Summary for PPIE Panel

CREPSING: Collective Reflective Equilibrium in Practice in SINGapore

Vision and Rationale of Program

Introduction

Imagine being offered a blood test to see if you carry a gene for a hereditary disease. Even if you don't have the disease, knowing you are a carrier could be helpful to allow surveillance and timely treatment or to inform other decisions such as family planning. especially if you are planning a family. However, while new cell and gene technologies such as genetic testing offers many benefits, they can also bring up complex ethical and social challenges. Our research program aims to address these concerns.

In a practical world where we have limited resources, using new cell and gene technologies means carefully balancing different important ethical values. These values are:

PUBLIC BENEFIT	COST
The technologies are good for many people. They help or improve our society. 	Developing the technologies is expensive and treatments can cost patients and Singapore's healthcare system a lot of money. 

PRIVACY Given that genetic data is sensitive and personal, protecting patient privacy is important. 	**FAIRNESS** Fairness ensures that everyone, including disadvantaged communities and the minorities, can afford treatments provided by gene technologies. 
SAFETY Safety ensures that individuals and groups are protected from potential harm. 	**RESPONSIBILITY** Scientists, policymakers, and healthcare providers are responsible when it comes to developing and using these technologies in an ethical way. 

To achieve this balance, we need to get public opinion. We need to understand which ethical values matter to Singaporeans, and how these values may change in different situations. We will use the Collective Reflective Equilibrium in Practice (CREP)[1, 2] method to combine public values, real-world data and ethical theories to develop practical solutions and policy recommendations that Singaporeans can accept.

Aims of our Program

We aim to examine:

1. how these new gene technologies and genetic tests affect individuals, families, and society;
2. how knowing about disease (genetic) risks may affect access to healthcare, insurance, education, and jobs;

3. what Singaporeans think about biobanks and how these should operate to better serve communities. Biobanks involve the collection of family history, lifestyle and genetic information and donation of biological material (such as DNA, cells, tissue etc.) by members of community.
4. how to make expensive new treatments fair and available to everyone.

Research Plan

The program involves four topics. We will invite interested people to sit on advisory panels for these topics.

Topic 1: Implementing universal screening	
Universal carrier screening 	• This is a genetic test that helps couples find out if they might pass on certain genetic health problems to their future children. • We are going to study the ethics of offering genetic testing to all couples in Singapore who might have children. • The goal is to create guidelines with patients, public, doctors, and policymakers on how to do this screening fairly and responsibly.
Cascade screening for families 	• This is a process where family members of a person diagnosed with a genetic condition are ALSO offered genetic testing to identify who may be at risk for the same condition. This is because certain health condition can run in families. • This project aims to address ethical concerns such as responsibility and obligations for informing family members; balancing consent and privacy concerns; addressing insurance concerns; and making sure everyone has fair access to the testing.

Topic 2: Consent and return of results for biobanks	
Returning genome analysis results 	• This is the initiative to return actionable genetic test results to those participants of the SG100K cohort who are at higher risk of developing a genetic condition. • The research aims to develop the best practice standards for the return of genetic test results in Singapore. • The research also aims to seek public views on how much active convincing should be done to individuals to take care of their own health. • You can read more about the SG100K cohort here: https://www.npm.sg/partners/precise-sg100k/ .

Optimal informed consent processes 	• Currently, lengthy consent forms are being used for cohort studies. • With the help of the public, the research aims to develop consent forms that are easy to use, make sure people understand what they are agreeing to, gives people all the important information, and address ethical concerns.

Topic 3: Use of biobank data by the government	
Allowing government access to national precision medicine data 	• This research will ask the public to make policy recommendations when the police requests to access genome data for crime investigations.

