PRECISE-SG100K Flagship Projects

S/N	Project Title	Team	Aims of Project
1	The SG100K cognitive health programme Topic: Mental Health	Lead PI: Dr Max Lam, Lee Kong Chian School of Medicine, Institute of Mental Health Co-Lead PI: Dr Jimmy Lee, Institute of Mental Health Co-Lead PI: Prof Liu Jianjun, Acting Executive Director, Genome Institute of Singapore	1. Establish the biological underpinnings for cognitive function in diverse Asian and global populations. 2. Establish the biological convergence between cognitive function and disease traits. 3. Establish epidemiological and genomic risk predictors of cognitive health.
	Institutions involved: Lee Kong Chian School of Medicine, Nanyang Technological University, Institute of Mental Health, National Neuroscience Institute, A*STAR Genome Institute of Singapore		
2	The SG100K_Med Alliance - clinical genetics researchers united for the analysis of mendelian disease variation in SG100K Topic: Mendelian Diseases	Lead PI: Dr Lim Weng Khong, Duke-NUS Medical School Co-Lead PI: Dr Joanne Ngeow, Lee Kong Chian School of Medicine Co-Lead PI: Dr Saumya Jamuar, KK Women's and Children's Hospital	1. Seek a deeper understanding of genetic disease burden in major Asian populations through a comprehensive analysis of structural variation and short tandem repeat expansions. 2. Demonstrate how SG100K data can resolve variants of uncertain significance. 3. Explore impact of polygenic backgrounds on penetrance in autosomal dominant conditions for under- represented Asian populations.
	Institutions involved: Duke-NUS Medical School, Lee Kong Chian School of Medicine, KK Women's and Children's Hospital, A*STAR Genome Institute of Singapore, Singapore National Eye Centre, Tan Tock Seng Hospital, National University of Singapore, National Heart Centre Singapore, National Neuroscience Institute, Khoo Teck Puat Hospital, Nanyang Technological University		
3	Identification of Asian-specific genetic association with fat and lean muscle mass distribution Topic: Fat and Lean Muscle Mass	Lead PI: Dr Liu Boxiang, National University of Singapore Co-Lead PI: A/P Sim Xueling, National University of Singapore Co-Lead PI: Prof Tai E Shyong, National University of Singapore	1. Perform multi-ethnic meta-analysis of fat and lean muscle mass using SG100K and UKBB datasets. 2. Mendelian randomisation analysis to identify the contribution of fat and lean muscle mass to cardiometabolic diseases. 3. Colocalisation analysis to identify risk genes affecting fat and lean muscle mass. 4. Conduct functional validation studies of

			identified genetic loci.
	Institution involved: National University of Singapore		
4	HLA alleles and its association with auto-immune diseases and pharmacogenomics in multi-ancestral Asian populations Topic: Human leukocyte antigen	Lead PI: A/P Sim Xueling, National University of Singapore Co-Lead PI: Dr Leong Khai Pang, Tan Tock Seng Hospital Co-Lead PI: Dr Wharton Chan, Duke-NUS Medical School	1. Generate a high-resolution human leukocyte antigen (HLA) reference panel in Asian populations. 2. Generate frequencies of HLA alleles and haplotypes in Asian populations for local reference and for global population comparisons. 3. Conduct association analyses of HLA alleles in outcomes including auto-immune diseases and pharmacogenomic responses.
	Institutions involved: National University of Singapore, Tan Tock Seng Hospital, Duke-NUS Medical School		
5	Unravelling the determinants of kidney health in a multi-ethnic Asian population Topic: Kidney Disease	Lead PI: Dr Yeo See Cheng, Tan Tock Seng Hospital Co-Lead PI: Prof John Chambers, Lee Kong Chian School of Medicine	1. Determine prevalence of chronic kidney disease (CKD) among adults. 2. Examine association of CKD with genetic, clinical and socio-behavioural predictors. 3. Examine relative contribution of key predictors driving differences in CKD risks across different sub- population. 4. Develop and validate an integrated risk score for the development of CKD in a representative multi-ethnic Asian population-based cohort in Singapore.
	Institutions involved: Tan Tock Seng Hospital, Lee Kong Chian School of Medicine		
6	The high variability of tandem repeats offers insights into population diversity and may explain the missing heritability of complex neurological and neurocognitive disorders in Asian populations Topic: Tandem Repeats	Lead PI: Prof Liu Jianjun, A*STAR Genome Institute of Singapore Co-Lead PI: Dr Nicolas Bertin, A*STAR Genome Institute of Singapore Co-Lead PI: Dr Lim Weng Khong, Duke-NUS Medical School	1. Generate SG100K genome wide tandem repeats (TR) variation catalogue and characterisation their respective prevalence in Asian populations. 2. Characterise contributions of TR variations to the aetiology of complex neurological and neurocognitive disorders.
	Institutions involved: A*STAR Genome Institute of Singapore, Duke-NUS Medical School, National Neuroscience Institute		

