The National Precision Medicine Strategy in Singapore: Securing Public and Community Trust for data sharing

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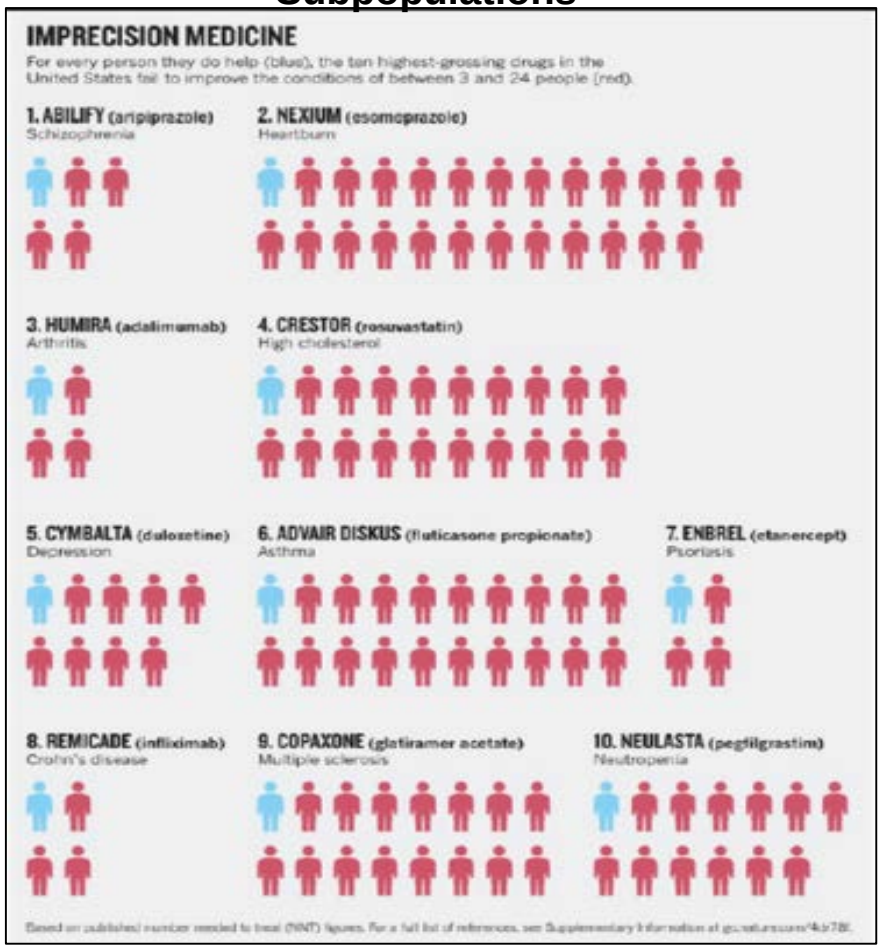
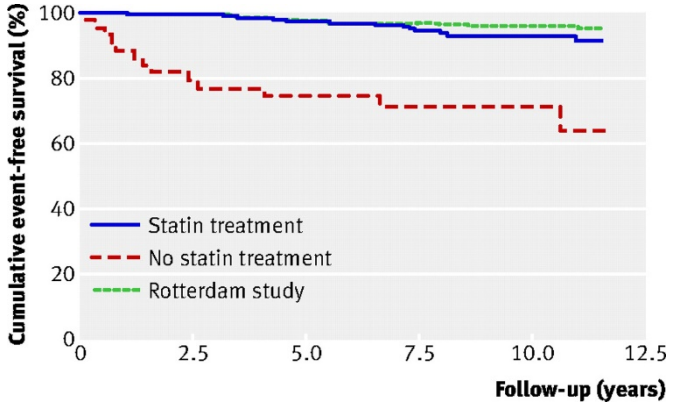
Why Precision Medicine?

