For Immediate Release

HKSH, HKUMed and HK Hereditary Breast Cancer Family Registry Collaborate to Advance Research on Gene Mutation of Hereditary Breast and Ovarian Cancers in Hong Kong

(15 November 2023, Hong Kong) HKSH Medical Group (HKSH), LKS Faculty of Medicine of the University of Hong Kong (HKUMed), and the Hong Kong Hereditary Breast Cancer Family Registry (Registry) today announced significant findings from their collaborative research studies on the germline mutation landscape of nearly 4,900 individuals with hereditary breast and/or ovarian cancers in Hong Kong. This pioneering collaboration, ongoing since 2007, aims to facilitate early detection of and targeted treatment strategies on breast and ovarian cancers among high-risk groups and their families.

Breast and ovarian cancers are leading causes of cancer deaths among females in Hong Kong, with breast cancer and ovarian cancer accounting for approximately one-third (32%) of newly diagnosed female cancer cases in 2020. Among breast cancer patients, there is a significant proportion (10-15%) of cases attributed to hereditary factors, and there is a concerning trend of younger age at diagnosis. Recognising the rising incidence of breast and ovarian cancer and the importance of identifying inherited mutations in genes, HKSH, HKUMed and the Registry have published 112 papers in international peer-reviewed journals, including *Cancers (Basel), International Journal of Molecular Sciences* and *Journal of Medical Genetics*. These publications have contributed to a deeper understanding of the genetic landscape of these diseases in Chinese population, and have aided in the improved management of inherited mutations.

Based on the database in the Registry, which includes about 4,900 individuals with breast and/or ovarian cancers, as well as high-risk individuals with a family history of breast, ovarian or prostate cancers, the studies revealed that approximately 10% of individuals in the database were found to have mutations in the Breast Cancer Susceptibility Genes - BRCA1 and BRCA2 genes. These gene mutations are widely known for their strong association with an increased risk of developing cancers (high-penetrance). Among the study targets, 4.3% were found to have mutations in other non-BRCA and high-to-moderate penetrance genes, such as PALB2, TP53 and PTEN, which also contribute to an elevated risk of developing hereditary breast, ovarian, prostate and other forms of cancers. According to a study published in the *Journal of Clinical Oncology*[1], the lifetime risk of developing breast cancer for women with PALB2 mutation is 52.8% by age 80. The risk is similar to that of individuals with BRCA2 mutations. TP53, another gene associated with breast cancer, has also gained attention. TP53 mutation carriers often experience an early onset of breast cancer at the age of 35 or younger, and may exhibit characteristics such as bilateral breast cancer or a strong family history of multiple cancers. The lifetime risk of developing breast cancer in women with TP53 mutation is 80-90% by age 80[2].

The research team concluded that by solely focusing on BRCA mutations during screening, there is a risk of overlooking the potential risks associated with other gene mutations. Therefore, it is crucial to identify and understand non-BRCA mutations to provide comprehensive evidence and support for managing risks and making informed decisions regarding preventive measures and treatment options for breast and ovarian cancer patients and their families. Comprehensive genetic testing that encompasses a broader panel of genes is essential to gain insights into a more accurate assessment of an individual's genetic risk profile.

Dr Edmond MA, Director, Clinical Pathology & Molecular Pathology Division and Specialist in Haematology of Hong Kong Sanatorium & Hospital, discussed the genetic screening methods employed in the study. He underscored that HKSH utilises multigene panel tests that incorporate both next-generation sequencing (NGS) and third-generation

[1] J Clin Oncol. 2020 Mar 1;38(7):674-685
[2] Cancer Treat Rev. 2023;114:102522

sequencing (TGS) technologies to examine a panel of genes simultaneously. This approach provides a comprehensive understanding of an individual's genetic predisposition to breast and ovarian cancers.

He highlighted the efficiency and cost-effectiveness of multigene panel test in identifying gene mutations beyond BRCA1/2 in breast and ovarian cancer patients as it can detect mutations in multiple genes with a single comprehensive test. NGS enables the simultaneous analysis of multiple genes, while TGS represents the most advanced screening technology available. TGS offers long-read length, real-time result and faster sequencing, all of which contribute to improved accuracy and efficiency in detecting genetic variants during the collaborative studies.

“Through collaboration with HKUMed and the Registry, valuable insights into the characteristics of gene mutation among local breast cancer patients have been gained. This collaboration has facilitated continuous surveillance and risk assessment, enabling early diagnosis for high-risk groups and their family members. Multigene panel can also help to identify tumour markers for targeted therapies, leading to more effective and personalised treatment strategies,” added Dr MA.