7	An integrated pharmacoeconomic-pharmacokinetic framework for prioritising and testing clinically important drug-gene interactions Topic: Pharmacogenomics	Lead PI: Dr Janice Goh, A*STAR Bioinformatics Institute Co-Lead PI: A/P Wee Hwee Lin, National University of Singapore Co-Lead PI: Dr Nicolas Bertin, A*STAR Genome Institute of Singapore	1. Evaluate the occurrence of known drug-gene interactions based on EHR data and its impact on efficacy and toxicity. 2. Explore genotype-drug response associations using SG100K and linked EHR datasets augmented by a dedicated pipeline for haplotyping highly polymorphic drug metabolising enzyme CYP2D6. 3. Develop a pharmacokinetics-informed framework for evaluating and ranking both known and novel drug-gene sets for clinical action to make dose recommendations.
	Institutions involved: A*STAR Bioinformatics Institute, National University of Singapore, A*STAR Genome Institute of Singapore		
8	Genetic variants contributing to clonal haematopoiesis across diverse Asian genomes Topic: Clonal haematopoiesis	Lead PI: Prof Ong Sin Tiong, Duke-NUS Medical School Co-Lead PI: Prof Ashok Venkitaraman, National University of Singapore Co-Lead PI: Prof Chng Wee Joo, National University of Singapore Co-Lead PI: Prof John Chambers, Lee Kong Chian School of Medicine Co-Lead PI: Dr Nicolas Bertin, A*STAR Genome Institute of Singapore	1. Determine age-related incidence of clonal haematopoiesis (CH) among our three major ancestry groups. 2. Correlate CH status with clinical metadata, measures of ageing and disease incidence, and disease-related variables including biomarkers. 3. Discover novel genetic associations with CH. 4. Integrate functional genomics for novel Asian CH driver mutation discovery and validation. 5. Correlate CH status with cell clusters and gene expression signatures in the AIDA scRNA-seq dataset.
	Institutions involved: Duke-NUS Medical School, National University of Singapore, Lee Kong Chian School of Medicine, A*STAR Genome Institute of Singapore, National University Hospital, Singapore General Hospital		
9	Advancing precision medicine for cardiovascular disease and diabetes in Asian populations	Lead PI: Prof John Chambers, Lee Kong Chian School of Medicine Co-Lead PI: A/P Sim Xueling, National University of Singapore Co-Lead PI: Prof Cheng	1. Determine the behavioural (including nutrition and physical activity), environmental, genetic and other molecular factors that underpin CVD and diabetes in the multi-ethnic Asian population of Singapore. 2. Develop and validate algorithms for accurate identification of Asian individuals

		Ching-yu, Duke-NUS Medical School Co-Lead PI: Prof Yeo Khung Keong, National Heart Centre Singapore	who are at increased risk of CVD and diabetes.
	Institutions involved: Lee Kong Chian School of Medicine, National University of Singapore, Duke-NUS Medical School, Singapore Eye Research Institute, National Heart Centre Singapore		