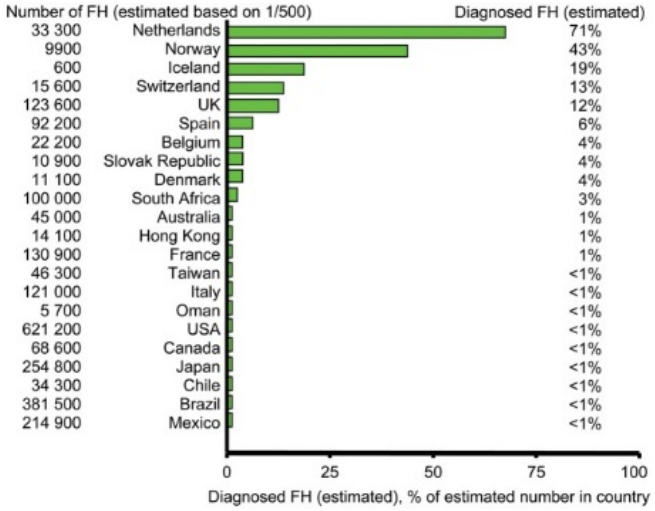
A Need for New Clinical Paradigms

Most Treatments Benefit or Harm Subpopulations

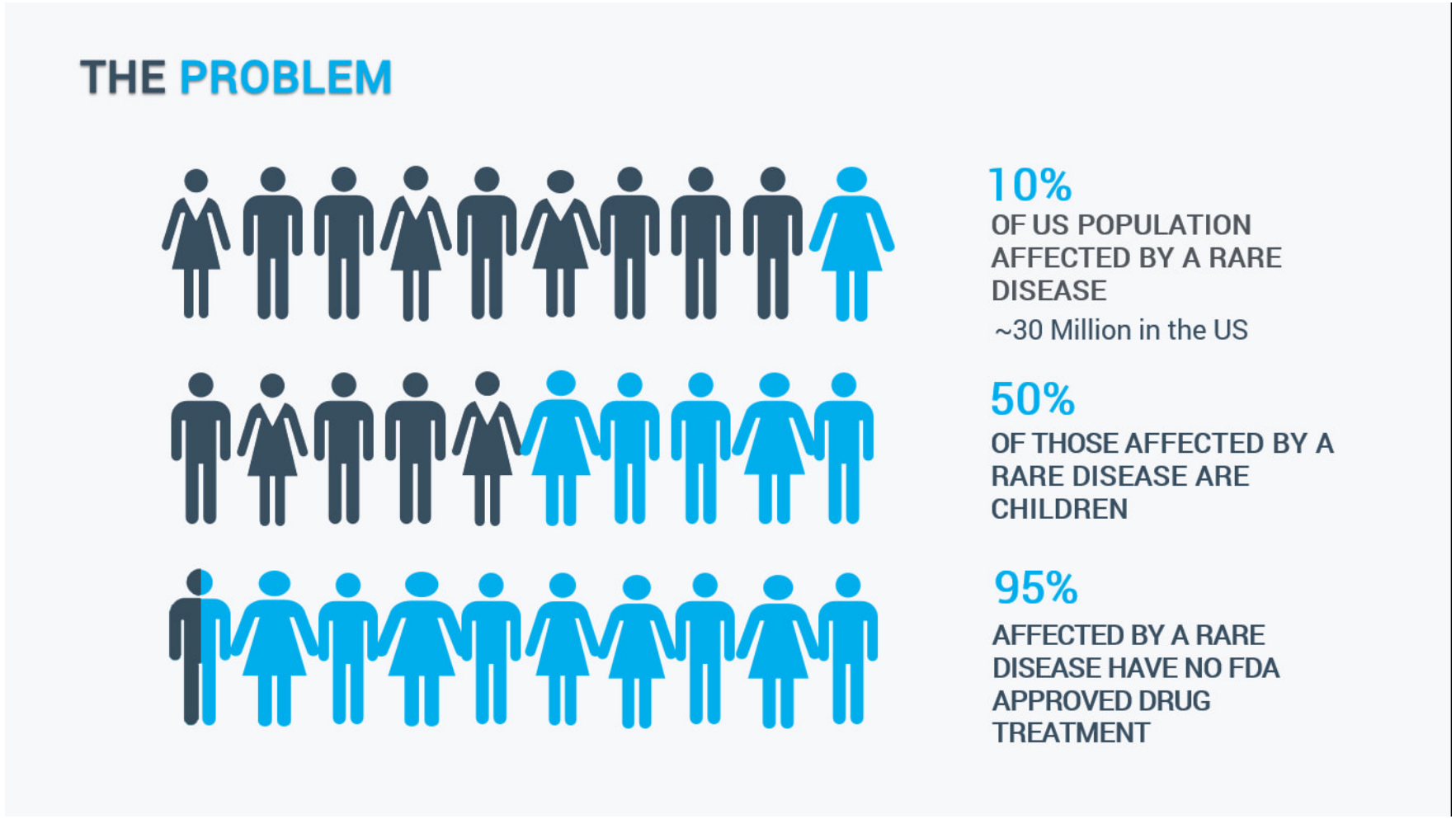


Some patients who would benefit from treatment are not being treated





A Need for New Therapies

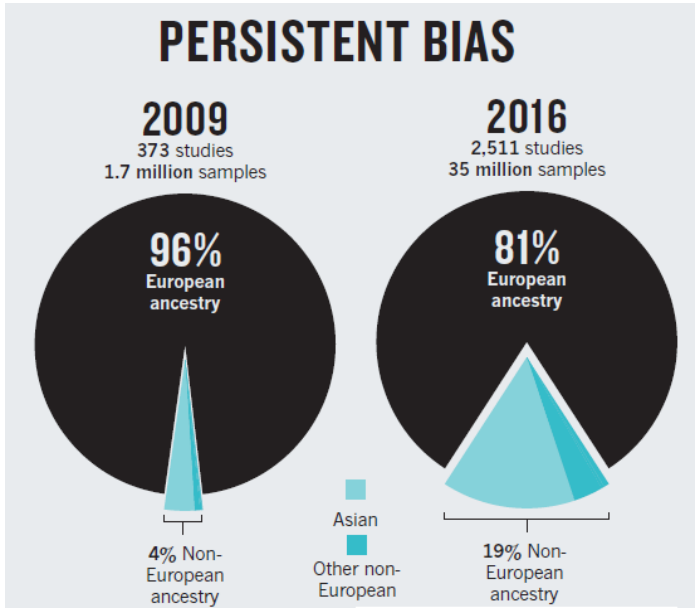


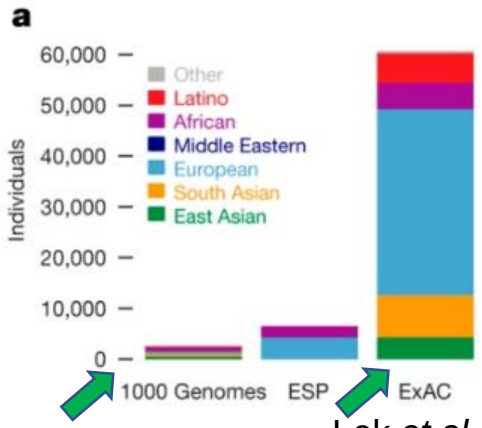
Why Asia?

A Global Missing Gap : Asian Genomic Data

Having trouble finding Chinese genomic data?

Charlotte Whicher | 08 September 2016 | Product, Team Blog Post, Data Collection, Chinese Control Data, Repository, The China Kadoorie Biobank, The Singapore Genome Variation Project, GigaDB, GigaScience, Beijing Genomics Institute, Genome Asia 100K





Lek *et al. Nature* **536,** 285–291 (2016)

Genetic Misdiagnoses and the Potential for Health Disparities

Arjun K. Manrai, Ph.D., Birgit H. Funke, Ph.D., Heidi L. Rehm, Ph.D., Morten S. Olesen, Ph.D., Bradley A. Maron, M.D., Peter Szolovits, Ph.D., David M. Margulies, M.D., Joseph Loscalzo, M.D., Ph.D., and Isaac S. Kohane, M.D., Ph.D.

NEJM, 2016

Diseases that manifest differently in Asians

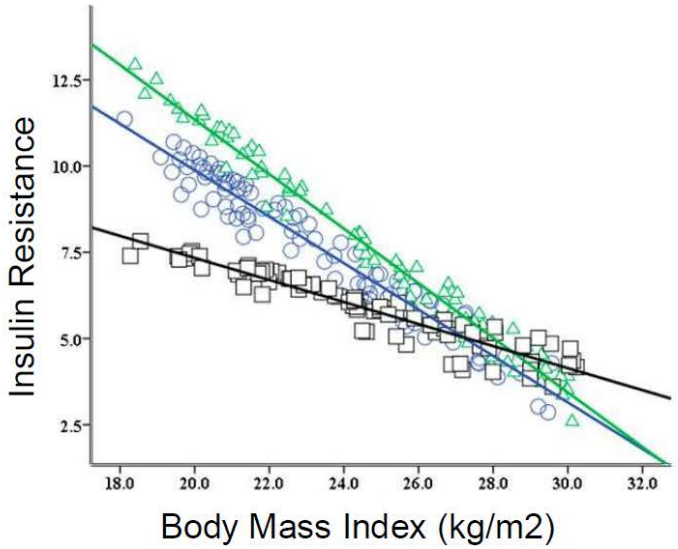
Disease Risk Factors and Asian Diversity

Chinese

Malay

Indian

Impact of obesity on insulin resistance is stronger in Chinese and Malay populations



Chin Meng Khoo et al. (2014) Diabetes

5

Diseases that are only seen in Asians

ARTICLE | Genetics inMedicine

Corrected: Correction

Population genomics in South East Asia captures unexpectedly high carrier frequency for treatable inherited disorders

Table 2 Summary of pathogenic variants detected

Disease name	Gene	Transcript	Genomic coordinates (hg19)	Gene change	AA change	Number of carriers	SEC/ExAC_All	SEC/ExAC_EAS
Citrin deficiency	*SLC25A13*	NM_014251.2	Chr7:95818684delCATA	c.852_855delTATG	p.M285fs	12	24.07	1.95
			Chr7:95822344C>T	c.615+5G>A	splicing	4	24.24	1.15
			Chr7:95751240insCCCGGG CAGCCACCTGTAATCTC	c.1663_1664insGAGATTA CAGGTGGCTGCCCGGG	p.A555fs	3	19.92	1.39
			Chr7:95822471G>A	c.493C>T	p.Q165X	1	NA*	NA*
Wilson disease	*ATP7B*	NM_000053.3	Chr13:52532469C>A	c.2333G>T	p.R778L	5	15.04	NA*
			Chr13:52520508G>A	c.2351C>T	p.T784M	2	0.93	12.03
			Chr13:52544627C>A	c.1543+1G>T	splicing	1	NA*	NA*
Phenylketonuria	*PAH*	NM_000277.1	Chr12:103246714G>A	c.721C>T	p.R241C	3	18.05	1.39
Glutaric aciduria, type I	*GCDH*	NM_000159.3	Chr19:13010280A>C	c.1244–2A>C	splicing	3	24.70	1.83
Molybdenum cofactor deficiency	*MOCS2*	NM_002203.3	Chr5:52405544G>A	c.16C>T	p.Q6X	2	NA**	NA**
Methylmalonic acidemia with homocystinuria	*MMACHC*	NM_015506.2	Chr1:45974001C>T	c.394C>T	p.R132X	1	6.05	NA**
			Chr1:45974520G>A	c.482G>A	p.R161Q	1	6.02	6.02
Methylmalonic aciduria	*MUT*	NM_000255.3	Chr6:49409685C>T	c.1677–1G>A	splicing	1	73.16	6.03
			Chr6:49425427->AA	c.729_730insTT	p.D244fs	1	36.03	3.03
Biotidinase deficiency	*BTD*	NM_000060.4	Chr3:15686120C>T	c.757C>T	p.P253S	1	NA*	NA*
Aceruloplasminemia	*CP*	NM_032383.4	Chr3:148927953C>-	c.607+1delG	splicing	1	24.36	2.01
PTS deficiency	*PTS*	NM_000317.2	Chr11:112103928G>A	c.286G>A	p.D96N	1	NA*	NA*
Segawa syndrome	*TH*	NM_000207.2	Chr11:2189135C>T	c.605G>A	p.R202H	1	6.02	6.02
Alpha Mannosidosis	*MAN2B1*	NM_000528.3	Chr19:12759988C>G	c.2398G>C	p.G800R	1	NA*	NA*
Holocarboxylase synthetase deficiency	*HLCS*	NM_000411.6	Chr21:38308963C>-	c.782delG	p.G261fs	1	25.11	2.08
TOTAL						**46**		