Topic 4: Emerging cell and gene therapies	
Predicting disease with polygenic risk scoring 	• Polygenic risk scoring is a number that calculates how likely you are to develop a certain disease compared to an average person, based on your genetic makeup. • This research aims to study how polygenic risk scores for heart failure might affect people's health behaviour. • In particular, the research aims to address ethical concerns together with the PPIE panel such as unnecessary worry or hopelessness, over-treatment or discrimination and whether it is ethical to use this information to try to change people's behaviour.
Access to high-cost gene therapies 	• New gene therapies can treat some rare and serious diseases, but they're very expensive- often costing hundreds of thousands or millions of dollars. • The research will ask for public opinions to evaluate related case scenarios.

Horizon scanning for new applications of genomics 	• This section will be dedicated to examining the ethical and societal implications of new gene technologies that have not reached Singapore. • Our focus will be on controversial technologies that could pose challenges to Asian societies. • Some examples include using whole genome sequencing to screen newborns, selecting embryos based on polygenic risk scoring, and editing genes that can be passed to future generations.

Patient-Public Involvement and Engagement (PPIE)

We would like to work together WITH members of public in this research. Patient and Public Involvement and Engagement (PPIE) means involving and engaging people with research as collaborators and advisors.

Patients and the public have perspectives based on their experiences, lives, and expertise in their own conditions and situations which may differ from researchers. These views have high value and need to be heard.[3]

We need your input to make sure that the research better serves the community, meets public's needs and is conducted in a way that is helpful and fair.

We would like to invite you to join our PPIE panel. You can email medthj@nus.edu.sg to register your interest with us.

Appendix / For Further Reading

What is CREP?

Collective Reflective Equilibrium in Practice (CREP) is a method that uses public values, moral theories, and real-world data to come up with fair and practical solutions for complex social issues. CREP has been used to make policy decisions on issues such as:

- how to distribute vaccines during COVID-19,[6-8]
- how self-driving cars should be programmed to make ethical choices,[9]
- how anaesthetic medicine could be used to manage pain and distress in terminally ill patients,[10]
- and how to include religious or cultural values in medical care.[11]

What does CREP involve?

First, CREP looks at the issue from multiple angles by gathering information from different sources, including experts and the general public. Then, CREP goes back and forth between ethical theory and practical considerations until a good solution is found. The goal is to find a practical solution that address ethical concerns effectively.

Genomics research in Singapore

What is genomics?

Genomics is the study of all the genes in a person. It is about understanding the complete genetic makeup that makes each person unique. In medicine, it helps understand diseases and why some people are more likely to get certain illnesses than others. It involves processing huge amounts of data. As technology improves, we are constantly learning new things about genomes and how they work.

What is precision medicine?

Precision medicine[12, 13] uses huge amounts of data to improve healthcare. It analyses a person's genetic makeup to understand disease risk and potential treatment responses. It aims to provide medical care that works best for every individual person based on their genetic, environmental, and lifestyle data.

Examples of how precision medicine is used include:

- Targeted treatments: Allows doctors to select treatments more likely to help patients based on studying their genes.
- Disease prevention: Predicts how likely someone is to get certain diseases and do early prevention.
- Drug efficacy: Improves prediction on which medical treatments will be most effective for specific patients.
- Reduced side effects: Helps avoid prescribing drugs that may cause side effects in certain individuals.

What is Singapore doing on genomics research?

Singapore is investing in precision medicine and genomics through the National Precision Medicine (NPM) program (https://www.npm.sg/). Genomic data can predict our disease risks, not just for ourselves but for our families and our future children too. A recent study in Singapore found that about 1 in 30 people have genes linked to serious diseases, and 1 in 250 couples might have a child with a severe genetic condition.[14]

Genomics can help predict risks for common diseases like heart disease and diabetes by looking at both genes and lifestyle factors. Genomics is also leading to new treatments of rare diseases, although these treatments can be very expensive. Overall, genomics will have a big impact on healthcare in Singapore and change how we understand and treat diseases.

Singapore is building on existing genomics research. Two related programs were introduced:

- ACTRIS (Advanced Cell Therapy and Research Institute): To expand on developing new cell and gene-based treatments.
- PRECISE (Precision Health Research, Singapore): To manage the NPM strategy of Singapore.

What is the NPM project about?

