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ABSTRACTS

Accepted Abstracts

1 SEPT–GD: a decision tree to prioritise potential RNA splice variants in cardiomyopathy genes for functional splicing assays in diagnostics

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Background:
Splice prediction algorithms currently used in routine DNA diagnostics have limited sensitivity and specificity, therefore many potential splice variants are classified as variants of uncertain significance (VUSs). However, functional assessment of VUSs to test splicing is labour-intensive and time-consuming. We developed a decision tree to prioritise potential splice variants for functional studies and functionally verified the outcome.

Materials and methods:
We built the decision tree, SEPT–GD, by setting thresholds for the splice prediction programs implemented in Alamut. A set of 343 variants with known effects on splicing was used as control for sensitivity and specificity. We tested SEPT–GD using variants from a Dutch cardiomyopathy cohort of 2002 patients that were previously classified as VUS and predicted to have a splice effect according to diagnostic rules. We then selected 12 VUSs ranked by SEPT–GD to functionally verify the predicted effect on splicing using a minigene assay: 10 variants predicted to have a strong effect and 2 with a weak effect. RT-PCR was performed for nine variants. Variant classification was re-evaluated based on the functional test outcome.

Results:
Compared to similar individually tested algorithms, SEPT–GD shows higher sensitivity (91%) and comparable specificity (88%) for both consensus and non-consensus splice-site variants. Using clinical diagnostic criteria, 1295 unique variants in our cardiomyopathy cohort had originally been classified as VUSs, with 57 predicted by Alamut to have an effect on splicing. Using SEPT–GD, we prioritised 31 variants in 40 patients. In the minigene assay, 12 variants showed results concordant with SEPT-GD predictions. RT-PCR confirmed the minigene results for two variants, *TMEM43* c.1000+5G>T and *TTN* c.25922-6T>G. Based on these outcomes, the *SGCD* c.4-1G>A and *CSRP3* c.282-5_285del variants were reclassified as likely pathogenic.

Conclusion:
SEPT–GD outperforms the tools commonly used for RNA splicing prediction and improves prioritisation of variants in cardiomyopathy genes for functional splicing analysis in a diagnostic setting.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Key words:
Cardiomyopathy, splicing, variants of unknown significance, molecular diagnosis, functional testing

2 Single-cell analysis of human diversity in circulating immune cells

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Background & Objectives:

Lack of diversity and proportionate representation in genomics datasets and databases contributes to inequity in healthcare outcomes globally. The relationships of human diversity

with biological and biomedical phenotypes are pervasive, yet remain understudied, particularly in a single-cell genomics context.

Methods and Results:
Here we present the Asian Immune Diversity Atlas (AIDA), a multi-national single-cell RNA-sequencing healthy reference atlas of immune cells. AIDA comprises 1,265,624 circulating immune cells from 619 healthy donors and 6 controls, spanning 7 population groups across 5 countries. AIDA is one of the largest healthy blood datasets in terms of number of cells, and also the most diverse in terms of number of population groups. Though ancestries are frequently compared at the continental level, we identified a pervasive impact of sub-continental ancestral diversity on cellular and molecular properties of immune cells. These included cell populations and genes implicated in disease risk and pathogenesis as well as those relevant for diagnostics. We detected single-cell signatures of human diversity not apparent at the level of cell types, as well as modulation of the effects of age and sex by ancestry. We discovered functional genetic variants influencing cell type-specific gene expression, including context-dependent effects, which were under-represented in analyses of non-Asian population groups, and which helped contextualise disease-associated variants. We validated our findings using multiple independent datasets and cohorts.

Conclusions (Significance and Impact of the Study):
AIDA provides fundamental insights into the relationships of human diversity with immune cell phenotypes, enables analyses of multi-ancestry disease datasets, and facilitates the development of precision medicine efforts in Asia and beyond.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial, or personal.

Keywords:
human diversity, ancestry, single-cell genomics, healthy baseline, circulating immune cells

3 Understanding the purpose of prescribing is key for enabling shared decision-making with hospitalised patients on antibiotic therapy: A cross-sectional study in Singapore

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Background & Objectives:
Antimicrobial resistance, driven by poor antibiotic use, threatens the global population with 10 million annual deaths by 2050. In Singapore, 50% of hospitalised patients are on antibiotics on any given day. Shared decision-making (SDM) on antibiotic therapy could improve appropriate antibiotic prescribing for these patients. In this study, we seek to identify gaps that can be targeted to improve SDM amongst hospitalised patients on their antibiotic therapies.

Method(s) and Results:
A survey was administered to 636 patients admitted in Tan Tock Seng Hospital with ≥1 day of antibiotic therapy in 2021-2022. Only 23% of respondents had a high-level of engagement in SDM (i.e. composite score >highest quartile of SDM-Q-9 scale, Kriston *et al*). Amongst patients who were aware that they were given antibiotic(s) (N=571), those who had received explanations on the purpose of the antibiotic(s) in an understandable manner (adjusted odds ratio 2.38 [95% CI 1.35-4.19]) were more likely than those who didn't, to have a high-level of engagement in SDM. Most respondents perceived it as very/extremely important to be informed by a doctor/nurse on the reason for taking antibiotic(s) (81%), and believed that protected time with the doctors to understand more about the use of antibiotics for their condition would effectively raise their awareness and knowledge on antibiotic use (75%).

Conclusions (Significance and Impact of the Study):
To engage hospitalised patients in SDM to improve appropriate antibiotic prescribing, it is important for doctors to proactively share information on the prescribed antibiotic therapies with their patients.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Antimicrobial resistance; Hospitalised patients; Shared decision-making; Antibiotic stewardship; Appropriate antibiotic prescribing

4 Transforming Genomics Research through Community Engagement: A Case Study from the Pukapuka Community in Aotearoa, New Zealand

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Background:
There is often scepticism about participating in genomics research within Indigenous and minority populations; indeed, less than 1% of GWAS have participants from Oceania[1]. All too often, researchers have neglected to address local priorities and power inequities when designing and implementing studies, and results are rarely communicated back to participating communities. Here we highlight an example of an accountable and collaborative approach to genomics research undertaken with the Pukapuka community in Aotearoa, NZ.

Methods and Results:
This approach prioritises building trust and empowering communities through in-depth community engagement, respecting cultural protocols, and equitable sharing of benefits and group-level genomic and health findings. In this case study, researchers in academia and industry from the US and NZ embarked on a genomics study in partnership with the Pukapuka community in Aotearoa, NZ. Crucially, the study was underpinned by principles of co-design and robust community engagement across all phases of the research. Additionally, this study committed to building local capacity by engaging and training a Pukapuka community-based implementation team.

The study successfully recruited 322 people into a project that reflected community health priorities and included genomics, metabolomics, and a comprehensive biomedical health assessment. To date, the process of community engagement is ongoing to ensure that imminent results return aligns with locally identified health concerns and guides the process for effectively communicating these findings back to the community.

[1] Sirugo G, Williams SM, Tishkoff SA. The Missing Diversity in Human Genetic Studies. Cell. 2019 Mar 21;177(1):26-31. doi: 10.1016/j.cell.2019.02.048. Erratum in: Cell. 2019 May 2;177(4):1080.

Conclusion and Significance:
In essence, this case study underscores the pivotal significance of community engagement in cultivating a locally meaningful partnership, thus fostering enhanced equity and justice for individuals involved in genomic studies.

Conflict of interest disclosure:
JM, OG, and KW are either current or former employees and/or options or shareholders of Variant Bio. TRM has research funding and a consultancy agreement with Variant Bio.

Keywords:
Indigenous, Health, Genomics, Equity, Community engagement

5 Harnessing AI for Precision Antibiotics: Enablers and Ethical Considerations

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Background & Objectives:
Clinical decision support systems (CDSSs) have been developed to guide doctors in antibiotic selection for empiric therapy, as optimal selection is complex when the causative pathogen is unknown. As existing antibiotic CDSSs are rule-based, doctors often choose to exercise their own or the clinical team's decision over the CDSSs' recommendations in complex patient situations. Artificial Intelligence(AI)-based CDSSs have the potential to address the individual patient's needs and enable precision antibiotic prescribing. Hence, we sought to understand the enablers and ethical considerations necessary for the diffusion and adoption of AI-based antibiotic CDSSs.

Method(s) and Results:
We performed a thematic analysis of 30 interviews with doctors (purposively sampled to achieve a maximum variation of medical and surgical specialties and seniority) practicing in Tan Tock Seng Hospital, concerning specific clinical case vignettes to explore their underlying opinions and attitudes regarding the introduction of an AI-based CDSS for antibiotic prescribing in their clinical practice. Four major themes were identified as enablers of doctors' acceptance of the AI-based antibiotic CDSS. First, trust in the CDSS's ability to improve patient outcomes compared with the current state. Second, ability of the CDSS to enhance decision-making by providing antibiotic recommendations based on explainable algorithms derived from local data. Third, accessibility of the system in terms of convenience, user-friendliness, efficiency, and reliability. Fourth, social acceptance by peers and seniors. With regards to ethical considerations, doctors required clarity on medico-legal liabilities.

Conclusions (Significance and Impact of the Study):
For the successful implementation of AI-based CDSSs for precision antibiotic prescribing, it is pertinent that the system is trustable, explainable, accessible, socially acceptable, and supported by an ethical framework.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Artificial intelligence; Clinical decision support; Precision antibiotic prescribing; Enablers; Ethics

Funding Source:
This project is supported by the NISTH Seed Grant from the NTU Institute of Science and Technology for Humanity, Nanyang Technological University.

6 Identifying the unmet needs of Neurofibromatosis Type 1 patients in Singapore

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Background and Objectives:
Neurofibromatosis type 1 (NF1) is a neurocutaneous condition associated with tumor predisposition. NF1 patients may also face neuropsychiatric and psychosocial problems, hence addressing the full scope of needs presented by NF1 patients can be challenging but is important for holistic management. This study aims to identify the unmet needs of NF1 patients in Singapore to guide the provision of patient care and service delivery.

Methods and Results:
A qualitative study involving patient interviews was conducted, and grounded theory with thematic analysis was applied. Twenty patients with NF1 were interviewed. Five themes were identified: 1) NF1 trajectory begins from childhood; 2) Coming to terms with body and self; 3) Expected acceptance drives disclosure patterns; 4) Need for specialized NF1 care; 5) Building local awareness and connections. From this study, the following unmet needs were identified: 1) Need for multidisciplinary NF1 care; 2) Need for management of neurological symptoms; 3) Need for treatment for cutaneous lesions; 4) Need for financial coverage for NF1; 5) Need for early NF1 screening; 6) Need for local awareness and support groups.

Conclusions:
This study identified the challenges and unmet needs of NF1 patients in Singapore, which can be translated into actionable steps to improve the care and quality of life of NF1 patients.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Neurofibromatosis, neurocutaneous, qualitative research

7 Germline pathogenic variants landscape of endometrial cancer in Singapore

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Background & Objectives:
Lynch syndrome-associated endometrial cancer (LS-EC) is the most common extra-intestinal cancer caused by germline pathogenic-variants (PVs) in mismatch-repair (MMR) genes. Emergence of germline testing have enabled targeted therapeutics. Data in Asia, however, is lacking. We aim to investigate EC PVs in Singapore.

Methods and Results:
We retrospectively reviewed patients, age >= 21 years with EC, seen at Cancer Genetics Service (CGS) between September 2014 and July 2022. P-value was derived using Fisher's test. Of 241 patients, 150 (62.2%) underwent germline testing. Median age diagnosis was 52.0 years. There were 113 (75.3%) Chinese, 18 (12.0%) Malays, 9 (6.0%) Indians. One-hundred-and-nineteen (82.0%) had endometrioid endometrial carcinoma (EEC), 15 (10.3%) high-grade serous, and 4 (2.8%) clear cell. Ninety-nine (66.0%) had MSI (microsatellite instability) performed - 57 MSI High and 42 MSS (microsatellite stable). Majority (97.3%) underwent multiple-panel testing, while 4 (2.7%) had single gene testing - 2 *MLH1*, and 2 *MSH6*. Forty-two patients (28%) had PVs. Twenty-nine patients (19%) had LS-PV (*MLH1, MSH2, MSH6, PMS2* and *EPCAM-MSH2*). Although not statically significant, Malays 5/7(71.4%) and Indians 2/3(66.7%) were more likely to carry LS-PV, and germline *MSH6* or *PMS2* were more likely to be diagnosed age >= 50 years compared to *MLH1, MSH2 or EPCAM-MSH2* (p=0.062). MSI High tumor tissue were more likely to have germline PVs (p=0.001) and LS-PV (p<0.001).

Conclusion:
Our proportion of EEC is consistent with global landscape, with early-stage presenting at younger age. Epigenetics may explain differences in LS-PV amongst various ethnicities. MSI testing should be standard practice.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal

Keywords:
Endometrial cancer germline variant mismatch-repair

8 10K Newborn Genome Project in Qingdao, China: clinical findings and precision health insights

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Background & Objectives:
While several large-scale newborn genome projects in multiple countries were launched in the past few years, the expanded newborn screening by whole genome sequencing (WGS) became one of the next frontlines of precision medicine. We initiated a 10K Newborn Genome Project in Qingdao, China in 2020, and previously published a pilot study of 321 unselected newborns. Here, we report the complete results of 10 thousand unselected newborns.

Method(s) and Results:
A total of 9992 newborns completed WGS with a mean depth of 65X for the analysis of 245 inheritable and metabolic diseases. About 2.7% (274/9992) of newborns were screen-positive, and 40.7% (4066/9992) of newborns contained at least one disease mutation. Compared with the newborn screening by mass spectrometry (MS), WGS confirmed 3 out of 17 MS-positive results and identified 43 extra WGS-positive cases. Among 7140 newborns we obtained additional consent for genomics analysis, a total of 155,636,120 single nucleotide polymorphisms (SNPs), InDels, and 49,209,955 structural variants were detected. Most newborns carry more than one SNPs and InDels on 257 pharmacogenomics genes. A total of 4,145 SNPs were strongly associated with newborn metabolite levels, including 1,326 novel SNPs. We also found the presence of virus sequences in the newborn genome and identified the associated SNPs.

Conclusions:
This is by far the largest report on WGS screening in unselected newborns. Our results show that newborn genome screening can effectively identify genetic diseases. Newborn genome data also provide scientific insight into precision health.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
newborn screening, whole genome sequencing, metabolic diseases, pharmacogenomics, virus

9 Social factors and health: Cohort creation to design innovative, targeted intervention strategies and community care models

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Background:
Social factors- such as the existing social and community environment- play an important role in determining health outcomes, but population health strategies have largely taken a biomedical approach to improve health. A rigorous assessment of social factors and changes in life circumstances, and their effects on health, would inform interventions to better address health inequalities.

Objectives:
We aim to collect comprehensive data on bio-psycho-social factors and health outcomes for residents of a residential region in central Singapore, and design tailored interventions to improve health for vulnerable groups with increased social risk factors.

Methods & Results:
We will construct a cohort of 4000 residents aged 35-70 years and follow them up longitudinally. Interviewer- or self-administered surveys will be employed to collect socio-demographic, psychological and life circumstances variables, which will be supplemented with biomedical and health outcomes data obtained through data linkages with national registries. Anchoring on precision public health principles and leveraging on epidemiological and implementation research methods, we will identify, and design intervention strategies tailored to different social risk groups. These strategies will tap on novel technologies and care models and be evaluated for their effectiveness, sustainability, and scalability for potential implementation in a broader geographical context.

Conclusion:
This project will provide valuable insights on the biopsychosocial risk factors and needs of Singaporeans in Central Singapore. By tailoring interventions to the specific needs of socially vulnerable groups, we can implement effective strategies to improve the health of these residents.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Precision population health, disease prevention, tailored intervention design, cohort, social determinants

10 Utilizing Asian Genomics Data to Identify Vulnerabilities in Hepatocellular Carcinoma Cells

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Background & Objectives:
Hepatocellular carcinoma (HCC) is the 6th most common cancer and 3rd highest mortality rate worldwide. Eastern Asia and South-Eastern Asia have the 1st and 4th highest incidence rate, respectively, with an average mortality rate of 15 per 100,000 individuals. Here we try to identify potential genomics vulnerabilities in Asian HCC patient tumors that can be exploited for personalized medicine.

Method(s) and Results:
Utilizing the prospective HCC surgical cohort in the Precision Medicine in Liver Cancer across an Asia-Pacific Network study (PLANet 1.0; NCT03267641), we have analysed whole-genome and RNA sequencing data from 103 local HCC patients. Each patient had multiple biopsies totalling 503 samples with a range of 2-7 per patient. This cohort had similar prevalence with the genes with the highest mutation frequency in The Cancer Gene Census. We identified a set of known cancer drivers with significantly higher mutational prevalence in this cohort. To identify vulnerabilities specific to this cohort we developed an analysis pipeline that predicted synthetic lethal gene pairs utilizing the patient's genomics and clinical data. We tested the top 146 predictions in a duel CRISPR screen and found that 17% of the pairs showed evidence of synthetic lethality. Screen hits were enriched for mitotic cell cycle, cellular senescence, and pathways in cancer.

Conclusions:
Potential opportunities for some of the screened positive synthetic lethal pairs include targets that have inhibitors in phase I/II clinical trials with biomarkers that are enriched in the local HCC patients.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Hepatocellular carcinoma, Synthetic Lethality, Cancer

11 Unlocking the potential of large-cohort proteomics studies with mass spectrometry-based proteomics solution

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Background & Objectives:
Large-cohort proteomics analysis using mass spectrometry is a powerful approach to discover and validate new biomarkers. In combination with clinical data and computational analysis, large-cohort proteomics study brings opportunities in improving early diagnosis, refining patient stratification, and predicting/monitoring treatment response. Yet, to achieve meaningful biological insights, robust, reproducible, and comprehensive proteome profiling in a high-throughput manner remains challenging. Here, we use a high-resolution accurate mass (HRAM) Oribtrap Astral mass spectrometry platform to enable high-quality and robust protein quantification across thousands of LC-MS/MS analyses.

Methods & Results:
Multiple LC-MS/MS systems were operated in a 24/7 operation mode at a throughput of 100 samples/day. Undepleted plasma digest was analyzed with >1000 injections on each LC-MS/MS setup. HeLa digest (QC) were inserted periodically. Automatically, the resulting data files were immediately transferred to a server, then processed by state-of-the-art intelligent search algorithm. With a throughput of 100 samples/day, we can reproducibly profile ~9000 proteins from human cell line and ~800 proteins from undepleted plasma across multiple instruments and more than 10 consecutive days in a 24/7 operation mode. More than 80% of the plasma proteins were reproducibly quantified, indicating a great reproducibility from run-to-run longitudinally. Stable and robust peptide quantitation was observed by extracting peptides with high, medium, and low abundant across the runs. Importantly, QC showed no performance degradation throughout the entire study, indicating high robustness of the entire setup.

Conclusion:
Orbitrap Astral mass spectrometry platform can comprehensively analyze the proteome of >1000s of sample robustly and reproducibly in a high-throughput manner, addressing the needs in large-cohort studies.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
large cohort analysis, mass spectrometry-based proteomics, plasma biomarkers, patient stratification, precision medicine

12 Systematic Review on the Effectiveness of Risk-Based Screening for Cancer Diagnosis

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Background & Objectives:
Cancer screening in Singapore relies on age-based stratification, with eligibility for screening starting at around 50 years old. Despite that, sufficient evidence showcased those below 50 are also susceptible to cancer, thereby prompting a re-evaluation of factors cancer screening be stratified upon. The purpose of this review was to examine the feasibility of adopting risk-based cancer screening (RBS) based on genetics with consideration for, (1) diagnostic accuracy, (2) improvements to survival and clinical outcomes and (3) cost-effectiveness and (4) Asian population.

Method(s) and Results:
MEDLINE and Embase on Ovid platform, PubMed, CINAHL, Web of Science, Cochrane Central and Scopus were systematically searched from their respective dates of inception up to 21 November 2023. Prospective and randomised controlled trials implementing risk-based screening of cancer in an asymptomatic population or studies retrospectively evaluating outcomes of the same were included. Two investigators independently screened title-abstracts and full-texts for inclusion, and similarly for risk-of-bias assessment and data extraction subsequently. We plan to derive the summary reporter operating characteristic curve (SROC) to meta-analyse diagnostic accuracy outcomes, and the summary odds ratios for mortality estimates. Geographic distribution of studies, study population characteristics, RBS model features and other outcomes will be narratively synthesised. 4265 title-abstracts were screened, and 120 full-texts were retrieved for inclusion.

Conclusions:
The review is ongoing but has potential to inform evidence-based practice changes to pre-existing age-based cancer screening guidelines.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Cancer; Screening; Genetics; Risk-based; Singapore

13 Microfluidic isolation of complete platelet-free plasma for enhanced detection of blood extracellular vesicles (EV) microRNAs and surface proteins

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Background & Objectives:
Blood extracellular vesicles (EVs) are promising prognostics and diagnostics biomarkers in diseases but the clinical translation remains challenging due to the laborious and non-standardized EV isolation methods. EV detection is also confounded by various preanalytical variabilities such as delayed centrifugation or incomplete platelet depletion. Herein, we develop centrifuge-free microfluidic technology (ExoArc) for onsite platelet-free plasma (PFP) and EV isolation within 30 min.

Methods and Results:
PFP was separated from blood directly using ExoArc by depleting larger blood particles (> 500 nm) based on hydrodynamic focusing. Flow cytometry analysis showed complete cell removal and 99.99% platelet depletion in ExoArc-isolated PFP. To characterize EV surface proteins, PFP were labelled with EV surface markers and analysed using fluorescent nanoparticle tracking analysis (fNTA). fNTA detected 2e9/mL CD9+ EVs and 3.9e8/mL CD81+ EVs in ExoArc-isolated PFP, with less (~ 5e7/mL) platelet (CD41+), neutrophil (CD66b+), and monocyte (CD14+) EVs, thus suggesting minimal blood cell activation during blood processing. Coupling ExoArc with size exclusion chromatography (SEC) further reduced background proteins to <100 µg/mL with 10x higher EV recovery as compared to ultracentrifugation. As a proof-of-concept for EV diagnostics, microRNAs in ExoArc+SEC-isolated EVs from type 2 diabetes mellitus (T2DM) and healthy subjects were studied using qPCR. Among 123 common microRNAs detected, upregulated miR-19a-3p, miR-129-5p, miR-21-5p and downregulated miR-141-3p were observed in T2DM subjects.

Conclusions:
ExoArc provides a robust, cost-effective and user-friendly EV isolation workflow without requiring any centrifugation steps. This significantly reduces labour, processing time and preanalytical variabilities in EV isolation which will be key to increase clinical adoption of EV-based diagnostics.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
platelet-free plasma, liquid biopsy, microfluidics, microRNAs, extracellular vesicles

15 Determination of genetic variants associated with Sarcoidosis in Sri Lankan population

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Background and objectives:
Sarcoidosis is a chronic inflammatory disease that affects multiple organs in the body, primarily the lungs and lymph nodes. The exact cause of sarcoidosis is unknown, but it is thought to be related to an abnormal immune response to certain environmental or genetic factors. Symptoms of sarcoidosis can vary widely depending on which organs are affected, but they often include persistent dry cough, shortness of breath etc.

Methods and Results:
The research involved an exhaustive review of existing literature to pinpoint potentially harmful genetic variants and subsequent optimization and validation of Tetra-primer Amplification Refractory Mutation System (tetra-primer ARMS) PCR-based assays for genotyping specific variants (*NOD2* gene rs104895462 (C>T), *LTA* gene rs1041981 (C>A), *ANXA11* gene rs1049550 (G>C), and *BTNL2* gene rs2076530 (T>C)), which were previously identified in Asian populations.

Regards to *LTA* gene variant 59% of the patients are having the variants genotype out of which 36.36% with heterozygous genotype and 22.72% with homozygous variant alleles and *BTNL2* gene rs2076530 (T>C) stand as the second most prominent with 40.90% heterozygous variant genotypes in the population with respect to the rs1041981 (C>A). For *ANXA11* and *NOD2* the samples cohort exhibited the wild-type allele genotype in twenty two patients.

Conclusion:
In conclusion, this study has successfully introduced four innovative tetra-primer ARMS PCR assays designed for the allele-specific detection of missense variants associated with sarcoidosis as well uncovered the most prominent sarcoidosis variant in Sri Lanka maidenly. The study identifies *LTA* and *BTNL2* as the pre-eminent genetic variant for sarcoidosis.

Disclosures:
No conflict of interest

Keywords:
Sarcoidosis, Tetra primer ARMS PCR**,** variants, genetics, granulomas

16 TAS-PGx: Targeted Adaptive Sampling-Long Read Sequencing for Enhanced Pharmacogenomics Profiling and Genome-Wide Variant Analysis

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Background & Objectives:
Genetic variants affecting drug therapy are widespread, impacting over 90% of the population and potentially leading to adverse drug reactions (ADRs). Pre-emptive pharmacogenomics (PGx) testing has demonstrated a 30% reduction in ADRs, resulting in decreased healthcare costs and improved patient outcomes. However, routine genotyping methods such as short-read sequencing and microarray genotyping face challenges in haplotype phasing and adequately resolving complex events. Long-read sequencing holds promise in improving the resolution of fully phased diplotypes, leading to more accurate phenotype prediction. In particular, adaptive sampling from Oxford Nanopore Technologies (ONT) emerges as a flexible and cost-competitive solution, since it offers in-silico driven enrichment of selected regions while generating a low-coverage signal across the entire genome.

Method(s) and Results:
Here, we assess long-read sequencing for PGx testing based on adaptive sampling. Multiple experiments were conducted using reference materials from various sources (GIAB, GeT-RM and 1KGP), as well as clinical samples previously challenging to characterize with genotyping. Our findings demonstrate that our workflow can accurately identify the expected diplotypes for Tier 1 pharmacogenes from PharmVar and elucidate complex haplotypes, including CYP2D6 hybrids. Additionally, we show off-target reads can be used to impute common SNVs genome-wide with high accuracy.

Conclusions:
Our TAS-LRS workflow effectively resolves diplotypes in actionable pharmacogenes, including complex structural and hybrid rearrangements, which were previously uncharacterized with other platforms. Moreover, it enables research applications by efficiently detecting genome-wide variants and methylation signals. By leveraging multiplexing, it offers great opportunities for accurate PGx testing at a lower cost.

Conflict of interest disclosure:
Pamela Gan Hui Peng, Audrey Ng Qi Hui, Muhammad Irfan Bin Hajis, Yusuf Maulana, Yeo Han Lin, Astrid Irwanto, Levana Sani and Mar Gonzalez-Porta are employees of Nalagenetics.