AA amino acid; *SEC* Singapore Exome Consortium; *ExAC* Exome Aggregation Consortium

* Allele count not available in ExAC

** Allele count = 0 in ExAC

10-year Singapore Precision Medicine Roadmap

Real-time Genomic-Clinical Data Vault of 1,000,000 Singaporeans

Three Phases : Term-Limited, with Clear Go/No-Go Milestones

Endorsed by HBMS IAC, RIEC (Non-Ministerial), NRF SAB

Phase I (2017-2019)
Establish "At-Scale" Infrastructure

a) Data Production (SG10K)
b) Data Analytics (NSCC)
c) Linkage to *EMRs (via ^BRAIN)

Phase II (2020-2022)
Capture Diversity

a) Sequence Population (100,000-150,000)
b) Disease cohorts (Cancer, CVMD, etc)
c) New Data Types (Metabolomics, Imaging, Epigenetics)

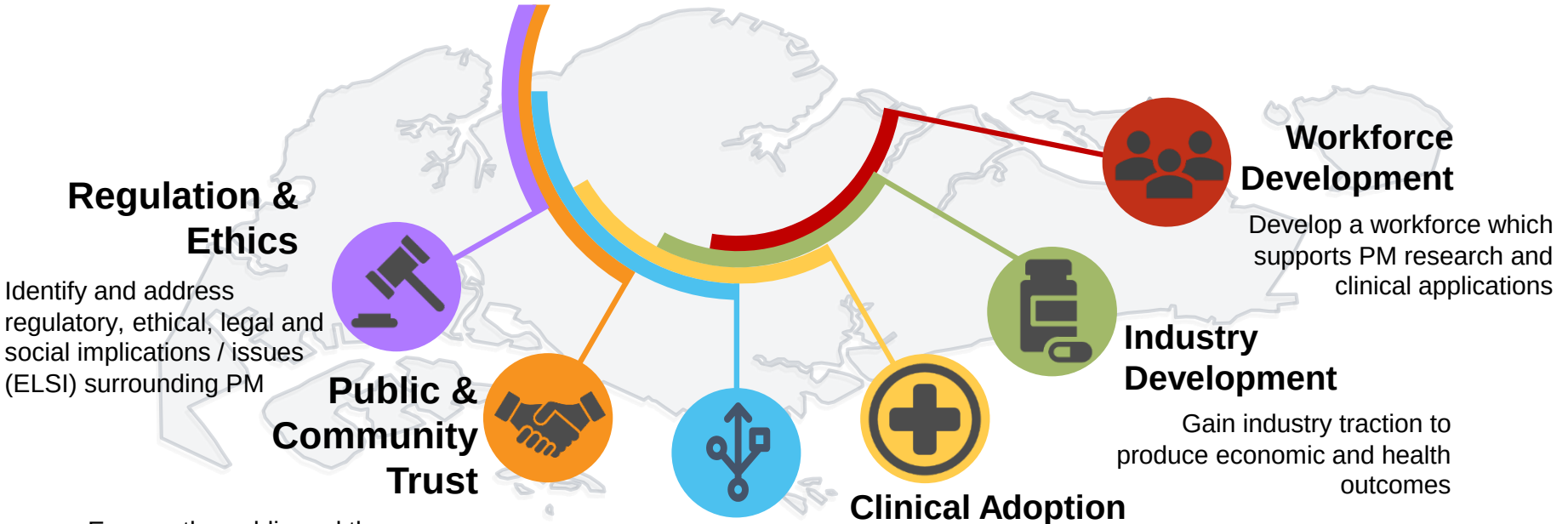
Phase III (2023-2026)
Population Health

a) Genotype 1 million ($10/patient)
a) Lifestyle and Environmental Data (SMART Nation)
c) Deploy PM Workforce (Training, Education)

ELSI Guidelines and Legislation
(Incidental Findings, Insurance, Secondary Use)

Public Engagement (incl Healthcare Practitioners)

NATIONAL PRECISION MEDICINE STEERING COMMITTEE- WORKGROUPS



Regulation & Ethics

Identify and address regulatory, ethical, legal and social implications / issues (ELSI) surrounding PM

Public & Community Trust

Engage the public and the scientific, medical and healthcare communities to survey and address their concerns of and aspirations for PM

Enabling Platforms

Develop technical infrastructure for data generation, analytics, storage and linkage

Clinical Adoption

Define priority areas for PM and bring PM into clinical applications in a cost-effective and sustainable manner