The NPM[15] program of Singapore aims to use advanced science to speed up medical research, help Singaporeans stay healthy, and grow new related industries. NPM has three phases:

- Phase 1 began in 2017 with the SG10K initiative, which studied the genes of 10,000 Singaporeans.
- Phase II was launched in 2021 and aimed to study the genes of 100,000 healthy Singaporeans and 50,000 people with specific diseases (SG100K cohort).
- Phase III will happen between 2025 and 2030. It aims to study the genes of about 10% of Singaporeans (about 500,000). The genomic data will be linked with health records and lifestyle data (e.g. diet and exercise) to create a big "health map" of Singapore. Doctors and scientists can use this health map to understand diseases better, find new ways to prevent diseases, and develop better treatments.

What does our previous research tell us?

Our previous research[16-18] show that Singaporeans generally support sharing precision medicine data, with the following values in place for sharing: public benefit, fairness, and transparency. In addition, based on views from patients and the public, we developed fair and clear processes for volunteers in genomics research.[19] These processes involve how to ask for consent and how to return genetic test results.[19] However, these research studies were conducted with smaller groups of Singaporeans. As NPM expands to include a large number of Singaporeans, we would need more research that can represent Singaporean views. Furthermore, these studies did not use CREP.

Why does Singapore need its own guidelines for genomics research?

Most research on public values related to genomics research comes from the United States and Europe. However, Singapore's culture and values are different. Past research shows that ethical values such as public benefit, fairness, and accountability are more important to Singaporeans, compared to personal privacy and individual choice.[16-18, 20] This is different from some Western countries, where personal privacy is often the top concern.[21, 22] Current international guidelines on genomics technologies research are broad and do not consider specific cultural contexts. Therefore, we need to create practical guidelines for gene technologies that fit Singapore's specific needs and values.

Research Plan

The aim of this research program is to create policies for using new cell and gene technologies in Singapore based on evidence and public opinions. This program involves three themes:

- Theme 1: Implementing universal genomic screening
- Theme 2: Characterising the social license for precision medicine; and
- Theme 3: Emerging cell and gene therapies

Theme 1: Implementing universal screening with genomics

This theme is based on studies at the Duke-NUS Institute of Precision Medicine (PRISM) in collaboration with KKH, NUS and PRECISE. It is made up of 3 topics: (i) universal carrier screening, (ii) cascade screening for families, and (iii) population genomic screening.

(i) Universal carrier screening

Carrier screening is a genetic test that helps couples find out if they might have children with certain genetic diseases.

How likely it is to have a child with a severe genetic disease in Singapore?

About 4 in 1,000 Singaporean couples (0.4%) might have a child with a severe genetic disease.[14, 23] This is about 150-200 babies each year. Treating these diseases in hospitals is very expensive and the cost is increasing.

What is the current practice of carrier screening in Singapore?

Singapore only routinely screens for one disease (thalassemia major).[24]

What are the international recommendations for carrier screening?

International experts suggest testing all couples pregnant or planning a pregnancy[25] for 70 genetic diseases that are common in Chinese, Malay, and Indian racial groups.[14] Of these diseases, 37 are severe diseases that begin in childhood.[26]

What is the aim of this study?

The aim is to create guidelines for how to do this screening in a way that works for Singapore. Based on the international recommendations, Singapore has come up with a list of common severe childhood diseases to screen for. In an upcoming preliminary study, we will screen 1,000 couples. If successful, all couples who visit the public hospitals for pregnancy related care will be screened. The eventual plan is to extend this screening to all healthcare institutions. We will use CREP to:

1. compare the costs with the benefits of screening all couples in Singapore
2. explore what Singaporeans think about disability, choice, and acceptance

(ii) Cascade screening for families

Cascade screening is a process where family members of a person diagnosed with a genetic condition are offered genetic testing to identify who may have risk for the same condition. This is because certain health condition can run in families. Their health can be improved through early treatment if their condition is detected early.

What is the current practice of cascade screening in Singapore?

Although experts worldwide recommend cascade screening, it has only been done for research and not yet in medical practice. So far, participation rates for research have been low.