Keywords:
pharmacogenomics, long-read sequencing, adaptive sampling, imputation, CYP2D6

17 Bridging Data and Clinical Decision-making: Case Study Analysis of Hepatocellular Carcinoma with Enhanced Microbiome Insights

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Abstract:
Our analysis of a clinical study on hepatocellular carcinoma employed leading analytical techniques such as machine learning and network analysis to address the challenge of interpreting large-scale high-throughput microbiome sequencing data for precision medicine applications. We identified individual microbial signatures indicative of hepatocellular carcinoma states and treatment responses, offering opportunities for personalized pathology studies and treatment. By integrating multi-dimensional data, including phenotypic and biochemical data, we enhanced predictive models for individual health and treatment outcome with unprecedented performance Ultimately, the AI-driven insights have been translated to provide guidance for better clinical decision-making within clinical trials, seamlessly integrated with existing workflows. We also discuss the use of these insights for patient monitoring and clinical asset development, while addressing the challenges in clinical adoption, emphasizing collaborative efforts to translate AI-driven insights on microbiome-host connection into personalized healthcare interventions.

Our emphasis lies in translating the elaborate microbiome data to meaningful and actionable insights that enable better patient impact. The human microbiome has become a pivotal component in precision medicine, reshaping healthcare by tailoring therapies to suit individual patients according to their distinct genetic, environmental, and lifestyle characteristics. This intricate ecosystem, known as the human microbiome, profoundly influences health and illness, intricately influencing diverse physiological functions and responses to treatment.

18 A learning and training agenda with a global focus: Delivering large-scale knowledge and skills development in real-time

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Background and Objectives:
The Wellcome Connecting Science (WCS) Learning and Training programme focusses on developing and delivering knowledge and skills-based tools, resources, and events, enabling global research and healthcare professional communities to apply genomics-based techniques, skills and understanding in their everyday practice.

Methods and Results:
Over the past five years the WCS programme has delivered 86 knowledge sharing-based conferences, 108 hands-on training courses, and published 17 massive open online courses with a collective 59 runs. Over this time the programme has reached over 200,000 people from more than 130 countries. All learning content is genomics-focussed but covers the breadth of this field from human biology to infectious diseases and the environment; and their intersections. Often based around collaboration with Wellcome Sanger Institute research programmes, the WCS learning outputs draw on genuinely cutting-edge genomic science, rapidly translating this knowledge into learning and training formats. The programme develops bespoke approaches, with each activity or event designed with an end-user in mind, to support the acceleration of genomics-based research and its application.

Conclusions:
Long-term evaluation data demonstrates the effectiveness of this approach; producing wide-reaching impacts, as well as addressing immediate training needs. In addition, partnership working with regional stakeholders in Africa, Asia, and Latin America has enabled effective capacity building, often complementing investment in research facilities and equipment, with the development of people based around the creation of communities of practice. The collective work of the WCS programme has therefore proven to deliver sustainable, longer-term impacts, which last beyond a single training event.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Key words:
education, training, global, communities of practice, impact evaluation

19 Whole-genome sequencing of half-a-million China Kadoorie Biobank participants

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Background & Objectives:
Whole-genome sequencing (WGS) is a powerful tool for obtaining a comprehensive view of the genome. However, the genomes available from large biobanks have predominantly been biased towards Western populations. Addressing this gap, our study aims to sequence the entire genomes of half a million participants from the China Kadoorie Biobank, building upon previous genotyping efforts (with a sample size of 100,000) and whole-genome sequencing projects (with a sample size of 10,000). This endeavor seeks to elucidate genetic variation within the Asian population on an unprecedented scale.

Methods and Results:
To achieve our objectives within a six-month timeframe, we developed a fully automated system for DNA extraction, sequencing, and data analysis. This comprehensive approach allowed us to decode genetic variations in the Asian population at an unprecedented scale in terms of both sample size and genome-wide resolution. Our evaluation of efficiency and accuracy, through comparisons with the Genome in a Bottle (GIAB) consortium and the Zhonghua Trio reference samples, confirmed the stability and precision of our sample-to-data solution. By integrating the sequenced genomes with China Kadoorie Biobank database, we were able to match half a million genomes with extensive phenotype and disease information.

Conclusions:
Our study represents a significant advancement in the field of genomics by providing a detailed genetic variation landscape of the Asian population, which has been underrepresented in global genomic databases. The successful implementation of a fully automated sequencing and analysis system demonstrates a scalable model for future large-scale genomic studies. By enhancing our understanding of the human genome and facilitating the discovery of novel diagnostics and therapeutics, this study holds the potential to improve precision medicine strategies significantly.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Whole-genome sequencing (WGS), Genetic variation, China Kadoorie Biobank, Automation system, Precision medicine

20 Addressing the 'Leaky Pipe' in Colorectal Cancer Genetics Referrals: The Critical Need for Optimization

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Background/Objectives:
Colorectal cancer significantly burdens Singapore, with over 1,865 cases diagnosed annually. Lynch syndrome, the most common hereditary colorectal cancer, affects 1 in 300 Singaporeans. Despite high prevalence, referrals to Cancer Genetics Service (CGS) remain low, highlighting a gap in Lynch syndrome detection. This study delves into referral discrepancies and barriers to timely hereditary cancer syndrome diagnosis among colorectal cancer patients in Singapore.

Methods:
We evaluated patients seen at the National Cancer Centre Singapore from 2017 to 2021, identifying 1,716 colorectal cancer cases diagnosed under age 50 or with a second Lynch syndrome-related cancer. Appropriate CGS referrals were determined based on age at cancer diagnosis, deficient mismatch repair protein expression, polyp pathology (adenomatous, hamartomatous, juvenile polyps), and presence of desmoid tumours.

Results:
We found that only 15% of the 878 colorectal cancer patients under the age of 50 were referred to CGS, while the referral rate for patients with a second Lynch syndrome-associated cancer was even lower at 9.8%. While most non-referred cases had MMR evaluation, 20% were not referred in spite of tumour pathology, indicating missed opportunities for hereditary cancer risk detection.

Conclusion:
This gap in referrals underscores the urgent need for increased awareness and improved referral practices among medical professionals. Prioritizing early detection through timely referrals is essential not only for initiating preventive strategies and enhancing patient outcomes but also for identifying at-risk relatives and substantially reducing the community's cancer burden. Proactively addressing these gaps is crucial, ensuring effective management of hereditary colorectal cancer syndromes in Singapore towards a more preventive healthcare model.

Conflict of interest disclosure:
Nothing to disclose

Keywords:
Hereditary colorectal cancer, lynch syndrome, polyposis, genetic testing, mismatch repair

21 A modular approach to compiling data sharing agreements to promote more equitable terms for data sharing.

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Background & Objectives:
Historical inequities resulting in the unidirectional flow of data and biospecimens from Africa have created reluctance by African researchers to openly share these resources. Secondary use of African data and biospecimens is urgently required to build an evidence base to address regional and global challenges, but must be equitable and respect the autonomy and agency of African stakeholders who created those resources. We present a data sharing agreement builder as a resource to equip African researchers, and the global research community, with resources they need to effectively set the terms for the onward use of the data and biospecimens they generate.

Method and Results:
Using a modular approach we have created an online, downloadable template which can be used to compile agreements for direct sharing, collaboration, federated analysis, trusted research environments and commercial use of data and/or biospecimens. This approach gives researchers the flexibility to create agreements that are fit-for-purpose by including only those clauses that are applicable to their sharing context. To address issues of equity, we included clauses addressing intellectual property and ownership of both the shared resources and new resources that will be generated, authorship in research outputs, acknowledgement statements, benefit sharing agreements and cost recovery models, to allow African researchers and participants to be equitably compensated for contributing data and biospecimens.

Conclusions:
The data sharing agreement builder can increase opportunities for African, and global researchers to share data and biospecimens by facilitating new opportunities for collaborations and benefit sharing through equitable agreements.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Data sharing, equitable collaborations, benefit sharing, equitable agreements, African data

22 Next Gen Sequencing-based proteomics and their utility in large population health cohorts

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Background & Objectives:
Understanding the dynamics of the human proteome is crucial for identifying biomarkers to be used as measurable indicators for disease severity and progression, patient stratification, and drug development. It can also help us translate the impact our genetics has on more real-time health.

Methods & Results:
The Proximity Extension Assay (PEA) translates protein information into actionable insights across large samples sizes in both healthy and disease samples. Here we have combined the PEA technology with automated sample preparation and a high-throughput sequencing readout for parallel measurement of over 5,400 proteins for up to 344 samples in a next generation sequencing run. Coverage includes low abundant proteins (e.g., cytokines), tissue leakage proteins (e.g., troponins), and overlap with high abundant proteins well served by mass spectrometry (e.g., globins). Characterizing the proteome alongside genetic and clinical data enables a protein quantitative trait loci (pQTL) framework to not only validate known clinical targets and identify new clinical targets but to also suggest repurposing opportunities of clinical candidates for new indications.

Conclusions:
We will discuss goals and results of large population health studies integrating proteomics, genomics and clinical data like the UK Biobank Pharma Proteomics Project and SCALLOP Consortium. We will also share details on publicly available data resulting from such efforts as well as examples where such insights are enabling disease and application specific clinical tools.

Conflict of interest disclosure:
CL, RB, LW, NN, JB, EA, SH, IA, CW, EW, AF, ML are employees of Olink, AM is an employee of Pfizer.

Keywords:
population health, multiomics, proteomics, precision health, genetics

23 Decoding the molecular ageing spectrum of Asians and its clinical prospects in the SG10K Health Study

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Abstract:
Singapore's population, like many others in Asia and the world, is rapidly aging. In this SG10K_Health study, we investigate the landscape of aging in 10,258 Singaporeans of Chinese, Malay, and Indian ethnicities, aged between birth and 85 years, across clinical phenotypes, genomics, epigenetics, and telomere length. We observe epigenetic age acceleration (EAA), determined through established DNA methylation clocks, is slower in Chinese adults, and in both female adults and neonates. EAA was also significantly associated in adults with various clinical phenotypes including heightened BMI, elevated triglyceride levels, and Type 2 Diabetes. EAA significantly associated with six genetic loci, including novel SNPs in the ZYG11A and WNT3A genes. Both were cis-meQTLs for CpGs significantly associated with chronological age. Epigenome-wide association studies of chronological age also identified 36,878 age-associated CpGs, 10.7% of which were also significantly associated with sex. This study addresses critical knowledge gaps in understanding Asian molecular phenotypes and laying the groundwork for future precision healthspan research.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Aging, Epigenetic Clock, EWAS, GWAS, Asian ethnicity

24 Spatial transcriptomic analysis of triple-negative breast cancer occurring during pregnancy and post-involution.

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Background:
In the *long term*, at least for women of European-ancestry, pregnancy before the age of 35 is thought to *decrease* breast cancer risk. However, in the *short term*, pregnancy paradoxically *increases* breast cancer risk - but much remains unknown, particularly for women of African-ancestry. Following the cessation of breast feeding (involution), women are at risk for highly aggressive breast cancers that carry a >2-3-fold increased risk of death. Risk for these highly aggressive breast cancers is 1) associated with immunosuppression and 2) is thought to persists - depending on the study - 1, 3, or even up to 10 years. The microenvironment cell state changes that drive this post-involution breast cancer risk are poorly understood, particularly in women of African-ancestry. In women of African-ancestry (unlike Europeans) it is not clear that risk ever normalizes.

Results:
Here we performed spatial transcriptomics using GeoMx-Digital Spatial Profiler (DSP) of 33 pre- and post-involution) Triple-Negative Breast Cancers (TNBC) from women of African- and European-ancestry. To be classified as post-involution, women were required to be less than 3 years from delivery and not breast feeding. In biopsy tissue that ranged from morphologically normal to invasive TNBC, we analyzed 1,0279 features and 773 AOIs - 282 AOIs were PanCK+ and 390 were PanCK-. Morphology and production of transcripts associated with lactation provided an agnostic means to validate whether women were lactating or post-involution.

Conclusions:
Our initial analysis of the pre- vs. post-involution microenvironment identified, in the atypical mammary epithelial cells adjacent to post-involution TNBC, upregulation of the beta-catenin signaling pathway, including CTNNB1, RUNX1, SMAD4, CCND1, TLE2. These findings open the potential for prevention of highly aggressive post-involution TNBC using natural products and non-toxic repurposed drugs that target beta-catenin signaling.

26 Broad-scale proteomics combined with genomics help identify early detection and causal biomarkers in cancer

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Background & Objectives:
The blood proteome reflects homeostatic and dynamic cellular processes across human organs. Understanding the dynamics of the human proteome has potential to be used as measurable and non-invasive indicators for not only early cancer detection and characterizing causal potential therapeutic targets for drug development. However, few blood proteomics studies of sufficient depth and size have reported causal vs consequential biomarkers relevant to diseases like breast cancer.

Methods & Results:
To comprehensively identify circulating proteins with a causal role in breast cancer we measured 2,929 unique proteins in plasma Karolinska Mammography Project to explore associations among protein levels, clinical characteristics, and gene variants. The analysis revealed 812 cis-acting protein quantitative trait loci (pQTL), which were used as instruments in Mendelian Randomization (MR) analysis of breast cancer. We identified a subset of 5 proteins ($P < 1.7x10-5$, Bonferroni-corrected) with a potential causal role in breast cancer risk and confirmed the MR findings in independent cohorts (FinnGen R9 and the UK Biobank).
Conclusions: We will put these findings in context of recent findings around identification of causal biomarkers as well as those showing utility in early detection of multiple cancers.

Conflict of interest disclosure:
CL, RB, SF, PE, MU, and MJ are employees of Olink. AM and AH are employees of Pfizer.

Keywords:
proteomics, biomarkers, cancers, therapeutic targets, early detection

27 Genomic Insights into COVID-19 Susceptibility and Severity Among Singaporeans: A Multi-National Platform Initiative

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Abstract:
The COVID pandemic has starkly exposed the profound gaps in our understanding of human variation in response to pathogens, from asymptomatic infections to severe illnesses and deaths. Hence, our study focuses on investigating host genetics to identify the biological mechanisms behind diverse COVID-19 outcomes, aiming for improved disease surveillance and personalized treatments. We targeted three objectives: surveying published genetic variants (predominantly western populations) linked with disease severity in Singapore's major ethnic groups (Chinese, Malay, and Indian); discovering novel genetic factors through genome-wide association studies (GWAS); and developing genetic risk scores (PRS) for predicting disease severity and susceptibility.

Leveraging the joint collaboration between PREPARE, SG10K_Health, and MOH-TRUST national platforms, we merged national COVID-19 case data with genomic information. A survey of 738 published covid severity risk variants, revealed significant ethnic disparities with Indians displaying the highest risk, followed by Malays and Chinese. Singapore-specific GWAS, identified new SNPs, at a suggestive threshold, indicative of COVID-19 severity and susceptibility. Additionally, the application of a multi-ethnic polygenic risk score (PRS) indicated higher risk of moderate and severe COVID among individuals in the top PRS quantile. There was also an ethnic variation in the PRS observed.

These Phase I findings show potential for stratifying causal variants for Covid susceptibility and severity. Moving forward, the expansion of our analysis to the larger SG100K cohort in Phase II can help solidify these insights, offering a stronger foundation for targeted public health surveillance and therapeutic development.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
infectious disease, COVID-19, GWAS, PRS, genetic risk

28 Is Genetic Testing Cost-effective to Detect and Manage Lynch Syndrome in Singapore?

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Background & Objectives:
Lynch Syndrome (LS) affects approximately 1 in 533 Singaporeans and contributes to about 3-5% of colorectal (CRC) and endometrial cancer (EC) cases. As a part of National Precision Medicine Clinical Implementation Pilots in Hereditary Cancers, the study aims to investigate whether genetic testing is cost-effective in newly diagnosed CRC and EC patients to detect and manage LS and evaluate the impact of subsidy on genetic testing uptake in Singapore.

Methods and Results:
A cost-utility analysis will be performed from both Singapore's healthcare system and societal perspective. Universal germline mutation testing of incident CRC and EC patients will be compared to universal tumour-based testing strategies (standard of care) and no testing. A decision tree will be utilized to detect the number of LS cases identified combined with a Markov model to estimate the cost-effectiveness of cancer surveillance and prophylactic surgery over the lifetime of the index case and their at-risk relatives (cascade testing). Model parameters will be derived from the MOH TRUST platform, the Cancer Genetic Service database, the Singapore Cancer Registry Annual Report, the Agency for Care Effectiveness healthcare resource sheet, ongoing local longitudinal study, and systematic reviews of published literature. The primary outcome is the incremental cost per quality-adjusted life-year (QALY) gained with a 3.5% annual discount. Parameter uncertainty will be explored using one-way and probabilistic sensitivity analyses.

Conclusions:
The study will provide insights into the clinical utility of genetic testing in assessing cancer risk in LS carriers, with implications for policy and decision-making regarding subsidy implementation.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial, and personal.

Keywords:
Lynch Syndrome, Genetic testing, Precision medicine, Cost-utility analysis, Cascade testing.

29 Dietary risk factors for visceral adiposity in multiethnic Asian population: An epidemiological and metabolomics study

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Background & Objectives:
Visceral adiposity is a risk factor for cardiometabolic and cardiovascular diseases. Compared to Europeans, visceral adiposity is elevated in Asians, particularly in Malay and Indian subgroups (representing ~1.65billion people). We aimed to i) identify dietary drivers of visceral adiposity in multiethnic Asian population and ii) discover population-specific disease mechanisms by dissecting key dietary-driven metabolites underlying excess visceral fat.

Methods and results:
We used dietary intake and visceral adiposity datasets of 8271 multiethnic Asians (Chinese: Malay: Indian= 69:12:19, 30-84 years old), quantified using a locally validated Food Frequency Questionnaire and Dual X-Ray Absorptiometry, respectively. We derived 69 dietary indices including macronutrients, food group, healthy eating indices (e.g., alternative Healthy Eating Index [aHEI]), and dietary patterns using hierarchical clustering. We shortlisted key dietary indices with univariate and LASSO regressions with Bonferroni-Hochberg correction. We used the Metabolon Global Discovery Panel Platform to generate 1073 unique fasted plasma metabolites and shortlisted those associated with both key dietary drivers and visceral fat. To establish causality, Mendelian Randomisations was conducted on shortlisted metabolites as exposure and visceral fat as outcome variables.

Ten of 69 (14.5%) dietary indices independently predicted visceral fat mass including healthy (fruits, β [SE]; p=-0.09[0.009]; 3.5x10-23) and unhealthy (flavoured rice, 0.04[0.009]; 9.9x10-6) indices, independent of demographics, lean mass, and physical activity levels. 419 of 1073 metabolites (39%) were associated with both key dietary indices and visceral fat. S-Methylcysteine sulfoxide was the strongest metabolite predicted by the dietary indices (aHEI score, 0.27[0.012]; 3.1x10-118) and was associated with reduced visceral fat (0.16[0.009];7.5x10-63). In contrast, 8 metabolites of xanthine metabolism including caffeine were associated with lower aHEI (>-0.21[0.011]; >2.9x10-67) and increased visceral fat (>0.05[0.010]; <6.7x10-65). The MR analysis for 419 metabolites is currently underway.

Conclusions:
Our findings demonstrate dietary risk factors for visceral adiposity in multiethnic Asian population.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial, and personal.

Keywords:
Obesity, visceral fat, epidemiology, precision nutrition, metabolomics

30 Multi-locus Inherited Neoplasia Alleles Syndromes in Cancer: An updated review and implications for clinical practice

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Background/Objectives:
With the support of Precision Health Research Singapore (PRECISE), the Cancer Genetics Service was able to offer multi-gene testing to more individuals, which identified carriers of two or more pathogenic variants (PV). They are at risk of suboptimal treatment, management and inaccurate cancer risk estimations as little on this topic is known. We trace double PV carriers within cancer predisposition genes, also known as multi-locus inherited neoplasia alleles syndromes (MINAS), to understand their association with more severe phenotypes.

Methods:
We conducted a systematic review of published MINAS cases. Statistical tests were performed to assess the association between patient characteristics and the number pathogenic variants identified. Variables examined were: first age of diagnosis, early onset of cancer defined as <5% age-stratified risk, number and type of primary cancers, and presence of phenotypes not associated with PV they have.

Results:
We analysed 394 cases, inclusive of 32 new patients from our local service. There was a greater proportion of MINAS presenting with more malignancies (32.0% vs 21.5% vs 10.3%; p <0.001), a younger median age of first diagnosis (40.5 vs. 44.0 vs. 49.0 years; p <0.001) and an early onset of cancer (24.9% vs 7.7% vs 4.7%; p<0.001) vs. monoallelic and non-carriers. Within MINAS, dominant-dominant combinations were more frequently observed with multiple malignancies (34.4% vs. 23.9% vs. 20.0%; p=0.042) and cancers outside of their PV-associated spectrum (87.5% vs. 82.1% vs. 40.0%; p=0.012) vs. dominant-recessive and recessive-recessive carriers.

Conclusion:
Findings suggest that MINAS presents with more malignancies, younger ages of diagnosis and early onset cancers. We suggest heightened awareness of early onset cancers, and a consideration that MINAS may develop malignancies outside of their PV-associated cancer spectrum.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
double germline carriers, double mutation, double het

32 Genetic counselling and testing for kidney disease by nephrologists – a single-center implementation study

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Introduction:
Adults suspected to have genetic kidney diseases were previously referred to another hospital as there was no accredited genetic service in our hospital. We aimed to evaluate the implementation of a genetic kidney disease service where nephrologists perform genetic counselling and testing.

Methods:
Single-center clinical implementation study with post design conducted between March 2023 and January 2024 at the Department of Renal Medicine, Singapore General Hospital. We identified barriers, facilitators, and implementation strategies[1,2,3] (Table 1) and evaluated clinical and implementation outcomes[1, 2]: adoption (number of referrals for genetic testing and number of nephrologists who referred patients), implementation fidelity (number and proportion of patients who completed the genetic counselling and testing), efficacy (proportion of genetic kidney disease diagnosed by genetic tests), and maintenance (self-administered, anonymized NoMAD survey among the nephrologists[4]).

Results:
145 probands with suspected genetic kidney disease were referred by 18 nephrologists and trainees (33.9%). 99 (68.3%) underwent genetic counselling and 61 (42.1%) consented to genetic testing. Among 52 with genetic test results, 5 (9.6%) had pathogenic variants and 14 (26.9%) had variants of uncertain significance of high pathogenic suspicion. 22 nephrologists and trainees (41.5%) completed the NoMAD survey. Among 16 (72.7%) respondents aware of the service, the majority recognized its value in patient care though they still found the service unfamiliar (Table 2).

Conclusion

The genetic kidney disease service facilitated genetic diagnoses among Renal Medicine patients. Lack of awareness of the service, its integration with current work practices and effects are potential barriers that need to be addressed.

Table 1. Barriers and facilitators according to the Practical, Robust Implementation and Sustainability Model (PRISM) domains with corresponding implementation strategies according to the Expert Recommendations for Implementing Change (ERIC) taxonomy

PRISM domains		Barriers and Facilitators		Implementation strategies
Intervention	Organization perspective	No existing genetic service in the department		*Stakeholder inter-relationships* (1) Identified and prepared champions to form the implementation team *Support clinicians* (1) Created new clinical teams for genetic service
		No existing clinic where genetic service could be conducted		*Infrastructure* (1) Changed physical structure and arranged clinic room for genetic kidney disease clinic
		Implementation team lacked knowledge on performing genetic counselling and testing		*Evaluative and iterative strategies* (1) Geneticists audited and provided feedback to implementation team *Stakeholder inter-relationships* (1) Developed academic partnerships – research project with geneticists (2) Captured and shared local knowledge (3) Organized clinician implementation team meetings *Train and educate stakeholders* (1) Geneticists conducted educational meetings for implementation team (2) Geneticists conducted ongoing training *Interactive assistance* (1) Geneticists provided clinical supervision to implementation team
	Recipient perspective	Nephrologists lack awareness about genetic counselling and testing		*Train and educate stakeholders* (1) Implementation team conducted educational meetings to nephrologists regarding referral criteria (2) Developed educational materials (3) Distributed educational materials
		Patients lack awareness about genetic counselling and testing		*Engage patients* (1) Increased demand via advertisement
Implementation and Sustainability Infrastructure		Costly genetic test		*Financial strategies* (1) Accessed new funding – genetic counselling and testing funded by research grant hence free of charge to patients

Table 2. The Normalization of Complex Interventions – Measure Development (NoMAD) survey responses

Question	Response		
When you use the program, how familiar does it feel?	2 (0, 6)[a]		
Do you feel the program is currently a normal part of your work?	4 (2, 6)[a]		
Do you feel the program will become a normal part of your work?	7 (4, 9)[a]		
	Strongly disagree or disagree	Neither agree or disagree	Strongly agree or agree
I can see how the program differs from usual ways of working (CI)	6.2%	6.2%	87.6%
Staff involved have a shared understanding of the purpose of the program (CI)	6.2%	6.2%	87.6%
I understand how the program affects the nature of my own work (CI)	0%	12.4%	87.6%
I can see the potential value of the program for my work (CI)	0%	0%	100.0%
There are key people who drive the program forward and get others involved (CP)	0%	6.2%	93.8%
I believe that participating in the program is a legitimate part of my role (CP)	0%	6.2%	93.8%
I'm open to working with colleagues in new ways to use the program (CP)	0%	0%	100.0%
I will continue to support the program (CP)	0%	6.2%	93.8%
I can easily integrate the program into my existing work (CA)	6.2%	31.3%	62.5%
The program disrupts working relationships (CA)	62.5%	25.0%	12.5%
I have confidence in other people's ability to use the program (CA)	6.2%	12.5%	81.3%
Work is assigned to those with skills appropriate to the program (CA)	0%	0%	100.0%
Sufficient training is provided to enable staff to implement the program (CA)	0%	37.5%	62.5%
Sufficient resources are available to support the program (CA)	18.7%	37.5%	43.8%
Management adequately supports the program (CA)	0%	6.2%	93.8%
I am aware of reports about the effects of the program (RM)	12.5%	31.3%	56.3%
The staff agree that the program is worthwhile (RM)	6.2%	12.5%	81.3%
I value the effects that the program has had on my work (RM)	0%	6.2%	93.8%
Feedback about the program can be used to improve it in the future (RM)	0%	0%	100.0%
I can modify how I work with the program (RM)	0%	6.2%	93.8%

[a]Scored from 0 "not at all" to 10 "completely"and reported as median (25th centile, 75th centile).
Abbreviations: CI, coherence insights (staff's comprehension of the purpose and perceived value within their practice), CP, cognitive participation (engagement and motivation levels among healthcare staff to adopt the tool); CA, collective action (integration into daily workflows and influence on existing practice assessed by questions); RM, reflexive monitoring (perceived impact on patient care and contribution to enhance existing practice)

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33 Strategies to improve implementation of cascade testing in hereditary cancer syndromes: A systematic review

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Background & Objectives:
Hereditary cancer syndromes constitute approximately 10% of all cancers. Cascade testing involves testing of at-risk relatives to determine if they carry the familial pathogenic variant. Despite growing efforts targeted at improving cascade testing uptake, current literature continues to reflect poor rates of uptake, typically below 30%. This study aims to systematically review current literature on intervention strategies to improve cascade testing, assess the quality of intervention descriptions and evaluate the implementation outcomes of listed interventions. Method(s) and Results: We searched major databases using keywords and subject heading of "cascade testing". Interventions proposed in each study were classified according to the Effective Practice and Organisation of Care (EPOC) taxonomy. Quality of intervention description was assessed using the TIDieR checklist, and evaluation of implementation outcomes was performed using Proctor's Implementation Outcomes Framework. Improvements in rates of genetic testing uptake was seen in interventions across the different EPOC taxonomy strategies. The average TIDieR score was 7.3 out of 12. Items least reported include modifications (18.5%), plans to assess fidelity/adherence (7.4%) and actual assessment of fidelity/adherence (7.4%). An average of 2.9 out of 8 aspects of implementation outcomes were examined. The most poorly reported outcomes were cost, fidelity and sustainability, with only 3.7% of studies reporting them. Conclusions: Most interventions have demonstrated success in improving cascade testing uptake. Uptake of cascade testing was highest with delivery arrangement (68%). However, the quality of description of interventions and assessment of implementation outcomes are often suboptimal, hindering their replication and implementation downstream. Therefore, further adoption of standardized guidelines in reporting of interventions and formal assessment of implementation outcomes may help promote translation of these interventions into routine practice.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
germline testing, cancer genetics, predictive testing, implementation science

34 Nephrologists' perspectives on facilitators and barriers of clinical implementation of genetic testing in Singapore

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Background & Objectives:
Lack of genetic literacy and expertise in genetic counselling among nephrologists is a major barrier to implement genetic testing in clinical nephrology practice in Singapore. As part of the efforts by the Renal Alliance for PrecIsion Diagnosis(RAPIDS) in Singapore, we provided structured genetic training for the nephrologists in order to allow for more widespread clinical implementation of genetic testing. Here, we aim to survey the nephrologists to understand the facilitators and barriers in implementing genetic testing within nephrology practice.