PRECISE-SG100K Driver Projects

S/N	Project Title	Team	Aims of Project
1	Computation of genome-wide LD scores and matrices from the SG100K resource	Lead PI: Li Jingmei, A*STAR Genome Institute of Singapore Co-Lead PI: Rajkumar s/o Dorajoo, A*STAR Genome Institute of Singapore Co-Lead PI: Khor Chiea Chuen, A*STAR Genome Institute of Singapore	Taking reference from similar work performed by the Pan-UK Biobank, the team will compute in-sample dosage-based LD matrices and scores for each of the three major ancestry groups in SG100K: • LD score regression analysis to estimate heritabilities • Fine-mapping analysis to identify causal variants of well-powered complex traits The plan is to make the LD matrices available in Hail's BlockMatrix format or similar. LD scores are also made available in LDSC-compatible flat files (.l2.ldscore.gz and .M_5_50).
	Institution involved: A*STAR Genome Institute of Singapore		
2	Chronic liver disease is a significant risk factor for adverse cardiometabolic outcomes	Lead PI: Mark Chan, National University Hospital, Cardiology Co-Lead PI: Nicholas Chew, National University Hospital, Cardiology	1. Investigate associations between established non-invasive Chronic Liver Disease (CLD) biomarkers and cardiometabolic outcomes 2. Evaluate how these associations relate to major adverse cardiac events. 3. Examine whether these associations with CLD are independent from associated metabolic disease.
	Institution involved: National University Hospital		
3	Nonlinear methods for genomic association analysis of eye diseases	Lead PI: Liu Dianbo, National University of Singapore, Ophthamology Co-Lead PI: Ching-Yu Cheng, National University of Singapore, Ophthamology Co-Lead PI: Tham Yih Chung, National University of Singapore, Ophthamology	1. Identify non-linear genetic associations contributing to the susceptibility and manifestation of diverse eye diseases. 2. Explore epistatic interactions and allelic heterogeneity within the genomic data to unravel the complex relationships between multiple genetic variants. 3. Investigate how non-linear responses to environmental variables contribute to the phenotypic variation, with a focus on refining our understanding of gene-environment interactions in the context of ocular health. 4. Investigate and interpret the biological relevance of non-linear genetic

			associations. Aim to gain insights into the underlying mechanisms linking identified genetic variants to specific eye diseases and contribute to a more comprehensive understanding of the biology involved. 5. Evaluate the public health implications of the identified non-linear genetic associations, considering their potential impact on disease prevention, intervention, and personalised treatment strategies. Assess the translational potential of the research findings to inform clinical practice, public health policies, and contribute to advancements in precision medicine for ocular health.
	Institution involved: National University of Singapore		
4	Advancing the understanding of biological mechanisms influencing chronic inflammatory skin diseases	Lead PI: Yew Yik Weng, National Skin Centre Co-Lead PI: Steven Thng Tien Guan, National Skin Centre Co-Lead PI: Marie Loh, Lee Kong Chian School of Medicine	1. Identify host genetic factors associated with chronic inflammatory skin diseases, specifically AD, psoriasis and chronic urticaria using genome wide association and rare variant analyses among SG100K study participants, taking advantage of whole genome sequence data and linkage to disease information from national electronic health records (NEHR). 2. Examine the relationship between genetic variants and polygenic risk scores (PRS) associated with skin phenotypes and real-world health data for skin diseases (including diagnosis, onset, severity and treatment outcomes) to identify genetic predictors of disease trajectories, complications and co-morbidities and treatment outcomes using the TRUST dataset.
	Institutions involved: National Skin Centre, Lee Kong Chian School of Medicine, A*STAR Skin Research Institute of Singapore		

5	Mood and diet in patients with irritable bowel syndrome (IBS) in Singapore	Lead PI: Kuang Ziyang Jonathan, Gastroenterology & Hepatology, Tan Tock Seng Hospital Co-Lead PI: Sunny Wong, Lee Kong Chian School of Medicine Co-Lead PI: Chen Kok Pun, Gastroenterology & Hepatology, Tan Tock Seng Hospital	1. Evaluate the dietary pattern and characteristics of patients with IBS in Singapore. 2. Identify patterns of mood disorders in patients with IBS in Singapore. 3. Identify genetic variants associated with IBS in the multi-ethnic Singaporean Population. Explore and characterise common genetic polymorphisms IBS within the diverse Singaporean population. This comprehensive genetic investigation aims to unravel the unique genetic landscape of IBS, considering the multi-ethnic composition of the population. 4. Investigate the effects of lifestyle factors on IBS Risk and progression. Systematically examine the impact of lifestyle factors, including diet, physical activity, sleep, stress, and mental health, on the risk and progression of IBS. This multifaceted investigation seeks to discern the intricate relationships between lifestyle choices and IBS, contributing valuable insights for developing targeted interventions and improving patient outcomes. 5. Elucidate potential interactions between genetic and environmental influences on IBS. Uncover and elucidate potential interactions between genetic factors and environmental influences in the development and progression of IBS. This integrated approach aims to provide a nuanced understanding of how genetic predispositions and environmental exposures collaboratively contribute to the manifestation of IBS, offering a foundation for personalised and precision medicine strategies.
	Institutions involved: Tan Tock Seng Hospital, Lee Kong Chian School of Medicine		