What does past research say about Singaporeans' views on cascade screening?

Past local research shows patients and families in Singapore are generally willing to hear about their genetic risks by health professionals.[27] This shows the potential of implementing cascade screening programs in Singapore.

What is the aim of this study?

The aim is to create guidelines to help health professionals share genetic risk results to patients and family in Singapore. To encourage more patients to disclose their genetic and more relatives to go for screening, we will first address the following ethical questions:

- Who has the responsibility to inform family members about genetic risks?
- How do we balance privacy concerns with health benefits?
- What do we address insurance concerns?
- How do we make sure cascade screening is available to everyone?
- How do we handle sensitive data from unexpected findings (e.g. finding out that a father is not biologically related to the child)?

(iii) Returning genome analysis results

Genomic screening can identify people at risk of or with undiagnosed medical conditions. In the SG10K Health cohort, about 3 in 100 people tested were found with higher risk of developing a genetic condition.[14] If discovered early, this condition could be prevented.

PRISM has developed a process to returning actionable genetic test results to a cohort of volunteers[19] and is also working with PRECISE to return findings related to cancer, high cholesterol, and heart problems to the SG100K cohort. Actionable genetic test results refer to useful health information that you and your doctor can do something about. For example, if a genetic test shows you have a high risk for high cholesterol, doctors might recommend medication and diet changes.

What is the aim of this study?

Past research shows Singaporeans are generally open to receiving genetic test results.[28, 29] For this study, we want to use CREP to develop best practices for returning actionable genetic test results in Singapore. Our aims are to examine:

- how knowledge of genetic test results affects people's willingness to get health screenings

- if being diagnosed with medical conditions makes people avoid genetic testing
- how much we should actively convince people to take care of their own health

We will conduct interviews with health professionals and do a national survey to come up with policy guidelines.

Theme 2: Characterising the social license for precision medicine

This theme aims to understand the "social license" for precision medicine in Singapore. Social license refers to getting permission from the members of the public to use public resources.[30] When research projects do not run their research activities based on what people expect, the public might stop trusting them.[31] This loss of trust can make it hard for big projects to continue their operations.[32] In the case of the NPM, loss of trust would make it challenging to reach the goal of recruiting up to 1 million volunteers.

For this theme, we will use CREP to develop policy recommendations for the NPM for the two challenges our previous research has found:

(i) government agencies using NPM data for reasons unrelated to health research; and
(ii) the types of consent and withdrawal choices

(i) Government agencies using NPM data for reasons unrelated to health research

Our past research shows most Singaporeans are agreeable with the government using NPM data for health-related work. However, it is unclear to us how they feel about using NPM data for criminal investigations.

In our more recent focus group discussions, we found that Singaporeans are unaware that the police might be able to use this data in the future. Singapore already has a national DNA database for the police to use. However, there are also currently laws that let police use almost any data in Singapore to solve crimes.[33]

The TraceTogether incident in 2020

In 2020, the police used data from the TraceTogether App to investigate a murder without informing the public beforehand. This caused a big negative reaction from the public.[34] The government then made a new law to limit police use of this data, allowing it to be used only for very serious crimes.[35] This new law is called the Registration of Criminals (Amendment) Bill 2022.

Although NPM data is <u>not</u> linked to personal information (such as names, address, NRIC etc),[33] police might be able to request to match it to DNA samples from crime scenes. Right now, with small numbers of volunteers in the NPM, such matches are unlikely. However, as more volunteers join the NPM, matches become more possible. Finding just a match in NPM data is not enough to arrest someone, but it could involve families in investigations. This might make people not want to join the NPM.

What is the aim of this study?

The aim of this study is to balance solving crimes with protecting people's privacy. We will use CREP to identify the ethical issues, theories and principles in this situation. We will survey Singaporeans to ask for their specific concerns (if any) about the police using NPM data for crime solving. Then, we will provide policy recommendations based on our findings.

(ii) The types of consent and withdrawal choices

What are the problems with current consent forms?

