

The Singapore National Precision Medicine Strategy

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Abstract

Precision medicine promises to transform healthcare for groups and individuals through early disease detection, refining diagnoses, and tailoring treatments. Analysis of large-scale genomic-phenotypic databases is a critical enabler of precision medicine. Although Asia is home to 60% of the world's population, many Asian ancestries are under-represented in existing databases leading to missed opportunities for novel discoveries, particularly for diseases most relevant for these populations. The Singapore National Precision Medicine initiative is a whole-of-government 10-year initiative aiming to generate precision medicine data of up to one million individuals, integrating genomic, lifestyle, health, social, and environmental data. Beyond technologies, routine adoption of precision medicine in clinical practice requires social, ethical, legal, and regulatory barriers to be addressed. Identifying driver use-cases where precision medicine results in standardized changes to clinical workflows or improvements in population health, coupled with health economic analysis to demonstrate value-based healthcare, are vital prerequisites for responsible health system adoption.

Precision Medicine and Healthcare Transformation

Advances in molecular biology and genetics have yielded remarkable achievements in medicine, including biological therapies targeting key proteins¹ and harnessing RNA molecules for pandemic vaccines². Despite these advancements, many national health systems remain under pressure, driven by aging populations, increasing prevalence of chronic conditions, and rising numbers of patients presenting with advanced stage disease. It is estimated that most individuals will spend 13.2% of their lives in ill-health, requiring a minimal global healthcare spending of 6.6% gross domestic product (GDP)^{3,4}. This is projected to increase over coming decades ultimately leading to unsustainable healthcare costs.

Faced with these challenges, healthcare systems and funders are exploring transformative approaches to deliver high-quality healthcare while maintaining equitable and fair access. Precision medicine involves the integration of biological, medical, lifestyle, and environmental information to inform treatments and intervention strategies for specific groups and individuals. Individual genomic profiling is a key enabler of precision medicine, as genetics has been proposed to explain up to 30% of healthcare outcomes⁵. Genomic signals have shown success in pharmacogenomics⁶ and patient stratification for cancer therapy⁷ (here, the term "genomics" is used to cover DNA-based information such as genetics and epigenetics and also RNA/transcriptomics and proteins/metabolites). Precision medicine can also be harnessed for Precision Public Health (PPH), where population health data is combined with genetics to identify multi-modal risk factors for targeted intervention and interception prior to overt disease⁸.

Precision medicine carries further potential for novel insights into disease mechanisms, facilitating drug target identification, repurposing, and asset development as therapies with supporting genetic evidence have higher clinical success^{1,9-12}. Together with PPH, precision medicine brings opportunities for public-private collaborations involving academic, public healthcare, and private entities to develop advanced technological and analytical capabilities leveraging data to provide a comprehensive picture of an individual's disease risk and strategies for promoting healthspan.

Driven by these promises, large-scale efforts in precision medicine have been initiated worldwide¹³, including the All-of-US program (USA), 100,000 genomes project (UK), and Australian Genomics¹⁴⁻¹⁶. While each program is tailored to the needs of funding agencies and stakeholders, a common foundational feature of these programs, driven by the falling cost of genome sequencing, is a focus on large-scale genomic databases where other data modalities

such as proteomics, clinical, and research phenotypes are layered. The increasing proportion of elderly populations in many countries has also raised significant interest in applying PPH to research and policies related to healthy aging. These efforts require the convergence of technology, ethics, education, industry, and social sciences to optimize national benefits and minimize potential harms.

Global Disparities in Asian Precision Medicine

Despite its promise, concerns are growing that the benefits of precision medicine will be restricted to a 'privileged few' sufficiently equipped to carry out such efforts, resulting in growing disparities between populations in this fast-emerging field^{17,18}. Potential inequities either globally or within countries can pervade multiple areas, including the transferability of findings across populations, access to innovative therapies, limited healthcare financing to introduce novel clinical workflows, and having a sufficiently skilled workforce to exploit precision medicine findings. These disparities are reflected by current biases in our understanding of global genomic variation, and specifically for this Perspective the underrepresentation of Asia. Currently, 78 percent of Genome Wide Association Studies (GWAS) predominantly contain participants from North America and Europe¹⁹. While recent efforts by gnomAD and TOPMed have attempted to increase diversity, the percentage of individuals with Asian ancestry in these two databases is below 10%^{20,21}. The lack of genomic diversity in precision medicine data comes with risks and missed opportunities. For instance, applying the wrong ancestral genetic background in managing patients with genetic conditions can lead to incorrect diagnoses²², and genetic risk models such as polygenic risk scores (PRS) constructed from one population may exhibit lower prediction accuracies when applied to others²³⁻²⁵. Relying only on one population for disease and genetic association studies may also limit potential discoveries, as evidenced by recent 'cross-ancestry' analyses²⁶⁻²⁸. Beyond genetics, many clinical conditions are known to manifest differently in Asia. For example, South Asians and East Asians develop Type II diabetes (T2D) at a lower body mass index (BMI) than Europeans^{29,30}, likely attributable to higher abdominal fat deposition in the former leading to increased insulin resistance.