6	The contribution of genetics to dietary habit and its relation to adiposity and cardiometabolic diseases in multiethnic Asian population	Lead PI: Theresia Mina, Lee Kong Chian School of Medicine Co-Lead PI: John Chambers, Lee Kong Chian School of Medicine Co-Lead PI: Sim Xueling, National University of Singapore	1. Conduct phenotypic associations of macronutrients with visceral adiposity as primary outcome, and the visceral fat-linked cardiometabolic traits and diseases as secondary outcomes in multiethnic Asian population. 2. Perform GWAS of macronutrients in multiethnic Asian population using the SG100K dataset and a GWAS meta-analysis using the UK Biobank macronutrient intake data. 3. Perform functional annotation of significant loci and estimate the genetic correlations of macronutrient intake with visceral adiposity as primary outcome, and the visceral fat-linked cardiometabolic traits and diseases as secondary outcomes. 4. Conduct one-sample and two-sample Mendelian Randomisation (MR) with macronutrient intake as exposure variables and visceral adiposity as outcome variables, with relevant sensitivity analyses.
	Institutions involved: Lee Kong Chian School of Medicine, National University of Singapore		
7	A structural variation catalogue across three ancestrally diverse Singaporean populations	Lead PI: Joanna Tan Hui Juan, A*STAR Genome Institute of Singapore Co-Lead PI: Shyam Prabhakar, A*STAR Genome Institute of Singapore Co-Lead PI: Patrick Tan Boon Ooi, A*STAR Genome Institute of Singapore	1. Build a catalogue of SVs (deletions, insertions, duplications, inversions, translocations, and tandem repeats) from the PRECISE-SG100K dataset. 2. Investigate the identified SVs to uncover population-specific trends. 3. Examine the functional consequences of SVs in different genomic regions as well as predict the impact of SVs in medically relevant genes. 4. Identify SVs that are associated with phenotypic traits within the PRECISE-SG100K dataset. **5.** Elucidate the impact of SVs on variation in cell type-specific gene expression (SV-eQTLs) and validate SVs through copy number variation inferences from scRNA-seq data.

	Institution involved: A*STAR Genome Institute of Singapore		
8	Genome-wide association study and population-based evaluation of patients with diabetic foot ulcers	Lead PI: Joseph Lo, Woodlands Health Co-Lead PI: Kavita Venkataraman, National University of Singapore Co-Lead PI: Yusuf Ali, Lee Kong Chian School of Medicine	Primary aim: Identify genetic loci associated with diabetic foot ulcers in Asian patients with diabetes mellitus. Secondary aims: o Identify differences in genetic loci within Malay/Indian ethnicities. o Identify genetic loci associated with diabetic peripheral neuropathy. o Identify potential gene-environment interactions (for example, tobacco smoking) associated with the risk of diabetic foot ulcers. o Identify socio-economical and other risk factors associated with diabetic foot ulcers. o Identify correlations between macro-angiopathy, micro-vascular reactivity nephropathy and retinopathy and diabetic foot ulcers. o Develop multi-polygenic risk score for developing diabetic foot ulcers.
	Institutions involved: Woodlands Health, National University of Singapore, Lee Kong Chian School of Medicine		
9	The SG100K_cancer and aging workgroup: Developing risk models for cancer associations	Lead PI: Joanne Ngeow, Lee Kong Chian School of Medicine Co-Lead PI: Rajkumar s/o Dorajoo, A*STAR Genome Institute of Singapore Co-Lead PI: Neerja Karnani, A*STAR Bioinformatics Institute	1. Generate common variant polygenic risk scores for common cancers (breast, colorectal, liver, lung, and prostate cancers) and identify potential functional rare coding genetic mutations in strong cancer related genes in the SG100K dataset. 2. Generate additional age-related biomarkers (i.e as telomere length estimates) related to cancer risk from the SG100K WGS data and identify genetic predispositions associated with these biomarkers. 3. Linkage of genetic datasets with TRUST to derive clinical data and determine common cancer status (breast, colorectal, liver, lung, and prostate cancers).
	Institutions involved: Lee Kong Chian School of Medicine, A*STAR Genome Institute of Singapore, Bioinformatics Institute		