We need people's permission to use their data for NPM research. However, the current consent forms are long and hard to understand. These forms can make it harder for people to make informed choices[36] and slow down hospital operations. The current way of asking for consent also takes up a lot of time and resources. The complex consent processes might not be needed since the risks of data breaches are small.

How do Singaporeans prefer in terms of consent?

Our past research shows that Singaporeans prefer simple, easy-to-understand consent forms.[18] They do not need high levels of control over their data if data protection measures are in place.[16]

What is the aim of this study?

We aim to look for a better way to ask for consent that is easier for research participants to understand, does not slow down hospital operations, and still protects people's privacy. The goal is to find a balance between giving people enough information for them to consent to genomics research and making the process simpler for everyone.

There are different methods of asking for consent. Some of the methods are:

- Meta consent[37]: A flexible type of consent where it allows people to decide in advance how they want to be asked for consent for different types of research. People can choose dynamic consent, broad consent, tiered consent or other types of consent.
- Dynamic consent[38]: Ongoing online consent where participants are informed about the studies' progress and can update their consent choices over time.
- Tiered consent[39]: Consent for some specific studies.
- Broad consent[40, 41]: Consent one time for all studies.

We will look at the different types of consent methods and explore which type might work best for the NPM groups (like SG100K cohorts). We will work with people in the SG100K cohort through focus group discussions to design the consent processes and survey Singaporeans what they think about these processes.

We will use CREP to come up with policy recommendations on the most suitable type of consent for the NPM participants. This includes deciding how much to tell the participants about when and how law enforcement might be allowed to use their data.

Theme 3: Emerging cell and gene therapies

For this theme, we will look at the ethics of the new technologies that use genetic information. Our research will focus on two technologies in particular:

- Polygenic risk scoring (PRS)
- Advanced cell and gene therapies

We plan to examine what experts have said about these technologies, look at how they are being used now and identify the gaps in ethical knowledge. Then, we will conduct workshops with stakeholders who work with or are affected by these technologies to point out specific areas of concern from these gaps. We will also survey Singaporeans to ask about their views on the ethics of these technologies. We aim to match theory with public inputs and develop ethical guidelines for policymakers and stakeholders.

We will also examine and predict ethical challenges of future gene-based technologies. These technologies are not ready to use in Singapore yet, but they might be important in the future and need further research. This work will help Singapore prepare for these new technologies in a way that is ethical and is aligned with what people expect.

(i) Predicting disease with polygenic risk scoring (PRS)

What is polygenic risk scoring (PRS)?

Polygenic risk scoring (PRS)[42] is a way to predict a person's chance of getting certain health problems by looking at their DNA. The RESET program (https://medicine.nus.edu.sg/reset_landing/) is creating a PRS tool to predict who might get heart failure in Singapore. The main purpose of PRS is that if people know they are at risk for heart problems, they might change their lifestyle habits to be healthier. This could help prevent heart failure. We will work with RESET to look at the ethical challenges that might come up when using PRS, how the challenges might affect society, and whether Singaporeans accept PRS use.

What is the aim of our study?

We will look at what PRS will predict, which will be the risk of heart failure and how long someone might live if they have this risk. Past limited research has shown that if people learn that they have high risk for a certain disease based on PRS, this information could help people plan their health better or they might feel distressed.[43-45] They might also feel anxious and lower their expectations of they want to achieve in life.[46] Other possible harms include unnecessary medical treatment, and the risk of discrimination based on genetic data.[46] There were also concerns about trying to motivate people to change their lifestyle based on PRS information might reduce their free will to make their own decisions, rather than increase it.[47]

We will use CREP to explore how to use PRS information ethically in Singapore and how much we can expect people to change their behaviours based on PRS. This involves reading up on what scientists and ethicists have reported, asking the public what they think and analyse the ethical issues. Then, we will write a short report. The report aims to help doctors and scientists who are working on PRS understand the ethical issues they need to think about when they use PRS.