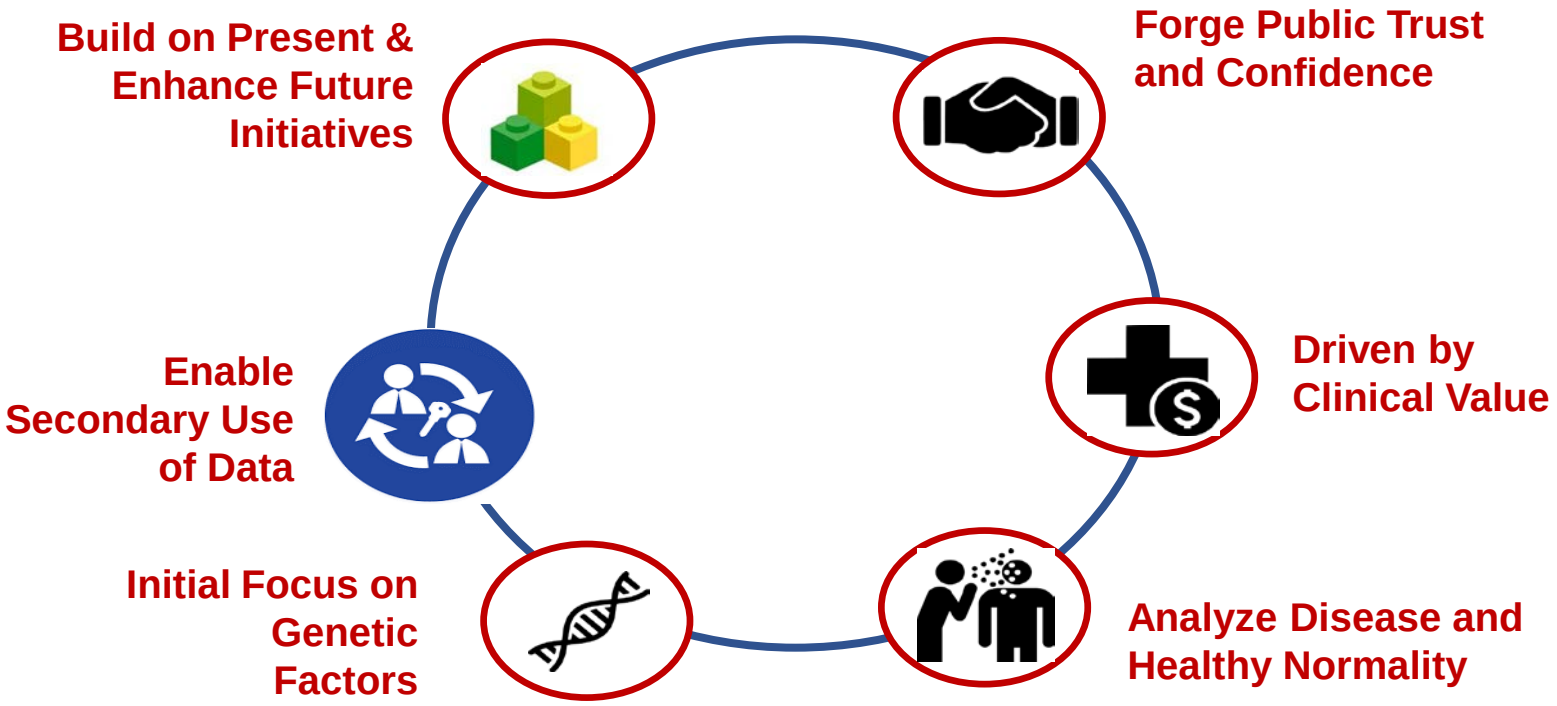
Industry Development

Gain industry traction to produce economic and health outcomes

Workforce Development

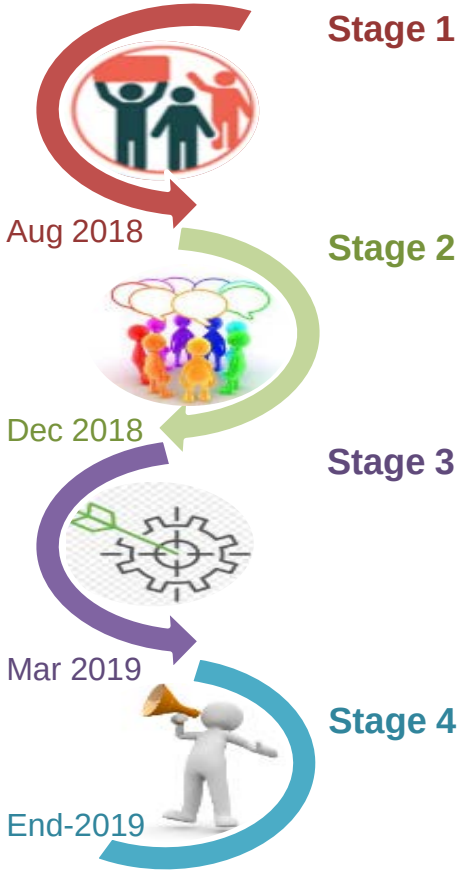
Develop a workforce which supports PM research and clinical applications

National Precision Medicine-Guiding Principles



Public and Community Trust Workgroup Roadmap

Public Communications and Engagement Plan for Precision Medicine in Singapore



Stage 1 — Introduce the Concept of Precision Medicine

Draft definition of Precision Medicine

Message testing & measure awareness and understanding; gauge public expectations for precision medicine as defined

Generate sufficient data to set the scene for Stage 2

Stage 2 — Engage in Dialogue to sharpen engagement strategy

Focus Groups with relevant groups to:

- Further test and refine messages among small groups of individuals
- Identify stories & use cases meaningful to the public (In collaboration with other WGs)
- Identify public concerns and understand motivations that would encourage participation & data sharing
- Begin to understand the means by which the public would like to be engaged

Stage 3 — Formulate policies and procedures to address public concerns

- Collaborate with Centre for Biomedical Ethics – Science, Health And Policy-relevant Ethics in Singapore (SHAPES) Initiative, tasked to develop an ethical decision-making framework to guide Big Data activities related to health & research – PM is included as one of the domains
- Evaluate measures and policies formulated by other WGs and access their ability to address public concerns related to the National PM Program in line with the values outlined in the ethical framework, and to provide feedback to the relevant work groups
- Collaborate and develop strategy for public engagement as the PM program moves forward

Stage 4 — Preparation for Rollout of Engagement Strategy

- Finalise National PM Engagement Strategy
- Alignment of strategy with broader national policies (where relevant)
- Develop & finalise communication and engagement related materials
- Preparations for the announcement of National PM Program

Public Concerns towards Precision Medicine

Survey Participants interviewed @Singapore Science Centre
- *Educators*
- *Student and Senior volunteers*

Public survey @Maker Faire (Tampines Hub)

Top Concerns (examples):

- **Affordability:** *"Precision medicine sounds expensive, like Chatterbox chicken rice versus Kopitiam chicken rice."*
  - Is sequencing to prevent disease more cost-effective than funding resources to encourage healthy lifestyles?

- **Personal benefit:** *"What's in it for me?"*
  - Would they get money, discounted/free treatment, or preferred access to precision medicine when it's available?

- Insurance companies and employers using information for discrimination

- Privacy and security of data: How would information be processed/kept?

Public Concerns on Contributing Data to National Platforms

Discrimination
Social stigma and employability

Data privacy
Medical records access by companies and others out of their 'circle of care'.

"it is like having your whole personhood exposed in terms of your condition, medication, past acts, and more".

Fear of exploitation
Inappropriate use of data, selling data to companies

Data security
Data breach and hacking risk

Public concerns

Benefits
Personal benefits: improve health or any monetary returns

Lack two-way communication
Public not well informed on how their data will be collected, used and shared.

"If it was actually something that met people's needs, then they would be more than willing to sign up for it and pressuring their practitioners to use it — that's not what we're seeing".

Warrant of trust
Data loaded in the system before public consent to data sharing

"When it becomes an opt out system and you find out all your data is on there, and oh by the way, you find out it's all being shared — I think that's one of the flaws. The rollout of this has been significantly flawed."

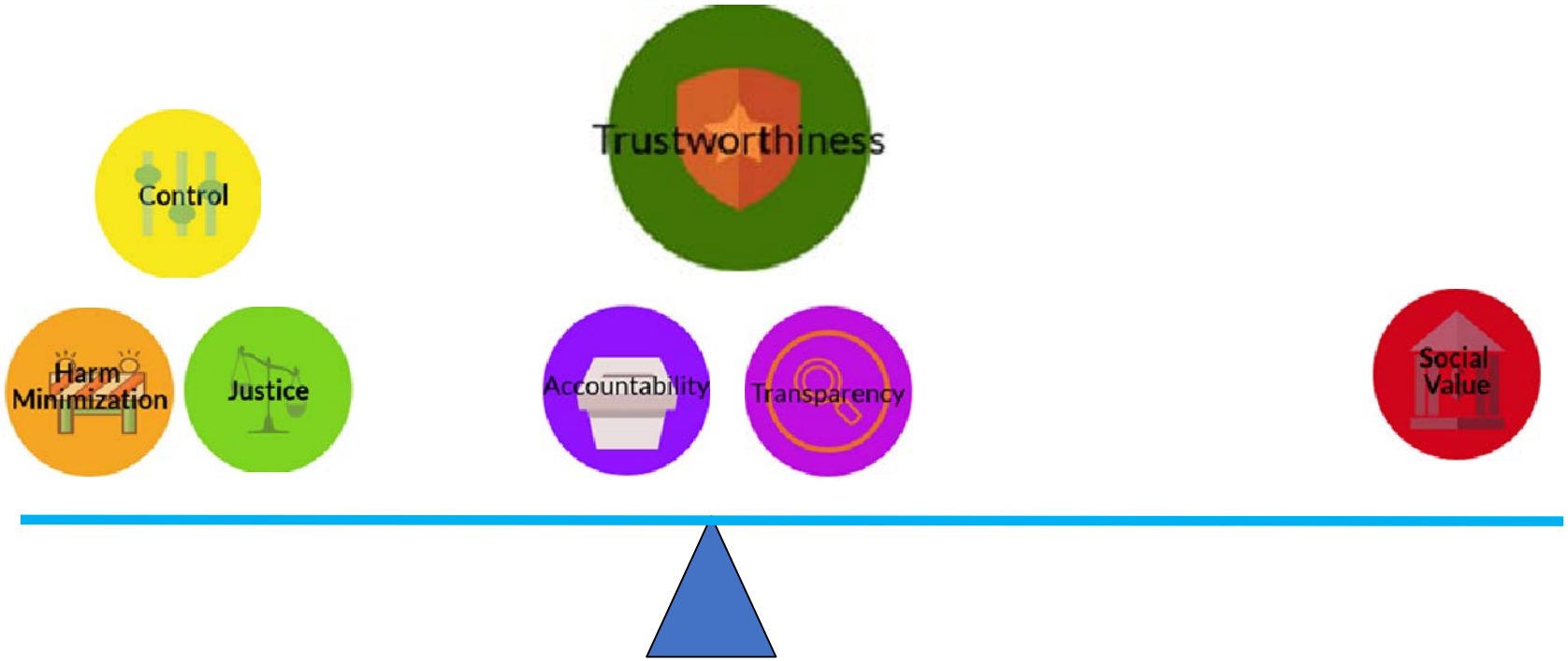
Source:
P&CT WG, Care.data, My Health Record, and Your DNA, Your Say

