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Editorial

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Personalised genomic medicine is shaping the future of healthcare

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The Human Genome Project, a pivotal moment in genomics, reached a significant milestone in 2003 by completing 92% of the sequencing map of the human genome. As genomic technologies advance, the Telomere-to-Telomere Consortium took on the task of filling in the remaining gaps in the genomic regions in 2022[1]. This endeavour has provided invaluable insights into the field of genomics and its implications for precision health. Precision medicine is an emerging paradigm in precise diagnosis, treatment, and efficient surveillance of diseases, taking into account individual variability in genetics, lifestyle, and environment of each patient[2]. The transformative potential of precision medicine lies in its ability to move away from a one-size-fits-all approach and embrace a patient-centric model[3]. Diverse precision medicine initiatives involving the sequencing of thousands to millions of human genomes have been launched worldwide, aiming to bring genomics into healthcare[2,4,5]. Notable examples include the 100,000 Genomes Project in the United Kingdom, the All of Us Research Program in the United States, and the China Precision Medicine Initiative in China. These collaborative efforts exemplify the global commitment to leveraging advanced technology to generate large-scale genomic data to predict or stratify the health risks of patients. Targeted treatment and personalised care could be provided, unlocking the potential of improving quality of life and helping to bring down healthcare costs. This special issue "Genomics & Precision Health" includes a total of nine publications, leading by showcasing the launch of a population-based genome project in Hong Kong,

namely the Hong Kong Genome Project (HKGP), where their four strategic directions are pertinently mapped with the eight publications in this special issue covering application and review of genomic advancement in rare and common diseases, experience sharing of high-quality sequencing and analysis platforms, and recommendations and strategies in fostering the development, wide adoption of, and access to the benefits of genomics and precision health.

Recognising the immense potential of genomic medicine and the lack of genomic data, many countries and regions have also launched their own genome projects to contribute to the advancement of healthcare in their communities. Hong Kong, as a world-recognised financial centre with a modern city standard and quality of living, also seizes the opportunity to embrace the era of precision medicine for more accurate diagnosis and personalised treatment. The Hong Kong Genome Institute (HKGI), established by the Government of Hong Kong in 2021, implements the city's first large-scale genome sequencing project, HKGP, aiming to perform whole genome sequencing (WGS) for up to 50,000 genomes by 2025. Chu *et al.* presented the potentials and challenges of launching the HKGP as their first paper after the successful implementation of the HKGP[6]. Four main strategic foci pertaining to (1) integrating genomic medicine into clinical care; (2) advancing research in genomic science; (3) nurturing talents in genomic medicine; and (4) enhancing public engagement and genomic literacy were mapped out to work toward achieving HKGI's vision and mission, "to avail genomic medicine to all for better health and well-being". They reviewed the current landscape and specific challenges encountered during the construction of the infrastructure, workflow, and implementation of the pilot phase of HKGP, highlighting the importance of governance, stakeholder engagement, the development of a patient-focused consent protocol, the unique three-tier informed consent process, and the aspiration for developing the genetic counselling profession in Hong Kong. This paper provides insights not only for international counterparts when building similar projects but also into setting a solid foundation for integrating genomics into routine clinical care by starting a new theme "Genomics and Precision Health" in addition to "Undiagnosed Diseases" and "Hereditary Cancers" after the pilot phase with the completion of the first 5,000 genomes. This new theme focuses on driving the incorporation of genomic medicine into mainstream healthcare development in Hong Kong by improving genomic diagnosis, personalised treatment, personalised prediction, and the prevention of disease risks. Collaborative research projects in diverse disease cohorts, beyond the existing undiagnosed diseases and hereditary cancers, that will benefit from WGS in disease diagnosis, treatment, and prevention have been initiated. Sequencing infrastructure and analysis platforms have also been further enhanced with the latest technologies incorporated to facilitate advanced genomic research development and discovery. These pave the way to move toward the four strategic directions to foster the development, wide adoption of, and access to the benefits of genomics and precision health.

