other reasons that are not yet known. Therefore, Controlled access is suitable as it would allow the databank/dataset to keep track of who has asked for access to data.

4

Framework Three: Public & Stakeholder Engagement

4.1 Introduction

SynBio has profound implications for society and the environment. By engineering standardised parts, SynBio enables unparalleled control over living systems and, arguably, redefines our relationship with nature.[38] This underscores the importance of engagement to ensure that the publics and the stakeholders are (1) properly informed of SynBio R&D developments, (2) able to participate in the public deliberations and (3) policymaking is informed not just by scientific evidence, but is also attentive to social needs and expectations. This goal-setting framework identifies key principles, factors (domains of concern) and engagement goals for informing SynBio policy.

It is not possible to engage publics on every scientific development. But, in the event that a SynBio development (technique, tool, product or line of research) is identified as potentially raising significant concerns for public health, environmental safety, or social norms, stakeholders should be consulted prior to or during development.

4.2 Guiding Principles for Public and Stakeholder Engagement

It is essential to establish guiding principles for engagement in this rapidly advancing field. Here we reduce them to 6 principles clustered into 2 categories: Trustworthiness and Comprehensiveness, to highlight the key factors for fostering informed public discourse, trust and integrating diverse perspectives.

A. How to approach communicating SynBio

Trustworthiness		
Transparent	Open	Accountable

[38] J. Dalziell & W. Rogers. (2022). "Are the Ethics of Synthetic Biology Fit for Purpose? A Case Study of Artemisinin [Point of View]," in *Proceedings of the IEEE*, vol. 110, no. 5, pp. 511-517, May 2022, https://doi.org/10.1109/JPROC.2022.3157825.

1. **Transparent**

   Transparency is essential for responsible science and innovation engagement. It requires clear communication about the scope and potential outcomes of emerging technologies, and honesty about uncertainties. While there are debates regarding how we communicate intended vs. unintended consequences of SynBio, transparency demands that the public be informed about factors shaping decisions to develop it, regardless of whether factors are positive or negative. Engagement should transparently acknowledge and address any limitations and uncertainties regarding SynBio, and the motivation for engagement should also be transparent.

2. **Open**

   Transparency means clear communication of the facts; openness means moving beyond viewing publics as a barrier, a common presumption in public engagement. Engagement must facilitate voicing criticisms, questions and concerns. Thus, openness entails active dialogue, empowering participants to scrutinise SynBio tools and solutions.

3. **Accountable**

   Accountability means engagement is more than a box-ticking exercise; it is a critical component of the science-policy-society interface. It should inform and shape decision making around SynBio's societal and environmental trade-offs. This means SynBio tools should be communicated accessibly and the public feedback documented thoroughly. Ultimately, this activity should link back to science and policy development through engagement with decision makers.

B. How to approach public & stakeholder views on SynBio

Comprehensiveness		
Context	Pluralism	Reflexivity

1. **Context**

   Recognising societal context is vital for innovation and science-policy endeavours. Therefore, beyond establishing trustworthiness.[39] In communication, engagement

[39] Goldenberg, M. J. (2022). 'Public trust in science.' Interdisciplinary Science Reviews, Vol. 48, No. 2, pp. 366–78. https://doi.org/10.1080/03080188.2022.2152243.

requires a comprehensive approach to understanding how stakeholders perceive SynBio. Gauging public views should extend beyond measuring their scientific accuracy or support levels. They can reflect local conditions, historical relationships, and differing priorities. Contextualisation calls for a more nuanced approach to engagement across design, analysis, interpretation and use of results.[40]

2. **Pluralism**

   Effective engagement means targeting a diverse range of stakeholders. Broadening the stakeholder base is essential in informing decisions, communication approaches and potentially reducing backlash.[41] Whether through statistically representative national surveys or smaller qualitative approaches like focus groups, pluralism remains key. Even specialised stakeholder interviews should strive for range of backgrounds, demographics and perspectives, in order to achieve saturation. Bidirectional engagement strategies should encourage a plurality of viewpoints and backgrounds within the target sample. Finally, scientists do not agree on every aspect of emerging SynBio, particularly the feasibility of proposed applications. Given its multidisciplinarity, it is important to recruit advice from experts in genetics, biochemistry and engineering.

3. **Reflexivity**

   Reflexivity is the practice of holding a mirror to one's personal views. It requires the researcher to critically examine why they are framing SynBio in a particular way and what assumptions they have about the public and SynBio. This is critical for any engagement design because it clarifies concepts and frees up the exchange of perspectives. It makes the researcher more aware of their own models of people and the world, fostering more productive deliberations.