10	Genetic susceptibility of age-related hearing loss	Lead PI: Liu Jianjun, A*STAR Genome Institute of Singapore Co-Lead PI: Nicolas Bertin, A*STAR Genome Institute of Singapore Co-Lead PI: Lim Weng Khong, Duke-NUS Medical School	1. Generate a SG100K genome wide TR variation catalogue and characterisation their respective prevalence in Asian populations. 2. Characterise the contributions of TR variations to the aetiology of complex neurological and neurocognitive disorders.
	Institutions involved: A*STAR Genome Institute of Singapore, Duke-NUS Medical School		
11	Evaluating the promise and perils of glucagon-like peptide-1 (GLP-1) receptor agonist: a deep dive into therapeutic potentials and adverse effects	Lead PI: Huang Jian, A*STAR Singapore Institute for Clinical Sciences and Bioinformatics Institute Co-Lead PI: Dennis Wan, A*STAR Singapore Institute for Clinical Sciences and Bioinformatics Institute	1. Investigate the effects of GLP-1 receptor agonist on various domains of health outcomes using an observational study design 2. Identify the non-synonymous single nucleotide polymorphisms (SNPs) of GLP-1 receptor agonist prescription and predict nsSNPs responsible for the differential response to GLP-1 receptor agonist. 3. Provide genetic evidence for the therapeutic potentials and adverse effects of GLP-1 receptor agonists by adopting a drug target Mendelian randomisation design.
	Institutions involved: A*STAR Singapore Institute for Clinical Sciences and Bioinformatics Institute		
12	Unravelling the pathogenesis of inflammatory bowel disease and associated immune- mediated disorders in the Singaporean population	Lead PI: Sunny Wong, Lee Kong Chian School of Medicine Co-Lead PI: Anselm Mak, National University of Singapore Co-Lead PI: Bernett Lee, Lee Kong Chian School of Medicine	1. Identify Genetic Variants Associated with IBD and Related Immune-Mediated Disorders in the Multi-Ethnic Singaporean Population. Explore and characterise both common and rare genetic variants linked to IBD, and spondyloarthropathies, uveitis, Behcet's disease, psoriasis, and other related immune-mediated conditions within the diverse Singaporean population. This comprehensive genetic investigation aims to unravel the unique genetic landscape of this disease cluster, considering the multi-ethnic composition of the population. 2. Investigate the Effects of Lifestyle Factors on IBD and Associated Diseases Risk and Progression.

			Systematically examine the impact of lifestyle factors, including diet, physical activity, sleep, stress, and mental health, on the risk and progression of IBD and associated immune-mediated diseases. This multifaceted investigation seeks to discern the intricate relationships between lifestyle choices and disease outcomes, contributing valuable insights for developing targeted interventions and improving patient wellbeing. 3. Delineate shared and distinct mechanisms underlying IBD, spondyloarthropathy, uveitis, psoriasis, Behcet's and other related conditions. Elucidate the shared and unique genetic and biological pathways driving IBD, spondyloarthropathy, uveitis, psoriasis, Behcet's disease, and other related conditions. This will provide critical insights into disease mechanisms to guide targeted prevention and treatment strategies for this nexus of related diseases. 4. Elucidate Potential Interactions Between Genetic and Environmental Influences on This Disease Cluster. Uncover and elucidate potential interactions between genetic factors and environmental influences in the development and progression of IBD and related conditions. This integrated approach aims to provide a nuanced understanding of how genetic predispositions and environmental exposures collaboratively contribute to the manifestation of this disease cluster, offering a foundation for personalised and precision medicine strategies.
	Institutions involved: Lee Kong Chian School of Medicine, National University of Singapore		