(1) Integrating genomic medicine into clinical care

The art of genome sequencing and analysis offers valuable insights into early and precise diagnosis, personalised treatment and management of various diseases, highlighting the expanding influence of genomics across diverse areas of clinical practice. In this special issue, we gathered an application of genomics in prenatal molecular diagnosis of a rare disease, X-linked Bartter Syndrome, as well as reviews on how genomics benefits clinical practice in various common disease cohorts, such as inherited cardiovascular conditions (ICCs), adult myeloid leukaemia (AML), and young-onset diabetes (YOD)[7-10]. Xu *et al.* presented an application of genomics in the prenatal diagnosis of Bartter syndrome (BS), which is important for the early onset of polyhydramnios related to BS[7]. They reported that severe transient X-linked antenatal BS was resulted by the fetus carrying the *MAGED2* hemizygous nonsense variant c.967C>T [p. (Asp323*)] inherited from the pregnant mother. Therefore, a prenatal genetic diagnosis can confirm that

initiating prenatal indomethacin therapy has a beneficial effect on the fetus, emphasising the importance of timely prenatal diagnosis of BS type 5 for guiding appropriate management of polyhydramnios and postnatal symptoms. Loong *et al.* shared the experience from the ICC research program at the National University Heart Centre, Singapore, bringing the notion that genomic medicine has opened the door to precision medicine in cardiology[8]. The clinical frameworks and considerations were presented, providing an overview of the operations of the clinic, including wet and dry lab conditions, work performed by a healthcare professional, and the variety of cases, ranging from cardiomyopathies and arrythmias to aortopathies. Their experience provides insights for international counterparts when implementing similar services in local healthcare centres to address the healthcare burden of ICCs. Leung *et al.* reviewed that the genomic revolution in AML has ushered in a new era of personalised medicine, shifting the treatment paradigm from a generalised approach, which has reached an impasse, to one that targets individual genetic alterations[9]. The integration of genomics, the detection of measurable residual disease, drug sensitivity testing, and single-cell transcriptomics hold tremendous potential for optimising AML management through personalised approach based on genomic and transcriptomic information. Chan *et al.* discussed various aspects of YOD, including the importance of correct diagnosis of maturity-onset diabetes of the young and monogenic diabetes, the use of genomic medicine in diagnosis and classification, and a clinical trial called PRISM that aims to re-define insulin secretion and monogenic diabetes in Chinese patients[10]. This paper emphasises the importance of clinical observations and person-oriented care, maximising the utility of genomic medicine in pursuit of early diagnosis and management of YOD.

(2) Advancing research in genomic science

To maximise the benefits of embedding genomics into routine clinical care, like the aforementioned examples in rare and common diseases, effort in advancing research in genomic science through the establishment and enhancement of standardised high-quality sequencing and analysis platforms with state-of-the-art technologies is extremely important. HKGI has enhanced its genome sequencing capacity and capability to increase patients' accessibility to this advanced technology for precise diagnosis and personalised clinical care. Chu *et al.* published their experience in designing the HKGI laboratory, establishing the genome sequencing workflow, and enhancing the sequencing and analysis platforms[11]. The HKGI drew on recommendations and experience from the Medical Genome Initiative and other sequencing projects to customise hardware and software components of the laboratory to optimise the laboratory design and layout, sequencing workflow, quality assurance and data information management system. A unidirectional workflow that employs a hybrid of manual and automated approaches for proper laboratory practice and operation was established. A list of stringent quality assessments of the samples and sequencing libraries was established. Systems for handling and housing different data types, such as Clinical FrontEnd and LabKey Sample Manager, were tailored and optimised at par with international standards to facilitate and standardise the patient recruitment process, clinical data collection, sample processing, and biobanking. The genome sequencing workflow has been optimised to boost weekly throughput to approximately 350-500 samples, enabling the processing of over 6,600 genomes in the first 24 months since launch. The laboratory has been further enhanced to include cutting-edge techniques, such as long-read sequencing. The performance of long-read GS in detecting variants in complex regions ("dark regions") of the human genome, which are challenging for short-read sequencing, was also illustrated in the example of the polycystic kidney disease 1 gene. Such a precise diagnosis can inform the patient's clinical management and treatment choices, such as the use of Tolvaptan to slow down the progression of kidney failure. The combination of long-read and short-read sequencing offers a more accurate understanding of the genome, enabling the detection of complex genomic rearrangements, large insertions or deletions, and allelic phasing. Broadly visioning the extent of further research advancement in favor of precision medicine, the