While established studies such as BioBank Japan, China Kadoorie Biobank, South Asia Biobank, and UK Biobank have begun to address the need for precision health research involving Asian populations, these resources have important limitations. Biobank Japan focuses on disease cases, limiting the identification of prospective disease relationships and

biomarkers. While China Kadoorie, South Asia Biobank, and UK Biobank have large sample sizes and a prospective design, none of these studies focus on Southeast Asia, a region of considerable genomic and cultural diversity.

Singapore National Precision Medicine Program

Singapore, with a land area of 724 km², has a total population of 5.5 million. These include three major groups - Chinese (74.2%), Malay (13.7%), and Indian (8.9%) of East Asian, Southeast Asian, and South Asian ancestry, respectively, along with Eurasian and Peranakan communities representing admixtures of European and Asian descent and Chinese with Malay/Indonesian heritage^{31,32}. This diverse composition allows the conduct of translational and clinical programs across multiple populations, particularly for ancestries under-represented in existing population genomics research. Singapore's stable socio-political environment, built on strong public trust in the government and robust collaborations between public agencies and local research communities, have allowed the country to embark on a large-scale precision medicine initiative. The nation's advanced research infrastructure enables comprehensive subject phenotyping and extensive biological sample collection, permitting generation of contemporary data types such as microbiomes and time-series behavioral profiles inferred through wearables. Singapore's data science capabilities facilitate accurate intellectual interpretation of precision medicine data with safe data governance and sharing, seeding opportunities for deep gene and environment interaction analyses distinctive to Southeast Asian populations. In parallel, the country's restricted geographical footprint facilitates the longitudinal analysis of consented patient trajectories in a 'birth-to-death' fashion, and the availability of a unique national identifier system not only enables automatic data capture of electronic health records (EHR) but also linkage with genomic and other national-level data sets, including disease registries, health-promotion programs, educational, financial, geospatial, and environmental records, all of which may contribute to health and disease.

In healthcare, Singapore is known for its impressive clinical outcomes with one of the world's longest life expectancies while utilizing only 2.2% GDP on healthcare in 2019. However, the nation is also one of Asia's most rapidly aging societies, with 22.5% of Singapore's population consisting of people >65 years by 2030^{4,33}. Unfortunately, many of these individuals will live with poor health; estimated at one in three elderly Singaporeans suffering from hypertension, one in seven from diabetes, and two in five from high

cholesterol³⁴. Driven by these concerns, the Singapore Ministry of Health (MOH) is exploring transformative approaches for healthy aging and sustainable healthcare, emphasizing pan-life-course health promotion, disease prevention, and affordable, high-quality medical services. Precision medicine has been identified as one promising approach.

Launched in 2017, the Singapore National Precision Medicine (NPM) program is a whole-of-government ten-year strategy to establish precision medicine as a peak of research excellence for Singapore, ultimately improving the nation's health by identifying clinical applications that are cost-effective, sustainable, and relevant to Singapore communities. Building upon initiatives both abroad and local pilot studies³⁵⁻³⁷, NPM adopted a three-phase approach to provide tangible short-term deliverables while having clear sight on long-term objectives (Fig. 1). NPM pursued a collaborative philosophy leveraging on existing infrastructure and national partners, including public healthcare systems, research agencies, and government agencies including the MOH, Chief Health Scientist Office (CHSO), Government Technology Agency (GovTech), and Integrated Health Information Systems (IHIS) for linkage of EHRs to genomic data for consented participants. Crucially, early engagement with these partners enabled the development of pathways to mitigate future barriers and concerns, thereby increasing the likelihood of adopting strategies adding value to local healthcare systems and national population health goals.

Phase I (2017-2021) was a "proof-of-concept" phase demonstrating the feasibility of large-scale genomic data generation with EHR linkage. Pathways were also developed to return incidental genetic findings to individuals participating in genomic research studies³⁸, and resource utilization studies (RUS) conducted to facilitate the clinical adoption of precision medicine. NPM Phase II (ongoing) is a "proof-of-value" phase, where NPM is expanding sequencing efforts to a large-scale population cohort incorporating other phenotypic and molecular data to enrich the genomics data, and clinical adoption of precision medicine pursued through clinical implementation pilots (CIPs). In Phase III, NPM will expand up to one million Singaporeans providing further depth and coverage of the Asian genotype incorporating social and environmental information. While the specific Phase III design is still under evaluation, it will certainly consider the most contemporary findings and lessons from other programs and the target of 1 million genomes is consistent with the guidance of key opinion leaders that realizing the value of population-scale sequencing will require sequencing tens of millions of individuals, to enable the unbiased, comprehensive study of our genome and the variation therein³⁹. At the end of NPM's three phases, it is envisioned

that validated precision medicine applications will be routinely used in Singapore, with a prepared healthcare system and workforce. NPM will also galvanize the Singapore research community to investigate deep multidisciplinary questions focused on Southeast Asian populations, and cultivate public-private partnerships strengthening not only the nation's genomics and biotech ecosystem but also adjacent sectors in information technology, cybersecurity, and artificial intelligence in line with national strategies for homegrown deep tech companies.