13	Genetics of allergic diseases and acne vulgaris in the Singapore population: validation and functional characterisation of candidates	Lead PI: Chew Fook Tim, National University of Singapore	1. Validate disease-associated genetic polymorphisms and environmental factors that were previously identified and functionally characterised in the SMCGES cohort, using the PRECISE-SG100K dataset. 2. Investigate the associations of previously identified asthma/AR/AD/acne candidate genes with the other clinical parameters relevant to the disease of interest. For instance, whether the allelic/genotypic differences of genetic variants would affect the treatment response, lung function (spirometry), skin condition (sites of flexural dermatitis and psoriasis, etc.), blood test results (compositions of immune cells, etc.) in complex disease. 3. Reproduce and validate the observed associations between specific dietary habits and allergic diseases, using a more extensive and culturally relevant FFQ. 4. Explore causal relationship between dietary habits and allergic diseases by understanding how changes in dietary patterns influence the development and progression of allergic diseases.
	Institution involved: National University of Singapore		
14	Modulation of cholesterol 7α-hydroxylase (CYP7A1) activity as an orthogonal approach to the management of hypercholesterolemia	Lead PI: Ho Han Kiat, National University of Singapore	1. Determine the prevalence of CYP7A1 single nucleotide polymorphisms (SNP) locally, and on extrapolation, to the region that presents similar ethnicities. 2. Ascertain the relationship between CYP7A1 SNPs and hypercholesterolemia in our local population. 3. Identify the target population most likely to benefit from targeting CYP7A1 as an orthogonal approach to cholesterol control. 4. Study the impact of non-genetic extrinsic

			factors, such as comorbidities and comedications, on the genotypes to discern the possibility of phenoconversion.
	Institution involved: National University of Singapore		
15	Multi-omics data analysis for novel depression mechanisms using deep learning tools	Lead PI: Mu Yuguang, Nanyang Technological University Co-Lead PI: Bernett Lee, Lee Kong Chian School of Medicine Co-Lead PI: Geoffrey Tan Chern-Yee, Institute of Mental Health	1.1 Build machine learning and deep learning models specific to Singaporean demographics which aid in prediction of depression. 1.2 To identify gene by marker and gene by environment interactions predicting depressive and anxiety symptoms with dietary, nutrient, metabolic, lifestyle, sociodemographic and cognitive factors 1.3 Apply feature selection approaches to discover important environmental and genetic features used by the machine learning and deep learning models to predict depression to ensure the model is explainable and reasonable to physicians. 1.4 Explore the potential for the depression machine learning models to be deployed in clinical settings. 2.1 Construct a language model which could extract complex interrelations between patient features under Singapore context. 2.2 Assess the capability of the language model in imputing missing features of a patient when other features were provided to extrapolate patient features in clinical settings. 2.3 Assess suitability of leveraging the trained language model for transfer learning.
	Institutions involved: Nanyang Technological University, Lee Kong Chian School of Medicine, Institute of Mental Health		
16	Asian-specific Parkinson's disease-linked genetic risk variants and systemic clinical outcomes	Lead PI: Tan Eng King, National Neuroscience Institute Co-Lead PI: Thomas Welton, Duke-NUS Medical School Co-Lead PI: Chan Ling Ling,	1a. Determine the prevalence of Asian specific LRRK2 coding variants and other PD risk genes (e.g., APOE, SNCA, GBA1, HLA alleles, etc) in Malays, Indians and Chinese in the SG100k cohort. 1b. Investigate the association of PD risk genes

		Duke-NUS Medical School	with comorbidities (Diabetes, Hypertension, Heart disease, Autoimmune diseases, Infectious diseases, vaccination history etc) in carriers and compare the associations with non-carriers. 2. Investigate the association with motor and non-motor features between PD risk gene carriers and non-carriers based on the quantitative outcome measures (e.g. eye, cognition, bone mass, etc). 3. Investigate the differences in MRI regional volumes, lesion burden and tissue microstructure between carriers and non-carriers.
	Institutions involved: National Neuroscience Institute, Duke-NUS Medical School		
17	Physiological, environmental and genetic determinants of heterogeneity in Singaporeans' health span	Lead PI: Neerja Karnani, A*STAR Bioinformatics Institute Co-Lead PI: Joanne Ngeow, Lee Kong Chian School of Medicine Co-Lead PI: Brian Kennedy, National University of Singapore Co-Lead PI: Rajkumar s/o Dorajoo, A*STAR Genome Institute of Singapore	1. Investigate the stressors associated with aging and identify the factors contributing to resilience. 2. Investigate gender-specific variations in aging stressors and assess the influence of reproductive aging. 3. Examine the effects of Asian ethnicity on the aging process and healthspan. 4. Evaluate the pharmacogenomic effects of medications on lifespan and overall health during aging
	Institutions involved: A*STAR Bioinformatics Institute and Genome Institute of Singapore, Lee Kong Chian School of Medicine, National University of Singapore		