Ethics of data use

From: Where is the human in the data? A guide to ethical data use

Gigascience. 2018;7(7). doi:10.1093/gigascience/giy076

Balancing our values



Our Survey Pool

300 attendees of Science Festival satellite events and One-North Festival

Makers Faire

- Science/tech inventions and crafts at **Tampines Hub**
- Public – students, parents, visitors to mall
- 10,000 attendees over 3 days
- 62 surveys (makers & public who paid $10 for Makers Faire entry)

Science Buskers

- Science/tech demonstrations at **Plaza Singapura**; competition
- Public – students, parents, visitors to mall
- 20,000 attendees over 2 days (free admission)
- 106 surveys (almost all students, parents, attendees of Buskers)

Case Studies

Please read the description of genes below.

Genes carry the codes that determine how our bodies function, the way we look and how we behave. Changes in the codes (gene variants) can cause disease, or determine how we respond to drugs or other things in our environment (food, exercise, toxins). Gene variants can be passed down from parents to children. Understanding how gene variants cause disease allows us to diagnose diseases, develop new drugs or choose the right drug or the right patient to maximize benefits and minimize side effects. The following are some examples of how this might occur.

Please read the case study, which is based on actual patient cases, then answer questions 1 and 2.

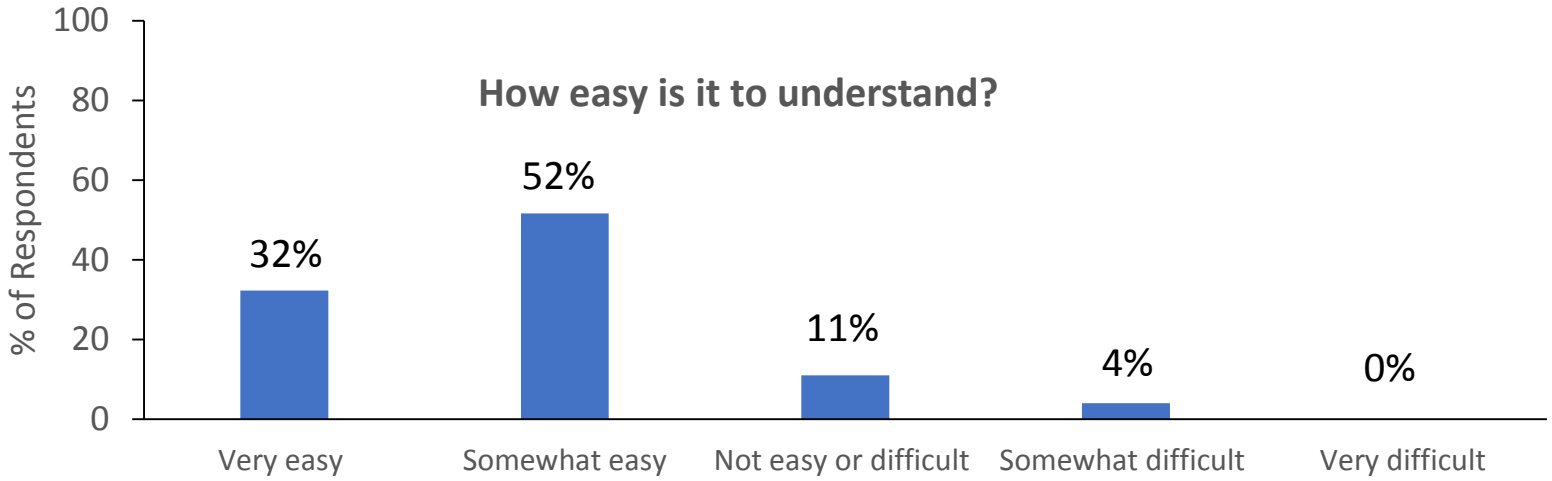
Case Study 1: Using Genetic Testing to Find an Elusive Diagnosis

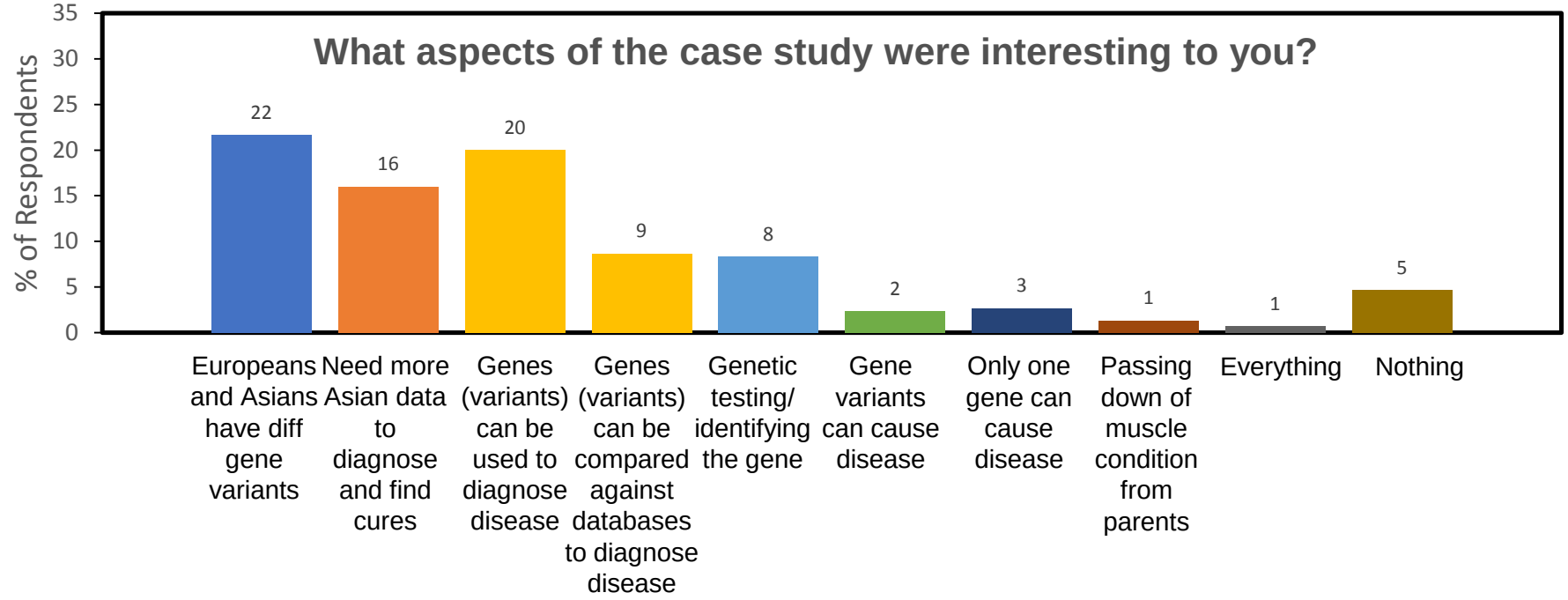
Access to data from Asian individuals can help diagnose rare genetic conditions in children. It helped the parents of Clara, 3, finally discover the cause of their daughter's severe breathing problems.

After many negative tests, Clara's doctor decided to try genetic sequencing. The test was performed on a blood sample from Clara. It revealed many gene variants, but only one was causing her disease. By comparing Clara's variants against databases containing thousands of genes from many people, Clara's doctor eliminated the variants that were also in healthy people. But he was stuck after that because the databases were mainly of European people.