NPM Workgroups and Early Insights into the Singapore Genome

Due to its multi-faceted nature covering ethics, law, society, technology, healthcare, and industry, the success of NPM Phase I required coordination and integration across multiple domains. Six NPM workgroups were established to engage, interact, and work with public agencies and stakeholders whose support and participation were deemed critical to ensure active representation. These workgroups included Regulation and Ethics; Public and Community Trust; Enabling Platforms; Clinical Adoption; Industry Development; and Workforce Development (Table 1). Each workgroup was tasked to identify critical barriers impeding precision medicine in Singapore and strategies to overcome these barriers. Some key achievements of the NPM Phase I workgroups included issuing a national moratorium⁴⁰ on the use of genetic information from biomedical research in insurance underwriting or employment, rolling out regulatory sandboxes for clinical genetic services, and public consultations to assess community attitudes in sharing precision medicine data with industry. Notably, public engagement exercises by the Public and Community Trust workgroup revealed that the Singapore community was comfortable with academic and healthcare researchers utilizing the data for research but were more cautious about sharing the information with specific industry segments, such as internet and social media companies, and also insurers unless there was clear evidence of public benefit⁴¹. While initial studies suggest that such risk perceptions are common across ethnicities^{41,42}, the workgroup also noted differences between community groups on the interpretation of specific words and language which required cultural sensitivity to accurately communicate the concepts of precision medicine⁴³. **Future investigations are planned to deepen our understanding of risk communication, perception, and management among different communities.**

A headline deliverable of the Enabling Platforms workgroup in Phase I was generating a genomic reference database of 10,000 healthy Singaporeans (SG10K_Health). While

underpowered to detect rare pathogenic genetic variants, SG10K_Health provided a starting catalog of common genetic variants in Chinese, Malay and Indian (allele frequency >1%) representing a baseline reference for population-based filtering based on allele frequency thresholds to better interpret related diseases. To establish SG10K_Health, NPM collaborated with six local prospective cohorts⁴⁴⁻⁴⁷ to sequence 10,323 healthy consented individuals. Key challenges included setting up a laboratory workflow with sufficient flexibility to accommodate DNA samples of varying quality from different cohorts, establishing a whole-genome analysis workflow for population-scale single-sample level variant calling, and performing joint calling of variants across the SG10K_Health cohort using cloud computing. After stringent quality control following GATK best practices^{48,49}, the SG10K_Health joint-called dataset was created for the community (n= 9,770 genomes; Chinese 58.4%, Indian 21.8%, and Malay 19.5%). To provide better coverage of the particularly underrepresented South Asian and Southeast Asian populations, SG10K_Health contained a higher proportion of Indian and Malay genomes compared to Singapore's resident population distribution (Methods). Analysis of SG10K_Health using human genome GRCh38 reference identified 179,418,917 small variants (158,331,366 single nucleotide variants (SNVs) and 21,087,551 indels), of which 92.8% (166,559,124) had minor allele frequencies of less than 1% (Table 2; see Methods). Using variant effort predictor (VEP)⁵⁰ and Loss-Of-Function Transcript Effect Estimator (LOFTEE)²¹ to predict functional consequences, 1,147,135 protein-coding missense, 595,783 protein-coding synonymous, and 104,569 (including 63,224 high confidence) protein-coding loss-of-function (LoF) variants were identified. 25% (278,715 out of 1.1 million) of human allelic variations previously associated with clinically-relevant phenotypes⁵¹ were also observed in SG10K_Health, of which nearly half (131,720 variants) were reported as benign (Table 3). The SG10K_Health dataset can be accessed via various NPM data access platforms (<https://npm.a-star.edu.sg/>).

Developing clinical pathways for precision medicine

Knowledge and insights derived from population-scale genomic data are necessary but insufficient to transform healthcare. Therefore, to drive the clinical adoption of precision medicine, the Clinical Adoption workgroup proactively engaged stakeholders, including clinicians, patients, funders, and healthcare systems, to comprehensively map the complete end-to-end journey for embedding genomic technologies in the clinic (Fig. 2). Such engagements were essential to identify barriers to implementation and potential strategies

for overcoming them, highlighting not only the essentiality of identifying appropriate clinical indications where outcomes would be improved by genomic testing, but also clinician champions for these indications.

One hurdle to implementation was the heterogeneity of lab-developed assays with no clear regulations around their use. Thus, the Regulation and Ethics workgroup developed a **Code Of Practice⁵²** to outline standards for providing clinical laboratory genetic testing and services, covering categories of tests needed to be prescribed by a qualified medical geneticist and scenarios in which pre-and post-test genetic counseling were required. **In parallel, the Workforce Development workgroup identified a shortfall in genetic counselors and initiated processes to clearly define competencies and licensing for counselors in a way that would offer "title protection" and career progression paths⁵³.** Refinement of the roles and functions of counselors also enabled assessment of the extent to which other allied health professionals (AHP) could be re-trained to facilitate the expansion of clinical capacity while avoiding counselor overloading. **For example, the workgroup found that the competency of constructing a three-generation pedigree could be readily delivered by AHPs after specific training, while applying knowledge of genetics in the risk assessment of patients would require deeper skillsets.**