4.3 Domains of Concern

Beyond being trustworthy and comprehensive, a well-formed public engagement strategy should consider the domains of concern that we already know emerge in debate. These

[40] The Contextualization Deficit: Reframing Trust in Science for Multilateral Policy'. The Centre for Science Futures, Paris. https://futures.council.science/publications/trust-in-science, 2023.
[41] Carter, L., Mankad, A., Zhang, A., Curnock, M. I., & Pollard, C. R. J. (2023). A Multidimensional Framework to Inform Stakeholder Engagement in the Science and Management of Invasive and Pest Animal Species. *Biol Invasions*, 23: 625-640. https://doi.org/10.1007/s10530-020-02391-6.

will influence the way SynBio attitudes develop. Thus, there are three broad domains of concern that typically frame SynBio[42]:

1. **Risk** - Safety risks that must be assessed with scientific evidence and stakeholder risk tolerance. This includes the risks of failing to develop and implement SynBio tools across a range of industries and environments.
2. **Economics** - Weighing economic gains and losses. This includes what might be forfeited without SynBio tools.
3. **Ethics** - SynBio involves social and moral questions that go beyond risks and cost-benefit analyses. Certain tools may provoke strong opposition and require broad ethical deliberation.

Transcending these three domains, public concerns regarding SynBio can be charted on two dimensions, agency and safety. The first dimension, agency, is the sense of personal control over one's use of or exposure to SynBio tools and products. The second, safety, is the perception of collective danger posed by SynBio, which encompasses both physical and moral risks to society.

4.4 Engagement Goal-Setting Matrix

This matrix should be used as a tool for continually assessing and updating SynBio engagement goals. Preliminary scoping should place an item within a quadrant; early engagement clarifies this placement; engagement goals are then set, and in-depth engagement, where necessary, proceeds according to those goals[43].

[42] Betten A. W., Broerse J. E. W., Kupper F. (2018). Dynamics of Problem Setting and Framing in Citizen Discussions on Synthetic Biology. Public Underst Sci 27(3): 294-309. https://doi.org/0.1177/0963662517712207.

[43] Note that the specific examples given in each quadrant are, by nature of the range of their uses and the dimensions they map onto in this matrix, debatable and moveable. For instance, *human genome editing* is classified as *low perceived agency* from the perspective of the subject receiving *in utero* editing. This constitutes a highly debated topic. Other forms of human genome editing, such as editing disease-causing DNA in full grown subjects, would likely not place within the same quadrant. Further, *low perceived agency* does not necessarily mean non-acceptance.

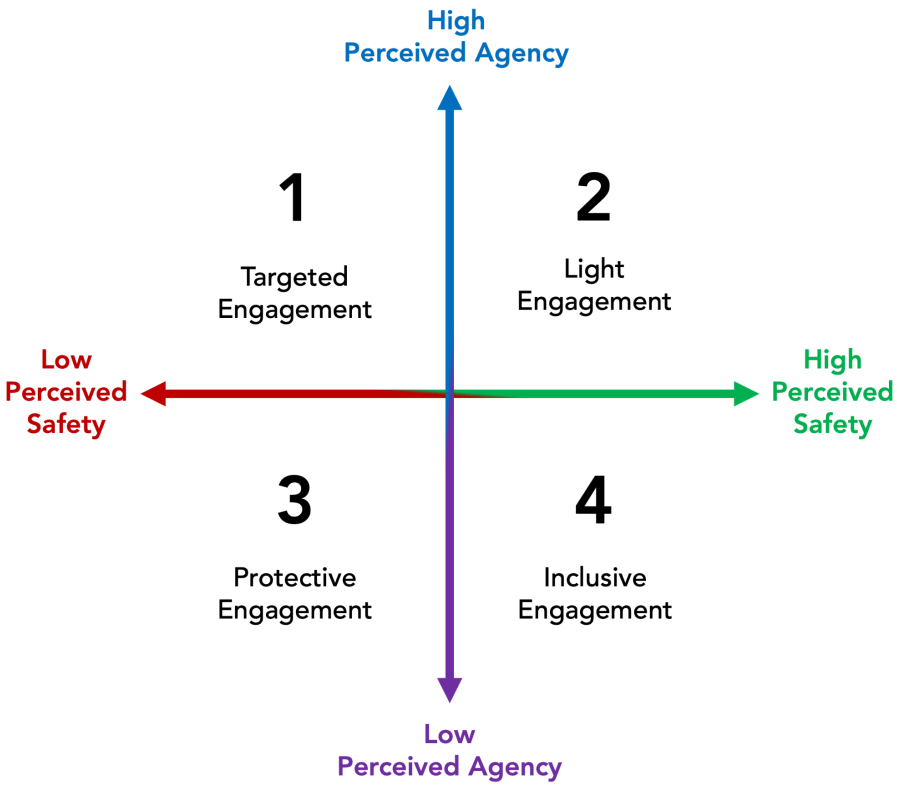

Figure 4: 2X2 Matrix for Public & Stakeholder Engagement

The matrix framework in Figure 4 leads to 4 types of engagement:

1. **High Agency; Low Safety - Targeted Engagement**

   Involves greater understanding of risks and broader assessment of their implications regarding public safety and values.