Method(s):
A survey was self-administered among nephrologists scheduled to undergo genetics training as part of the RAPIDS initiative.

Results:
Twenty-two nephrologists (12 from adult services;10 from paediatrics services) from 4 restructured hospitals in Singapore completed the survey. Three nephrologists had received formal genetic training outside of undergraduate studies. Nephrologists learn genetics mainly from self-directed study (literature/books/internet) (12/22,54%), discussing with knowledgeable colleagues (9/22,41%) and participating in genomics-related research projects (8/22,36%). For restructured hospitals with only adult nephrology services, the nephrologists (8/12,67%) found it hard to access genetics services. The barriers toward implementing genetic testing in clinical practices include costs to patients (16/22,73%), lack of expertise in interpreting genetic reports (14/22,64%) and lack of training in genetic counselling (13/22,59%). Thirty-six percent(8/22) of them felt uncomfortable dealing with genetic issues of their patients prior to this study.

Conclusions:
In conclusion, the lack of formal genetic training among the nephrologists is one of the key barriers for clinically implementing genetic testing. A structured genetics training program could resolve most of these gaps.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Nephrologists, genetic testing, barriers, clinical implementation

35 Understanding Women's Preferences for Undergoing Breast Cancer Risk Assessment: Insights from a Discrete Choice Experiment

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Background & Objectives:
Risk-based breast cancer screening offers a potentially more effective and cost-effective approach compared to age-based screening. Besides age, factors such as breast density, family history and genetic tests for calculating polygenic risk scores influence one's risk. This study aims to understand women's preferences and willingness to undergo such tests.

Methods:
A discrete choice experiment (DCE) was conducted. Through literature review and discussion with domain experts, six attributes were selected to construct the DCE questionnaire: one-time cost of the test, annual breast cancer screening expenses, methods for reducing late-stage breast cancer, insurance coverage for early-stage breast cancer, family risk correlation, and risk communication methods. Women aged between 21 and 59 were recruited from Singapore. Demographic information were collected. Latent class analysis was performed.

Results:
After excluding 67 invalid responses, 328 women were included in the final analysis and classified into two classes: test supporters and non-supporters. Class shares of test supporters and non-supporters were 65% and 35% respectively. Both classes prioritised test and screening costs. Insurance coverage increased willingness to undergo testing. Risk communication methods were not found to be significant. Interestingly, non-supporters were less inclined if family risk correlation was high. Age, family history, concern about breast cancer, education level, and employment status influenced support for testing.

Conclusion:
Our study identified key factors affecting women's willingness to undergo breast cancer risk assessment, offering insights for shaping policies in risk-based screening.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Breast cancer, risk stratification, risk-based screening, preference, discrete choice experiment

36 Beyond Lipid Profile: Enhancing Electronic Phenotyping with Unstructured Data

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Background & Objectives:
Familial Hypercholesterolemia (FH) is a prevalent yet often undiagnosed hereditary cardiovascular disease. Addressing the critical need for improved FH identification, our study introduces the ELPHA-FH framework that harnesses structured and unstructured data in electronic health records (EHR) to identify possible/probable/definite FH cases for further genetic testing.

Method(s) and Results:
EHR data from 2015 to 2018 of patients aged 18 years and older who had valid low-density lipoprotein cholesterol (LDL-C) tests (N=23,659) were extracted, stored and analyzed on the Discovery AI platform developed at the National University Health System. Applying the Mayo Clinic algorithm, 1,238 patients with primary hypercholesterolemia (LDL-C >4.9mmol/L) were identified initially, with an additional 426 (34%) patients (total = 1,664) identified when cholesterol-lowering treatment history was considered. When unstructured data on personal history, family history and physical examination based on the Dutch Lipid Clinic Network criteria were included, we reduced the number of patients who would have been sent for genetic testing from 1,664 possible FH cases to 171 patients probable/definite FH cases. Of these 171 patients, 130 definite FH cases would have been misclassified as possible–were it not for additional information on personal and family history.

Conclusions (Significance and Impact of the Study):
The ELPHA-FH framework allows scalable, automated and non-intrusive identification of possible/probable/ definite FH cases to be referred for further genetic testing and picks up definite clinical FH cases that would have been missed due to lack of information.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial, or personal.

Keywords:
text mining; electronic medical records; familial hypercholesterolemia; genetic testing; electronic phenotyping

37 Adherence to risk management guidelines in individuals with hereditary cancer conditions in Singapore

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Background:
Genetic predispositions account for up to 10% of all cancers. Cancer risk management guidelines for inherited cancer conditions describe modalities to prevent cancer and detect cancer early. Assessing adherence to guidelines is essential for service improvement and economic benefits to the patients and healthcare system. We aim to report adherence in such individuals seen in the Cancer Genetics Service in Singapore.

Methods and results:
Medical charts of individuals with genetic predispositions identified between January 2014 to August 2023 were reviewed. Information on cancer screening, preventative surgeries and cancer detected post-genetic testing was collected for 604 eligible patients. The overall adherence to cancer screening and preventative surgeries was 87.6%, comprising of 381 (63.1%) fully adherent and 148 (24.5%) partially adherent subjects. Twenty-nine individuals (4.8%) were diagnosed with tumours/cancer through risk management post-genetic testing. Adherence was higher in females (90.3%), individuals without family history of cancer (95.2%), and individuals diagnosed with cancer (88.9%). There were 244 individuals (40.4%) with hereditary breast and ovarian cancer syndrome.

Of which, 36.2% females opted for bilateral mastectomy, and 80.4% underwent bilateral salpingoophorectomy. Adherence to annual breast screening recommendations in this group was 94.8%. Lynch syndrome carriers showed similar adherence to colonoscopy and gastroscopy (76.8% and 78.1% respectively).

Conclusion:
High adherence rate to recommended risk management was reported among individuals with genetic predispositions to cancer. This demonstrates value in increasing accessibility to genetic testing, which is offer by PRECISE, to identify high-risk individuals and families to reduce cancer incidence, mortality and to improve an individual's health-related quality of life.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Cancer, inherited, hereditary, adherence, risk

39 Vasculature damage and dysmetabolism in heart failure with preserved ejection fraction.

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Background:
Pathophysiological differences between heart failure (HF) with preserved (HFpEF) and reduced ejection fraction (HFrEF) remain poorly understood. We aimed to associate metabolite-metabolite interactions with 2-year outcomes by comparing HFpEF with HFrEF.

Methods and Results:
We used a mass-spectrometry-based assay to measure 289 plasma metabolites within six months post-HF-decompensation in two matched protocol, prospective cohorts, in New Zealand and Singapore (PEOPLE and SHOP; N=1,520; mean age 65.6; 25.1% women). We simplified the plasma metabolite profiles with weighted co-expression network analysis. Two metabolite pathways relevant to vascular health were perturbed upon HF consistently in PEOPLE-HF and SHOP-HF, including arginine-nitric oxide (Arg-NO) and purine metabolites. However, they are only relevant to prognosis in pEF but not in rEF.Ascending quintiles of the Arg-NO module (adjusted-HR = 0.64 [0.49–0.84] and 0.40 [0.20–0.83] in PEOPLE and SHOP; P<0.05) paralleled reduction of mortality hazard in HFpEF. In contrast, the purine metabolism pathway (adjusted-HR = 1.71 [1.30–2.24] and 1.96 [1.08–3.55]; P<0.05) paralleled increment of mortality hazard in HFpEF. These associations were broadly recapitulated in terms of the composite outcome. Metabolites with glycaemic control and nitrosative stress relevance co-regulated with the Arg-NO metabolites in pEF. The concentration of the individual metabolites relevant to nitric oxide and nitrosative stress control also independently parallels HF outcomes in both PEOPLE-HF and SHOP-HF.

Conclusion:
Metabolites relevant to vascular tone regulation, reactive species action, and glucose metabolism were prominent in HFpEF prognostic network but not in HFrEF. These findings support the metainflammation and endothelial damage paradigm for HFpEF pathogenesis.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
heart failure, metabolome, nitric oxide, oxidative and nitrosative stress

40 Metabolic variation reflects dietary intake in a multi-ethnic Asian population

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Background & Objectives:
Biomarkers reflecting habitual diet are explored largely in European and American populations. However, the food metabolome is highly complex; its composition varies with region and culture.

Method(s) and Results:
We assessed 1,055 plasma metabolites and 169 foods/beverages in 8,391 comprehensively phenotyped multi-ethnic Asian individuals y (69% Chinese, 12% Malay, 19% South Asian).We report multiple novel observations for ethnic-relevant and common foods. Using machine-learning, we developed multi-biomarker panels (3-39 metabolites) for key foods and beverages. These panels comprised distinct and shared metabolite networks, and captured variances in intake prediction models better than single biomarkers. Diet-metabolite relationships were robust and reproducible over time. Metabolite scores, derived from biomarker panels, associated significantly and more strongly with clinical phenotypes (HOMA-IR, diabetes, BMI, fat mass index, carotid intima-media thickness and hypertension), compared to self-reported intakes.

Conclusions (Significance and Impact of the Study):
Altogether, our findings show new insights into multi-ethnic diet-related metabolic variations and new opportunity to link exposure to population health outcomes.

Conflict of interest disclosure:
Kari E Wong, Patricia A Sheridan, Rangaprasad Sarangarajan and Gregory A Michelotti are employees of Metabolon. The other authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
metabolomics, nutrition, health outcomes

41 Creating an efficient and truly federated international data market for genomic and health data

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Abstract:
The exponential growth of human genomic data, outpacing even the most prolific Big Data generators such as astronomy or YouTube, underscores its pivotal role in revolutionising drug discovery and personalised medicine. Realising the full potential of this vast resource necessitates not only extracting value from the data but also overcoming significant barriers hindering its effective utilisation.

Despite the declining costs of data generation and the emergence of new resources, challenges persist across legal, political, and economic landscapes, impeding access to multi-institutional and multi-national fragmented data. Furthermore, the laborious and time-intensive nature of data preparation and analysis, coupled with the multidisciplinary skills required for genetic data analysis and the substantial computational resources needed, present formidable obstacles. Over several years of research we developed a technology that addresses those problems. By ensuring that the data is never exposed, not even to the analyst, and leveraging the unprecedented performance of the system (e.g. an analysis on datasets >1M individuals with millions of variants within a few seconds), our solution can move the field from the current situation where an analyst struggles to reach data and then spends weeks in an iterative cycle of data preparation and analysis, to a situation where multi-organization fragmented data is accessed easily, and queried interactively and on-demand. Meanwhile, the data holder never exposes their data, thus keeping full control over it. They can trace detailed data usage from who and from where. Finally, they can revoke access at any time, being guaranteed users retain no data.

Conflict of interest disclosure:
The authors founded a spin out based on the technology they developed at the university.

Keywords:
federated data, genetics, -omics, high performance computing, health data

42 Bravo automation of Agilent Avida targeted enrichment for high-throughput detection of genomic alteration and DNA methylation

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Background:
Current genomic and epigenomic profiling of cancer tissue DNA or cfDNA (cell-free DNA) in liquid biopsy relies upon separate, time- and sample-consuming technologies for somatic variant detection or methylation analysis. Here we describe workflow and performance of the Agilent Bravo automated liquid handling platform with the Agilent Avida targeted enrichment solution for somatic variant and methylation profiling. **This solution can effectively analyze low-input tumor DNA or cfDNA samples.** The Avida Duo workflow enables highly sensitive detection of single nucleotide variant (SNV), insertions and deletion (INDEL), copy number variation (CNV) and DNA methylation profiles from a single sample, without any sample splitting.

Methods and Results:
Panels, reagents, and automated workflows for Avida DNA, Avida Methyl, and Avida Duo Methyl (combined DNA & methylation) kits were developed to accommodate up to 96 samples on the Bravo NGS workstation. The automated solution supports independent single-day workflows for somatic variants or methylation sample preparation. The Avida Duo analysis combines both workflows without sample splitting, streamlining the process and reducing sample consumption. Leveraging a focused cancer hotspot panel, we demonstrate excellent reproducibility and low allele frequency (SNV at sub 1%) variant detection in cfDNA samples and reference standards with as little as 10ng DNA input. We exhibit similar performance with a larger ~300 kb target region tumor profiling panel. Finally, we demonstrate DNA methylation detection in the standalone or combined ("Duo") workflows across differentially methylated regions (DMRs) with a panel of ~3400 targets.

Conclusions:
Automation of the Avida targeted enrichment solution with the Bravo NGS workstation enables a sensitive, high-throughput, end-to-end analysis for detecting genomic alterations and DNA methylation changes from a single low-input cfDNA or tumor DNA samples.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Agilent Avida, cfDNA, epigenetic, genomic, dual workflow

43 Obesity increases susceptibility to symptomatic flaviviral infection and alters host response to infection

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Background and Objectives:
Dengue affects approximately 100 million people annually, with some developing severe dengue. Several factors predispose individuals to severe dengue, one of which is obesity. However, how obesity alters the host response to dengue virus infection to increase the risk of severe dengue remains poorly understood. In this study, we used the live attenuated yellow fever vaccine (YF17D-204 strain and hereon referred to as YF17D) that simulates an acute flaviviral infection to test: 1) the hypothesis that obese participants would display higher rates of systemic adverse events (AEs) compared to non-obese controls; and 2) how obesity affects the host immune response to YF17D inoculation.

Methods and Results:
We enrolled, with written informed consent, 34 non-obese (BMI<25) and 35 obese (BMI≥25) participants. Participants were administered the YF17D vaccine and were assessed for their clinical and molecular outcomes. Despite comparable levels of YF17D RNAemia between the two groups, obese participants reported significantly more systemic symptoms, namely myalgia and axillary swelling (from lymphadenopathy). Significant differences in hematological parameters were also found in obese compared to non-obese individuals. Multiplex cytokine measurements identified several abnormalities in obese individuals at pre-infection baseline, along with more accentuated pro-inflammatory cytokine response to YF17D infection compared to non-obese controls.

Conclusions:
Our findings reveal obesity-driven host response to flaviviral infection as well as potential therapeutic strategy to reduce their risk of severe dengue and other flaviviral infection.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Dengue; flavivirus; obesity; infection; host immune response

44 The use of optical genome mapping in prenatal evaluation for translocation carriers

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Background and objectives:
An estimated 1/560 of individuals are carriers of balanced chromosomal translocations. Such individuals are at risk of offspring with chromosomal imbalances that may result in miscarriage or children with congenital malformations, developmental delay and other problems. Currently, chromosomal karyotype and microarray are typically performed to but this practice is limited in that it cannot evaluate if the breakpoints disrupt a critical gene with consequent effect.

We present a case report of a family where the father is a balanced translocation carrier 46,XY,t(15;18)(q25;q22) with an 7-year old child with dysmorphic intellectual disability who carries a 15q25.3 duplication and 18q22.3 deletion related to the paternal translocation. His wife was 9 weeks pregnant and they hoped to exclude abnormal offspring.

Method(s) and Results:
Prenatal whole genome sequencing and optical genome mapping quad for the father, mother, affected child and fetus was performed at a clinical laboratory. Whole blood was used for father, mother and affected child. Amniocytes obtained at 16weeks gestation was used for the fetus.

We were able to demonstrate that the unborn fetus was a balanced translocation carrier, and that the breakpoints of the translocation lay in intergenic regions that did not disrupt critical genes.

Conclusions:
We were able to definitively demonstrate that this fetus would be unaffected because of the paternal translocation which facilitated prenatal counselling.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest in relation to this work, whether scientific, financial and personal.

Keywords:
Optical Genome Mapping, Prenatal genetics, Chromosomal translocation, Genetic counselling.

Acknowledgements:
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45 Fetal Akinesia and biallelic variants in *TNNI2*

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Background and objectives:
Fetal akinesia is a condition characterized by decreased fetal movement and limb arthrogryposis. It is associated with gene dysfunction at any point in the motor system pathway. *TNNI2* encodes Troponin I, a myofibrillar protein involved in calcium-mediated regulation of muscle contraction. Monoallelic gain of function variants in *TNNI2* cause autosomal dominant distal arthrogryposis. This gene has no annotated disease related to biallelic recessive pathogenic variation. We present a case report of a family with possible *TNNI2* recessive disorder.

Case Report:
A consanguineous healthy couple had 4 children. Their first and third child were male who demised early in life. They were suspected to have fetal akinesia. Their second child had autism, with no muscle weakness. Their fourth child, a female, had an antenatal history of extended breech and polyhydramnios. The baby, born at term, had akinesia and demised at day 11 of life.

Method(s) and Results:
Exome sequencing was performed for the third child. Targeted variant testing was performed on the couple, their second child, and their fourth child.

The third child and fourth child were homozygous for *TNNI2* (NM_003282.3:c.[232_234del];[=],(p.Glu78del)). The parents and the second child were heterozygous for the same variant. The variant is an in-frame deletion affecting a highly conserved amino acid in the H1 alpha-helical domain predicted to disrupt the coiled coil interphase typically formed with Troponin T in the Ca^{2+} saturated state.

Conclusions:
We postulate that biallelic loss of function variants affecting the H1-alpha helical domain results in autosomal recessive *TNNI2*-fetal akinesia.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest in relation to this work, whether scientific, financial and personal.

Keywords:
Fetal akinesia, TNNI2, Arthrogryposis, Polyhydramnios, recessive

46 Precision Medicine for Diabetic Individuals - A Joint Malaysia-UK Effort (PRIME): Exploiting The Malaysian Cohort resource for translational research and clinical applications

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Background and objectives:
The Malaysian Cohort is the largest population-based and multi-ethnic cohort project in Malaysia with a total recruitment of nearly 120,000 individuals. We set up a sub-cohort called the PRIME focusing on those with T2D with the aim of identifying risk groups and predictors of outcomes.

Methods and results:
We recruited 5000 individuals with T2D (Malays, Chinese and Indians) who had baseline and follow-up data. We performed genotyping (using the Infinium Asian Screening Array) on all the 5000 participants, and in 556 of them we performed retinal scans and measured the high sensitivity troponin and NT-proBNP levels. The VAMPIRE software was used to analyse the retinal scans. Standard biostatistical and machine learning approaches were used to analyse the data. *Results*: Phenotypic clustering revealed distinct clinical groups. The genotype data identified CETP gene variants that were significantly associated with high-density lipoprotein (HDL) levels and their differential effects across ethnic groups. Malays had a higher incidence of chronic kidney disease while Indians had a higher incidence of coronary heart disease at follow-up. We identified 3 clusters based on the retinal scan results that showed different cardiovascular disease risk. We also discovered that fractal dimensions based on the branching patterns of the retinal vasculature correlated well with the hs-troponin and NT-proBNP.

Conclusions:
This study underscores the PRIME's pivotal role in advancing precision medicine for T2D in Malaysia, and will likely pave the way for a precision approach intervention tailored to the unique genotypic and phenotypic data of each patient.

Conflict of interest disclosure:
We declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
precision medicine, Type 2 diabetes, multi-ethnic cohort, risk groups, predictors

47 A proposed framework prioritizing pharmacogenomic drug-gene interactions in an Asian context for chemotherapy

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Background & Objectives:
Asian genomes are under-characterized. A recent large-scale whole genome sequencing initiative in Singapore SG10K, has described the pharmacogenomic polymorphisms that are enriched in our population.[1] To better understand how Asian-specific pharmacogenes (Pgx) impact health, we thus need to develop a framework for prioritizing drug-gene interactions to develop Singaporean-specific guidance for drug dosing. Chemotherapy drugs in particular, have a narrow therapeutic index and high toxicity, warranting urgent attention to look for potential PGx-drug interactions.

Method(s) and Results:
A database of chemotherapy drugs, their significant metabolic and transporter pathways, and the functional variant frequencies of these pathways were compiled.[2,3] Significant PGx-drug interaction was defined as > 10% of the population having functional variants for the gene, and the gene as a major clearance pathway for the drug. Pharmacokinetic simulations comparing wild type vs PGx variant were then carried out using Singaporean demographics, and a significant change in drug exposure (>30%) was considered to be a significant interaction.

CYP2B6, UGT1A1, CYP2D6, SLCO1B1, NUDT15, and CYP2C9 were identified genes with a high frequency of variants, and responsible for major metabolism/transport pathways in chemotherapy drugs. Chemotherapy drugs that were impacted via these pathways were tamoxifen, cyclophosphamide, doxorubicin, irinotecan, darolutamide, docetaxel, mercaptopurine and erdafitinib. A PK simulation of tamoxifen[4] showed CYP2D6 intermediate metabolizers could benefit from an increased dose of tamoxifen from 20mg to 40mg to achieve similar therapeutic levels of active metabolite endoxifen.

Conclusions:
We thus describe a systematic method of evaluating Pgx-drug interactions for prioritization, and the utility of population PK models to evaluate these interactions.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
pharmacokinetics, pharmacogenomics, precision medicine

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48 Empiric treatment with aspirin and ticagrelor is the most cost-effective strategy in patients with minor stroke or transient ischemic attack

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Background & Objectives:
Patients with minor ischemic stroke or transient ischemic attacks (TIAs) are often treated with dual antiplatelet therapy regimens as part of secondary stroke prevention. Clopidogrel, an antiplatelet used in these regimens, is metabolized into its active form by the *CYP2C19* enzyme. Patients with loss of function (LOF) mutations in *CYP2C19* are at risk for poorer secondary outcomes when prescribed clopidogrel.

Method(s) and Results:
Markov models were developed to look at the cost-effectiveness of empiric treatment with aspirin and clopidogrel versus empiric treatment with aspirin and ticagrelor, versus genotype-guided therapy for either 21 or 30 days. Effect ratios were obtained from the literature, and incidence rates and costs were obtained from the national data. The primary endpoints were the incremental cost-effectiveness ratios (ICERs). Empiric treatment with aspirin and ticagrelor was the most cost-effective treatment. Genotype-guided therapy was more cost-effective than empiric aspirin and clopidogrel if the LOF was above 48%. Empiric ticagrelor and aspirin was cost saving when compared to genotype-guided therapy. Results in models of dual antiplatelet therapy for 30 days were similar.

Conclusions:
This study suggests that in patients with minor stroke and TIA planned for dual antiplatelet regimens, empiric ticagrelor and aspirin is the most cost-effective treatment regimen. If ticagrelor is not available, genotype-guided therapy is the most cost-effective treatment regimen if the LOF prevalence in the population is more than 48%.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Genotype guided therapy, Cost effectiveness, Stroke, Antiplatelet, CYP2C19

49 Genomic landscape of drug binding and pharmacogenetic variation across diverse populations using SNPdrug3D

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Background & Objectives:
Pharmacogenetic (PGx) variants occur at least 5 times in a genome, are generally more common than monogenic variants and are clinically actionable. However, they remain understudied when compared to disease variants especially in Asian populations although they are implicated in therapeutic failure and adverse side effects. To interpret such variants, we have created SNPdrug3D – a webserver that maps and visualizes missense single nucleotide variants (SNV) in a protein-drug structural context.

Method(s) and Results:
SNPdrug3D integrates protein sequence, structure, drug, and variation data to analyze SNVs that may affect drug binding across the human proteome and at population-wide level. In total, 5.8 million SNVs in 20,442 genes from Singapore SG10K_Health and gnomAD populations were mapped to 202,299 protein structures (experimental or predicted) containing 5962 drugs. In these cohorts, comprising variations in over 80,000 individuals, we identified ~ 1.17 million variants mapped to residues within 8Å of one or more drug in at least one protein structure. Using SNPdrug3D, we identified and experimentally validated effects of selected SNVs, including previously uncharacterized and SG10K_Health-specific SNVs, on drug binding in relevant proteins ranging from kinases to cytochrome P450s (CYPs). We also demonstrate that information derived from SNPdrug3D serves as useful predictive features to build PGx-inclusive missense variant prediction tools such as CYPVarPred that outperforms existing tools in the prediction of PGx effects for CYP variants.