Another challenge addressed by the Clinical Adoption workgroup, in preparation for large population studies, was the establishment of clinical pathways for returning incidental findings, in keeping with growing expectations that such findings should be proactively managed^{54,55}. Similar to other studies⁵⁶⁻⁵⁹, 1-2% of participants in NPM harbored previously undetected pathogenic variants in clinically actionable genes. The workgroup collaborated with local healthcare institutions to establish clinical frameworks where participants consented for recall were re-contacted and guided through a systematic workflow conducted by qualified medical geneticists and counselors, involving a full health assessment, redrawing of blood samples, validation of sequencing results in a clinically accredited laboratory, and collecting detailed family medical histories³⁸. After evaluation by a multi-disciplinary team, the results were returned to participants by a genetic counselor with subsequent referral to appropriate specialty clinics. This return-of-findings platform will be expanded in future NPM phases, to cope with increasing levels of population-scale sequencing and as additional variants of medical relevance are identified.

A third important challenge was assessing the true impact of precision medicine on healthcare costs since most healthcare interventions are cost-effective rather than cost-

saving. Given finite resources, NPM's stakeholders posited that adopting new technologies such as genome sequencing would likely involve significant trade-offs with other medical services or treatments. While health technology assessment is often used to guide the evaluation of these trade-offs, deeper conversations revealed uncertainties if current health economic models, frequently used to evaluate novel therapeutics, were relevant to precision medicine. Stakeholders also raised concerns about the specific indications where genomic tests would be warranted, how downstream therapeutic decisions would be influenced based on the test results as such information is required for economic assessment, and the potential for technologies such as whole-genome/exome sequencing (WGS/WES) to generate large numbers of incidental findings ironically resulting in more, rather than less, healthcare demand. These concerns are not unique to Singapore, as policymakers, administrators, and regulators require a compelling value proposition to approve more therapies incorporating precision medicine^{60,61}.

In an initial attempt to generate models that would inform implementation, NPM commissioned RUSs in rare pediatric diseases, familial hypercholesterolemia, and hereditary cancer (Table 4). The RUSs focused on establishing national consensus on clinical pathways where genomic tests could guide diagnosis and treatment locally. To limit uncertainties around incidental findings, for familial hypercholesterolemia and hereditary cancer the technology considered was a targeted panel rather than WGS/WES. In the RUSs, clinicians worked with health economists to construct economic models comparing the proposed pathways (with genomic testing) to existing pathways to evaluate potential impacts on resource utilization. Notably, sensitivity analyses identified certain parameters likely to significantly impact the cost and the cost-effectiveness of the identified clinical pathway, highlighting important but sometimes under-appreciated considerations for improving the economics of genomic testing. For example, the familial hypercholesterolemia and hereditary cancer RUSs underscored the need to improve processes to increase the proportion of first-degree relatives coming forward for testing after identifying an index case. The familial hypercholesterolemia study also identified a need to optimize treatment with low-cost cholesterol-lowering medications (statins) to reduce the number of patients who require high-cost medications (PCSK9 inhibitors). These parameters thus represent targets for focused experiments to improve the economics of precision medicine by modulating these factors.

Ambitions and Goals of NPM Phase II

NPM Phase II (2021-2024) is a key initiative under Singapore's Research, Innovation and Enterprise 2025 (RIE2025) master plan. Reflecting Phase II's expanded scope and ambition, "Precision Health Research, Singapore" (PRECISE, www.npm.sg) was established under MOH to coordinate and administer the program. Key activities to be undertaken in NPM Phase II include establishing the PRECISE-SG100K longitudinal population cohort and CIPs to continue the clinical adoption of precision medicine.

The PRECISE-SG100K Population Cohort

Identifying mechanisms underlying disease risk in the Singapore population and developing affordable, effective, and scalable strategies for disease risk stratification and prevention are urgent national priorities. Longitudinal population studies, comprising phenotypic measurements and biological sample collection at baseline, coupled with long-term follow-up for clinical outcomes, can provide unique insights into complex behavioral, environmental, and genetic interactions causing subsequent disease or health. A key strength of prospective cohorts is that behavioral and environmental exposures are measured before the onset of disease, thus avoiding selection bias and problems of reverse causality. SG100K is a longitudinal population study of >100,000 Singaporeans comprising comprehensive phenotypic characterization and high-quality biological samples. The cohort was established by harmonizing existing prospective cohorts (N=50,000) with additional prospective recruitment of ~50,000 new participants. These new participants have expanded phenotypic characterization in key cardiovascular and metabolic domains through deep phenotyping (including nutrition, diet, and advanced imaging tests) and enhanced biological sample collection to enable genomic, transcriptomic, and microbiome studies. To ensure significant numbers of participants and incident events from different genetic ancestries, SG100K recruited men and women aged over 21 years, with sociodemographic features representative of the broader Singapore population and purposive sampling of **South Asian and Southeast Asian individuals**.