Fortunately, he knew researchers who were studying Asian patients. With their help, he found a variant in Clara that was also in another person with similar symptoms. He diagnosed Clara with a rare genetic muscle condition, and started her on a medication to strengthen her muscles.

What We Found: How easy was the case to understand?



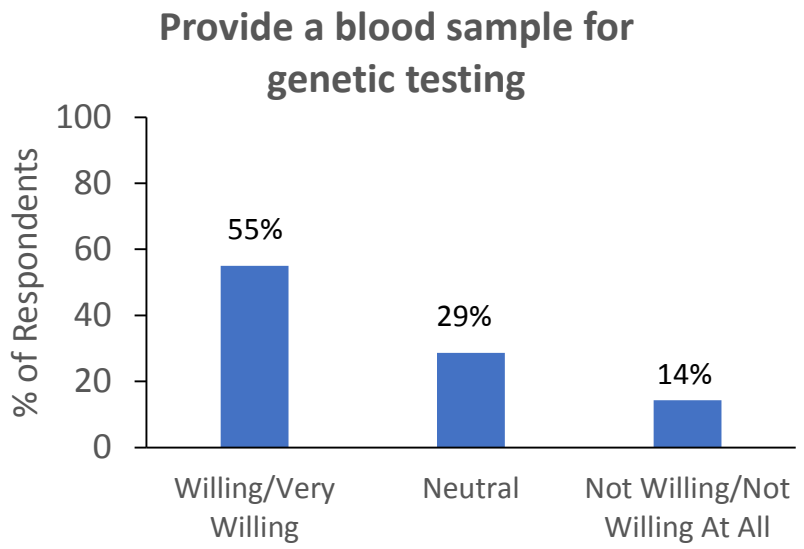


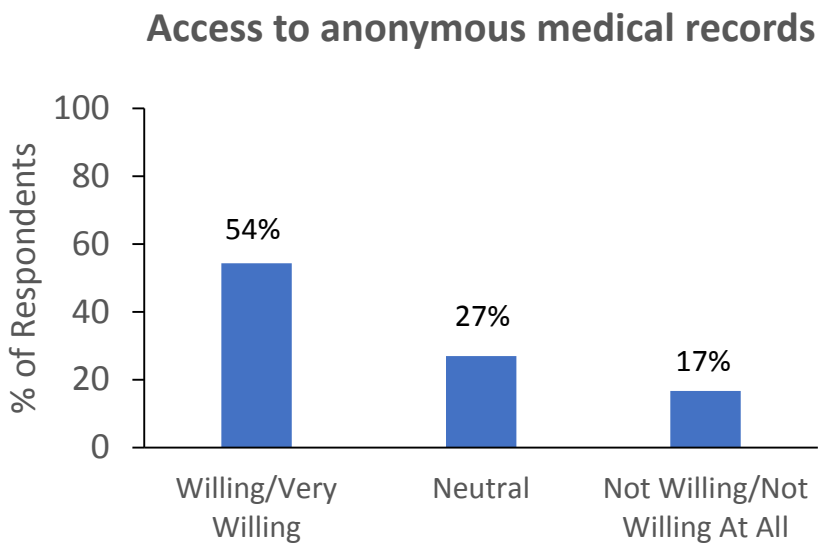
Explanation of a Potential Precision Medicine Program

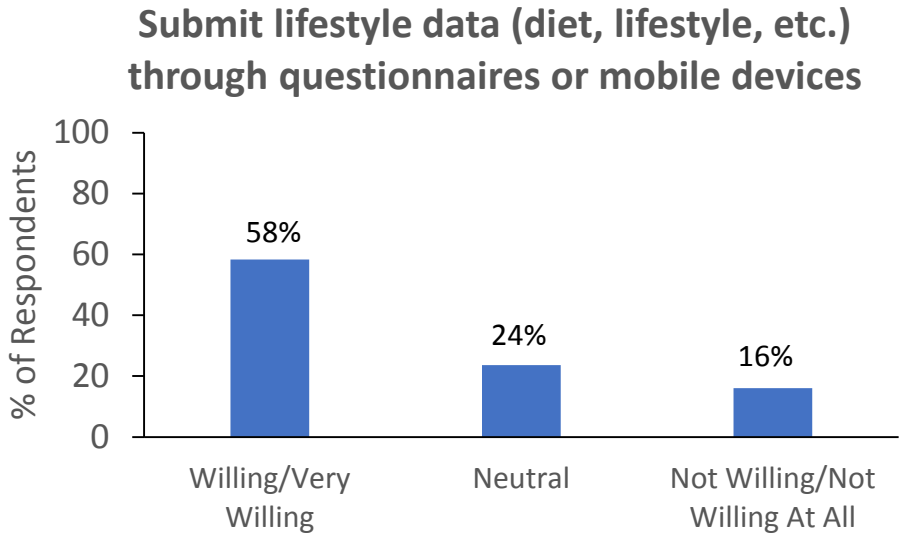
What a Precision Medicine Program Could Involve

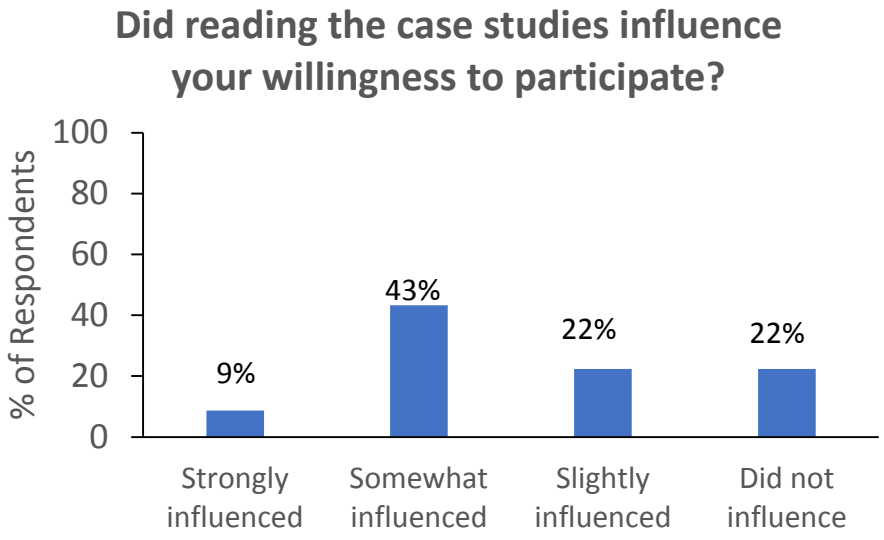
Since each individual is unique, doctors and scientists ne ed access to genetic, medical and lifestyle data from a lar ge number of individuals to understand how different in dividuals develop disease and respond to different treat ments. This information will be stored in a database and will be as secure as your banking data. Doctors and scien tists can access this anonymous information and use it to better prevent and treat diseases.