Conclusions (Significance and Impact of the Study):
By placing variants and drugs in a structural context, SNPdrug3D provides comprehensive interrogation of the molecular phenotype associated with missense variants of unknown significance and their relation to inter-individual variation in drug responses and diseases.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Pharmacogenetics, variant effect prediction, protein structure, missense variants

50 Cascade testing for hereditary cancer in Singapore: how population genomics help guide clinical policy

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Background & Objectives:
Hereditary Cancer makes up around 5-10% of all cancers. A timely diagnosis of hereditary cancer is important, as not only do patients require long-term care from a young age, but their relatives also require management. The main approach to capture at-risk relatives is cascade testing. It involves genetic testing of relatives of the first detected carrier of a pathogenic variant in a family i.e. the proband. Probands are then advised to inform and encourage family members to undergo genetic testing. In Singapore, cascade testing is inefficient, around 10-15%, lower than the 30% global average. PRECISE, a central entity to oversee Singapore's National Precision Medicine programme, has awarded five clinical implementation pilots, with one of them seeking to identify strategies for how cascade testing for hereditary cancer can be increased in a safe and cost-efficient manner.

Method(s) and Results:
Achieving this will be done through addressing barriers such as cost, manpower shortages, improving the way at-risk relatives of probands will be informed about genetic testing (e.g. digitalization of the cascade testing process through a genetic registry) and getting a deeper insight into why genetic testing gets declined.

Conclusions:
Addressing these barriers is a crucial step towards increasing cascade testing. If successful, it will likely result in care pathways that are a cost-effective public health intervention for identifying individuals at risk when compared to the current standard of care. Surveillance and management of those unaffected at-risk individuals, if caught early, will result in improved patient outcomes, and further reduce the healthcare burden for the economy.

Keywords:
cascade testing, hereditary cancer, Singapore's clinical implementation pilots, population genomics, clinical policy

51 Genetic model predicts lifelong cardiometabolic risks in women.

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Background and Objectives:
The development and evaluation of a polygenic model for metabolic syndrome (MetS), designed to predict cardiometabolic risks across cohorts, ages and sexes, remains a critical unmet public health need especially in the Asian population. We studied into the genetic bases of MetS among young adult women from Singapore birth cohorts, leading to the creation of a novel polygenic model, GenMetS. This model was subsequently validated with 370,246 individuals from diverse cohorts, including children from GUSTO, aged and diseased subjects from ATTRaCT, elderly individuals from UK Biobank and East Asians from Biobank Japan, to assess its effectiveness in predicting risks associated with cardiometabolic diseases.

Method and Results:
We applied a generalized linear model on SNPs from GWAS data for waist circumference, blood triglycerides, high density lipoprotein cholesterol, blood pressure and glucose, targeting the MetS scores from young adult women. The best fit resulted 4,726 SNPs. The GenMetS scores was the sum of the weighted SNPs from individual genotype in the studied cohorts. GenMetS explained 5-12% of MetS variations in Asian women and predicted cardiometabolic diseases, including type 2 diabetes, hypertension, and heart failure of aging individuals of Asian descent in the UK Biobank, ATTRaCT and Biobank Japan. Combined with age, GenMetS achieved a 70.0% accuracy in predicting cardiometabolic multimorbidity. Variability in GenMetS scores in children aged 0-6 years was associated with obesogenic growth patterns.

Conclusions:
These findings underscore an inherent genetic risk for metabolic traits across a woman's lifespan and as well as her offspring.

Keywords:
metabolic syndrome, polygenic model, cardiometabolic diseases, multi-cohorts.

Acknowledgement:
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52 Whole genome sequencing reveals a high incidence of germline pathogenic variants in genes associated with sarcoma across subtypes

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Background & Objectives:
Sarcomas are heterogeneous mesenchymal cancers originating from the bone and soft tissue. They account for 1% of adult solid tumours and a significant proportion of 21% of paediatric solid tumours [1]. Although sporadic, sarcomas have been linked to genetic risk due to their high frequency of occurrence among children [2]. However, sarcomas carry a poor prognosis due to their rarity. Furthermore, subtypes present differences in genomic alterations and driver mutations [3].

Method & Results:
To investigate the variants that predispose to sarcomas, we included 115 probands with 50% liposarcomas, 45% leiomyosarcomas, and 5% MPNST from the National Cancer Centre Singapore. The median age of diagnosis was 54 years with a balanced gender ratio. Whole genome sequencing was performed on peripheral blood DNA, and germline single nucleotide and frameshift variants were called with HaplotypeCaller [4]. Likely pathogenic (LP) missense variants were observed in 7.8% (9/115) of the probands carrying at least one variant in genes associated with the risk of developing sarcomas in *CCND2*, *DNMT3A*, *MLH1*, *MSH2*, *MSH6*, *NTRK1*, and *TP53*. LP frameshift variants were observed in 6.1% (7/115) of the probands carrying at least one variant in *ATR*, *BRCA2*, *CHEK1*, *ERCC3*, *NF1*, and *PMS1*. One variant in *ATR*, *CCND2*, *MLH1*, *NTRK1* and two variants in *TP53* were reviewed to be pathogenic. Additionally, variants in *DNMT3A*, *ERCC3*, *MLH1* and *MSH2* have allele frequencies of less than 1%, while the remaining variants were not present in SG10K.

Conclusions:
Our findings revealed the underlying need for genetic screening in patients who develop sporadic sarcomas over their lifetime.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Sarcomas, Genetic screening, Germline predisposition, Hereditary cancer, Pathogenic variants

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53 STCC Unified PD1/PD-L1 Evaluation of Response (SUPER) – a Use-Case Study of the Translational Research Integration and Support Platform

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Background & Objectives:
Immune Checkpoint Inhibitors hold a significant proportion of the cancer drug market, yet varied responses they elicit present challenges in the clinical setting. Patients who show exceptional and poor responses to this cancer treatment, provide invaluable insights into the factors determining survival outcomes. The SUPER study, a collaboration among multiple institutions, aims to develop and validate a combined assay of predictive biomarkers for PD-1/PD-L1 inhibition leveraging on Singapore Translational Cancer Consortium (STCC)'s Translational and Pre-clinical Research Pipeline.

Methods & Results:
The study sought to identify one hundred exceptional responders, case-control matched with one hundred hyperprogressors, to PD-1/PD-L1 inhibition across diverse cancer types within two prominent cancer centers in Singapore (NCCS and NCIS). Their archival histopathological specimens were extensively profiled with a suite of genomic and proteomic assays (DNA/RNA sequencing, highly-plexed immunohistochemistry, digital spatial profiling and others) to establish a comprehensive multi-dimensional molecular data repository. This invaluable resource will serve as a foundational tool for developing biomarkers and predictive models that will impact cancer management, optimize public healthcare expenditure, and improve cancer outcomes locally and globally. The process of case identification, coupled with extensive molecular profiling, will be finalized in 2024, with resources and initial analyses slated for public release in 2025.

Conclusions:
The SUPER study stands as a prime example of conducting cutting-edge, large-scale clinical research studies involving multiple public institutions in Singapore (STCC, NCIS, NCCS, SGH, NUS, GIS, IMCB, DxD Hub, and BII). STCC, a national cancer consortium, operates as an one-stop-shop platform created to meet the demand for a synergized, nationwide translational cancer research.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
cancer, molecular profiling, PD1/PD-L1 inhibitors, biomarkers, exceptional responders

54 Unlocking Skin's Defenses: Repurposing Belinostat for Atopic Dermatitis Treatment

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Background & Objectives:
Atopic dermatitis (AD) is a prevalent chronic inflammatory skin disorder characterized by compromised skin barrier integrity and heightened sensitivity to allergens. Addressing the urgent need for a systematic approach aimed at restoring barrier function, our research focuses on the identification and repurposing of therapeutic agents for the treatment of AD. Our investigation aims to identify pivotal regulators in keratinocyte differentiation and cornification, critical processes for establishing a robust skin barrier, and to repurpose Belinostat, a broad-spectrum HDAC inhibitor, as a topical cream for AD treatment.

Method(s) and Results:
We identified microRNA-335 (miR-335) as a crucial regulator of keratinocyte differentiation and cornification, mediated through direct repression of SOX6. In AD-afflicted skin, we observed reduced miR-335 expression and abnormal SOX6 expression, hindering proper skin barrier development. Further investigation revealed an epigenetic regulatory mechanism involving histone deacetylases (HDACs), leading us to identify Belinostat as a promising HDAC inhibitor. In pre-clinical human skin models, Belinostat restored epidermal miR-335 expression.

Conclusions:
Our study proposes repurposing Belinostat as a therapeutic for AD. We hypothesize that analogues of Belinostat, designed for facile degradation upon systemic entry, can deliver high efficacy with minimal toxicity in treating AD. The research unfolds through three specific aims: designing and validating Belinostat analogues, identifying and validating these analogues in in-vitro, ex-vivo, and in-vivo settings, and formulating and clinically assessing the lead analogues. This innovative therapeutic approach holds potential for effectively ameliorating the compromised skin barrier in AD, translating into improved patient outcomes.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial, or personal.

Keywords:
Atopic dermatitis, microRNA-335, SOX6, histone deacetylases, Belinostat analogues

55 An End-to-end Privacy-preserving Framework for Predicting Cancer Outcomes

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Background & Objectives:

Genomic factors are strongly associated with cancer treatment outcomes and survival rates of patients. Although such factors have traditionally been extracted via expert knowledge and annotations, the advancements in artificial intelligence have led to an increasing focus on automated feature extraction based on training on large amounts of genomic data. However, genomic data is widely considered as sensitive, as their missuse can lead to dire ramifications such as social stigmatization, limited employment prospects, and loaded insurance policies. For instance, it has been shown that reidentification of patients can be achieved with a set of less than 80 independent single nucleotide polymorphisms (SNPs). As such, researchers often face difficulties in performing analysis across national borders, which relies on data access agreements that are often cumbersome to navigate.

Precision medicine is fundamentally a data-driven endeavour which relies on the availability of large amounts of multi-modal data, and the challenges in securing access to relevant datasets hinders the advancement of the field. In this work, we address the privacy concerns regarding the sharing of sensitive genomic data, by demonstrating a privacy-preserving framework to train models securely based on datasets across multiple sites.

Methods and Results:

We present an end-to-end framework that trains a model across multiple parties securely without sharing actual data, and then classifies new samples privately so that the owner of the model is unable to access the data of the new samples. The framework is based on Federated Learning, Differential Privacy and Homomorphic Encryption.

Private model training is achieved with Federated Learning (FL) and Differential Privacy (DP). A round of federated feature selection using Fed-χ^2 is first executed to select the top 15 most informative features. Data contributors then jointly build a classification model without revealing their data with FL. A privacy budget is subsequently applied to the model to enhance the privacy of the dataset using DP. We split the data into different combinations to simulate different real-world scenarios. We also compared the performance of the private model against a baseline model which was trained with all the data locally without DP. For a moderate privacy budget of ε=1, there appears to be little to no degradation of the model.

Private classification allows new samples to be first encrypted before being evaluated by the private model. We chose a Fully Homomorphic Encryption (FHE) setting that provides a security level of at least 128 bits. We are also able to evaluate batches of 4096 samples each time. We report no loss in accuracy between evaluating the model privately with HE and without HE.

Conclusion:
We demonstrated how a machine learning model can be trained jointly and securely from several data sources with FL and DP, and how inference on new samples can be achieved in a privacy-preserving manner via FHE. Data from each owner stays locally on-premise and is never exposed to other owners in the system throughout the whole process from model training to inference. Each data owner will not be able to learn anything about the data from other owners, beyond what can be inferred via the global model.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Fully Homomorphic Encryption, Federated Learning, Differential Privacy, Private Genomic Analysis, Cancer

56 Understanding baseline determinates for mRNA vaccine immunogenicity

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Abstract:
The unprecedented use of mRNA vaccines to prevent COVID-19 has been an urgent public health need. Despite conferring a high level of immunogenicity and efficacy induced by the mRNA vaccines, the molecular underpinnings of these immune responses are still unknown. Leveraging on an -omics approach that integrates transcriptomics and cytokine profiling, we examined baseline blood transcriptome and its correlation to adaptive immunity in 20 healthy volunteers who were vaccinated with two doses of Pfizer-BioNTech mRNA vaccine (BNT162b2). We identified distinct baseline signatures that regulates T cells and antibody responses after vaccination, as with cellular and humoral immunity being major components that mediate protection. The magnitude of the vaccine induced cellular and humoral responses were also influenced by the frequency and activation status of immune cell subsets at baseline. Overall, our findings support that different early transcriptional correlates in the form of baseline signatures can predict for a varied of T cell and antibody responses towards mRNA vaccines. These immune transcriptomes underpinning the differences in immunogenicity underscore the potential of informing future vaccine design strategies.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
mRNA vaccine, immmuogenicity, transcriptomics

57 Statin Lactone Metabolism is a Determinant of 5-year Cardiovascular Outcomes Independent of Serum Cholesterol

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Background & Objectives:
Statins are a first line treatment for reducing cardiovascular risk, however the individual clinical benefit of statins remains highly variable.

We seek to quantify statin biotransformation phenotypes in cardiology patients and validate predictors of 5-year clinical outcomes in two independent cohorts of the SAPhIRE study.

Method(s) and Results:
We conducted a 5-year, multicentre, prospective, observational trial of 1362 cardiology patients across two independent healthcare systems in Singapore. In addition to genotyping, subjects were also phenotyped based on mass spectrometry quantification of all known plasma statin metabolites, sampled at two time points in late elimination phase.

The atorvastatin lactone metabolite (ATVLAC) ≥3.9ng/mL 13 hours post-dose predicted Major Adverse Cardiovascular Events (MACE) (HR=2.45) and all-cause mortality (HR=3.18), independently of drug dose and achieved LDL. *UGT1A*, a lactone-producing gene, associated with ATVLAC at genome-wide significance, independently predicted MACE (HR=1.40). Simvastatin Lactone (SMVLAC) also associated with MACE and *UGT1A*, suggesting a class effect. Among 51 co-prescribed non-statin drugs, omeprazole (a UGT inducer) was the strongest predictor of plasma ATVLAC (1.41-fold) and MACE (HR=1.46).

Conclusions (Significance and Impact of the Study):
These results suggest the statin lactone metabolite is a determinant of differential outcomes in statin takers and omeprazole co-prescription is a novel, potential risk factor. Genotyping the enzymatic source of statin lactone, *UGT1A*, may play a role in pharmacogenetic risk prediction.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Statins, Precision Medicine, Pharmacogenetics, Clinical Trials, Major Cardiovascular Adverse Events

58 Genetic Architecture of plasma metabolites in the Southeast Asian population

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Background:
Metabolites and variation in their levels provide key information about the wellbeing of humans and the mechanisms that control key physiological processes involved in health and disease. Genome wide association studies (GWAS) have identified many genetic loci associated with metabolic variation, but most of these studies have been conducted in individuals of European ancestry. Here, we conduct the first large scale GWAS of 1073 plasma metabolite levels in 8200 individuals in the multi-ethnic HELIOS dataset (53±12 years, female=59%, Chinese=67%, Malay=14%, Indian=19%).

Methods and Results:
Linear mixed model-based ancestry specific GWAS analysis was performed followed by inverse variance weighted fixed effect meta-analysis. We identified 477 genomic loci associated with 836 metabolites at genome-wide significance ($P < 5x10^{-8}$) with over 100 loci previously unreported in other metabolite GWAS studies. We observed that the genomic loci are highly pleiotropic with a median of 2 associations per loci, especially the FADS1/FADS2 loci which was found to be associated with 115 metabolites. Integrating gene expression quantitative trait loci (eQTL) data, we identified significant associations for 649 metabolites and expression of 1568 genes, with the strongest association observed with the Kynurenine aminotransferase (KYAT3) and amino acid pathway metabolites: 2-hydroxy-4-(methylthio) butanoic acid ($p = 1.94x10^{-81}$) and imidazole lactate ($p = 1.94x10^{-74}$).

Conclusion:
This study provides a valuable resource to understand the genetic architecture of metabolites in Asian populations and help identify novel genetic loci previously undiscovered in large-scale European GWAS studies. The study delivers insights into the roles of metabolites in human health, thereby offering opportunities to determine novel diagnostic and therapeutic targets.

Conflicts of interest disclosure:
J.C.C. is the Chief Scientific Officer of PRECISE. M.Lam is an organizer of the PRECISE-IHCC conference. The rest of the authors have no conflicting interests.

Keywords:
GWAS, Metabolites, Asian population, Multi-omics

59 Phenotypic variability in Ornithine Transcarbamylase deficiency males with the *OTC* R277W variant: A case report and review of the literature.

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Background & Objectives:
Ornithine Transcarbamylase deficiency (OTCD) is caused by disease-causing variants in *OTC* gene. Males with OTCD typically present in the neonatal period with hyperammonemia. We present an adult male newly diagnosed with OTCD and compare this with other previously reported individuals with the same variant.

Method and Results:
We present a male proband, hemizygous for a pathogenic variant, *OTC(*c.829C>T), p.R277W, diagnosed with OTCD at 38-years of age when he presented acutely with altered mental state due to hyperammonemia. His elder brother aged 40 years was clinically diagnosed with OTCD at 11-months of age and treated with protein restriction diet. Further we compared the variability in age of onset, clinical expression, and outcomes in previously reported individuals with same variant, retrospectively. Twenty-three cases were collected. Two were diagnosed via newborn screening and the rest were diagnosed post symptomatically. The mean age of onset was 6.5 years of age, ranging between day 1 of life and 34 years of age. The highest level of ammonia in the study was 901 umol/L. The neurological outcome was normal in 52%, severe neurologic damage in 26% and unknown in 22%. The individuals with early intervention had better clinical outcomes.

Conclusions:
This demonstrates the variable age of onset of OTCD in individuals with R277W. This highlights the importance of still considering OTCD as a potential diagnosis in adult males with hyperammonaemia as individuals with mild variants can present later. This ensures timely diagnosis and treatment and minimizes mortality or morbidity.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest in relation to this work, whether scientific, financial, and personal.

Keywords:
Hyperammonaemia, ornithine Transcarbamylase deficiency (OTCD), variable heterogeneity, Late onset OTCD, OTC gene

60 The Dementias Platform UK (DPUK) IHCC Remote Mentoring Programme: Democratizing collaboration and mentoring for Early Career Researchers (ECRs)

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Background & Objectives:
The aim of the DPUK-IHCC Remote Mentoring Programme (RMP) is to provide affordable, convenient and cost-effective international mentoring opportunities for researchers. Using the infrastructure of the Dementias Platform UK (DPUK) Data Portal, datasets can be accessed from anywhere in the world using a virtual desktop interface (VDI). The VDI has preinstalled statistical software tools and the datasets are accessed upon approval of a project proposal. Multi-modal analysis is enabled (genomics and imaging) through a Linux environment. DPUK also provides researchers with a training programme which includes an Elementary Academy for foundation statistical analysis, an Advanced Academy for longitudinal data analysis and a Datathon workshop for group working on a scientific question across multiple cohorts.

Objectives:
1. To provide mentoring opportunities for ECRs
2. To provide affordable training and site-visit opportunities for ECRs.
3. To foster multi-disciplinary and multi-cohort collaborations within a scientific field.

Methods and Results:
Once the application has been accepted by DPUK and the cohort owners, data access is provided by provision of a DPUK Data Portal account requiring the signing of a Data Access Agreement (DAA). The DAA needs to be signed by the researcher and an institutional signatory for contracts (Appendix III). Data owners approve the datasets (median time – 28 days) and once one cohort has approved (regardless of total number of requested datasets), the DPUK account set up process is initiated.

Conclusions:
The DPUK-IHCC RMC is an initiative that will extend mentoring beyond global borders without the need for expensive long visits.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
mentoring, ECR, training, remote, analysis

61 Cascade screening for family members of patients with Familial Hypercholesterolemia in Singapore: FHCARE program

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Introduction:

Familial Hypercholesterolemia (FH), often undiagnosed and undertreated, is an autosomal dominant genetic disease characterized by high levels of plasma low density lipoproteins cholesterol (LDL-C), increasing risk for premature coronary artery disease (CAD).

Cascade screening (CS) is a cost-effective strategy in diagnosing. In this study, we aimed to investigate the effectiveness of CS and describe the clinical attributes of family members (FM).

Methods:

FM biologically related to proband with genetic diagnosis of FH were enrolled and underwent genetic testing based on proband's detected variant by Sanger sequencing. Lipid levels, together with clinical characteristics were compared with outcome of genetic testing.

Results:

A total of 1411 patients with clinical diagnosis of FH had genetic testing. Mean age 41.2 years (±14.4), male 62.9%, ethnic distribution (C:75.1%, M:14.1%, I:7.1 %). FH causing variant was detected in 412 (29.2%), with variant of uncertain significance (VUS) in another 15.1%.

Of the 634 probands offered CS, 39.3% consented. With an average of 2.1 family members per proband, a total of 523 attended CS. Mean age 35.6 (±19.6) years, 42.8% males. FH was detected in 210 (40.2%) of whom 57.1% were previously undiagnosed for hypercholesterolemia and unaware of FH.

Comparing those with mutation positive, negative and VUS FM, total cholesterol (TC) was 7.25 (±1.73), 5.24 (±1.10), 6.10 (±1.20)mmol/L respectively, while LDL-C: 5.37 (±1.69), 3.40

(±1.00), 4.25 (±1.24)mmol/L respectively ($p<0.0001$). In FM with confirmed with FH and already on treatment, their mean LDL-C was 3.12 mmol/l, with 3.8% having LDL-C below 2.6mmol.

Conclusion:
CS is effective in detecting undiagnosed FM with FH. A central dedicated program with designated genetic workers and healthcare professionals, allows effective CS to lower the number of undiagnosed FH, potentially allowing for future better LDL-C goal achievement and prevention of premature CAD.

Conflict of interest disclosure:
I, Madhuumetaa D/O Selvakumar, hereby declare no potential conflicts of interest, whether scientific, financial, and personal.

Keywords:
Familial Hypercholesterolemia (FH), Family, Cholesterol, FHCARE

62 Targeted Full-Genomic Gene Panel as Diagnostics for Uncovering Deep Intronic Variants in Genetic Disorders

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Background & Objectives:
Genetic diagnostics play a crucial role in identifying pathogenic variants associated with genetic disorders. Deep intronic variants can disrupt splicing and lead to disease, yet they are often neglected by conventional sequencing approaches such as WES or gene panels. To address this limitation, we developed two full-genomic gene panels (FG-GP), which target both exonic and deep intronic regions of genes associated with ABCA4-retinopathy or Urea Cycle Disorder (UCD). This study aims to develop and evaluate the performance of the gene panel in detecting pathogenic variants, particularly in deep intronic regions, compared to whole-genome sequencing (WGS) and whole-exome sequencing (WES).

Method(s) and Results:
We designed the DNA baits using IDT xGENTM and optimized them through a custom algorithm, “Prune”. The FG-GP was benchmarked against seven Genome in a Bottle (GIAB HG001-007) truth sets. Our results demonstrate that the gene panel achieves high sensitivity and specificity in detecting variants, including splicing variants in the deep intronic regions, with an optimized variant calling pipeline. Furthermore, the FG-GP requires fewer read counts compared to WGS/WES, making it a cost-effective alternative for clinical genetic testing. With the FG-GP, we found a novel deep intronic variant in the Japan cohort causal for urea cycle disorder.

Conclusions (Significance and Impact of the Study):
The successful development of FG-GP paves the way to create gene panels for the analysis of the entirety of a gene’s content. Its economic and rapid approach, paired with today’s computational prowess in identifying splice variants, makes FG-GP a valuable tool to identify previously neglected variants in the deep intronic space for improved diagnosis in Mendelian diseases.

Conflict of interest disclosure:
Two authors involved in this study, Munfai Loke and Johnson Ng, are industrial partners who may have a financial interest in the commercialization of the gene panel discussed in this work.

Keywords:
Hybridization-based targeted enrichment, gene panel, deep intron, splice variant, genetic diagnosis

63 Spectrum of Compound Heterozygous, Double Heterozygous and Homozygous variants in Patients with Familial Hypercholesterolemia in Singapore

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Background & Objectives:
Familial Hypercholesterolemia (FH) is an autosomal dominant disease characterised by increased low-density lipoprotein cholesterol (LDL-C) levels, resulting in increased risk of premature cardiovascular disease. Patients with compound heterozygous, double heterozygous and homozygous variants have a more severe form of FH. The study aims to assess genetic variants, baseline lipid profiles and response to therapy in patients with severe FH.

Method(s):
Index patients with untreated/highest on-treatment LDL-C levels >4.9mmol/L were recruited. Fasted lipid and clinical characteristics were collected. DNA extraction, next generation sequencing, sanger sequencing, multiplex-ligation probe analyses, single nucleotide polymorphism microarray and in-house targeted array were performed. Baseline (untreated/imputed) LDL-C levels were compared against lowest on-treatment or lowest available LDL-C levels.

Results:
Of the 1411 index patients sequenced, 9 patients had compound heterozygous, double heterozygous or homozygous FH. Mean age was (40.7±15.6) years. For LDL-receptor, 5 were compound heterozygous [mean baseline LDL-C = (10.86±4.71) mmol/L] and 2 were homozygous [mean baseline LDL-C = (7.50±1.12) mmol/L]. For LDL-receptor and Apolipoprotein B (APOB), 1 was double heterozygous [baseline LDL-C = 5.34 mmol/L]. For LDL-receptor Adaptor Protein 1 (LDLRAP1), 1 was homozygous [baseline LDL-C = 16 mmol/L].

All patients were treated with high intensity lipid lowering medication. After treatment, for LDL-receptor, patients who were compound heterozygous had mean LDL-C level of (5.29±2.03) mmol/L while patients who were homozygous had mean LDL-C level of (3.23±0.47) mmol/L. Double heterozygous patient had LDL-C reduced to 1.87 mmol/L after treatment, while patient homozygous for LDLRAP1 had LDL-C reduced to 7 mmol/L.

Conclusions (Significance and Impact of the Study):
This report illustrates the spectrum of genetic variants within patients with compound heterozygous, double heterozygous and homozygous variants in Singapore. It provides an insight into the severity of these variants, where untreated patients had very high LDL-C levels. Majority of the patients achieved 50% LDL-C lowering, with none achieving target LDL-C levels. Cascade testing of family members is needed as every first degree relative is likely to have heterozygous FH, requiring early preventive treatment.

Conflict of interest disclosure:
I, Chen Hoe Meng, declare no potential conflicts of interest, whether scientific, financial, and personal.

Keywords:
Familial Hypercholesterolemia, Spectrum, Variants, LDL-receptor, LDL-C

64 To test or not to test? A measure of informed choice for Hereditary Breast and Ovarian Cancer Syndrome testing.

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Background & Objectives:
Informed decision-making is a key aspect to patient-centric care. Particularly for hereditary cancer genetics testing, where one's choice for testing can result in health spillovers for relatives, ensuring informed choice for testing is warranted. Hence, this study aimed to pilot a measure of informed choice for hereditary breast and ovarian cancer syndrome (HBOC) testing.