In Phase II, PRECISE is partnering with SG100K to sequence the SG100K participants, jointly creating a PRECISE-SG100K resource of comprehensive genomic and research phenotypes. In parallel, PRECISE also collaborated with MOH CHSO to establish national-scale infrastructure linking consented participants to their longitudinal EHRs through the Trusted Research/Real world-data Utilization and Sharing Tech (TRUST) platform

(<https://trustplatform.sg/>). Integration of PRECISE-SG100K baseline data with EHRs will allow the identification of individuals who develop disease, alongside their laboratory measurements, diagnosis codes, and drug prescriptions. PRECISE-SG100K thus represents a unique platform for state-of-the-art epidemiological, translational, and precision medicine research in the genetically distinct and culturally diverse Singapore population that may also contribute to chronic disease management at a regional and international scale.

Clinical Adoption via Clinical Implementation Pilots

In Phase II, informed by design choices and learning lessons from the Phase I RUSs, a competitive grant call for prospective CIPs was performed. Clinician teams, with health economists as co-investigators, submitted proposals suggesting suitable clinical use-cases, genomic tests to conduct, and treatments to prescribe based on test results. CIP applicants were also asked to propose economic models assessing the adoption of the proposed new clinical pathways in a manner where studies could be conducted to improve their health economics. This exercise demonstrated that through a focused request for proposals, clinicians from diverse healthcare institutions could reach consensus, agree on downstream clinical pathways, and generate economic models to inform healthcare decisions. To date, PRECISE has commissioned five CIPs, evaluating breast cancer PRS, familial hypercholesterolemia, hereditary cancer, pharmacogenomics, and primary glomerular kidney disease.

In a "competition/collaboration" model, clinicians and health economists of separate shortlisted CIP applications were converged to identify commonalities across the selected CIPs where joint development of infrastructure or shared services would enable further economies of scale and reduce variation in implementing precision medicine across use-cases. Economic models were further refined through discussions with stakeholders. For influential model parameters where data is unavailable or deemed unsuitable for the Singapore context, this information will be collected either through the CIPs or from additional data sources facilitated by NPM. Clinical teams in the CIPs will also work closely with PRECISE-SG100K investigators to actively reclassify variants of unknown significance in Asian populations utilizing data generated by the former. We foresee that the CIP results will be pivotal to underpin informed healthcare decisions about which clinical pathways to adopt into Singapore's mainstream clinical practice.

NPM as part of the global precision medicine community

As a small country, Singapore's NPM will not operate in isolation but will consciously advocate responsible sharing of genomic and health-related data through a three-pillar strategy. First, NPM will contribute to the global precision medicine community through international collaborations and participation in major international consortiums such as the Global Alliance for Genomics and Health (GA4GH), Global Genomic Medicine Collaborative (G2MC), the International HundredK+ Cohorts Consortium (www.ihccglobal.org), and the International Common Disease Alliance (ICDA). Second, NPM will seek to strategically partner with regional genomic initiatives, such as the Tohoku Biobank Project and the Genomics Thailand Initiative (www.genomicsthailand.com). Notably, NPM is already working with the Thailand Health Intervention and Technology Assessment Program (HITAP) to generate frameworks for health economic analysis. Third, NPM recognizes the importance of data reusability to further value-add to the data. The current lack of interoperable healthcare data presents significant challenges with a plethora of diverse medical standards widening interoperability gaps. To counter this, NPM will adopt international standards such as OMOP Common Data Models, FAIR principles, and participate in GA4GH workstreams involving genomic and phenotypic data.

Conclusion

Translating an individual's genetic profile, in conjunction with traditional forms of health information, will enable clinicians to make more accurate diagnoses, appropriate targeted interventions, and reduce potential incompatibilities of medication. However, the current lack of diversity in genetic databases, particularly for Asian populations, poses challenges for realizing precision medicine for the 4.6 billion people in the Asia-Pacific region. Hence, defining Asian genomic diversity through initiatives like Singapore's NPM and other Asian-focused initiatives are vital for advancing healthcare globally. Beyond research, implementing precision medicine in routine clinical workflows will require investment and infrastructure development, with ongoing efforts to maintain public trust. Partnerships will be vital in creating new opportunities, whether in translating research, driving industry innovation or creating high-value jobs in the healthcare and biotech sectors. Finally, forging a common ethical and legal framework with dedicated cultural discussions with community, religious, and social leaders in a sensitive and respectful manner is necessary to enable the potential of precision medicine in healthcare transformation.

SG10K_Health Consortium

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Author contributions

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Competing interests

All authors declare no competing interests.

Fig. 1 Overview of Singapore's National Precision Medicine program

Singapore's National Precision Medicine (NPM) program is a whole-of-government ten-year roadmap. The program adopted a three-phased approach designed to have tangible short-term deliverables while having a clear vision of long-term objectives to prepare Singapore to introduce precision medicine.