18	Portability of catalogued polygenic risk scores across ancestrally diverse Singaporean populations	Lead PI: Pierre-Alexis Goy, A*STAR Genome Institute of Singapore Co-Lead PI: Li Jingmei, A*STAR Genome Institute of Singapore	1. Integration of Research Phenotypes with PRS Catalogue Ontologies and Identification of Applicable PRS Models: • Align research phenotypes with the trait ontologies in the EBI-maintained PRS catalogue. • Systematically select pertinent PRS models based on the relevance to mapped research phenotypes. 2. Assessment of Performance Across Diverse Ancestries within SG100K: • Evaluate the effectiveness of selected PRS models across the major ancestries represented in the SG100K dataset (i.e. distribution, discrimination, calibration). • Analyse and compare performance metrics to identify any ancestry-specific nuances in predictive accuracy. • Recommendations and portability assessment of EBI-catalogued published PRS in a Singapore context.
	Institution involved: A*STAR Genome Institute of Singapore		
19	Advancing Asian-centric liver disease treatment: machine learning applications in MASLD and MetALD precision medicine	Lead PI: Tan Nguan Soon, Lee Kong Chian School of Medicine Co-Lead PI: Yew Kuo Chao, Tan Tock Seng Hospital Co-Lead PI: Cheng Hong Sheng, Lee Kong Chian School of Medicine	1. Investigate the genomic risk of MASLD and associated metabolic traits in Asian populations. 2. Interrogate the contribution of dietary components, alcohol intake and physical activity to MASLD and MetALD disease spectrum. 3. Develop machine learning frameworks for risk stratification and identification of predictive markers for MASLD disease spectrum.
	Institutions involved: Lee Kong Chian School of Medicine, Tan Tock Seng Hospital		
20	Unravelling the correlation between sarcopenia with lifestyle, genetics, and comorbid diseases	Lead PI: Teh Bin Tean, National Cancer Centre Singapore Co-Lead PI: Frederick Koh Hong Xiang, SingHealth	1. Validate the multi-omics signature of people with various stages of sarcopenia. 2. Identify the influence of sarcopenia on comorbidities and its impact on clinically relevant outcomes.

			3. Evaluate correlation of biomarkers of sarcopenia with social economic status
	Institutions involved: National Cancer Centre Singapore, SingHealth		
21	Young-onset obesity and determinants of cancer prevalence	Lead PI: Yusuf Ali, Lee Kong Chian School of Medicine Co-Lead PI: Sunny Wong, Lee Kong Chian School of Medicine Co-Lead PI: Fan Xiuyi, Lee Kong Chian School of Medicine	1. Correlates of obesity before age 45 and incidence of cancer (EHR). Compare risk relationships by ethnicity and sex. 2. Develop a dietary pattern score characterising inflammatory potential of diet. Relate this score to circulating markers of inflammation and metabolic health among PRECISE-SG100K participants under age 45. 3. Determine whether medications and bariatric surgery mitigate cancer risk in young onset obese PRECISE-SG100K participants. Compare effectiveness across ethnic groups and cancer sites.
	Institution involved: Lee Kong Chian School of Medicine		
22	Implications of alternative splicing of voltage-gated calcium channels in schizophrenia	Lead PI: Soong Tuck Wah	Profile the frequency of splicing associated genetic variations of VGCCs and their auxiliary subunits, and their potential association with schizophrenia in the SG100K cohort.
	Institution involved: National University of Singapore		
23	Exploring the impact and origins of somatic mutagenesis in cardiovascular disease	Lead PI: Tan Kar-Tong	1. Assess the impact of genetic variations the rate of somatic mutagenesis, and the risk of CVDs. 2. Assess the impact of environmental exposures on the rate of somatic mutagenesis, and the risk of CVDs. 3. Assess the impact of DNA damaging drugs on the rate of somatic mutagenesis and CVDs.
	Institution involved: National University of Singapore		