Method(s) and Results:
Informed choice was defined using the Multidimensional Measure of Informed Choice (MMIC), which requires a testing choice to be 1) made with **adequate knowledge**, and 2) with congruence between testing **attitude** and actual **uptake** of testing, to be deemed informed. A measure of MMIC for HBOC was developed to measure informed choice in patients considering HBOC testing. The decision conflict scale was also administered to patients.

217 patients were recruited, of which 189 (87.1%) accepted testing. Patients with financial assistance were more likely to accept testing X^2 (1, N=201)=12.60, p<.01. Testers (74.2%) were **more likely** than non-testers (8.0%) to make an informed choice for genetic testing, X^2(1, N=194)=43.10, p<.01. No difference in knowledge was found between testers or non-testers. Attitudes scores for testers were positively skewed, while non-testers were found to have ambivalent attitudes. No difference in decisional conflict was found.

Conclusions:
Most participants (73.3%) had adequate knowledge prior to HBOC testing. Informed choices were largely influenced by testing attitudes, and possibly influenced by the presence of financial assistance. Efforts should be directed towards resolving incongruence between testing attitudes and actual uptake.

Conflict of interest disclosure:
Joanne Ngeow receives funding from AstraZeneca. All other authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Cancer Genetic Testing, Behavioural Health, HBOC Syndrome, Informed-Choice, Precision Medicine

65 From cohorts to the clinic: interactively visualising amyotrophic lateral sclerosis (ALS) future risk projections

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Background and Objectives:
ALS is a rare neurodegenerative disease affecting motor neurons, leading to progressive weakness and ultimately death. Management is multidisciplinary and supportive, aimed at symptom control, including gastrostomy tube insertion for dysphagia and non-invasive ventilation for respiratory muscle weakness. Patients vary in their presentation and progress, and disease trajectories can be challenging to understand and communicate. Using a predictive model developed from cohort data, we developed a tool that clinicians can use in the clinic to visualize current status and stratify future risk of gastrotomy insertion for patients.

Methods and Results:
We studied 3517 patients from three ALS databases (PROACT, IDPP and ArQ), with at least four observation timepoints. As a first step, we examined the patterns of evolution of patients' disease using markers such as ALSFRS scores, weight velocity, markers of respiratory function and event survival curves using a joint growth mixture–discrete time survival analysis model based on a multivariate Cox Proportional Hazards model. With this model, we detected two classes of decline patterns (rapid and slower). On back of these results, we created a bespoke interactive web-based visualisation tool for clinicians.

Conclusions:
Clinicians can use this tool to visualize the current status of patients and predict individual patient progress and risk of gastrotomy insertion at future timepoints to provide more comprehensive and anticipatory care. Patients can also benefit from understanding of expected outcomes.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Visualisation, Prediction, Model, ALS, Cohort

66 Cost-effectiveness of Pre-emptive Pharmacogenetic Panel Testing versus No Testing in a Multi-ethnic Asian Population

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Background and Objective:
The cost-effectiveness of a panel-based pre-emptive pharmacogenomic (PPGx) test has not been evaluated for a multi-ethnic Asian population. Previous studies focused on reactive, single drug-gene test.

Methods:
We evaluated the cost-effectiveness of four drug-gene pairs within a PPGx panel test compared to no PGx test. The assessment employed a framework developed through Discretely Integrated Condition Event (DICE) simulation, which allowed simultaneous analysis of multiple diseases and treatments of varying duration. The study focused on a hypothetical cohort of healthy 40-year-old Singaporeans, considered lifelong downstream effects of one-time panel test, and encompassed outcomes such as disease occurrence and serious adverse drug reactions (ADR). We adopted a health payer's perspective with a 3% discount rate. Costs reflect local clinical practice pattern.

Results:
We evaluated Clopidogrel–CYP2C19, Capecitabine–DPYD, Allopurinol–HLA-B*58:01 and Simvastatin–SLCO1B1 considering their frequent prescription and presence of variant alleles locally. In the base-case analysis, panel testing was a dominant strategy (i.e. less costly with more benefits), resulting in savings of 107,049 Singaporean Dollars and benefits gain of 30.93 Quality-Adjusted Life Years compared to no testing. The cost-effectiveness of panel testing further improves with a higher prevalence of variant alleles, higher disease and ADR incidence, and lower costs of alternative drugs used for carriers of variant alleles.

Conclusion:
PPGx panel testing is cost-effective. The framework can be customised to assess cost-effectiveness of additional drug-gene pairs. Any drug-gene pair added to the panel will provide information useful for clinical decision making at a minimal extra cost.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Cost-effectiveness, Pharmacogenetics, Panel test, Pre-emptive testing, Asian

67 Genomic co-localisation, child proteomics and brain imaging support a link between obesity-associated genotype and child language development.

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Background & Objectives:

Language is the primary medium for conveying thoughts and emotions. It is deeply intertwined with the way individuals process and interpret information. This interconnection highlights the critical role of language development as a cornerstone of cognitive growth, setting the foundation for future academic and personal achievement. Beyond the social environment, language development is also shaped by biological processes, such as brain myelination. The inhibitory role of obesity in myelination may contribute to its association with cognitive development and educational outcomes. An interplay between obesity and genetically predicted body mass index (BMI) has been observed, highlighting differences between environmentally and genetically influenced obesity. Here, we aim to explore the mechanisms between BMI and language development, using longitudinal and multi-omic data from the Growing Up in Singapore Towards healthy Outcomes (GUSTO) cohort.

Method(s) and Results:

We constructed polygenic risk score (PRS) for obesity for the GUSTO children and parents using an East Asian genome-wide association study (GWAS) of BMI from BioBank Japan (N=163,835) and a European GWAS of BMI from a meta-analysis of GIANT and UK BioBank (N=681,275). Child PRS for obesity was inversely associated with child language scores as assessed by the Wechsler Individual Achievement Test, Third Edition (WIAT-III) composite score assessed at age 9. These associations were stronger in boys (β=-0.56, 95%CI -0.81 to -0.31, *P* value=2.5×10^{-5}) compared to girls (β=-0.27, 95%CI -0.53 to 9.8×10^{-5}, *P* value=0.050). Genetic correlations and colocalization suggest a complex interaction between obesity-related traits and language-related skills. Specifically, investigation in the neurology-related proteins and brain imaging suggested potential roles of inflammation mechanisms. However, we did not identify a causal relationship between obesity-related traits and language-related skills using two-sample Mendelian randomization. Intriguingly, we identified a connection between

obesity predisposition and elevated MSR1 protein levels, whereas EFNA4, VWC2, and CNTN5 protein levels were associated with a higher WIAT-III composite score. Expression levels of MSR1, EFNA4 and VWC2 were also associated with fractional anisotropy in white matter tracts.

Conclusions (Significance and Impact of the Study):
Our study shows that common genetic constructs may have contributed to the link between obesity and language development. We have also identified early-life neurology-related proteins that are influenced by obesity-associated genotypes and those implicated in language development.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
obesity, language development, polygenic risk score, neurology-related protein, genetic colocalisation

68 From Cohort to Clinic: Return of genetic secondary findings from the population-based Multi-Ethnic Cohort

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Background & Objectives:
Secondary findings involving actionable genetic variants for known diseases may be detected in individuals from population-based cohort studies. The process of notifying, providing support through genetic counselling, and understanding their concerns on future preventive actions have not been performed in large-scale cohorts.

Method(s) and Results:
A total of 4,277 participants from the Multi-Ethnic Cohorts (MEC) were sequenced through (i) National Precision Medicine Programme Phase 1 (NPM I - SG10K) and (ii) Breast Cancer Risk after Diagnostic Gene Sequencing (BRIDGES) initiative. We identified 24 carriers for hereditary breast and ovarian cancer (BRCA) and 14 carriers for familial hypercholesterolemia (FH). Working with SingHealth Duke-NUS Institute of PRecISion Medicine (PRISM), we recontacted participants through a first contact letter, short message service (SMS) and a follow-up phone call. A total of 14 participants (4 BRCA, 10 FH) attended a first meeting with a genetic counsellor, and were invited to a semi-structured interview six months later. Six participants (FH carriers) who agreed to the interview were aged above 50 and had been diagnosed with high or borderline cholesterol, with the condition being common among their family members. The level of understanding of FH and genetic implications to their family members varied, as well as their decision to proceed to clinical validation, or to share the findings with their family members.

Conclusion:
We established a process of returning genetic secondary findings to population cohort participants. This provided valuable insights to better communications for return of findings to the next 30,000 participants from NPM II.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
secondary findings, BRCA, familial hypercholesterolemia, genetic counselling, population-based cohort.

71 A Partially Connected Neural Network for Enhanced Polygenic Risk Score Prediction

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Background & Objectives:
Polygenic risk scores (PRS) are a crucial tool in precision medicine, enabling the prediction of an individual's susceptibility to complex traits or diseases based on their genetic profile. Recent advancements in machine learning, particularly neural networks, have shown promise in generating more precise and accurate PRS. We, therefore, introduce a novel partially connected neural network (PCNN) approach to enhance PRS prediction.

Method(s) and Results:
Our innovative PCNN model computes PRS by integrating C+T scores calculated for each chromosome using various parameters. The unique PCNN architecture allows for the capture of complex interactions and non-linear relationships between traits and genetic variants within and across chromosomes. We rigorously evaluated the PCNN's predictive performance against state-of-the-art models (C+T, LDpred, PRScs, and Lassosum) using both simulated and real data from diverse cohorts. The PCNN has superior or comparable performance relative to other methods that require a higher order of computational time, demonstrating its potential for improved genetic risk prediction in clinical settings.

Conclusions (Significance and Impact of the Study):
The PCNN approach represents a significant leap forward in PRS prediction, offering a novel method for enhancing the accuracy of genetic risk assessment. This study not only underscores the importance of developing innovative computational methods but also holds promise for improving patient outcomes and precision medicine strategies on a global scale.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial, or personal.

Keywords:
polygenic risk scores, partially connected neural network, complex traits, genetic prediction, precision medicine

72 Telomere Length Distribution and Genome-wide Association Study Among Singaporean Cohorts

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Background and Objectives:
Leukocyte telomere length (LTL) serves as an inheritable indicator of cellular aging and is a potential risk factor for several chronic diseases. Comprehensive studies on LTL distribution and its association are essential for gaining insights into telomere homeostasis, as well as its correlation with metabolic traits and age-related conditions. Such investigations have been limited in Asian population groups. Here, we utilized whole-genome sequencing data from 8,045 Singaporean samples across three major ethnic groups - Chinese, Indian, and Malay divided into six cohorts: GUSTO, HELIOS, MEC, PRISM, SERI, and TTSH.

Methods and Results:
LTLs were assessed using TelSeq, with normalized LTL as phenotype in subsequent analyses. Our results reported a robustly longer average LTL in the childhood cohort (GUSTO) compared to the adult cohorts ($P<1.19\times10^{-195}$). Ethnic differences were observed, with adult Singaporean-Chinese samples exhibiting the longest LTL (5.08kb), followed by Malay (4.87kb) and Indian (4.65kb) ($P<4.98\times10^{-12}$). Our genetic association analyses replicated multiple previously reported LTL-associated variants, validating the methodologies used. Additionally, a novel East-Asian-specific variant at the *COL28A1/MIOS* gene associated with LTL was identified beyond genome-wide association levels (meta-$P=2.05\times10^{-08}$). Individual analysis of the childhood GUSTO dataset uncovered a second novel genome-wide hit at *RAD17* gene locus and simultaneously suggested that the previously reported variant at the *TINF2* locus may have significantly opposing effects compared to adults during early developmental stages.

Significance of Study:
This study enhances our understanding of LTL distribution and its associated genetic characteristics in both childhood and adult Singaporean populations.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
telomere length, genetic association, gwas, novel risk loci, SG10K

73 Plasma proteomic signatures of adiposity are associated with cardiovascular risk factors and type 2 diabetes risk in a multi-ethnic Asian population.

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Background & Objectives:
The biological mechanisms connecting obesity and cardiometabolic diseases are not fully understood.

Method(s) and Results:
We evaluated the associations between body mass index (BMI), waist circumference (WC), and ~5,000 plasma proteins in the Singapore Multi-Ethnic Cohort (MEC1). Among 410 BMI-associated and 385 WC-associated proteins, we identified protein signatures of BMI and WC and validated them in an independent dataset from MEC1 across two timepoints and externally in the Atherosclerosis Risk in Communities (ARIC) study. The BMI- and WC-protein signatures were highly correlated with total and visceral body fat, respectively. Furthermore, the protein signatures were significantly associated with cardiometabolic risk factors and were able to differentiate between metabolically healthy and unhealthy obesity. In prospective analyses, the protein signatures were strongly associated with type 2 diabetes risk in MEC1 (odds ratio per SD increment in WC-protein signature = 2.84, 95% CI 2.47 to 3.25) and ARIC (hazard ratio = 1.97, 95% CI 1.87 to 2.07). Pathways related to post-translational protein phosphorylation, regulation of insulin-like growth factor, coagulation cascades, adenosine monophosphate-activated protein kinase signaling, extracellular matrix receptor interaction, and cell adhesion were overrepresented in the BMI- and WC-protein signatures.

Conclusions:
Our findings on adiposity-related proteins were robust across ethnic and geographically diverse groups and have potential uses for assessing and monitoring metabolically adverse adiposity.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Adiposity, abdominal adiposity, type 2 diabetes, proteomics, metabolic abnormalities

74 Metabolome-wide association of carotid intima media thickness in an Asian population cohort identifies FDX1 as a determinant of cholesterol metabolism and cardiovascular risk.

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Background & Objectives:
The burden of cardiovascular disease (CVD), and CVD-related mortality is rising in the Asia-Pacific region, in contrast to its stable or falling incidence and mortality rates in Europe and North America. With the objective of exploring the metabolic signature of atherosclerosis, and discovering new insights into the underlying pathways influencing cardiovascular risk in Asian populations, we performed a metabolome-wide study of carotid intima media thickness (cIMT), among 8,124 participants from the HELIOS-SG100K study (53±12 years, female=59%, Chinese=67%, Malay=14%, Indian=19%).

Methods & Results:
cIMT, a marker of atherosclerosis, was assessed in the carotid bulb and distal common carotid artery using 2D/3D carotid ultrasonography. 883 metabolites were semi-quantified by untargeted mass spectrometry on the Metabolon's Global Discovery Panel. Using linear regressions, controlled for age, sex, ethnicity, batch and CVD risk factors (BMI, blood pressure, total cholesterol, smoking and diabetes status), we identified 126 independent metabolic markers of cIMT. We found that increased plasma concentrations of 3-beta-5-hydroxy-

cholestenoate (3BH5C) were potentially causally associated with decreased risk of coronary artery disease (OR=0.89, [95%CI=0.87-0.92], P=$1.5x10^{-16}$). Through colocalization studies, using whole blood cis-expression data from HELIOS (N=1,228) and GTEx (N=670), we identified a shared causal variant associated with 3BH5C levels and ferredoxin (FDX1) expression. We validated the role of *FDX1* as a key regulator of cholesterol metabolism via the acidic pathway in hepatocytes and macrophages, demonstrating that depletion of *FDX1* reduced 3BH5C production.

Significance & Impact:
This study advances our understanding of the metabolic underpinnings of atherosclerosis in Asian populations, and identifies a potential therapeutic target for atherosclerosis.

Conflicts of interest disclosure:
J.C.C. is the Chief Scientific Officer of PRECISE. M.Lam is an organizer of the PRECISE-IHCC conference. K.E.W, P.A.S, R.S and G.A.M are employees of Metabolon, and may hold stock/stock options in Metabolon. The rest of the authors have no conflicting interests.

Keywords:
Asian population, Atherosclerosis, Cardiovascular disease, Ferredoxin, Metabolomics

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75 Integrative analysis of omics summary data reveals putative mechanisms underlying dilated cardiomyopathy.

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Background & Objectives:
Understanding complex trait etiology involves pinpointing causal genes and exploring their regulation. DCM-linked methylation alterations have been shown to influence the expression of genes crucial to cardiac disease. Our primary objective is to clarify DCM mechanisms influenced by CpG methylation using multi-omics and causal analyses in the largest existing DCM cohort of left ventricular tissues (n = 235 DCM, n =179 control).

Method(s) and Results:
We used the EPIC array to map DNA methylation at approximately 850k CpG sites in left-ventricular tissue samples from failing and non-failing hearts across two independent DCM cohorts (discovery n = 329, replication n = 85). This surfaced 194 replicated, independent methylation signals robustly associated with DCM (discovery cohort Bonferroni-corrected P <0.05) enriched in regions of active transcriptional regulation. Array-based genotyping and RNA sequencing were performed on the same samples (discovery n = 306, replication n = 85). We identified and replicated significant relationships between 183 sentinel CpGs and 849 proximal genes (±1Mb). Subsequently, we leveraged genetic variants linked to sentinel CpG methylation to assess causal relationships between sentinel CpGs and DCM as well as proximal gene expression using Summary data-based Mendelian Randomisation (SMR). Three sentinel CpGs were causally linked to DCM (SMR P <0.05) and 33 sentinel CpGs to the expression of one or more proximal genes (SMR P <0.05).

Conclusions:
To our knowledge, this study is the first to infer causal mechanisms involving DCM-linked methylation alterations by integrating multi-omics data from independent cohorts.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
DNA methylation; dilated cardiomyopathy; epigenetics; heart failure; Summary data-based Mendelian Randomisation (SMR)

Acknowledgments:
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76 Leveraging existing large-scale genomic studies for assessment of genetic risk within Singapore.

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Abstract:
In the early stages of a population sequencing program (particularly of a healthy cohort), the number of sequenced individuals is not yet large enough for well-powered genome-wide association studies (GWAS). However, given the availability of GWAS and rare variant association tests (RVATs) results from prior cohorts, it is feasible to estimate the polygenic risk scores (PRS) for various traits for individuals of the nascent cohorts. We are developing methods to leverage insights from GWAS and RVAT of large population sequencing cohorts (such as UKBB) to produce the PRSs from common and rare variants within Singapore. Our study utilizes genomic data of 10,000 participants from the Singapore's National Precision Medicine program's initial SG10K_health cohort. Common PRSs were built using PRS-CSx, amalgamating GWAS summary statistics from multiple populations. This enhances cross-population polygenic predictions by inferring posterior SNP effect sizes across populations. Rare variant PRSs were developed from genes identified from RVATs in the UKBB, where rare genetic variants are scored for pathogenicity using PrimateAI-3D. With AI-driven variant effect prediction, population-specific rare variants can be scored and incorporated, a task previously challenging, into the development of localized rare variant PRSs. Using a linear combination of PRSs, our preliminary analyses on LDL-cholesterol have revealed a 3-fold increase in odds (within the top PRS quintile) for predicting genetic risk. By demonstrating the feasibility for translating genetic insights from other cohorts into polygenic risk prediction early in sequencing projects, we accelerate the deployment of genomics in local precision medicine efforts.

Conflict of interest disclosure:
AJWL and GLC are both employees of Illumina Inc. AJWL is a joint PhD student with National University of Singapore.

Keywords:
Polygenic Risk Scores, Genome-wide Association, Genetic Variations, Artificial Intelligence, Precision Medicine

77 Necessity of case-control joint calling for accurate evaluation of rare variant disease contribution

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Abstract:
Polygenic risk scores (PRS) quantify disease risk, using genetic variants from genome-wide association studies (GWAS). However, PRSs from European cohorts have shown low portability to non-European populations, whereas rare variant association testing (RVAT) in UKBiobank demonstrated good portability. Here we use GWAS and RVAT to generate a unified PRS for rheumatoid arthritis (RA) with common and rare variants, to quantify RA risk in the Singaporean population. The common variant (allele frequencies (AF) > 1%) PRS was built by combining six multi-ancestry GWASs for RA and correlated traits using clump and threshold with lasso, and the rare variant (AF < 0.1%) PRS was built from significant genes identified in Illumina's RVAT on UKBiobank traits, including RA. The cohort contained 978 RA Chinese whole exomes and 2732 SG5K Chinese whole genomes. Our model achieved an adjusted R2 of 0.55 and AUROC of 0.90, and the pipeline can be easily applied to other disease cohorts.

However, sensitivity analysis identified a subpopulation of RA cases (~60%) with twice as rare variants, resulting in an artifact-induced bimodal distribution amongst the cases, inflating its performance. We fix this by joint calling of cases, but the inability to joint call cases and controls together led to cases having twice as many rare variants as the controls, even after appropriate quality controls. This was replicated in UKBiobank RA cohort by excluding variants with higher AFs in the controls than cases and highlights the necessity of joint calling for consistent rare variant calling.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial, and personal.

Keywords:
rare variants, rheumatoid arthritis, polygenic risk scores, joint calling, multi-trait

78 Can polygenic risk scores from different genotyping arrays be used interchangeably?

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Background & Objectives:
Difference in coverage of known GWAS markers across arrays is minimal. However, polygenic risk scores (PRS) are derived from a small subset of variants. We assessed the concordance of risk classification by PRS calculated from different arrays.

Methods:
DNA was extracted from 92 saliva samples, genotyped on three Infinium arrays (Global Screening Array, OncoArray-500K, Global Diversity Array), and imputed on the Michigan server. We assessed the concordance (Fleiss's Kappa) of 313 variants in the breast cancer risk PRS, correlation of PRS between arrays, and concordance in risk classification. High risk was defined as PRS>0.6 (the 80th centile PRS of the reference dataset [distribution: *Normal(mean=0.130, standard deviation=0.565)*]).

Results:
Of the 313 variants, 40 and 180 variants were typed and imputed on all arrays, respectively. PRS_{313}, were similar for the three arrays, with $P_{pairwise,\ t\text{-}test}>0.05$ ($correlation_{GSA\sim OncoArray}=0.910$, $correlation_{GDA\sim OncoArray}=0.943$, $correlation_{GDA\sim GSA}=0.920$). We observed reduced correlation ($correlation_{highest}=0.828$) when only variants with high imputation quality ($R^2>0.9$) were included from each array ($PRS_{R2>0.9}$).

PRS_{313} SD ranged from 0.549 to 0.566, similar to $SD_{reference\text{-}dataset}=0.565$. Lower SD (0.414-0.515) was observed for $PRS_{R2>0.9}$. Moderate concordance (Kappa=0.781) was observed for risk classification after correcting for mean differences ($difference=mean_{array}-mean_{reference}$) using PRS_{313}; 20-23% (expected=20%) of our sample were classified as high-risk. Weak concordance (Kappa=0.532) was observed for $PRS_{R2>0.9,}$ with lower proportion (10-21%) classified as high-risk.

Conclusion:
In our application of PRS for risk classification, all variants should be included to achieve similar SD as the reference. Mean correction is required for different arrays to achieve similar high-risk proportion as the reference.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Genome-wide association studies, polygenic risk scores, breast cancer, risk-based screening, concordance

79 Predictors for Positive Genetic Diagnosis of Monogenic Kidney Disease.

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Background & Objectives:
The genetic diagnostic yield for monogenic kidney disease varies between 25-30% in paediatric patients and 10-30% in adults. Genetic testing is recommended for chronic kidney disease (CKD) patients showing hereditary clinical features. This local clinical implementation pilot study aims to identify predictors for a genetic diagnosis.

Method(s) and Results:
This study enrolled 147 probands with primary glomerular diseases or CKD of unknown etiology, of whom 102 (69.4%) were adults and 45 (30.6%) were paediatric patients. The mean age at recruitment was 33.1 ± 18.4 years and 61 (41.5%) were females. The mean age of disease onset was 24.5 ± 17.4 years. These probands comprised of 118 (80.2%) Chinese, 12 (8.2%) Malays, 10 (6.8%) Indians, and 7 (4.8%) from other ethnicities. Clinical-grade targeted panel testing or whole exome sequencing was performed. The overall genetic diagnostic rate was 34/147 (23.1%) while 4 probands (2.7%) had variants of uncertain significance that were of high pathogenic suspicion. Through multivariate logistic regression, factors associated with a genetic diagnosis included female gender (OR 6.7; 95% CI 2.1-21.8; p=0.001), presence of extrarenal malformations (OR 3.5; 95% CI 1.1-11.5; p=0.039), and Alport features on renal biopsy (OR 17.7; CI 1.4-23.3; p=0.029). Surprisingly, younger onset of kidney disease at presentation and a positive family history did not predict the presence of genetic kidney disease in our cohort.

Conclusions:
The genetic diagnostic rate in our cohort mirrors existing international data. Female gender, extrarenal malformations, and Alport features on renal biopsy are associated with a positive genetic result.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Genetic Testing, Monogenic Kidney Disease, Predictors

80 Early life proteomic markers for child depressive symptoms

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Background & Objectives:
Depression is common mental disorder and a leading risk for the mental health of children and adolescents. Proteins being the main component in biological processes, proteomics offers insights into the disease mechanisms for depressive disorder. This study investigated the impact of neurology-related proteomic biomarkers on child depressive symptoms, in the Growing Up in Singapore Towards healthy Outcomes (GUSTO) cohort.

Method(s) and Results:
Neurology-related proteins were measured using plasma samples collected at ~8 years (N=528) on the Olink Target 96 Proteomics Panel. Depressive symptoms, specifically emotional problems and functional problems, were assessed using Children's Depression Inventory 2nd Edition (CDI-2) at visits from year 8 to year 10.5. We employed Empirical Bayesian method with Elastic Net prior (EBEN) to prioritise protein markers associated with the CDI-2 scores. We found that Cathepsin C (CTSC, posterior beta=0.09, p=0.033) and poliovirus receptor (PVR, posterior beta=0.12, p=0.007) to be significantly associated with emotional problems, and secreted frizzled-related protein 3 (sFRP-3, posterior beta=0.002, p=0.031) with functional problems. Moreover, from the multiple linear regression model, higher sFRP-3 is associated with more functional problems (beta=0.40, p=0.010, 95% CI 0.09~0.70) and higher PVR (beta=0.38, p=0.002, 95% CI 0.14~0.61) is associated with more emotional problems, while CTSC is associated with more emotional problems, particularly in boys (beta=0.33, p=0.001, 95% CI 0.14~0.53).

Conclusions (Significance and Impact of the Study):
We found that higher PVR, CTSC, SFRP-3 protein markers were associated with more emotional and functional problems, with potential sex-specific association between CTSC and emotional problems.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
mental health, child depressive symptoms, proteomic markers, elastic net, birth cohort

81 Genetics and Genomics Education Programmes in Singapore

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Background:
The Singapore National Precision Medicine program is a 10-year strategy to establish active application of precision medicine in the research and clinical settings to improve the nation's health. Training for healthcare professionals on genetics, genomics and counselling is a key component for the implementation of cost-effective clinical genetic services in healthcare institutions. Genetics Education for Medical Professionals Workshop and Executive Certificate Programme in Clinical Genomics are the two genetics and genomics education programs in Singapore to address the genomics education gap in healthcare professionals.