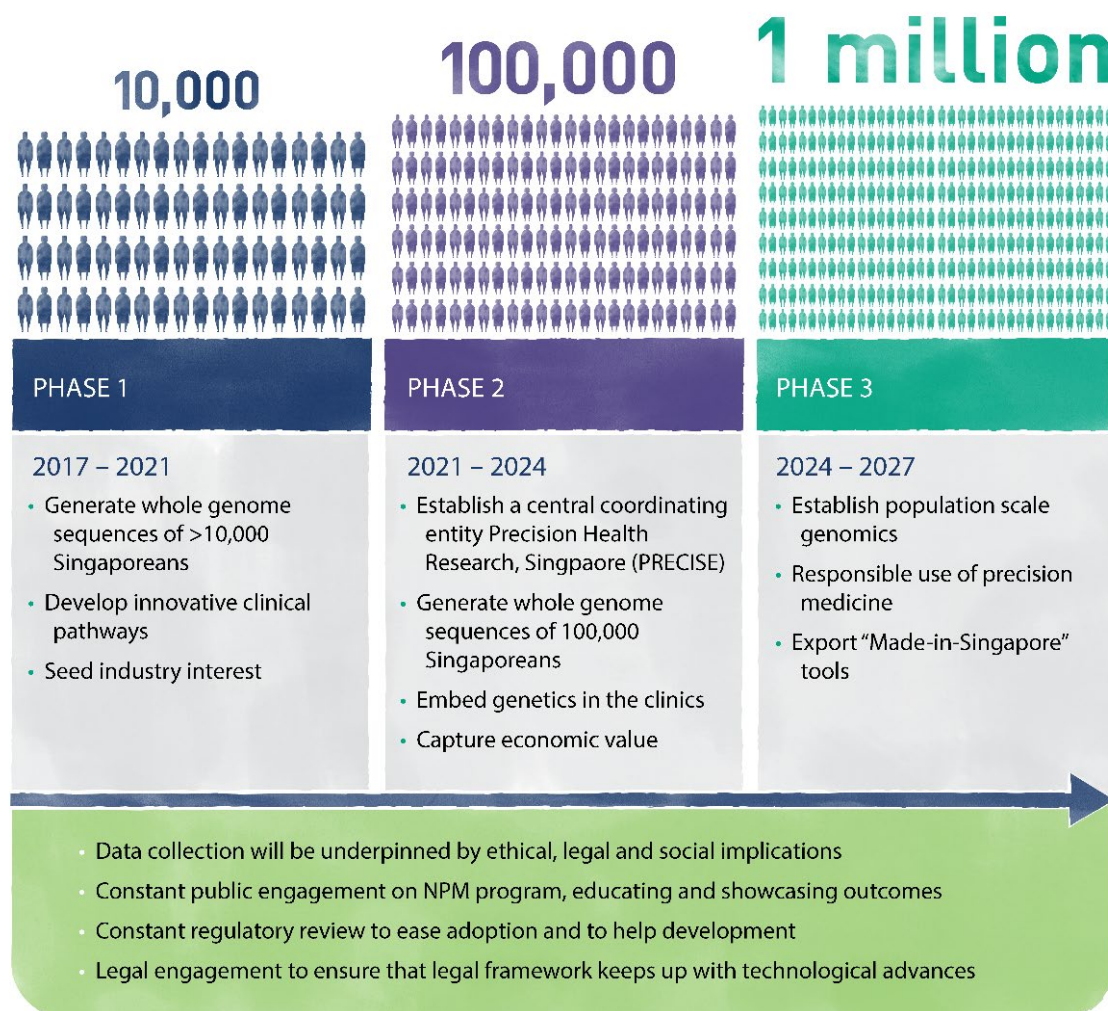


Fig. 2 Singapore National Precision Medicine program clinical adoption strategy

A systematic landscape survey of barriers and potential strategies for clinical adoption of precision medicine in Singapore.