(ii) Access to high-cost gene therapies

In the last five years, new gene therapies have become available worldwide. Singapore has approved four of these treatments so far.[48] The number of approved treatments is likely to increase as many others have been approved in other countries.[48]

These treatments can be very effective for rare diseases that were hard to treat before. They can help with certain types of blood cancers, muscle diseases, blood disorders and eye diseases. The big problem is that these treatments are extremely expensive. They can cost hundreds of thousands or even millions of dollars per patient. As more of these treatments are developed, including some for more common

cancers,[49, 50] the challenge becomes figuring out how to pay for them.[46] For example, the most expensive gene therapy approved in Singapore is called Zolgensma. It costs about €1.9 million (or roughly 2.8 million Singapore dollars) for one treatment.[51] Despite the high cost, some studies show these treatments might be worth the money, as the treatment greatly improves and extends a person's life.[52]

There are also concerns that these expensive treatments might disproportionately increase the healthcare costs and make health inequalities worse (where only rich people can afford certain treatments). Therefore, we need to ask the following ethical questions about what we value as a society, to inform policymaking.

1. Is it fair to spend millions on one person when that money could help many others?
2. How do we balance helping the most people (utility) with being fair to everyone?

What is the aim of our study?

Given the lack of research on public attitudes towards high-cost treatments and their accessibility, we propose to explore ethics of covering expensive cell and gene therapies in Singapore's health financing systems. We will survey patients, families, healthcare providers, insurers, economists on priorities and preferred justice theories for coverage decisions. We will also conduct a scoping review and stakeholder workshop. Based on what we find, we will come up with a policy brief.

(iii) Horizon-scanning for new applications of genomics

We will reserve this space to study the ethical and social issues of new genomics technologies. We will focus on controversial technologies that could cause big societal challenges when they reach Asia. Some examples are:

- using whole genome sequencing to screen newborns,[53]
- selecting embryos based on PRS,[54] and
- editing genes that can be passed to future generations. [55, 56]

We want to understand how the public and experts in Singapore feel about these potential uses. This research will help fill gaps in our knowledge about how Asian societies view genomics. Since this is preliminary research, we will not make firm policy suggestions. Instead, we will lay the foundation to use CREP if these technologies come to Singapore.

Potential Impact of this research program

In doing this research, the potential impacts are:

1. This program will support important national scientific projects by creating evidence-based policies, practical guidelines and standards for best practices.
2. This program will help shape global discussions on how to use genetic and personalized health technologies in an ethical and responsible way.
3. This program will improve the CREP method for evidence-based bioethics and scientific policymaking.
4. The program will study how valuable and practical it is to involve patients and the public in genomics research in Singapore.
5. This program will support advanced health research by creating new knowledge in developing an ethical and socially responsible way to introduce genomics that fits Singapore's specific needs.
6. This program will help understand society in the digital age, create better ways to govern the use of genomics and personalized medicine, and build public trust in these health technologies.

Research Team

Team leadership

This research program is led by the Principal Investigator, Professor Julia Savulescu. Professor Savulescu is the director of the Centre for Biomedical Ethics, National University of Singapore. He is an award-winning ethicist and a moral philosopher, and has background training in neuroscience, medicine, and philosophy.

Research team

The research team is diverse and highly qualified, with expertise relevant to implementing genomics and precision health in Singapore. Key members include:

- Associate Professor Tamra Lysaght, University of Sydney: Bioethicist experienced in genomics and precision health ethics, regulation, and policy.
- Assistant Professor Owen Schaefer, National University of Singapore: Specialist in normative bioethics and biotechnology ethics.
- Associate Professor Konstadina Griva, Nanyang Technological University: Health Psychologist expert in health interventions and mixed research methods.
- Professor Roger Foo, National University of Singapore: Expert in cardiac epigenetics, experienced with large personal data sets.
- Professor John Chambers, Nanyang Technological University: Clinical Scientist leading large population studies.
- Assistant Professor Lim Weng Khong, Duke-NUS Medical School: Bioinformatics expert focused on genome analytics and genetic disorders in Singaporeans.

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