24	Alport syndrome in the Singapore population: an under-recognised kidney disease?	Lead PI: Ng Kar Hui, National University of Singapore Co-Lead PI: David Bruce Matchar, Duke-NUS Medical School Co-Lead PI: Jason Choo Chon Jun, Duke-NUS Medical School	1. Determine the prevalence of autosomal dominant (AD), X-linked (XL), autosomal recessive (AR) and digenic Alport syndrome in Singapore; and differences in these prevalences among the Chinese, Malay and Indian populations in Singapore. 2a. Determine the penetrance of kidney, eye and hearing phenotypes in AD Alport, XL male Alport and XL female Alport syndrome, stratified according to age groups and gender in Singapore. 2b. Estimate the number of diagnosed Alport and versus mis-diagnosed or undiagnosed Alport cases in Singapore and the differences in healthcare costs, service utilisation and patterns of care among these groups. 2c. Correlate the severity of the kidney phenotypes with the genotypes in COL4A3 and COL4A4, specifically comparing collagenous domain glycine missense variants with other types of genetic variants. 3a. Determine the clinical features that predict an Alport genetic diagnosis. 3b. Determine the added risk of AD Alport on bad kidney outcomes (ESKD, rapid GFR decline or heavy proteinuria). 3c. Determine the clinical features that predict a poor kidney outcome in AD Alport subjects.
	Institutions involved: National University of Singapore, Duke-NUS Medical School		
25	Risk prediction for congenital and early-onset hearing loss	Lead PI: Joshua Tay, National University of Singapore Co-Lead PI: Tan Ene Choo, KK Women's & Children's Hospital Co-Lead PI: Goh Xueying, National University Hospital	1. Describe the genetic landscape of congenital and early-onset hearing loss in multi-ethnic Singapore. Identify the prevalence of known genetic variants and novel variants associated with hearing loss. 2. Analyse interactions between hearing loss-associated genetic variants and clinical events that may potentiate hearing loss (e.g. use of ototoxic drugs). 3. Develop and validate a polygenic risk score for congenital and early onset hearing loss based on an individual's genotype.

	Institutions involved: National University of Singapore, KK Women's & Children's Hospital, National University Hospital		
26	Biological age clocks for multiple organ systems and the lifestyle and genetic risk factors of advanced biological age	Lead PI: Andrea B. Maier, National University of Singapore Co-Lead PI: Weilan Wang, National University of Singapore	1. Investigate the optimal versus current reference ranges of organ systems against the risk of age-related diseases using Singaporean data. 2. Develop and validate a biological clock on organ systems (cardiovascular, pulmonary, metabolic, immune, hepatic, and musculoskeletal systems) based on Singaporean data. 3. Explore the lifestyle and genetic risk factors associated with advanced biological organ age.
	Institution involved: National University of Singapore		
27	Identification of risk factors for gastrointestinal cancers through analysis of genetic and phenotypic data	Lead PI: Patrick Tan, Duke-NUS Medical School Co-Lead PI: Lim Weng Khong, Duke-NUS Medical School Co-Lead PI: Rajkumar s/o Dorajoo, A*STAR Genome Institute of Singapore	1. Systematically identify genes associated with gastrointestinal cancer risks and survival and estimate penetrance (the cancer risk associated with gene variants) of both novel and known pathogenic genes in gastrointestinal cancer. 2. Investigate the interactions between the human genome, lifestyle factors and presence of precursor lesions. This aim to determine the extent that a healthier lifestyle can mitigate gastrointestinal cancer risk in subjects with premalignant lesions or carrying a cancer predisposition gene. 3. Quantify the proportional contribution of human genome and lifestyle factors to risks and survival outcomes of gastrointestinal cancers. We also aim to develop predictive models for gastrointestinal risks by integrating these factors.
	Institutions involved: Duke-NUS Medical School, A*STAR Genome Institute of Singapore		
28	Genomic associations of	Lead PI: Kelvin Bryan Tan,	1. Mine and catalogue published disease

	COVID-19 susceptibility & severity in Singapore	Ministry of Health	severity and susceptibility host genetic variants and testing their prevalence in Singaporeans. This will include not just previously published variants but identify potential new variants which are associated with COVID severity, susceptibility and long COVID outcomes. Prevalence and allele frequencies of these variants will be further studied. 2. Genome wide association study (GWAS) to identify novel host genetic factors in our population. 3. Assessing and developing genetic risk scores of disease severity, susceptibility and long COVID outcomes in our population.
	Institution involved: Ministry of Health		