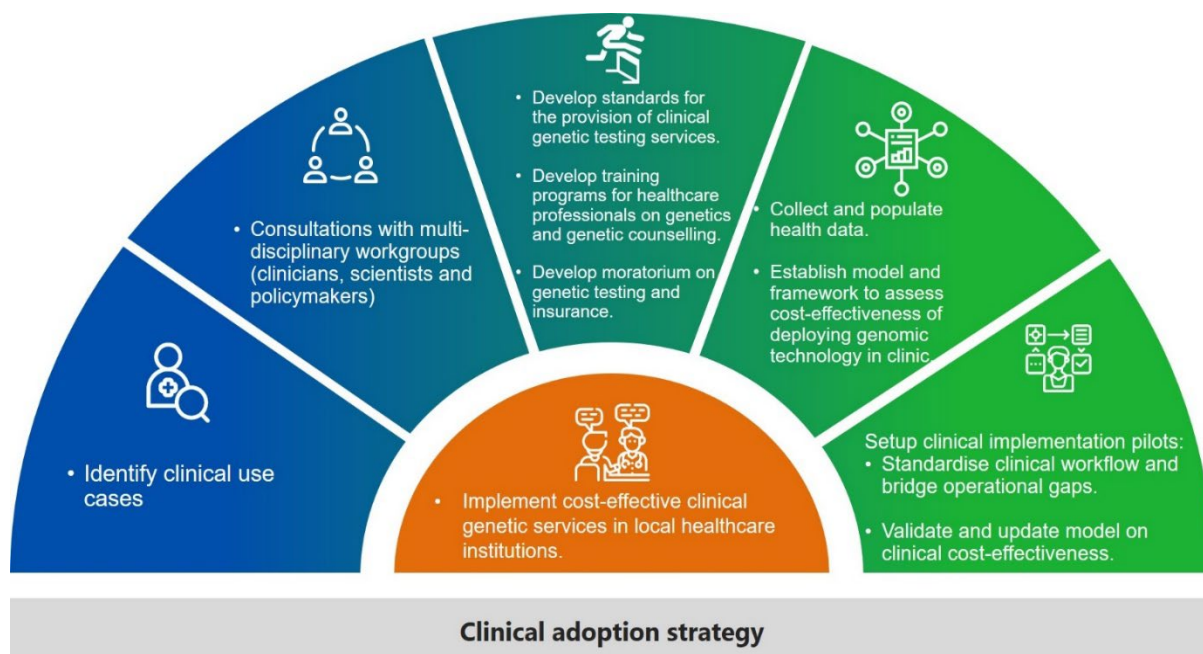


Table 1. National Precision Medicine program Phase I Workgroups

Workgroups	Challenges and Objectives	Major NPM Phase I Achievements
Regulation and Ethics	<ul style="list-style-type: none"> • Lack of guidelines for the provision of clinical genomic services • Lack of legal frameworks for preventing discrimination due to genetics 	<ul style="list-style-type: none"> • Issued code of practice for delivery of clinical genetic services⁵² • Passed moratorium on the use of genetic information for insurance underwriting⁴⁰
Public and Community Trust	<ul style="list-style-type: none"> • Little data on Singapore public's understanding and acceptance of precision medicine and sharing of healthcare data • Conduct public & community consultation, education and outreach 	<ul style="list-style-type: none"> • Population surveys on public acceptance of precision medicine^{41,42} • Citizen's jury on sharing of precision medicine data with industry
Enabling Platforms	<ul style="list-style-type: none"> • Lack of scalable infrastructure for large-scale genomic sequence data production • Lack of IT software pipelines for at-scale whole-genome analysis • Formulate data sharing policies and platforms for accessing NPM data 	<ul style="list-style-type: none"> • Generation of 10,323 whole genome sequences • Established genomic analytic pipeline compatible with international gold standards • Successful proof-of-concept of integrating genomic data with national-scale electronic health records
Clinical Adoption	<ul style="list-style-type: none"> • Absence of defined processes for converting research-grade findings into clinical management • Lack of accepted economic models for assessing the cost-effectiveness of precision medicine • Lack of a Singapore genome database as a reference for patients with genetic disease 	<ul style="list-style-type: none"> • Development of clinical pathways for return of genetic incidental findings • Commissioning of resource utilization studies for precision medicine use-cases • Accelerate clinical workflows through provision of Asian reference of genomic normality
Industry Development	<ul style="list-style-type: none"> • Overall unfamiliarity with overseas companies in the Singapore precision medicine and research ecosystem • Promotion of Singapore as a gateway to Asia 	<ul style="list-style-type: none"> • Establish public-private partnerships for genomic data production • Consortium framework for companies interested in engaging NPM
Workforce Development	<ul style="list-style-type: none"> • Overall lack of critical mass in workforce skillsets required for precision medicine • Map overall numbers of staff required for different areas of precision medicine (e.g., genetic counselors, bioinformatics staff) • Define pathways to send qualified staff for external training or repurposing staff from adjacent industry sectors 	<ul style="list-style-type: none"> • Workforce projections to estimate numbers of qualified staff required for national-scale PM • Provision of in-service scholarships for clinical genetics training • Developed workforce development roadmap for tiered genetic counseling services

Table 2. Variants observed in all individuals in NPM Phase 1-SG10K_Health whole genome sequencing (WGS). Median counts and standard deviation (SD) counts per genome are also presented. See Methods for details on genome mapping, joint variant calling and QC filters.

	Variants in WGS		Median variants per genome			
	Number of variants	Number of variants with MAF < 1%	Number of variants	SD	Number of variants with MAF < 1%	SD
Total variants	179,418,917	166,559,124	4,106,905	207,880.84	393,367	37,222.15
Variant type						
SNVs	158,331,366	148,665,318	3,501,477	129,196.15	346,317	32,594.75
INDELS	21,087,551	17,893,806	602,448	84,126.34	47,139	4,794.15
Functional prediction						
Synonymous	595,783	566,740	10,940	405.29	1,084	123.49
Missense	1,147,135	1,114,839	11,147	447.75	1,469	155.03
LoF	104,569	101,917	722	44.33	82	11.64
LoF (High Confidence)	63,224	62,324	207	19.61	35	6.23

Table 3. Observed number of clinically relevant variants categorized based on ClinVar clinical significance values: benign, likely benign, likely pathogenic, pathogenic and variants of unknown significance (VUS). Number of Private (variant found in only one individual), Rare ($AF \leq 1\%$ and more than one individual) and Common ($AF > 1\%$). See Methods for details on the on variant classification.