   Examples: GM pesticide resistant crops; DIY genetic engineering

2. **High Agency; High Safety - Light Engagement**

   Aim is to improve user experience and outcomes.

   Examples: synthetic milk; custom probiotics

3. **Low Agency; Low Safety - Protective engagement**

   Awareness, regulatory change and civil redress. Advice on alternatives.

   Examples: Gene drive organism release; Human genome editing

4. **Low Agency; High Safety - Inclusive Engagement**

   Involves awareness, assessment of public values, and co-design of implementation.

   Examples: engineered pseudo-organisms for bioremediation

These challenges and goals are relevant to all emerging technologies. However, SynBio's unique capacity to reshape our relationship with natural processes across various scales (from individuals to entire populations, ecosystems and evolutionary processes) increases the need to clarify and address these issues in engagement. Each quadrant implies different engagement goals based on the relationship between agency and safety concerns. Only quadrant 2 (high agency and high safety) represents cases that do not meet the above conditionality clause. All other quadrants should contain cases with low agency, safety, or both, meeting the conditionality clause.

There is no perfect engagement strategy, or strict rules for when or when not to use different tools (e.g., focus groups, information campaigns, surveys, panels). Instead, this matrix provides a tool for identifying engagement goals rather than determining a specific form of engagement. Further, the above goals are not necessarily exclusive to a single quadrant and may be useful across all cases. However, we highlight goals that address the negative effects of shifting levels of agency or safety in each quadrant.

5

Conclusion

SynBio and its ever-increasing array of applications pose many difficult ethical questions, with clear transnational ramifications. It feels qualitatively different to what has come before.

This document was made with the Indo-Pacific in mind. It is a region with half of humanity and a huge amount of unique biodiversity. It is a region that stands to be transformed by biological engineering, not least because it is home to much of the world's genetic resources. Yet, voices from the region have been constrained in global discussions. This document represents the authors' best efforts to respond to the wide-ranging input of stakeholders across the region. It is an attempt to give the region more say over the future of SynBio.

The document prioritises the most pressing SynBio ethics questions for resource-constrained countries across the region. The selection of three distinct frameworks (ahead of many other potential issues) focuses the ethics discussion on the most consequential areas.

The use of matrices and decision trees is designed to provide clear guidance on how to think about managing individual SynBio applications. It is designed to bring in stakeholders who are not ethics specialists. Because in many cases, these decisions will be made by scientists, companies, and governments with limited knowledge of SynBio.

The framework for SynBio applications steers away from blanket bans and considers phenotyping changes caused by SynBio applications and the reproducibility of it in a non-contained environment. This is, hopefully, a way forward for governments and other stakeholders to progress the benefits without going too far. It is an important point that resource-constrained countries in the Indo-Pacific are going to be on the receiving end of climate change effects. Economic development concerns are also a higher priority in many countries in the region. SynBio is one solution to both economic development and climate change. Being too cautious also causes harm.

Similarly, the data framework looks for ways to share data better. We see a lot of data-sharing suspicion across the region because of biopiracy concerns. Yet, denying data sharing also causes harm. The framework's proposal to define tiered sharing depending on the benefits vs the degree of endemism of (non-human) organisms can overcome the instinctive desire to protect data or stop data sharing. Much of the data being protected now is not particularly unique to one country, or it is being shared anyway despite laws against it. A more open data-sharing environment could also reduce the monitoring requirements on data transfer.

Finally, the public framework introduces the concept of agency and perceived safety. The public cares whether they have control over the effects of SynBio applications. In cases where agency is low, public engagement becomes all the more important. This will hopefully help governments define when they need to emphasise public engagement.

These frameworks will help guide a broad range of stakeholders on the question of SynBio ethics, while providing sufficient flexibility for nations (and individual stakeholders) to consider their specific contexts when making these difficult decisions.

In the longer term, hopefully, this is part of a trend to make global decision-making on SynBio more pluralised and better incorporate the views of the Indo-Pacific.