Willingness to Participate



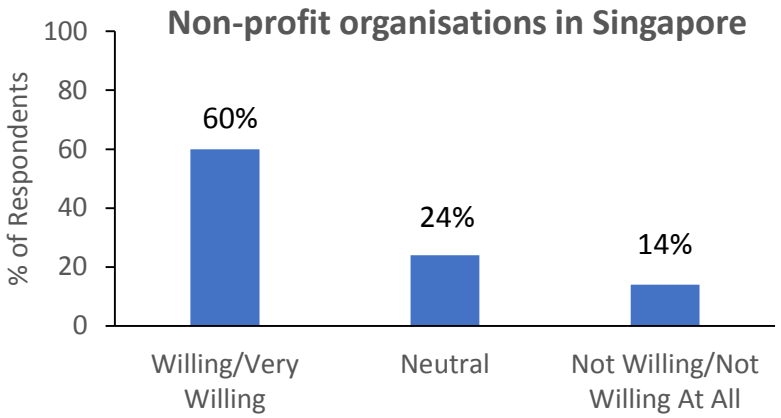


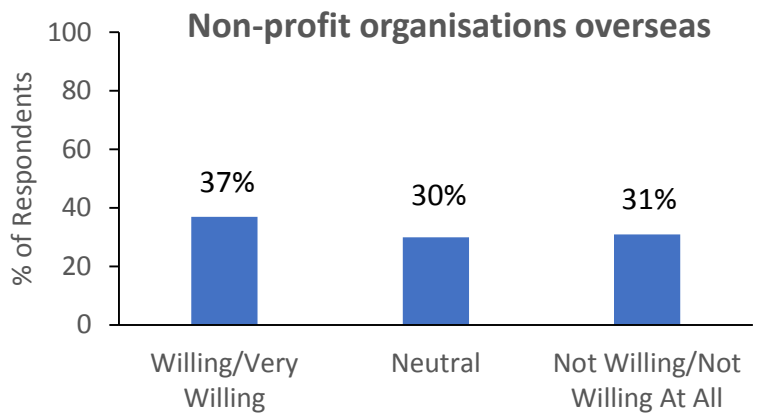


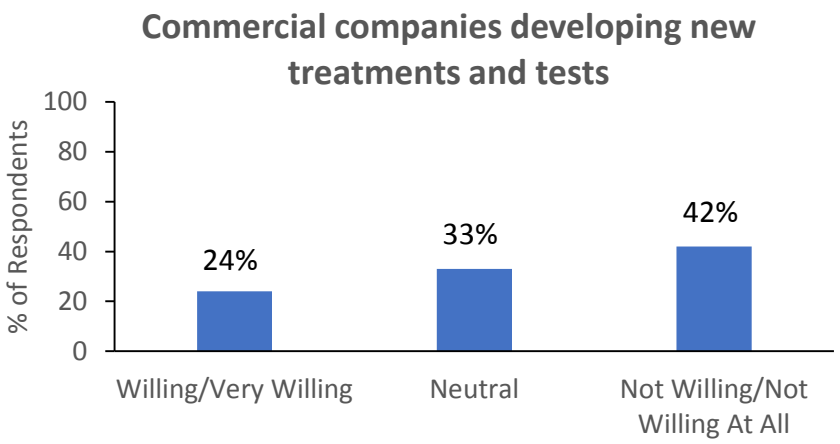


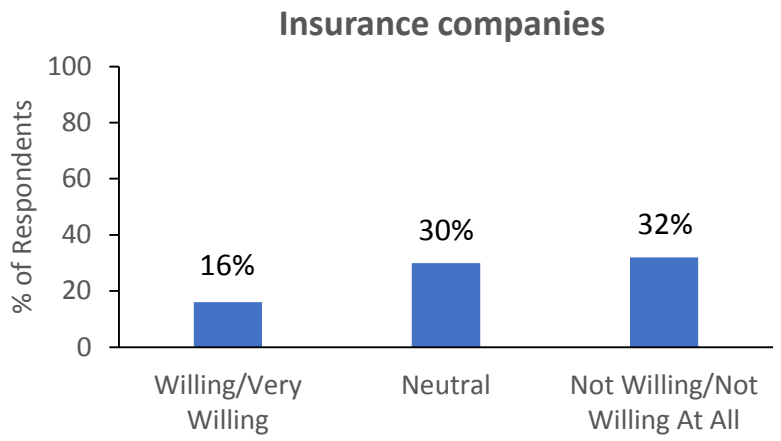
Willingness to Participate

How willing would you be for **researchers from the following organisations** to access your anonymous information, including genetic and medical records?