Clinical significance	Total variants		
	Private	Rare	Common
Benign	10,888	37,397	83,435
Likely benign	19,547	46,116	7,214
Likely pathogenic	1,029	756	3
Pathogenic	1,315	1,072	20
VUS	25,150	41,735	1,352
Other	328	704	654

Table 4. NPM Phase I Resource Utilization Studies

Resource Utilization Studies to Assess Feasibility of Precision Medicine
Aims: <ol style="list-style-type: none">I. Assess resource utilization with/without precision medicine interventionII. Determine minimum data sets required for health economics analysesIII. Identify and address the barriers to precision medicine implementation
Clinical use cases: <ol style="list-style-type: none">I. Pediatric Genetic DiseasesII. Familial HypercholesterolemiaIII. Hereditary Breast and Ovarian Cancers
Outcomes: <ul style="list-style-type: none">• All three studies reported that utilizing genomic testing in their identified clinical pathways is likely to be beneficial.• The pilot studies also showed that it is feasible to have clinicians agree on a clinical pathway, and generate an economic model that could be used to inform healthcare decisions.
Modifiable factors that have a large impact on the cost-effectiveness of the pathway: <ul style="list-style-type: none">• A more efficient process that increase the proportion of first degree relatives coming forward for testing after identifying an index case.• Improve adoption and adherence to therapeutic and screening guidelines in tested positive patients.

Supplementary information

Methods

SG10K Health project subject details

The SG10K_Health project comprises 10,323 healthy individuals of three major ethnic groups: Chinese (C), Indian (I), Malay (M) and Others (O), from six prospective cohorts, including (i) The Singapore Multi-Ethnic Cohort (MEC, n=3,082; C:1,148, I:950, M:981, O:3), (ii) The Health for Life in Singapore Study (HELIOS, n=2400; C:1,907, I:210, M:178, O:105), (iii) The Singapore Epidemiology of Eye Diseases cohort (SEED, n = 1,534; C:602, I:654, M:278), (iv) The Growing Up in Singapore Toward healthy Outcomes study (GUSTO, n= 1000; C:581, I:175, M:243, O:1), (v) SingHealth Duke-NUS Institute of Precision Medicine (PRISM, n= 1,350; C:1,181, I:69, M:71, O:29) and (vi) Tan Tock Seng Hospital (TTSH, n= 957; C:517, I:244, M:196). Genomic DNA was extracted from whole blood or buffy coat except for the GUSTO cohort, where DNA was extracted from cord blood. All participants have provided informed consent for research. IRB approvals from each participating cohort were obtained from their respective contributing organizations: MEC cohort (National University of Singapore IRB, B-16-158), HELIOS (Nanyang Technological University IRB, 2016-11-030 and 2017-11-006-01), SEED (SingHealth Centralised Institutional Review Board, 2012/487/A, 2010/392/A and 2015/2279), GUSTO (SingHealth Centralised Institutional Review Board, 2018/2767 and National Health Group Domain Specific Review Board, D/2009/00021 and B/2014/00406), PRISM (SingHealth Centralised Institutional Review Board, 2013/605/C) and TTSH (National Health Group R&D office, TTSH/2014-00040).

Whole genome sequencing

Paired-end 151 bp whole genome sequencing was performed on Illumina HiSeq X with 15x and 30x sequencing depth. The paired-end reads were adaptor-trimmed using Trimadap and mapped using BWA-MEM to GRCh38 reference. Duplicated reads were discarded using Picard MarkDuplicates with GATK "germline short variant per-sample calling" Reference Implementation defined parameters. Base quality scores were recalibrated using GATK BaseRecalibrator / ApplyBQSR on a per library basis.

Joint variant calling, QC filters and annotation

Single-sample level CRAM files were used to call individual SNPs and INDELS with GATK HaplotypeCaller in gVCF mode, using GATK "germline short variant per-sample calling" reference implementation defined parameters and companion files (GATK resource bundle GRCh38). Single-sample gVCF files were indexed for cohort-wide and collection-wide joint-variant calling steps. Variants failing VQSR filter were removed, sex was imputed based on the mean depth ratio of chrX/chr20 and chrY/chr20 of each sample, and samples with abnormal ploidy were also excluded. Subsequently, samples with call rate < 95%, contamination rate > 2%, and error rate > 1.5% were also excluded. Next, Median Average Deviation (MAD) was computed on autosome only for ratio insertion/deletion, ratio transition/transversion, and ratio heterozygote/homozygote alternative, where samples with a deviation of more than 6xMAD were excluded to derive the final SG10K_Health dataset of 9,770 genomes. Finally, genotypes on chr X and Y were corrected according to the imputed sex. Then, genotype with allele balance (AB) > 0.8 or AB < 0.2, read depth (DP) < 5 or genotype quality < 20 were excluded. The remaining variants were annotated using VEP95 in merged mode (Gencode + Refseq reference).

Characterization of ClinVar clinical significance values

The ClinVar public archive reporting evidence-supported relationships between human variations and phenotypes (clinvar_20220328.vcf.gz) was downloaded and used to annotate the SG10K_Health variant catalogue based on ClinVar interpretations. We grouped 'ClinVar's "Uncertain_significance" and "Conflicting_interpretations_of_pathogenicity" interpretations as "VUS"- Variants of Unknown Significance. We further grouped ClinVar's "Pathogenic/Likely pathogenic" and "Likely Pathogenic" as "Likely Pathogenic". We retained ClinVar's interpretation of "Likely benign", "Pathogenic", and "Benign", and all other ClinVar reported interpretations were grouped as "Other".

Full data descriptions, methods and results will be described in subsequent manuscripts.

The codes to perform all analyses in this manuscript are available at <https://github.com/C-BIG/sg10k-health>