The Genetics Education for Medical Professionals Workshop:
The half-day interactive workshop focuses on educating healthcare professionals on clinical application of genetic testing, practical aspects of genetic counselling and current legal framework regulating genetic testing. Blended teaching with flipped classroom teaching approach allows more time to be allocated for role-playing to develop communication and genetic counselling skills. Each participant has an opportunity to role-play to be a counsellor, counselee and observer(s) in different case scenarios.

Executive Certificate Programme in Clinical Genomics:
The intensive 5-day programme is offered to healthcare professionals who wish to develop a deeper understanding of clinical genomics and to equip themselves with genetic counselling skills. The programme consists of four modules: i) Basics in genetics and genetic testing; ii) Application of clinical genetics; iii) The role and application of genetic counselling; iv) A practical approach in the application of genetic counselling. The assessment for the participants includes multiple choice questions on various topics in clinical genomics and genetic counselling and their participation during the role-play session. Post-course evaluation showed positive learning impact on the participants' knowledge/skills on genetics/genomics and counselling.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Genomics Education, Genetic counselling, Blended teaching, Role play, Learning impact

82 Association of thyroid peroxidase antibodies and high-sensitivity C-reactive protein: a cross-sectional analysis from the ELSA-Brasil study

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Background & Objectives:
Previous studies have suggested that increased thyroid peroxidase antibodies (TPOAb) levels are a low-grade inflammation marker; however, little information is available about its association with high-sensitivity C-reactive protein (hs-CRP). Our aim was to explore the association between TPOAb titers and high hs-CRP using baseline data from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil).

Method(s) and Results:
Participants with hs-CRP <10mg/L and without previous cardiovascular disease or stroke were included (n=12,078; mean age 51.6±8.9; 54.6% women). Fasting serum of hs-CRP and TPOAb were measured. High hs-CRP was defined as values between 3-10 mg/L. TPOAb was categorized as undetectable (≤5.00 IU/mL), low detectable (5.01-14.99 IU/mL), high detectable (15.00-33.99 IU/mL), and positive TPOAb (≥34.00 IU/mL). Univariate and multivariate logistic regression models were assessed. For sensitivity analysis, we excluded individuals with subclinical and clinical thyroid diseases and those on medications that affect thyroid function.

In the univariate analysis, participants with high detectable (OR:1.34; 95%CI: 1.07-1.68; p=0.011) and positive (OR:1.30; 95%CI: 1.03-1.65; p=0.027) TPOAb levels were more likely to have high hs-CRP. After multivariable adjustment, only the high detectable group showed higher odds of having high hs-CRP (OR:1.33; 95%CI: 1.04-1.68; p=0.020). In the sensitivity analyses, the association was attenuated by risk factors (OR: 1.28; 95%CI: 0.99-1.67; p=0.061) and by thyroid function markers (OR:1.30; 95%CI: 1.00-1.70; p=0.048).

Conclusions:
There was an association between TPOAb and hs-CRP, and this association was consistent even when considering thyroid function. These findings suggest a potential relevance of TPOAb detectability as a marker of low-grade inflammation.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Systemic inflammation, thyroid autoimmunity, C-reactive protein, iodide peroxidase, thyroid function

83 Thyroid peroxidase antibodies are associated with incidence, but not progression, of coronary artery calcification: analysis of the ELSA-Brasil cohort study

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Background & Objectives:
Previous studies have reported contradictory results regarding the association between thyroid peroxidase antibodies (TPOAb) and subclinical atherosclerosis. We explored the association of TPOAb levels with CAC incidence and progression in an ethnically diverse cohort.

Method(s) and Results:
We included individuals with no prior cardiovascular disease and two CAC measurements in ELSA-Brasil (3015 individuals, 57.2% women, 49.3±8.1 years). Fasting plasma TPOAb levels were used as continuous data (log-transformed), categorized in quartiles and as positive TPOAb. We defined incident CAC as a baseline CAC=0 followed by CAC>0 on the second visit. CAC progression was defined according to Berry and Hokanson methods. We performed Cox and logistic regression models were used.

The mean interscan period was 5.0 ± 1.0 years. CAC incidence occurred in 333 (14.5%) of 2292 individuals. Among the 723 participants with CAC > 0 at baseline, 45.4% (Berry) and 60% (Hokanson) had progression of CAC. The highest quartile of TPOAb was associated with a higher risk of CAC incidence when compared to the lowest quartile, even after multiple adjustment (HR: 1.53 95%CI: 1.11-2.11). Similar result was observed for euthyroid participants (HR: 1.62 95%CI: 1.11-2.37); which also showed that higher levels of TPOAb, as a continuous variable, were associated with a higher risk of CAC incidence (HR: 1.23 95%CI: 1.05-1.44). There was no significant association between TPOAb titers and CAC progression (p=NS).

Conclusions:
Individuals identified with higher normal-range TPOAb levels seems to present an elevated risk for developing incident CAC and may need an earlier reassessment compared to those with lower levels of TPOAb.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Systemic inflammation, thyroid autoimmunity, subclinical atherosclerosis, epidemiology, iodide peroxidase.

84 Constructing a 3D anatomical atlas of hepatic vasculature variants for surgical planning

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Background & Objectives:
Anatomical variation is a key facet of phenotypic diversity within populations. Our objective is to develop a 3D anatomical variation atlas of hepatic vasculature (hepatic artery, portal veins and hepatic veins). This atlas will serve to aid surgeons in pre-operative surgical planning and to provide guidance for deep learning segmentation models to achieve precise segmentation of hepatic vasculature from medical images.

Methods and Results:
Methods: To identify anatomy variations through literature and textbooks review and collaborate with hospitals to collect images for the related variations. Where actual CT/MR images are available, use the image processing software Hexa3D to create the 3D model. For the known variations without available images, Hexa3D will be used to construct 3D models using generative AI.

Results: At present, we have gathered approximately 500 anonymized patient CT or MR liver images with patients' consent. An initial data base of 14 anatomical variants are available, which include 5 portal vein, 3 hepatic artery and 6 hepatic vein variations.

Conclusions:
The atlas will provide valuable insights and play a crucial role in precision surgery when used to develop accurate 3D models for segmentation.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
anatomical variation, hepatic vasculature, surgical planning, precision medicine, quantitative imaging

85 The Genetic Heterogeneity & Phenotypic Continuum of Developmental and Epileptic Encephalopathies: Data from a Sri Lankan Cohort

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Background & Objectives:
Developmental and epileptic encephalopathies (DEEs) is a subtype of epilepsy syndromes, which has a negative impact on neurodevelopment, life expectancy and seizure control. This study was done to determine the genetic and phenotypic characteristics of children who underwent exome sequencing on the suspicion of an epilepsy syndrome.

Method(s) and Results:
All eighteen children referred to the Centre for Genetics & Genomics over a period of eight years for the evaluation of an epilepsy syndrome was included. Average age at genetic testing was two years and the average time elapsed from onset of seizures to genetic diagnosis was eighteen months. Almost all infants had developed seizures by six months of age and 70% had drug resistant convulsions. Only one family was consanguineous and one third had a family history of seizures.

The overall diagnostic yield by whole exome sequencing was 40% which included six cases of Dravet Syndrome, two each with DEE subtype 4 and 62 and the rest spanned the spectrum of DEE; Type 2, 9, 11, 13, 36, 54, 94 and 99. A total of eighteen variants in eleven genes was detected. 70% were likely pathogenic or pathogenic variants and almost 40% were novel variants.

Conclusions (Significance and Impact of the Study):
Whole exome sequencing is a powerful early diagnostic tool to drive therapeutic decisions and empower families to make reproductive and prognostic decisions. This study is among the first to report the unique genetic landscape and phenotypic features of developmental and epileptic encephalopathies in the Sri Lankan population.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Developmental and epileptic encephalopathy (DEE), Dravet syndrome, Epilepsy syndromes, early infantile developmental and epileptic encephalopathy (EIDEE), Epilepsy

86 De-novo Sub-clustering of Young-Onset Type 2 Diabetes Identify Subgroups with Distinct Clinical Characteristics

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Background & Objectives:
Data-driven subclassification approaches have been used to refine type 2 diabetes (T2D) into relatively homogeneous subgroups using clinical variables. In this study, we aim to perform sub-clustering of individuals with young-onset T2D using a similar approach to identify more homogeneous subgroups for disease-risk stratification.

Method(s) and Results:
661 patients with young-onset T2D (onset age ≤40 years old) recruited through two ongoing prospective studies (NHG-KTPH monogenic diabetes (MODY) registry and young-onset T2D (YT2D)) were included in this study. Genetic testing and autoantibody assays were performed to exclude monogenic diabetes and autoimmune-related diabetes, respectively. De-novo k-means clustering was performed using four clinical variables (BMI, HbA1c, HOMA2-B and HOMA2-IR). We identified three subgroups with distinct clinical features: Cluster 1 (33%) was characterised by insulin insufficiency attributed to poor β-cell function (severe insulin-deficiency diabetes). Cluster 2 (38%) had obesity-related insulin resistance and preserved β-cell function (mild obesity-related diabetes). Cluster 3 (29%) had the worse glycaemic control attributable to long standing diabetes duration and insulin resistance (severe insulin-resistant diabetes).

Conclusions (Significance and Impact of the Study):
Sub-clustering of young-onset T2D into homogenous subgroups allows the identification of individuals at greater risk of developing diabetes-related complications and enable individualised treatment regimens. Future studies will be required to correlate the subgroups with long-term disease outcomes to inform clinical decisions.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
diabetes subtypes, young-onset diabetes, sub-clustering, personalised medicine, machine learning

87 Circulating proteomic profiles are associated with the onset of type 2 diabetes in a multi-ethnic Asian population – a longitudinal study

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Background & Objectives:
Type 2 diabetes (T2D) is a major global concern, with Asia at its epicenter in recent years. Proteins serve as dynamic biomarkers for pinpointing perturbed pathways in disease development. As the pathogenesis of T2D varies across populations, the transferability of previously reported T2D associated proteins and novel discoveries in Asian populations can highlight similar and unique pathways associated with the onset of T2D to aid in the understanding of complex molecular mediation mechanisms.

Method(s) and Results:
We examined the association of 4,775 plasma proteins with incident T2D in a Singapore multi-ethnic cohort of 1,659 Asian participants (539 cases and 1,120 controls). Our analysis revealed 522 proteins were associated with incident T2D after adjusting for age, sex, and ethnicity. Of 479 proteins previously reported to be associated with T2D, 382 (79.75%) showed the same direction of effect in our study. Among the 522 proteins associated with incident T2D, changes in 198 proteins measured at two timepoints were further associated with incident T2D. These proteins showed enrichment in neuron generation, glycosaminoglycan binding, and insulin-like growth factor binding. Two-sample Mendelian randomization analysis suggested that three plasma proteins, GSTA1, INHBC, and FGL1, may have causal roles in the development of T2D, with colocalization evidence supporting GSTA1 and INHBC.

Conclusions:
Our findings reveal plasma protein profiles linked to the onset of T2D in Asian populations, offering insights into the biological mechanisms of T2D development.

Conflict of interest:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Type 2 diabetes, circulating proteomics, longitudinal change, Mendelian randomization, colocalization.

88 Deciphering the Epigenetic Role of Small Non-coding RNA in Obesity

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Abstract:
Obesity is a metabolic disorder that can be transmitted to the next generation by small non-coding RNAs (sncRNAs) through a mechanism known as "Transgenerational Epigenetic Inheritance". The sncRNAs are a crucial component of the human epigenome that are highly vulnerable to environmental effects. Bariatric surgery induced-weight loss could serve as a surrogate weight loss model to investigate the alteration of sncRNAs. Through this "BEACON" study we aim to carry out an extensive profiling of saliva, plasma, and sperm sncRNA pre- and post-gastric bariatric surgery: (i) To identify the characteristic sncRNA (miRNAs, piRNAs and tRFs) signature of obesity (ii) To determine the surgery-altered sncRNAs and their downstream targets.

Pre-surgery recruitment has been completed and samples have been collected from 17 men and 16 women (N=33). Post-surgery sample collections are on-going; and so far, collections from 21 volunteers (9 men and 12 women) have been completed. The bariatric surgery as expected has brought about significant weight loss and reduction in HbA1c and Trigylcerides. After the completion of all post-surgery sample collections, profiling and comparison of salivary appetite related hormones, blood cardiometabolic markers, sperm quality parameters will be carried out. RNA will be extracted and sent for sequencing, following which sncRNA profiles will be generated and compared (post vs pre-surgery) to determine the sncRNA biomarkers linked to obesity.

A deeper understanding of obesity and weight loss related epigenetic mechanisms will help unravel distinct small non-coding RNA signature of obesity that influence the metabolic health and raise societal and social awareness of preconception behaviour.
Conflict of interest disclosure: The authors declare no potential conflicts of interest, whether scientific, financial, and personal.

Keywords:
obesity, weight loss, bariatric surgery, epigenetics, small non-coding RNAs

89 Can deep learning-based retinal omics personalise cardiovascular disease prediction?

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Background and objectives:
Cardiovascular disease (CVD) is ubiquitous and imposes high costs and mortality for patients and healthcare systems globally. Early and tailored diagnosis and treatment modalities may reduce CVD deaths and spending.

We aim to improve early CVD detection by using deep learning to find and refine biomarkers specific to the early stages of different CVD subtypes.

Methods:
We performed a targeted literature review to find the latest cardio-oculomics deep learning algorithm (DLAs) that discover CVD biomarkers. RetiAGE is a novel DLA that uses retinal photographs to estimate biological age and risk level for CVD mortality.
We examined 57,297 retinal fundal photographs (RFPs) from the UK Biobank (UKBB) after quality control. We generated RetiAge scores of these samples and confirmed that the RetiAGE scores were statistically significant in forecasting CVD events via multivariate Cox proportional hazards (CoxPH) regression analysis adjusted for age and sex. We performed subgroup analysis via univariate CoxPH analysis on subtypes and divided the cohort into quartiles based on RetiAge scores.

Results:
RetiAGE predicts specific CVD subtypes, especially valvulopathies, embolic stroke, and arrythmias. RetiAge can capture subclinical changes in the retina in early-stage CVD, especially in essential (primary) hypertension. Subgroup analyses showed that the trend of hazard ratios of CVD events increasing from quartiles 2 to 4 was generally present in most subtypes.

Conclusion:
DLAs can detect subclinical changes to predict and stratify CVD morbidity. As CVD is heterogenous, adjusting the RetiAge score to specific subtypes may allow personalised CVD subtype risk ranking, which may improve health outcomes.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
cardiovascular disease, ophthalmology, retinal fundal photographs, predict, deep learning

Layman abstract:
Heart disease is common and serious. We can prevent or treat it better if we find it early. To do this more efficiently and accurately, we used deep learning to look for clues in eye pictures that predict future heart disease risk. We used a new method called RetiAGE that tells biological age and death risk from eye pictures to check 57,297 samples from a health database. We assigned a RetiAGE score to each eye picture and found that the RetiAGE score is good at predicting heart disease. Moreover, the RetiAGE score is especially good at predicting certain types of heart disease, namely: high blood pressure, chest pain, heart attack, irregular heartbeat, brain damage, and stroke. Our results suggested that deep learning can use eye pictures to find hidden heart disease and estimate its severity. This can help us personalise earlier prevention and treatment, thereby saving lives.

90 Coronary calcium score levels and risk for fatal and non-fatal cardiovascular events – the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

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Background & Objectives:
The coronary artery calcium score (CAC) is an indicator of atherosclerosis and levels above zero are associated with higher cardiovascular events (CVE). This study investigated the risk for CVE according to CAC levels in the ELSA-Brasil cohort study.

Methods and Results:
A sample of 4,389 participants (50.8 ±8.8 years, 54.4% women), without cardiovascular disease at baseline, were assessed. CAC was evaluated by computed tomography and classified into 0, 1-99, 100-199, 200-299, and ≥300 Agatston units. Non-fatal CVE were recorded in 5-year follow-up, while fatal CVE were counted from baseline (2008-2010) until December 31, 2022. Kaplan-Meier curves of cumulative risk for CVE were compared by log-rank test, and risk ratio (RR, 95% confidence interval) was analyzed by Cox regression, adjusted for sociodemographic and traditional risk factors. A total of 121 CVE was adjudicated (16 fatal and 105 non-fatal). CAC>0 was observed in 27.7% of sample. Log-rank test showed increased risk for CVE according to CAC increase ($p<0.001$). When compared to CAC=0, the risk for fatal and non-fatal CVE was RR=2.46 (1.45; 4.18) for CAC=1-99; RR=3.63 (1.77; 7.46) for CAC=100-199; RR=9.60 (4.46; 20.62) for CAC=200-299; and RR=5.91 (3.12; 11.22) for CAC≥300. When stratified according to fatal and non-fatal CVE, no significant association was observed between CAC levels and fatal CVE, while non-fatal CVE remained associated with CAC.

Conclusions:
A higher RR for CVE was observed at higher levels of CAC. The low occurrence of fatal CVE in ELSA-Brasil cohort limited its association with CAC beyond traditional risk factors.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Atherosclerosis; Coronary calcification; Cardiovascular events; Cardiovascular risk factors; Mortality

92 Nurturing minds, nourishing bodies: Associations between maternal mental health, feeding practices and child eating behaviours in the GUSTO cohort.

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Background & Objectives:
Poor maternal mental health is associated with childhood obesity, though specific pathways are unclear. Mothers with mental health issues may struggle with caregiving, which could lead to poor feeding practices and, in consequence, poor child eating behaviours. We investigate the relationship between maternal mental health, maternal feeding practices and child appetitive traits in the first three years of life in the Growing Up in Singapore Towards healthy Outcomes (GUSTO) cohort.

Method(s) and Results:
Data from 242 GUSTO children and mothers were analyzed. Child appetitive traits were measured at 36 months using the Child Eating Behaviour Questionnaire (CEBQ). Maternal mental health scores were measured at five time points (pregnancy week 26; 3, 12, 24 and 36 months) using the Edinburgh Postnatal Depression Scale (EPDS), Beck's Depression Inventory (BDI) and the State-Trait Anxiety Inventory (STAI). Maternal feeding practices were measured at 36 months using the Preschooler Feeding Questionnaire (PFQ). We conducted exploratory mediation analysis to assess if maternal feeding practices mediate the association between maternal mental health and child appetitive traits. Preliminary findings suggest that maternal mental health indirectly influences child appetitive traits through the mediating role of feeding practices.

Conclusions (Significance and Impact of the Study):
We found a mediating effect of feeding practices on the relationship between maternal mental health and child appetitive traits - complete mediation effects for two subscales CEBQ subscales, partial mediation effects for four CEBQ subscales and two weak partial mediation effects for two CEBQ subscales. Mothers with mental health concerns may require targeted child feeding interventions to prevent childhood obesity.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Maternal mental health, appetitive traits, eating behaviours, feeding practices, child obesity

93 Predicting early-life BMI Trajectories through Proteomics Data by learning Parametric Koopman Decomposition

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Background & Objectives:
Influences of obesity in early life can persist in adulthood and contribute to an increase risk of chronic diseases in later life. The rising prevalence of child obesity poses significant challenges to optimal human healthy longevity. The prediction of body mass index (BMI) trajectories is essential for early management of obesity. While much of the existing research has concentrated on retrospective analyses to pinpoint biomarkers linked to BMI, the intricate dynamics between proteomics and the progression of BMI have yet to be fully explored.

Method(s) and Results:
Using 92 neurology-related proteins measured in plasma using the Olink Target 96 Proteomics Panelof the 355 children at year 8 (49.2% girls) from Growing Up in Singapore Towards healthy Outcomes (GUSTO) cohort, we designed a novel deep-learning (DL) model named EDMD-proteomics to reconstruct and predict the children's BMI trajectories from year 3 to year 9. EDMD-proteomics employed the Parametric Koopman Decompositions, as an Extended Dynamic Mode Decomposition (EDMD) to frame BMI trajectory prediction as a parametric problem, considering proteomics as the control input for each child. EDMD-proteomics model outperformed three baselines: shallow neural network using proteomics (NN-proteomics), linear model using proteomics, and spline regression using historical BMI, in predicting the children's year 9 BMI with a leading test RMSE of 1.589, significantly better than the second-best competitor, NN-proteomics, at 2.159.

Conclusions:
In this work, we developed a novel DL framework, EDMD-proteomics, to reconstruct and predict the trajectory of children's BMI. EDMD-proteomics demonstrates its potential to aid clinicians in identifying early-life intervention strategies for child obesity.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Child BMI Trajectory, Proteomics, Birth Cohort, Parametric Koopman Decompositions, Deep Learning

94 Public expectations about the public interest of research

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Background & Objectives:
A number of regulatory frameworks governing access to health data require research to be in the public interest (or similar concepts). However, the concept of 'public interest' is rarely clearly defined, and the meaning of public interest may be depend in part on public perception and platform-specific context.

To help define context-sensitive criteria for the national data-sharing platform in Singapore, we gathered empirical data on Singaporeans' views and expectations about the public interest of research.

Method(s) and Results:
We applied a mixed-method approach consisting of in-depth exploratory focus group interviews followed by quantitative surveying, which allowed scope to generalise the qualitative findings. The research builds on our prior research exploring trust in health data-sharing among Singaporeans.

'Potential benefits for Singapore' was considered an important but not a necessary condition for research being in the public interest, as long as the research would promote health and wellbeing in general. Research performed by private companies could be considered to be in the public interest, as long as the produced benefits would be accessible to Singaporeans. Most doubts about public interest revolved around research involving sensitive data of minors.

Conclusions (Significance and Impact of the Study):
Those tasked with assessing the public interest criterion in Singapore and elsewhere should take into consideration how the Singaporean public understands the concept. Our research suggests various ways to specify and operationalize the concept, such as more careful scrutiny when sharing with for-profit entities and allowing public interest evaluations to include a wide range of impacts.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Data sharing, data access, public interest, public good

95 Spectrum of FBN1 Variants and Their Phenotypic Correlations in a Cohort of Twelve Sri Lankan Patients

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Background & Objectives:
Variations in the FBN1 gene result in a spectrum of overlapping clinical manifestations, such as Marfan syndrome (MFS), MASS syndrome, and ectopia lentis syndrome (ELS). Our aim was to investigate the correlation between genetic variants and clinical manifestations in Sri Lankan patients with FBN1 variants

Methods:
Clinical data were gathered retrospectively. This study included patients identified with pathogenic FBN1 variants through whole exome sequencing of the proband. The sequencing was conducted by the Human Genetics Unit, Faculty of Medicine, University of Colombo, between 2019 and 2023. Novel variants were thoroughly evaluated using in-silico prediction tools and protein modelling. The clinical diagnoses were made using the revised Ghent nosology criteria.

Results:
Twelve patients (50% male, mean age at presentation: 10.5 years) with FBN1 variants were identified, with no cases reporting a positive family history. According to the revised Ghent criteria, 50% (6/12) were diagnosed with MFS, 41.7% (5/12) with MASS syndrome, and 8.3% (1/12) with ELS. Plain pes planus and hindfoot deformities were the predominant presenting complaints and was evident in 83% (10/12) and 75% (9/12) respectively. All FBN1 variants were heterozygous: 75% (9/12) missense, 16.7% (2/12) frameshifts, and 8.3% (1/12) splice site variant. Of those, five were identified as novel. Frameshift and splice site variants were associated with pronounced facial features and severe skeletal abnormalities.

Conclusion:
This study highlighted the genetic and clinical profiles of twelve Sri Lankan patients carrying pathogenic FBN1 variants, including the discovery of five novel variants causing damaging effects on the fibrillin-1 protein.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
FBN1, Marfan syndrome, Exome sequencing, Fibrillin-1, Sri Lanka,

96 Evaluating quantitative proximity extension assay as a monitoring tool for precision health

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Background & Objectives:
The human plasma proteome comprises a myriad of proteins with concentrations spanning more than 9 logs. Multiplex proteomic profiling suffers from a mismatch in dynamic range amongst the various cytokines, chemokines and other inflammatory markers frequently used to assess safety and immunogenicity in vaccine and drug trials.

Methods and Results:
Technical evaluation showed robust performance of Olink Target 48 Cytokine, a tool based on proximity extension assay, to provide quantitative readouts for 45 human protein biomarkers that mediate inflammation and immunity. We consistently observe 8 protein biomarkers with low detectability in healthy baseline samples. High concordance was observed for between day samples tested by two different operators, suggesting assay precision and reproducibility.

Conclusions:
The Olink Target 48 Cytokine assay shows robust performance for quantitative measurement of 45 protein biomarkers, demonstrating its suitability for monitoring human plasma profiles in precision health studies.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
proximity extension assay, precision health

97 Next generation proteomic profiling of a pan-cancer cohort for the development of screening tools for cancer

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Abstract:
A comprehensive characterization of blood proteome profiles in cancer patients could provide a better understanding of disease biology, enabling earlier diagnosis, risk stratification and better monitoring of the different cancer subtypes.

Here, we describe the use of next generation protein profiling to explore the proteome signature in blood across patients representing 12 major cancer types. Plasma profiles of 1463 proteins from more than 1400 cancer patients of the Uppsala-Umeå Comprehensive Cancer Consortium

(U-CAN) biobank was measured at the time of diagnosis and before treatment. Using machine learning methods, the differentially expressed proteins identified were used to derive models to discriminate among different cancer types. A panel of 83 proteins was found to identify the correct cancer types with AUCs ranging between 0.93 and 1. Preliminary analysis indicated that the protein panel was able to discriminate all cancers from healthy controls and showed promising performance in both staging some of the cancer types, and in detecting very early-stage cancer. The data from this study was made available via the Disease Blood Atlas, an open-access resource.

The results were used as a foundation to establish the Olink Insight platform, an open-access digital data resource to accelerate adoption of proteomics in the research community. In Olink Insight, we are creating a collection of proteomic profiles for important diseases, beginning with cancer. Olink Insight and the Human Disease Blood Atlas represent a significant step towards uncovering human disease proteome and will be a valuable resource for researchers in many areas of medicine and biology.

Conflict of interest disclosure:
RB, MR, RL, OC, HA, LF are employees of Olink Proteomics

Keywords:
Proteomics, pan-cancer cohort, cancer detection, cancer staging, Olink Insight

98 Severe Combined Immunodeficiency (SCID) Screening in Singapore

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Introduction:
SCID is a rare but life-threatening disorder characterized by a group of inherited immune disorders in which T-lymphocytes fail to develop, and B-lymphocytes are either absent or compromised. Untreated patients develop life-threatening infections caused by bacteria, viruses, and fungi. Timely diagnosis is crucial for early intervention and improved clinical outcomes. Here, we discuss the implementation of SCID screening in Singapore in the last 4 years.