laboratory has also established a single-cell sequencing platform to integrate multi-omics information to enhance the characterisation of disease at the cellular and tissue levels and to enable the discovery of biomarkers for therapeutic targets. These hold the promise of transforming healthcare through precise diagnosis, targeted treatment, prognostic prediction, and targeted therapeutic development.

(3) Nurturing talents in genomic medicine

Expediting the advancement of genomic medicine and the promotion of precision health in the healthcare system worldwide cannot be achieved without enlightening work in other disciplinary aspects, like nurturing talents in genomic medicine by facilitating genomic education for medical professionals. Maher *et al*. shared their experience in developing continuing genomics education programs for non-genetics medical specialists to increase their understanding of genomic medicine and its clinical application in Australia, providing insights into the place of online learning and workshops as implementation strategies to translate the use of genomics from research settings to health systems[12]. Additionally, the inclusion of non-genetic specialty peer experts in the co-design and delivery of education is highly recommended to mediate and translate the evidence for the use of genomics in a specialty, to adapt clinical genetics practice as appropriate to the specialty, and to strengthen cross-specialty relationships to practice genomic medicine.

(4) Enhancing public engagement and genomic literacy

The promotion of public engagement and genomic literacy is crucial work in support of genomics and precision health in healthcare service development. Collaboration in research with members of the public and patients is recognised to be indispensable. Hunter *et al*. shared five case studies in a variety of clinical genomic studies in the United Kingdom, highlighting that public and patient involvement has a significant and beneficial influence on research that addresses sensitive and ethically challenging topics in genomic service development[13]. Key recommendations in planning, recruitment and involvement are also identified to further embed good practices across genomic and other health service research. Sharing the same view that public support and engagement in promoting genomics and precision health in the healthcare system is the key to success, especially in the Chinese culture with different socio-cultural views, Chu *et al*. explored the views and concerns of patients and family members participating in the HKGP[14]. A quest for a patient-oriented, transparent, and decommercialised WGS campaign for the population-based genome project is highly important to address the challenge of public distrust as a common obstacle to genomic advancement. Age-specific marketing and publicity strategies are vital for raising public awareness and encouraging public engagement for genomic initiatives. Genomic literacy through tailoring complex genomic topics to diverse audiences ranging from the public and patients of different ages to highly educated professionals is a priority to facilitate the integration of genomic medicine into mainstream healthcare. Insights into the long-term promotion of public engagement and education can serve as a guiding beacon for international counterparts in navigating the genomic medicine era.

In conclusion, the publications gathered in this special issue "Genomics & Precision Health" aim to showcase collaborative efforts in multidisciplinary aspects to promote genomics and precision health. Implementation of a population-based genome project with advanced sequencing and analysis technology can bring the era of precision medicine into clinical practice. Equipping healthcare professionals and the general public for a better understanding of genomics and precision health leads the journey to unlock the full potential of genomics for personalised and patient-centred care. With strategies to integrate genomic medicine into clinical care, advance research in genomic science, nurture talents in genomic medicine, and

enhance public engagement and genomic literacy, the goal of bringing genomic and precision medicine into our healthcare with substantial clinical and economic benefits is not far to reach.

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