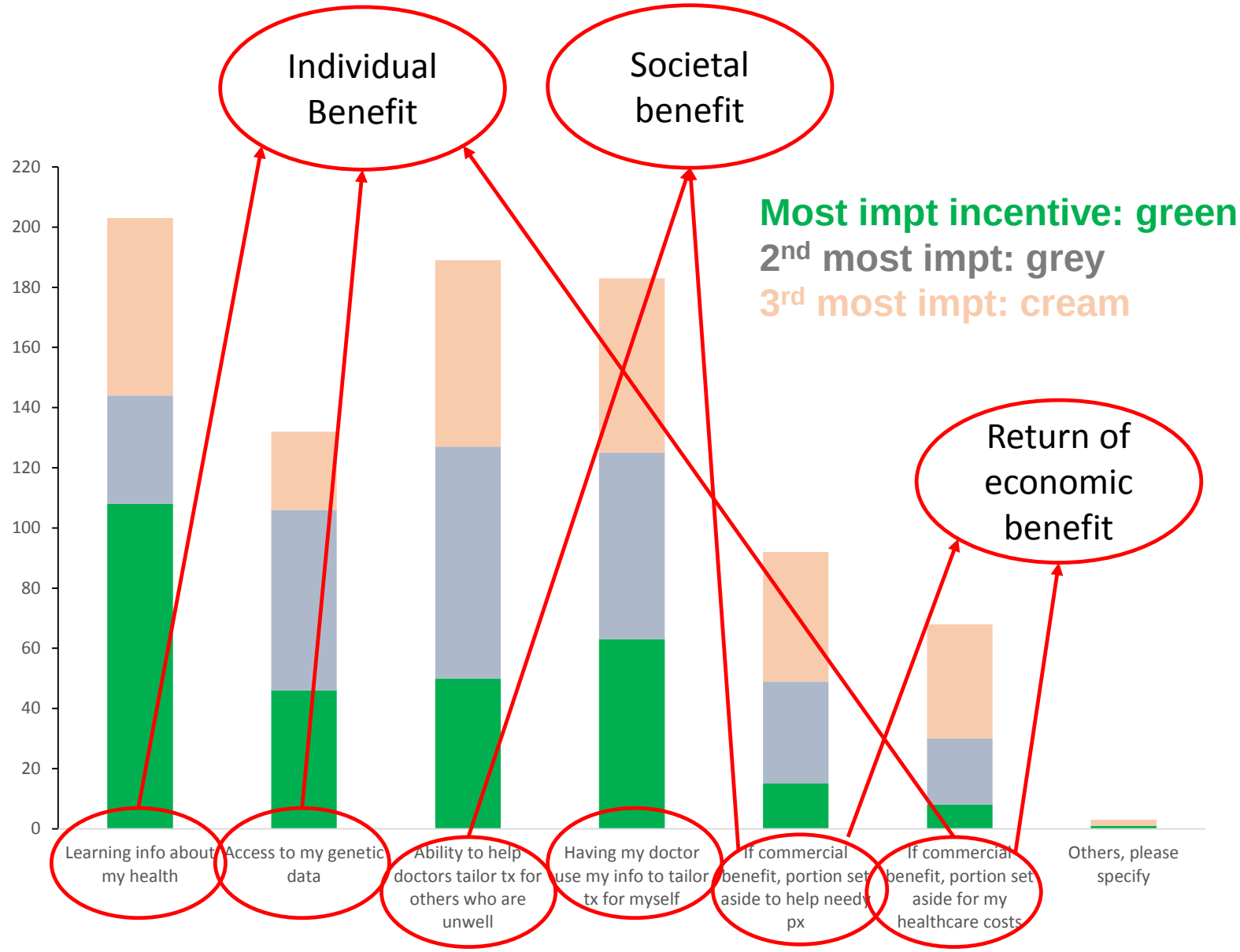




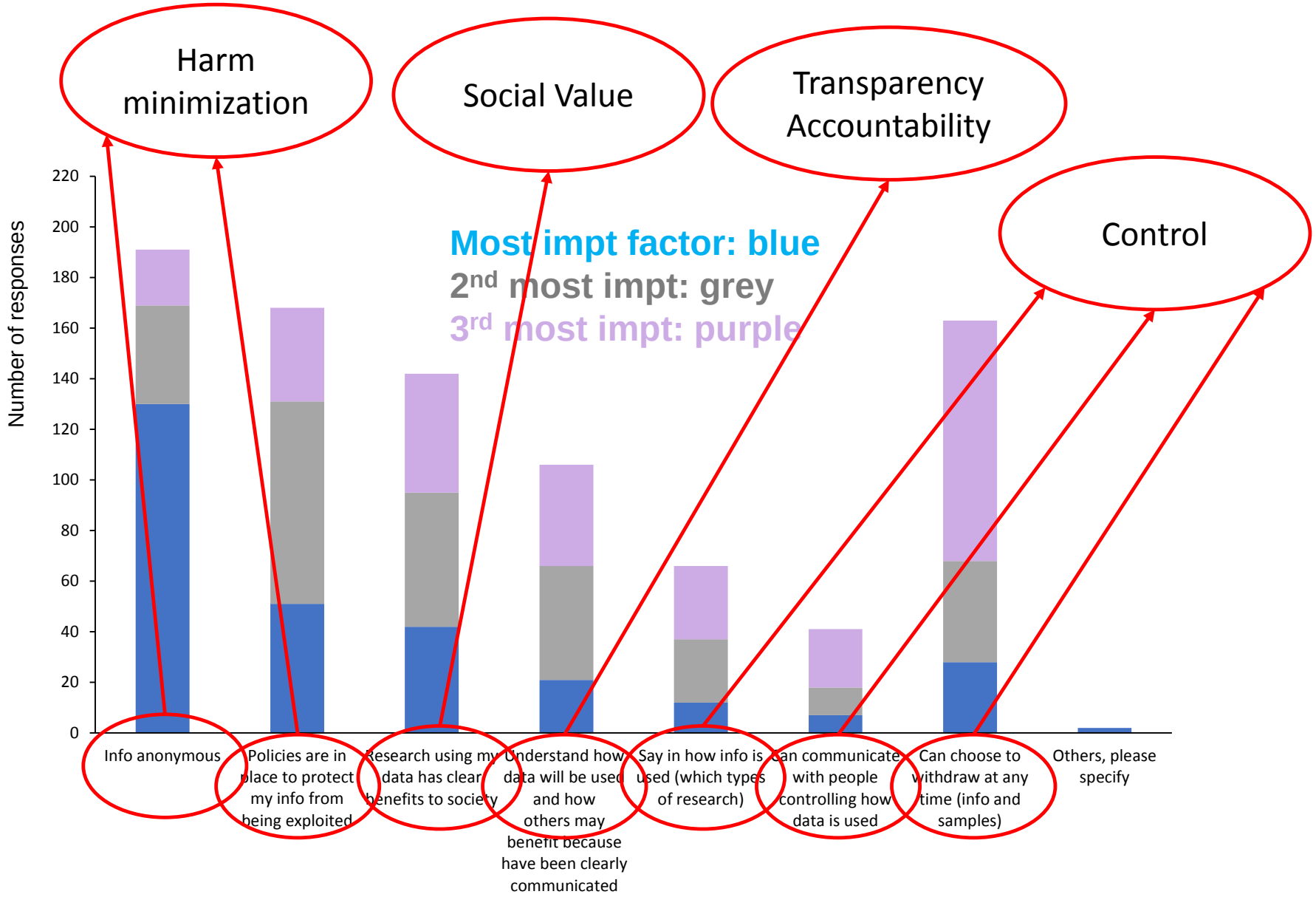




Incentives For Participation



Factors Determining Participation



Genetic data may be inherently identifiable in today's e nvironment

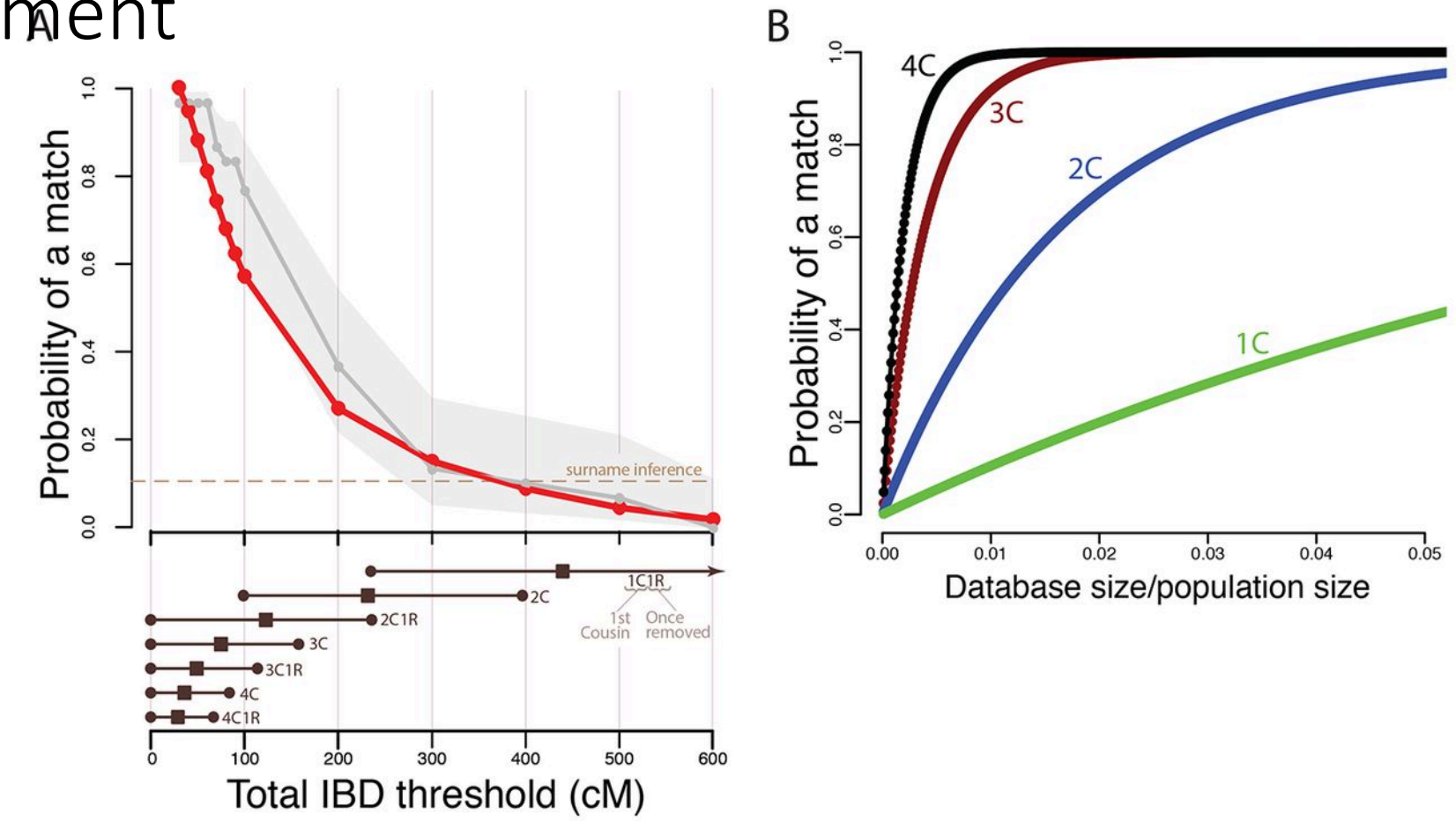


Fig. 1 The performance of long range familial searches for various database sizes.

Yaniv Erlich et al. Science 2018;science.aau4832

Key aspects of Public Trust and Engagement that are required for a successful program

Establishing a Social License

- Requires consistent messaging and engagement with the public and
  - Articulation of the benefits (societal/individual) of participation and manage the return of benefits
    - Stories Matter
    - Return of individual level data for healthcare
  - Articulation of the risks of participation and the steps taken to mitigate those risks
    - Risk of re-identification
    - Protection against discrimination

Governance and Data Access

- Policies and regulations need to be uniformly applied across data derived from multiple institutions
  - Ensure transparency and accountability
    - Who is using the data?
    - How is the data used?
  - Enable appropriate attribution of contributions and return of economic benefit
  - Allow for Co-governance (particularly by vulnerable populations) as a way to complement Consent

Security and Access Control

- Data security Framework
- encryption

Current & Proposed Capabilities