Methods:
TREC assay was carried out using EnLite™ Neonatal TREC kit using dried blood spot collected on Guthrie filter card between 1-7 days. TREC > 18 copies/µL on a single DBS obtained at any age were considered normal. Low TREC value with a low beta-actin < 30 copies/µL was considered invalid, and a repeat blood spot is required.

Samples whose TREC was ≤18 copies/µL and beta-actin >30 copies/µL were considered positive if the baby was ≥32 weeks gestational age and ≥1500g, and urgently positive if the TREC was <4 copies/µL regardless of the baby's gestational age. Presumptive positive cases were immediately referred to the on-duty pediatric immunologist for further clinical and immunological evaluation. If the TREC was between 4 to 18 copies/µL and the baby was <32 weeks or <1500g the result was deemed inconclusive (premature) and a repeat sample was collected at 2 weeks of life.

Results:
From Oct 2019 to Dec 2023, 147,562 newborns were screened. Of these, 159 samples (~0.10%) were recalled for repeat testing. 3 syndromic babies with T-cell lymphopenia and one primary SCID screened positive.

Conclusion:
SCID screening is successfully implemented in Singapore.

99 The Human Gut Microbiome in Pregnancy and Early Life: Insights from the GUSTO and S-PRESTO multi-ethnic Asian Cohorts

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Objective:
Pregnancy and infant development are two critical time windows, as the gut microbiome's initial establishment and maturation during these stages lay the foundation for long-term human health and are key in preventing non-communicable diseases. We aim to understand: 1) how women's microbiome alter from preconception to post-delivery, and its link with women's metabolic health; 2) the colonization of gut microbiome in early life and how various intrinsic and early-life factors influence their acquisition; 3) how modern world practices delay or endanger the colonization of certain beneficial microbes in the human gut.

Methods:
Gut microbiome was analyzed longitudinally at preconception, 1st, 3rd trimester and 6 weeks post-delivery in the S-PRESTO cohort (n = 1304). Infant or child gut microbiome was analyzed at Day 3, week 3, Month 3, 6, 12 and 24. Demographic, detailed body composition, and other metabolic measurements were analyzed in both cohorts.

Results:
The gut microbiome were dynamically altered from perception to postpartum, with alterations during pregnancy were subtle, while those during the transition from preconception to pregnancy and pregnancy to postpartum were more pronounced. Ethnicity and BMI had longitudinal influences on the mother's gut microbiome. The inter-individual variation in the gut microbiome at preconception was significantly associated with BMI, HbA1c, age, ethnicity, education, and parity, while delivery mode and antibiotics usage influenced the postnatal maternal gut microbiome. *Streptococcus anginosus* and *S. salivarius* significantly increased from preconception to pregnancy but decreased post-delivery after accounting the effects of the maternal phenotypic variables. *S. salivarius* positively correlated with visceral and subcutaneous adipose tissue volumes post-delivery. Differential microbes were identified for the early prediction of gestational diabetes (GDM). Ethnicity, mode of delivery, breastfeeding status, *Fucosyltransferase* 2 (*FUT2*) genotype, and repeated antibiotics exposure were the key

factors affecting the early-life gut microbiome after mutual adjustment. Metagenomics analysis identified phylogenetically related Bifidobacteria species to have opposite abundance trends in the gut of children with different *FUT2* genotypes. Generational immigration delayed the colonization of *Bifidobacterium* in early life, and 95.6% of the infants surveyed in this study had undetectable *B. infantis*.

Conclusions:
Our findings underscore the critical importance of the gut microbiome's development from preconception to early life as foundational to human health. By elucidating the dynamics of microbiome changes during these pivotal stages and the adverse effects of modern practices on beneficial microbial colonization, our research highlights the potential for targeted interventions in these windows to forge a healthier start for future generations. This work lays the groundwork for innovative public health strategies and underscores the urgent need for further research to explore the full potential of microbiome-focused interventions in disease prevention and health promotion.

100 Comparing Polygenic risk, Elastic Nets and Interpretable Artificial Intelligence Approaches in the Prediction of Vitamin D Insufficiency in Pregnant Women and their Children

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Abstract:
Vitamin D deficiency presents significant health risks, particularly for pregnant women and children. With the increasing adoption of personalised genetics, there is a potential utility for genetic models to predict nutrient levels. To address this gap, this study focuses on developing a predictive model for maternal and child Vitamin D insufficiency using genetic factors.

The data for this study was collected from participants, including both mothers and children, from the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) cohort. Genetic data, specifically single nucleotide polymorphisms associated with vitamin D levels, was obtained along with serum vitamin D3 levels.

In our analysis, we utilized elastic nets and interpretable artificial intelligence (IAI) models. IAI models used include Optimal trees, Optimal feature selection and Optimal trees refitted with logistic regression models, namely optimal feature selection and elastic nets. The performance of these models in classification tasks was evaluated using the AUC, while regression tasks were evaluated using the MSE.

The Optimal Trees model refit with Elastic Nets performed the best in the prediction of maternal plasma vitamin D using maternal genetics(AUC 0.674). The same model also performed the best in the prediction of child plasma vitamin D using child genetics and maternal vitamin D levels, (AUC 0.739). The Optimal Feature Selection model performed the best in the prediction of child vitamin D using child genetics only(AUC 0.714).

Although these models require further validation with independent datasets, they lay a crucial foundation for using machine learning to predict nutritional deficiencies with a combination of genetic and environmental factors.

Keywords:
Vitamin D, Machine Learning, Pregnancy

101 Genetic adaptations of humans to the diverse environments of South America

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Abstract:
South America harbours diverse human populations inhabiting environmentally divergent habitats, such as high-altitude Andes, Amazon rainforest, semi-arid lowlands of Chaco, and frigid subarctic-regions of Patagonia. Indigenous populations inhabiting such harsh environments survive through environment-mediated lifestyles and could have built up genetic resilience against such harsh conditions, including endemic pathogens, through genetic adaptations. However, beyond Andean highlanders, genetic adaptations to other challenging environments in South America remain understudied. To detect the evidence of adaptation, we applied Population Branch Statistics (PBS) and Cross-Population Extended Haplotype Homozygosity (XP-EHH) selection test to high-quality whole genome data of indigenous populations from the Andes, Amazon, Chaco, and Patagonia. Our analysis applied high-resolution HLA allele calls across South American and worldwide populations, revealing population-specific immune adaptations in their HLA genes across different environments in South America. We identify several positively selected genes related to cardiovascular traits among Andean highlanders. Amazonians and Chaco populations showed strong adaptive signals in skeletomuscular and immunity trait genes, suggesting the influence of mobile hunter-gatherer lifestyle and high pathogen-endemicity. Subarctic Patagonians showed selection signals in genes influencing fat and developmental traits. Our study also revealed a potentially adaptive population-specific HLA allele frequency distribution in South Americans. For example, the elevated population-specific frequency of endemic Chagas disease protective HLA-A*39:09:01 allele in Patagonian populations. The study emphasizes how varied environmental challenges and pathogens have shaped the population-specific genetic adaptations of South American groups, offering profound implications for understanding human resilience and the environmental determinants of human health. The inferences from this study could also inform targeted functional studies on the adaptive genetic variants which could have crucial medical significances, vital for human health.

102 Virtual panels have a superior diagnostic yield for inherited rare diseases relative to static panels

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Background/Objectives:
Exome-base panels – also known as slices or virtual panels – are now a popular, cost-effective and efficient method of analyzing a capture backbone using a phenotype guided set of genes, especially in heterogenous disorders, performed in clinical laboratories optimizing genetic testing diagnosis. Given the advantages of potential interrogation of all the known human genes in exome slices, this strategy allows analysis flexibility by enabling frequent gene updates based on disease association and specific order requests.

Methods:
Here we perform exome slice testing on 949 mostly pediatric patients (50.7% females; age rage 3 months–82 years old) referred from multiple pediatric /clinics within a single Center in the Middle East specialties (82.8% Arabs; 17.2% non-Arabs).

Results:
The overall diagnostic yield was 27% out of the total exome slices reported. Interestingly, 13.2% of the positive cases were due to pathogenic variants identified in genes outside the “panel” gene list at the time of testing, and could have been missed in “static” panels as result of novel gene-disease associations and phenotype spectrum broadening.

Conclusion:
We highlight specific cases where this practice has resulted in better clinical management of patient upon the extracurricular findings; suggesting regular and guided disease-centric updates and modifications to gene lists composed and maintained by clinical laboratories for best practices and high-quality analysis of exome slices.

103 From North Asia to South America: Tracing the longest human migration through genomic sequencing

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*Presenting author: Hie Lim Kim

Abstract:
Within the GenomeAsia 100K project, aimed at generating comprehensive high-coverage whole genome sequencing datasets from diverse Asian populations, we conducted an extensive analysis on genome sequencing datasets from 1,537 individuals representing 139 ethnic groups. Our findings revealed the contrast population histories between North Asia and Native Americas. We were able to infer the complex genetic ancestries of North Asian populations, including 17 indigenous Siberian ethnicities, owing to frequent population admixture. Additionally, we demonstrated the migration history of peoples across Beringia, extending their journey to the southern tip of South America. Beringian populations, including the Eskimo, Chukchi, and Koryaks, were the closest ancestral groups to Native Americans, with recent gene flow between them. Furthermore, our analysis identified four distinct genetic ancestries among the earliest inhabitants of South America - Amazonians, Andeans, Chaco Amerindians, and Patagonians – and revealed population splits around 13,900 years ago. This population structure corresponds closely with biogeographic boundaries in South America, suggesting the impact of environmental factors on population history and their genetic background. The vastness of the South American continent likely resulted in immediate spatial isolation, leading to a significant reduction in genetic diversity following migration. The Patagonian ethnicities, including the Yagan and Kawésqar, have traveled the longest path out of Africa, leading to a small effective population size due to genetic drift. This, in turn, has resulted in reduced immunogenic diversity, increasing their vulnerability to past and current pathogens.

104 The Nile Delta of Precision Medicine: Prenatal Genomic Care in Highly Inbred Population

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Background and Objectives:
Beside its enormous impact on the patients and their families, genetic disorders pose a "huge" burden on the health care sector in Saudi Arabia due to the high rate of consanguinity, large family size, and the tribal nature of the Saudi society. There may be as many as 7000 genetic diseases that can be unraveled by next-generation sequencing. This number increases as novel rare genes are discovered every year. Prevention of these diseases is the objective through a pioneer prenatal program that integrates the essence of precision medicine.

Methods and Results:
Major prevention initiative has been undertaken to prevent these genetic diseases using prenatal genetic diagnosis at King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia. A comprehensive prenatal service has been re-organized to address the complexities and challenges related to the genetic diagnosis, heavy volume (≈30 prenatal cases/week), multiple referral sources, and time-pressure due to the 120-day fetal ensoulment (critical date prior to which fetal termination may be allowed for medical reason). A prenatal checklist has been developed to eliminate potential harm, and prenatal board formulated that consists of a team of consultant clinical geneticists, consultant obstetricians, molecular geneticists, genetic counsellors, and clinical coordinators. The team discusses the challenging prenatal cases and makes a collectively intelligent decision. Vigorous communication with various stakeholders inside and outside the institution and across the country is undertaken to ensure proper phenotyping and genotyping of the cases. Quality clinical, laboratory, and logistic issues are also discussed to provide a safe service. Multiple virtual prenatal clinics have been launched to keep the family well-informed and provide the best patient experience. Each family receives a personalized care through the state-of-the-art insightful precision medicine plan. The program has been expanded to two other major medical centers in Saudi Arabia. All these measures have been introduced for the first time in our institution in late 2023. Illustrative examples are to be presented. Regional clinical practice guidelines and research are being developed and written for the country. The program received a welcome note from the top leadership of the institution.

Conclusion:
Precision prenatal medicine embraces a theme of prevention. This unique program incorporates the current literature, collective group intelligence, effective communication, and optimal patient experience to provide the best personalized patient care in the best safe environment. Thousands of genetic diseases converge for prevention in this ambitious program from all over of the country analogous to the "Nile Delta" of Ancient Egypt.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Prenatal, precision medicine, consanguinity, inbred population, prevention

105 Genomics for KIDS in ASEAN: Improving access to genomic medicine for paediatric rare disease in Southeast Asia

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Background:
Application of clinical whole exome sequencing (WES) is especially transformative for paediatric rare diseases; however, equitable access remains a key barrier to implementation in the clinic. The Genomics for KIDS in ASEAN project aims to establish a clinical workflow for providing clinical WES to 500 under-resourced families in Southeast Asia and to build a knowledgebase in collaboration with regional experts to better serve the specific needs of Southeast Asian families.

Methods & Results:
We developed an end-to-end clinical workflow for constitutional DNA analysis with our regional partners, encompassing patient recruitment and consent, specimen collection and processing, sequencing, and bioinformatics analysis, variant interpretation, and reporting. The ISO-accredited workflow involved WES on genomic DNA using Illumina short-read platform and a custom-developed clinical bioinformatics framework. Notably, integration of ethnically-matched SG10K_Health population allele frequencies in our variant prioritization pipeline led to an average 13% decrease in total ultra-rare variants relevant for evaluation, with up to 30% less variants among the under-represented Malay ethnic group. To date, we have 38 participating Southeast Asian families across five nationalities and multiple ethnicities. Most are proband-parent trio analyses; 50% (19/38) involved a child with multisystem/congenital abnormalities, 47% (18/38) with neurodevelopmental disorders and 1 case with immune-related condition. Probands ranged from age 7 days to 22 years, with median age 2 years. Diagnostic yield was 59% (n=16) of 27 completed cases, with reportable findings mostly detected in neurodevelopmental (n=9) and multisystem/congenital abnormalities (n=7) cases.

Conclusion:
We demonstrated clinical utility of integrating ethnically-matched population genomic data in variant interpretation for paediatric rare diseases and showed 59% diagnostic yield among under-resourced Southeast Asian families using this optimized workflow.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Paediatric rare disease, genomic medicine, whole exome sequencing, Southeast Asia, clinical genetics

107 Defining and Reducing Variant Classification Disparities Across Human Populations

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Background:
Multiplexed Assays of Variant Effects (MAVEs) can test all possible single variants in a gene of interest. The resulting saturation-style data may help resolve variant classification disparities between populations, especially for variants of uncertain significance (VUS).

Methods and Results:
We analyzed clinical significance classifications in 213,663 individuals of European-like genetic ancestry versus 206,975 individuals of non-European-like genetic ancestry from *All of Us* and the Genome Aggregation Database. Then, we incorporated clinically calibrated MAVE data into the Clinical Genome Resource's Variant Curation Expert Panel rules to automate VUS reclassification for *BRCA1, TP53, and PTEN*.

Using two orthogonal statistical approaches, we show a higher prevalence ($p \leq 5.95e\text{-}06$) of VUS in individuals of non-European-like genetic ancestry across all medical specialties assessed in all three databases. Further, in the non-European-like genetic ancestry group, higher rates of Benign or Likely Benign and variants with no clinical designation ($p \leq 2.5e\text{-}05$) were found across many medical specialties, whereas Pathogenic or Likely Pathogenic assignments were higher in individuals of European-like genetic ancestry ($p \leq 2.5e\text{-}05$).

Using MAVE data, we reclassified VUS in individuals of non-European-like genetic ancestry at a significantly higher rate in comparison to reclassified VUS from European-like genetic ancestry (p=9.1e-03) effectively compensating for the VUS disparity. Further, essential code analysis showed equitable impact of MAVE evidence codes but inequitable impact of allele frequency (p=7.47e-06) and computational predictor (p=6.92e-05) evidence codes for individuals of non-European-like genetic ancestry.

Conclusions:
Generation of saturation-style MAVE data should be a priority to reduce VUS disparities and produce equitable training data for future computational predictors.

Conflict of interest disclosure:
JRL has stock ownership in 23andMe, is a paid consultant for Regeneron Genetics Center, and is a coinventor on multiple U.S. and European patents related to molecular diagnostics for inherited neuropathies, eye diseases, and bacterial genomic fingerprinting. JRL serves on the Scientific Advisory Board of Baylor Genetics. EV, JRL, and RAG declare that Baylor Genetics is a Baylor College of Medicine affiliate that derives revenue from genetic testing. BCM and Miraca Holdings have formed a joint venture with shared ownership and governance of Baylor Genetics which performs clinical microarray analysis and other genomic studies (exome sequencing and whole genome sequencing) for patient and family care. EV is a co-founder of Codified Genomics, a provider of genetic interpretation.

Keywords:
Variants of Uncertain Significance, genetic ancestry, multiplexed assays of variant effects, equity, precision medicine

108 Higher blood biochemistry-based biological age developed by advanced deep learning techniques is associated with frailty in geriatric rehabilitation inpatients: RESORT

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Background and objectives:
Accelerated biological ageing is a major underlying mechanism of frailty development. This study aimed to investigate if the biological age measured by a blood biochemistry-based ageing clock is associated with frailty in geriatric rehabilitation inpatients.

Methods:
Within the REStORing health of acutely unwell adulTs (RESORT) cohort, patients' biological age was measured by an ageing clock based on completed data of 30 routine blood test variables measured at rehabilitation admission. The delta of biological age minus chronological age (years) was calculated. Ordinal logistic regression and multinomial logistic regression were performed to evaluate the association of the delta of ages with frailty assessed by the Clinical Frailty Scale. Effect modification of Cumulative Illness Rating Scale (CIRS) score was tested.

Results:
A total of 1187 geriatric rehabilitation patients were included (median age: 83.4 years, IQR: 77.7-88.5; 57.4% female). The biochemistry-based biological age was strongly correlated with chronological age (Spearman r = 0.883). After adjustment for age, sex and primary reasons for acute admission, higher biological age (per 1 year higher in delta of ages) was associated with more severe frailty at admission (OR: 1.053, 95% CI:1.012-1.096) in patients who had a CIRS score of less than 12 not in patients with a CIRS score more than 12. The delta of ages was not associated with frailty change from admission to discharge. The specific frailty manifestations as cardiac, hematological, respiratory, renal, and endocrine conditions were associated with higher biological age.

Conclusions:
Higher biological age was associated with severe frailty in geriatric rehabilitation inpatients with less comorbidity burden.

Conflict of interest disclosure:
Alex Zhavoronkov and Fedor Galkin are employees at Deep Longevity, a for-profit Hong Kong company, subsidiary of a public company Endurance RP (0575.HK). The blood ageing clock described in this article is available for commercial use via the Senoclock online platform. Lihuan Guan, Camilla S.L. Tuttle and Andrea B. Maier declare no conflicts of interest.

Keywords:
Ageing; frailty; deep learning; laboratories; rehabilitation

109 The Federated EGA: A global network for discovery and access for sensitive human data

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Background & Objectives:
With increasingly strict regulations for managing sensitive human omics including healthcare-derived data, solutions are required to ensure research and clinical data can benefit the entire society. Safely sharing sensitive data is vital for successful data reuse to support biomedical research and personalised medicine programs.

Method(s) and Results:
The Federated European Genome-phenome Archive (FEGA) provides a data sharing solution of infrastructure and governance frameworks to support discovery of and secure access to human data globally, while respecting national data protection regulations. Initially motivated by European initiatives such as the 1+ Million Genomes and European Health Data Space, the Federated EGA was formally launched in 2022 with a network of nodes in the United Kingdom, Spain, Norway, Sweden, Finland, and Germany. Nowadays, in 2024, FEGA counts with 7 official nodes and over 16 at different levels of engagement. The next phase of Federated EGA will build upon these early successes to expand data sharing both within and outside of Europe. Accelerating this expansion can be achieved through collaboration with more initiatives working towards human data sharing, for example: Genome Data Infrastructure (GDI), Data Science for Health Discovery and Innovation in Africa (DS-I Africa), and Australian BioCommons.

Conclusions (Significance and Impact of the Study):
The Federated EGA is achieving its vision: to build a global, interoperable discovery and access network of human data resources, to accelerate disease research, understanding and improving human health.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
genomics, federation, node, FAIR, global, data, sequencing

110 Clinical Benefits of *CYP2C19* Genotype-Guided Therapy of Antiplatelets against Standard Care in Stroke Patients: Meta-Analysis

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Background and objectives:
Aggregated risk of composite vascular events for the stroke patients inheriting *CYP2C19* loss-of-function (LoF) alleles and administering alternative antiplatelets i.e. prasugrel/ticagrelor against standard antiplatelet therapy i.e. clopidogrel has not been investigated yet. It was aimed to perform a meta-analysis to assess the risk/benefit ratio of *CYP2C19* genotype guided antiplatelets therapy against standard care in these patients.

Methods and results:
Comprehensive literature search was carried out in different databases from the inception to December 31, 2023, following PRISMA guidelines. End points were composite vascular events and moderate to severe bleeding events. Odds ratio (OR) was calculated using RevMan software, in which $p<0.05$ was set as statistical significance. In total, five studies comprising of 9,221 stroke patients were finally considered in this meta-analysis, in which 4607 patients were in the *CYP2C19* genotype-guided group (taking prasugrel/ticagrelor) and 4614 patients were in the standard care group (taking clopidogrel). After pooled estimation, it was found that *CYP2C19* genotype-guided group administered prasugrel/ticagrelor significantly reduced the risk of composite vascular events compared to standard care group (OR 0.52, 96% CI 0.36–0.77; $p=0.0009$). However, there was no significant difference in bleeding toxicity between these two treatment groups (OR 1.06, 96% CI 0.65–1.73; $p=0.80$).

Conclusions:
The novel findings of this analysis demonstrates that *CYP2C19* genotype guided antiplatelets therapy can significantly reduce the composite vascular events, without raising the bleeding events. Robust evidence of this analysis may support and accelerate the implementation of precision medicine of antiplatelets in routine clinical practice for stroke patients.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Stroke, antiplatelets, *CYP2C19*, vascular events, precision medicine

111 Lipidomic signatures of insulin resistance and metabolic flexibility in Asian subjects identified from hyperinsulinemic-euglycemic clamp studies

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Background and objectives:
Insulin resistance (IR) is fundamental to the development of type 2 diabetes and usually precedes the disease by several years. However, the underlying molecular pathogenesis of insulin resistance remains to be understood. Here we wanted to perform metabolic phenotyping of non-diabetic Asian subjects according to their insulin sensitivity indices derived from the hyperinsulinemic-euglycemic clamp (HIEC) procedures.

Methods and results:
We used an integrated approach of anthropometric and biochemical measures in conjunction with serum lipidomics for metabolic phenotyping of multi-ethnic male subjects with varied insulin sensitivity. We stratified the study subjects (n=235) into tertiles of insulin sensitivity indices measured from HIEC procedures. By detailed characterization of the serum lipidomic profiles in fasting state as well as temporal changes during HIEC procedure, we identified a systemic metabolic response to HIEC procedure, represented by the marked changes in acylcarnitines, non-esterified fatty acids, lysophospholipids, sphingosine-1-phosphate and phosphatidylserine lipids. We demonstrate that a shared lipidomic signature between IR and liver fat shows gradual increase with increasing liver fat content. This shared lipid signature outperforms traditional lipid indices in predicting HIEC-derived insulin sensitivity indices.

Conclusions:
By stratifying non-diabetic subjects according to the insulin sensitivity indices derived from HIEC procedures, we identified a circulating lipidomic signature of insulin resistance and metabolic plasticity with a potential to aid in better management of metabolic health before the onset of development of type 2 diabetes and other metabolic diseases.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Insulin resistance, Metabolic syndrome, Metabolic dysfuction- associated steatotic liver disease, Dyslipidemia, Fatty acid and lipid metabolism, Lipidomics, Metabolic phenotyping

113 Advancing Personalized Medicine and Public Health: The Role and Impact of Qatar Biobank

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Abstract:
The Qatar Biobank (QBB) aims to collect comprehensive lifestyle, clinical, and biological data from up to 60,000 Qatari citizens and long-term residents aged 18 and above. Participants are invited to return every five years to monitor disease development, investigate its causes, and identify risk factors specific to the Qatari population. This presentation highlights the significant impact of QBB in identifying and reporting incidental findings (IFs).

Methods and Results:
Consented participants undergo a thorough collection of clinical, genetic data and imaging data from MRI scans, ultrasounds and other at QBB facilities. QBB has established a comprehensive framework to manage Ifs, ensuring ethical considerations, participant engagement, and data integrity. QBB reports IFs found in MRI scans, laboratory results, mental health assessments, and actionable genetic findings, facilitating timely referrals. Participants receive feedback from QBB physicians and are referred to appropriate healthcare services. In urgent cases, emergency referrals are made.

Case presentation:
On May 7, 2024, a 54-year-old female participant attended her MRI appointment at QBB. During the imaging, the radiographer detected an abnormality and notified the medical office. The attending physician identified the mass as a meningioma. After completing the MRI, the QBB physician issued an emergency referral, explained the diagnosis to the participant, and advised her to go to the emergency department immediately. The participant promptly went to HMC, where a contrast MRI confirmed the diagnosis. On May 12, she underwent surgery to remove the tumor and is now recovering well.

Conclusion:
Qatar Biobank's (QBB) comprehensive framework for managing Ifs significantly enhances personalized medicine by ensuring early disease detection leading to improved health outcomes and well-being.

Figures:

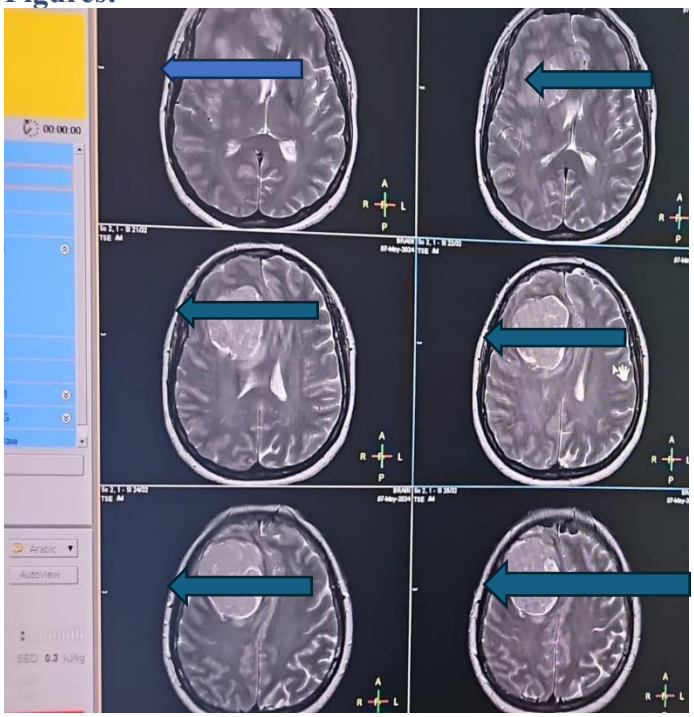

Figure 1 T2 MRI images showing the incidentally discovered large right frontal intracranial mass lesion with mild mass effect and midline shift suggestive of convexity meningioma.

Conflict of interest disclosure:

The authors declare no potential conflicts of interest, whether scientific, financial, and personal

Keywords:

Qatar biobank; precision medicine; biobanking; health care; incidental findings

114 A 15-year Pharmacogenomics Tests in a Thai Pharmacogenomic and Personalized Medicine Center

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Background and objectives:
Pharmacogenomics (PGx) assesses the effects of individuals' genetic variants on drug responses towards precision medicine. In this study, we evaluated 15 years of PGx testing performed in a Thai pharmacogenomics and personalized medicine clinic from January 2009 to January 2024.

Methods and results:
The targeted PGx variants were genotyped by polymerase chain reaction sequence-specific oligonucleotide probes (PCR-SSOP) method for Human Leucocyte Antigens (*HLA)* genes and the Real Time-PCR with pyrosequencing technique for non-*HLA* pharmacogenes. The results showed that most of the PGx tests were reactive which were requested by physicians in the hospital, where *HLA-B* for Carbamazepine (CBZ), Allopurinol (ALL), Abacavir and Co-trimoxazole revealed high-rate tests followed by *HLA-A*, *DRP*, *DQA1* and *DQB*. In total of 34910 tests were performed including 27059 *HLA* tests *(-A, -B, -DRP1, -DQB1, -DQA1*) to detect high risk alleles and 7851 for Non-*HLA* tests (*CYPs*: *1A2, 2A6, 2C9, 2C19, 2B6, 2D6, 3A4, 3A5* Non-*CYPs*: *APOE, DPYD, ITPA, MTHFR, NAT2, NUDT15, SLCO1B1, TPMT, UGT1A1, VKORC1*) to predict risk phenotypes, affecting safety or effectiveness of medications. The policies of screening variants were considerable in genotyping of *HLA-B*15:02* for CBZ and *HLA-B*58:01* for ALL, also rapidly rising in preemptive tests for *TPMT* and *NUTD15*.

Conclusions:
Both reactive and preemptive PGx tests were increased in considerable proportions after introducing national PGx screening policy in Thailand. The PGx testing panel may optimize the safety or effectiveness of medications to achieve precision medicine.

Keywords:
Pharmacogenomic tests, human leukocyte antigen (HLA), Cytochrome P450 (CYP) enzymes, national screening policy, precision medicine

115 Analysis of 100,000 Whole Genomes Reveals Genetic Basis of Pregnancy Phenotypes and Complications in Chinese Population

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Background & Objectives:
Over the past decade, significant advancements have been made in Genome-wide Association Studies (GWAS). However, a primary challenge remains the underrepresentation of non-European populations and the limited availability of studies on pregnancy phenotypes. Non-Invasive Prenatal Testing (NIPT) for fetal trisomies, which utilizes maternal plasma cell-free DNA for whole genome sequencing, has become a globally adopted molecular test with over 10 million participants. Our previous research demonstrated the potential of NIPT data for human genetic studies.

Methods and Results:
We expanded this approach to include a range of maternal and neonatal phenotypes and common pregnancy complications. We conducted a genetic analysis of 104 pregnancy-related phenotypes from over 100,000 Chinese women, marking this as the largest such genetic study in the Asian population. Our GWAS revealed 410 genome-wide trait-locus associations, with 71.71% previously reported. Among the 116 novel hits, 83 were reproduced in independent replication studies. Notably, we discovered a significant association of the gene *ESR1* with fasting glucose, hemoglobin, hematocrit, and leukocyte counts. Considering the dramatic fluctuations in estrogen levels during pregnancy, we propose that these *ESR1* associations may be pregnancy-specific and warrant further exploration. Additionally, we investigated the genetic background of Gestational Diabetes Mellitus (GDM) and Intrahepatic Cholestasis of Pregnancy (ICP). For GDM, we replicated two known genes, *CDKAL1* and *MTNR1B*, and for ICP, we discovered a novel association with *SLC39A9*. We have established a website to provide access to all the GWAS results[2].

Conclusions:
Our findings underscore the power of leveraging low-pass whole genomes generated by NIPT to gain genetic insights into pregnancy-related phenotypes, accelerating future mechanistic studies into complex pregnancy traits and diseases.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial, and personal.

Reference:
1. Liu, Siyang, et al. "Genomic analyses from non-invasive prenatal testing reveal genetic associations, patterns of viral infections, and Chinese population history." *Cell* 175.2 (2018): 347-359.
2. GWAS summary result available at https://db.cngb.org/MANE.PheWeb

116 Unlocking Medical Insights through the Power of Taiwan Biobank Whole Genome Data

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Background & Objectives:
The Taiwan Biobank (TWB) has established a comprehensive nationwide database, representing a significant repository for the East Asian demographic. This resource facilitates many collaborative translational research domestically and internationally. In the past years, we have been reanalyzing the TWB whole-genome sequence (WGS) data with the calibration by GIAB benchmarked procedures for single nucleotide variants (SNV), small insertion-deletion (INDEL) and other types of genetic variants.

Method(s) and Results:
Our findings reveal that, on average, each Taiwanese harbors approximately 6,871 globally novel variants. Besides, we identified 23 small variants from the American College of Medical Genetics and Genomics (ACMG) secondary finding V3 gene list among participants, indicating a 1.67% (25/1496) prevalence of medically actionable variants in the population. Besides, one in 25 couples (3.94%) are at risk having offspring with at least one pathogenic variant. Clinically significant variants have been curated by multiple practicing clinicians. Detailed variant annotations are available on TaiwanGenomes (https://genomes.tw).

Furthermore, our analysis of pharmacogenomic (PGx) drug-associated alleles revealed that 75.3% (831/1103) of Taiwanese harbor at least one PharmGKB-selected Human Leukocyte Antigen (HLA) risk allele. Besides, we identified carrier rates of 5.1% for alpha thalassemia and 1.3% for spinal muscular atrophy (SMA) for population-prevalent pathogenic copy number variants (CNV).

Conclusions:
As the WGS becomes affordable, personal genomic profiling offers invaluable medical insights, providing a comprehensive perspective for both populations and individuals. With robust minor allele frequency (MAF) from a unified cohort, we provide extensive clinical insights for characterizing genetic disease susceptibility within the Taiwanese population.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Allele frequency, Whole Genome Sequence, Actionable variant, Pharmacogenomic, Carrier rates

117 Familial coaggregation and shared genetic loading of psychiatric and gastrointestinal disorders

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Background:
To investigate comorbidity, familial coaggregation, and shared genetic loading between psychiatric and gastrointestinal disorders.

Methods:
This study used the Taiwan National Health Insurance Research Database; 4,504,612 individuals born 1970-1999 with parental information, 51,664 same-sex twins, and 3,322,959 persons with full-sibling(s) were enrolled. Genotyping was available for 106,796 unrelated participants from the Taiwan Biobank. A logistic regression model was used to examine the associations of individual history, affected relatives, and polygenic risk scores (PRS) for schizophrenia (SCZ), bipolar disorder (BPD), major depressive disorder (MDD), and obsessive-compulsive disorder (OCD), with the risk of peptic ulcer disease (PUD), gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS), and inflammatory bowel disease (IBD), and vice versa.

Results:
Psychiatric disorders were associated with comorbid gastrointestinal disorders. Parental psychiatric disorders were associated with gastrointestinal disorders, and the magnitude of association when both parents were affected was higher than that when either parent was affected. Full-siblings of psychiatric cases had an increased risk of gastrointestinal disorders except for SCZ/BPD and IBD; the magnitude of coaggregation was higher in same-sex twins than in full-siblings. The results of bidirectional analyses mostly remained unchanged. PRS for SCZ, MDD, and OCD were associated with IBS, PUD/GERD/IBS/IBD, and PUD/GERD/IBS,

respectively. PRS for PUD, GERD, IBS, and IBD were associated with MDD, BPD/MDD, SCZ/BPD/MDD, and BPD, respectively.

Conclusions:
There was familial coaggregation and shared genetic etiology between psychiatric and gastrointestinal comorbidity. Individuals with psychiatric disorder-affected relatives or with higher genetic risk for psychiatric disorders should be monitored for gastrointestinal disorders, and vice versa.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
familial coaggregation, genetic correlation, psychiatric disorder, gastrointestinal disorder, biobank

118 Incorporating polygenic liability and family history for predicting psychiatric diseases in the Taiwan biobank

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Background:
This study investigated the transferability of European-derived polygenic risk score (PRS) in community samples of East Asian populations and the interplay of the molecular measure of PRS and conventional measure of family history (FH) through nationwide healthcare registries on the risk of four psychiatric disorders, including schizophrenia (SCZ), bipolar disorder (BPD), major depressive disorder (MDD), and obsessive-compulsive disorder (OCD). We examined the individual and joint associations and relative contributions of PRS and FH, and further evaluated the potential of combining transdiagnostic PRSs and FHs to improve risk prediction.

Methods:
Genotyping for 106,581 unrelated participants from the Taiwan Biobank was linked to Taiwan National Health Insurance Research Database to retrieve ICD-defined diseases and FH. A logistic regression model was used to examine the associations of PRS, FH in father, mother, and full-sibling with the psychiatric risks.

Results:
The PRS for SCZ, BPD, MDD, and OCD explained 2.0%, 0.4%, 0.6%, and 0.6%, respectively, and the FH explained 1.3%, 1.4%, 2.3%, and 3.4%, respectively, of the variance of the corresponding disease. Incorporating PRS and FH increased explained variance of SCZ, BPD, MDD, and OCD to 3.2%, 1.7%, 2.8%, and 4.1%, respectively. The effect sizes for PRS and FH in the PRS/FH-alone and PRS-FH-combined models were generally similar. Incorporating four PRSs and FHs simultaneously increased explained variance of SCZ, BPD, MDD, and OCD to 4.7%, 4.7%, 3.3%, and 7.3%, respectively.

Conclusions:
PRS and FH provide independent and complementary information for identification for psychiatric disorders. Incorporating transdiagnostic PRSs and FHs improve the risk prediction.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
polygenic risk score, family history, Biobank, psychiatric disorders, prediction

119 Gene therapy for Spinal Muscular Atrophy with Onasemnogene Abeparvovec: real-world experience, challenges and ethical concern in Malaysia

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Background and objectives:
Onasemnogene abeparvovec (Zolgensma®) is a novel targeted therapy, FDA-approved in May 2019 to treat patients with Spinal muscular atrophy (SMA) under 2 years of age. Real-world data on Zolgensma ® used in developing country is scanty. This study described the safety and clinical efficacy, and explore the main ethical issues related to this therapy.

Methods and results:
Eight SMA patients (7 SMA type 1 and 1 with SMA type 2) aged 22-59 months, with five treatment naïve patients, were treated in University Malaya Medical Center (UMMC), Malaysia, between June 2020 and July 2023. Median age of infusion was 15.5 months (7-23months) with duration of follow up for 10-47 months. Five patients received gene therapy under Novartis global managed access program (GMAP) and three patients via crowd funding. Post treatment, 7/8 patients showed raised liver transaminases level and resolved with recommended dose of oral prednisolone. Asymptomatic thrombocytopenia occurred within 7 days post treatment in 2/8 patients with no intervention required. All patients experienced improvement in motor function with increase in CHOP-INTEND scores. However, there was no remarkable improvement in respiratory and bulbar function.

Conclusions:
With proper pre-treatment screening, immunization, respiratory and nutritional support, and post-gene transfer management, Zolgensma® was safe and early efficacy was promising. The main ethical issue relates to the high cost of the drug which is prohibitive in a developing country. This will require further discussion with all stakeholders, support groups and governmental intervention to ensure equity of care and appropriate funding model.

Conflict of interest disclosure:
Sub-investigator in STEER study
Received speaker honorarium by Norvatis on “Local Experience with Zolgensma”

Key words:
Onasemnogene Abeparvovec, spinal muscular atrophy, real-world experience, challenges, developing country

120 Bridging Gaps in Genomic Research: Insights from Diverse Indonesian Populations

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Abstract:
Indonesia, a vast archipelago with rich cultural diversity, offers an immense potential in advancing precision medicine. Its human population genetic diversity, influenced by complex history of multilayered migrations, natural selection, and drift, reflects its wide-ranging health challenges, from infectious diseases to non-communicable diseases. Precision medicine seeks to adapt treatments for individuals based on their unique genetic profiles, unique environmental factors, and also unique population lifestyle. Thus, evolutionary forces, which have shaped the genetic landscape of Indonesian populations over tens of thousands of years, provide critical insights into precision medicine for its modern populations. Here, we explore over 1,000 whole genomes from diverse Indonesian populations across the archipelago. This dataset sheds light on the population's history, adaptation due to environmental pressures, and variations in important pharmacogenomics variants. A large majority of biomedical research and databases has focused on populations of European descent, leaving a significant gap in our understanding of many under-represented groups. We aim to bridge this gap, offering new insights into genetic diversity and its impact on disease. Our continuing research will not only support the global push for precision medicine but will also highlight the crucial need to include diverse populations in genomic and biomedical studies to achieve unbiased healthcare outcomes.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Indonesia, diversity, genomics, population genetics

121 CREATION OF THE PHILIPPINE LIST OF RARE DISEASES USING A SCORING SYSTEM

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Background/Objectives:
The passage of the Rare Disease Act aimed to provide equitable access to comprehensive medical care for patients diagnosed with rare disease (RD) in the Philippines, defined as disease having a prevalence of 1:20,000 population. In 2018, a list of RD mainly composed of inherited metabolic disorders was prepared by the Institute of Human Genetics to be covered by the law. Due to the recognition of the need to expand the list and be more inclusive and comprehensive, it was aimed to expand the list through the creation of a scoring system.

Methods/Results:
A rare disease scoring system was developed which aimed to aid in deciding which RD are the most important to be included in the initial RD list that will be covered by the law. It covers questions on prevalence, impact, diagnosis and treatment. The different medical societies were met and instructed to submit their 5 rare diseases using the scoring system. A total of 166 diseases were submitted. Out of the 23 member societies of the Philippine Pediatric Society, only 16 submitted a total of 59 diseases. Meanwhile, 12 of 15 member societies of the Philippine Obstetrical and Gynecological Society submitted 49 diseases. The Philippine College of Surgeons has 22 member societies and 6 of them submitted a total of 24 diseases. Lastly, 7 of 16 member societies of the Philippine College of Physicians submitted 34 diseases. After the adjudication, a total of 96 diseases passed the Rare Disease Scoring System and were included in the list.

Conclusion:
The use of the RD scoring system provided guidance in prioritizing RD in the initial list of RD in the Philippines.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
rare disease, scoring system, orphan disorders, rare disease act, rare disease list

122 XY Leap Clinical Decision Support Software delivers DNA-guided Individualized Medicine 3.0 therapeutics at the Point-of-Care

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Abstract:
Recent medical technological developments in New Zealand allows for the clinical implementation of individualized medicine at the point-of-care. The translational software that is presented represents a significant global advancement in genomic and precision medicine. The clinical decision support software guides healthcare professionals to deliver individualised therapeutic interventions to prevent and treat diabetes, depression, obesity, hypertension, and cardiovascular disease in patients from all populations. The XY Leap software works as an offline precision medicine calculator, so the patient's raw DNA data never goes online. The results of the bioinformatic analysis [including over 900 DNA-guided longevity hacks] are reported online to optimize the clinical utility of existing therapeutics at the bedside, in the theatre, and in the outpatient clinic. The non-diagnostic decision support software includes pharmacogenomic [PGx] reporting for >800 medications, 15 predictive clinical genetic tests for family physicians, >50 personalised complementary medicines (including precision Chinese medicines), and >100 predictive and participatory exercise and nutrigenomic interventions. A phenoconversion sub-analysis increases the predictive value of the results. Patients, scientists, and clinicians can use their DNA datasets and the genomic and precision medicine reporting software to expand the field of precision medical science. The platform's security architecture is guided by traditional Māori laws regarding data governance *tino rangatiratanga* to deliver the new international gold standard in patient data security that protects against data colonisation, genetic discrimination, and dystopian genetic futures. The new landscape of global healthcare is optimized DNA data security and ubiquitous DNA-guided therapeutics at point-of-care to maximise the safety and clinical utility of existing medical interventions.

Conflict of interest disclosure:
The author declares no potential conflicts of interest, whether scientific, financial and personal with the Conference.

Keywords:
Pharmacogenomics, Nutrigenomics, Clinical Genetics, DNA Security

124 Pharmacogenomics at Scale: Database Construction and Variation Analysis of 257 Pharmacogenes from a Chinese Newborn Cohort with 6,442 Individuals

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Background & Objectives:
The efficacy, dosage or side effects of drugs for different people may be pre-determined by their genetic makeups.

Method(s) and Results:
We investigated genetic variations in 257 pharmacogenes for 6,442 individuals within a newborn cohort from Qingdao, China. Whole-genome sequencing to 40X coverage were conducted to assess the potential impact of known actionable pharmacogenomic variants and predict the effects of newly identified variants. 593,206 variants were identified in the selected pharmacogenes. Notably, 45.37% of these variants were reported for the first time in East Asians, with 96.06% being rare. Significant genetic diversity in variants and haplotypes known to influence therapeutic efficacy of drugs was observed when comparing our cohort to other ethnic groups globally. Notably, we identified a higher prevalence of actionable pharmacogenetic (PGx) variants in newborn individuals compared with the rates in previous studies. Furthermore, 97% of newborns carried at least one potentially damaging variant as predicted by both the CADD and AlphaMissense. Among the 57 drugs recommended by PharmGKB, 26 (45%) required dosage adjustments and were associated with adverse drug reactions in over 10% of participants, and four drugs associated with the *CYP2C19* gene had these associations in 57% of the individuals.

Conclusion:
Our findings provide novel insights into the pharmacogenetic background of East Asians and highlight the importance of further investigations of potentially damaging pharmacogenetic variants. In addition, we constructed a web-based database for this study serves as a valuable resource for future pharmacogenetic genotype analyses, facilitating the development of personalized medicine strategies.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords:
Pharmacogenomics, whole-genome sequencing, actionable PGx, adverse drug reaction, AlphaMissense, precision medicine

125 Pharmacogenetic Variability of UGT2B7, CYP3A4, CYP3A5 and CYP2B6 genes in an African-American Sickle Cell Disease Patient Cohort

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Background & Objectives:
Interindividual variability in analgesic effects of opioids prescribed for sickle cell disease (SCD) pain is attributed to polymorphisms in drug metabolizing enzymes and transporters (DMET). We describe UGT2B7, CYP3A4, CYP3A5, and CYP2B6 allelic variants characterized in opioid pharmacokinetic and pharmacodynamic pathways for determination of potential suboptimal opioid exposure in SCD patients.

Method(s) and Results:
DNA from 165 unrelated SCD patients was genotyped for 2 UGT2B7 alleles, 4 CYP3A4 alleles, 6 CYP3A5 alleles, and 7 CYP2B6 alleles using the iPLEX® ADME PGx multiplexed panel. We reported genotype frequencies as homozygous wild-type, heterozygous, and homozygous variant/compound heterozygous; and predicted phenotypes as extensive, intermediate, ultra-rapid, and poor metabolizers. Four CYP2B6 alleles were detected in the cohort. The most common alleles were *1 (0.482) and *6 (0.442). Phenotypes were distributed into EM (21.8%), IM (72%), and UNK (6%). The CYP3A4 *1 frequency was 0.994 and the *20 was 0.006. The phenotypes were distributed as EM (98.8) and IM (1.2%). For the CYP3A5*1, the allelic frequency was 0.461. The combined frequency for the *3, *6 & *7 was 0.539. Phenotypically, 23% of the cohort were EM, 30% were PM, and 46.1% were IM. The UGT2BT*1 frequency was 0.785 and the *2 was 0.215. The phenotypes were EM (64.2%), UM/EM (28.5%), and UM (7.3%) respectively.

Conclusions:
Our study provides important data on the pattern of the UGT2B7, CYP3A4, CYP3A5, and CYP2B6 allelic variants for the first time in an African American SCD cohort. For SCD pain, preemptive genotyping of selected DMET variants could empower clinicians to communicate pharmacologic risk and drug response prediction with SCD patients using biological evidence as opposed to explaining statistical risk without biological significance. Additional pharmacokinetic studies are necessary to determine the genotype - metabolic phenotype concordance in SCD patients due to the influence of disease state on DMET expression.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial, or personal.

Keywords:
Pharmacogenetics, preemptive genotypic, drug response, African-American, Sickle Cell Disease

126 Genetic Counseling for Sickle Cell Hemoglobinopathies in Sub-Saharan Africa: A Nursing Champion Implementation Science Study Protocol

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Background and Objectives:
Sickle cell disease (SCD) is a significant contributor to child morbidity and mortality. In sub-Saharan Africa (SSA), 90% of the children born annually with SCD will die before their fifth birthday, often undiagnosed. Decreasing the high birth incidence of SCD requires identifying at-risk individuals through carrier screening, genetic counseling, and informed reproductive decision-making. The professional genetic counseling workforce capacity is severely limited in SSA. Nurses, however, comprise the single largest category of available health workers. Therefore, upskilling nurses to provide genetic counseling offers a logical alternative workforce solution. We showcase an integrated Nurse Champion Model for genetic counseling for SCD.

Methods and Results:
The Nurse Champion model task-shifts the provision of genetic services to nurses in primary care. Nurse champions with requisite technical assistance and education are tasked to effectively provide preconception counseling for SCD, and perform carrier screening for sickle cell trait with novel point-of-care tests in young Africans of marriageable ages and childbirth. A type-2 hybrid implementation-effectiveness design is used to evaluate patient uptake of genetic services and satisfaction, organizational readiness, provider acceptance, workflows, and resource use. The model intervention includes developing and assisting local hospitals in implementing the protocol, evaluating processes/determinants of the model's implementation, and evaluating the model's acceptability and effects on provider and client outcomes. Sierra Leone, a SCD endemic country presents an ideal site for the intervention. The Nurse Champion Model provides an evidence-based understanding of the implementation processes (i.e., implementation outcomes, program outcomes, and patient and provider outcomes) for alternative health workforce utilization for clinical genetic services in SSA. The protocol showcases the utility of the Nurse Champion model to increase the capacity for genetic counseling in limited resource settings; enhance communication of genomic information to patients and family members with limited health literacy; and understand the needs of patients and relatives in the communication of genomic information and the potential impact of genetic counseling processes on patient outcomes.

Conclusion:
The Nurse Champion Model is a tested, scalable model for implementing and maintaining genomic health service intervention for nurses, readily adaptable to low-resource settings in SSA where there is a profound need for such an approach.

Conflict of interest disclosure:
The authors declare no potential conflicts of interest, whether scientific, financial, or personal.

Keywords:
Nurse Champion, genetic counseling, genetic literacy, implementation science

127 Large-scale protein-disease risk association analysis in the UK Biobank: Introducing an extensive and freely available research resource in Olink® Insight

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Abstract:
Proteomics has emerged as an indispensable tool in biomarker discovery for the detection, prognosis, and treatment of disease. The UK Biobank (UKB) Pharma Proteomics Project represents the prime example of large-scale proteomics, using Olink® Explore to quantify levels of nearly 3,000 proteins in plasma samples from over 50,000 individuals. When combined with e.g., genomic or healthcare data in UKB, the opportunities for biomarker research in biology and medicine are tremendous.

This study aimed to estimate the future risk of a large and diverse set of diseases for all protein biomarkers available in UKB, thus generating a library of protein-disease risk associations freely available to researchers worldwide. In total, 107 diseases were selected from the PheWAS ontology and mapped to diagnosis codes in UKB. For each protein, the association between plasma levels and time to first occurrence (up to 10 years) of each disease was assessed using Cox regression, generating over 300,000 protein-disease risk associations adjusted for sex, age, BMI, and smoking.

Our results reveal a large heterogeneity in strength and number of associations both across diseases and proteins. Some proteins, for example GDF15, have statistically significant associations to a high proportion of all included diseases. Several strong associations, e.g., TNFRSF13B with leukemia, have been previously reported in independent research.

The complete set of results has been made freely available via Olink Insight, an online portal to support proteomic research. This new resource can enhance future studies by guiding biomarker selection or acting as a cross-reference post study.

Conflict of interest disclosure:
The authors are employees of Olink Proteomics.

128 Genetic Variants on Genes Related to Endomembrane System are Associated with Longevity

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Background/Objectives:
The exploration of genetic determinants contributing to human longevity unveils novel biological pathways crucial for studying aging. Earlier investigations into longevity suffered from limited statistical power, resulting in the identification of only a handful of genes. One probable explanation lies in the high heterogeneity observed among control samples.
Methods: In this study, we selected control samples from a vast pool of 177,099 participants enrolled in the China Chronic Disease and Risk Factor Surveillance in 2013, tracking their long-lived or mortality status until 2020. Employing self-organizing maps, we assembled a control group that matched the lifestyle factors of long-lived individuals while succumbing to early mortality. The refined approach culminated in a case-control whole-genome sequencing endeavor encompassing 512 long-lived (>90 years) and 502 controls (<78 years) individuals.

Results:
A genome-wide significant signal (P = 4.58e-08) within the TTYH1/LENG9 gene region has been identified through common variants association. Additional suggestive signals surfaced in genes such as COG3 and ATP2B4. One genome-wide significant signal, EVI5 (P = 3.12E-06), for rare variants association were identified. Gene-set-based rare variant association pinpointed the regulatory mechanisms of the synaptic vesicle endocytosis pathway was correlated with longevity, with COG3 and EVI5 emerging as pivotal components of Golgi functions.

Conclusion:
Refined study design for selecting controls according to lifestyles could enhance power of GWAS. Collectively, the elucidation of signals across various analyses underscored the pivotal role of endomembrane systems, including endocytosis, Golgi apparatus, and lysosomes, in shaping molecular mechanism of aging or longevity.

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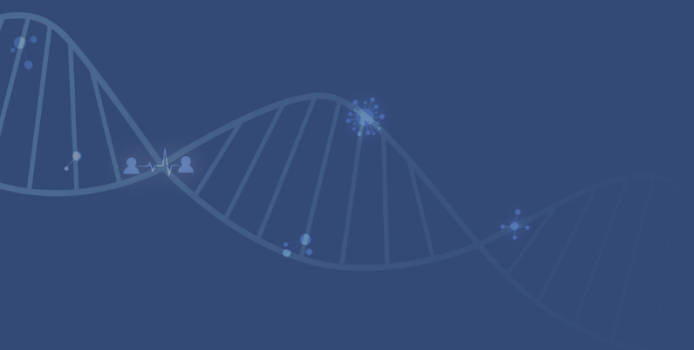

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