The collaboration between HKSH, HKUMed, and the Registry on genetic testing facilitates long-term follow-up for patients and high-risk groups. It allows for re-testing using improved technologies over time, leading to a more accurate assessment of an individual's genetic risk profile. Based on accrual and interpretation of genetic variants in the local Chinese population collected over years, reclassification of variants of unknown significance (VUS) cases can be performed. For instance, a cohort review study found that 31.8% of VUS cases were reclassified as either pathogenic or benign. This reclassification of VUS cases has led to changes in disease management based on identified risks. Regular updates on genetic databases and familial studies are crucial for precision medicine and personalised treatment, ensuring accurate and relevant genetic information and achieving scientific discoveries in the field.

Professor Ava KWONG, Clinical Professor of the Department of Surgery, School of Clinical Medicine, HKUMed, Chairman of the Hong Kong Hereditary Breast Cancer Family Registry and **Honorary Consultant in Breast Surgery and Specialist in General Surgery of Hong Kong Sanatorium & Hospital**, emphasised the long-term benefits of the collaborative effort. She said, “Over the course of 16 years, the Registry has made significant efforts to establish a comprehensive biobank for the Chinese population and high-risk families affected by hereditary breast and ovarian cancers. Through our ongoing collaboration and utilisation of cutting-edge laboratory technologies, we have the ability to revisit cases with variants of unknown significance (VUS) over time. This allows us to leverage the latest scientific findings and provide more personalised clinical services. By gaining a deeper understanding of the spectrum of breast and ovarian cancer in the Chinese population, we can introduce timely interventions and continuously improve preventive and management options. Ultimately, this comprehensive approach not only benefits the patients themselves but also has a far-reaching impact on healthcare policy planning."

HKSH, HKUMed, and the Registry are committed to conducting ongoing research to enhance understanding of the risks and causes of hereditary breast and ovarian cancer in the Chinese population. This research aims to personalise screening and surveillance for high-risk individuals and their families, enabling early detection, refining precision treatment strategies, and ultimately leading to improved patient outcomes and a reduced cancer burden in Hong Kong.

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About HKSH Medical Group

Officially launched in September 2017, HKSH Medical Group promotes public health and advanced medicine through a multi-faceted, coordinated approach across clinical services, medical education, scientific research and public health education. Members of the Group, including Hong Kong Sanatorium & Hospital, HKSH Healthcare and HKSH Eastern Medical Centre, are dedicated to offering top-quality holistic care to patients, upholding the motto 'Quality in Service, Excellence in Care.'

Established in 1922, Hong Kong Sanatorium & Hospital is one of the key members of HKSH Medical Group and a leading private hospital in Hong Kong. Living up to its motto of 'Quality in Service, Excellence in Care', the Hospital is committed to serving the public as well as promoting medical education and research.

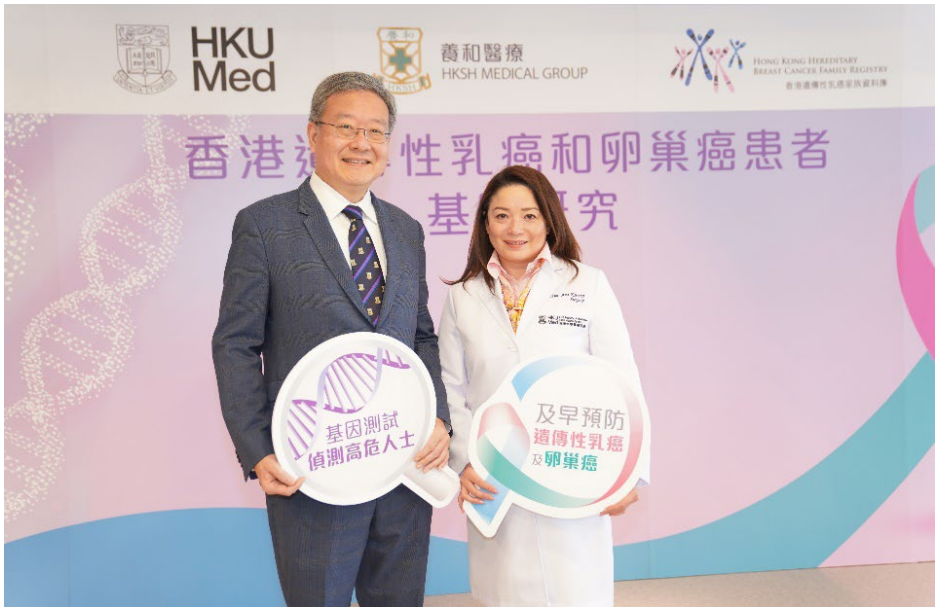
About LKS Faculty of Medicine, the University of Hong Kong (HKUMed)

HKUMed is the oldest local institution of higher education in Hong Kong. It was founded as the Hong Kong College of Medicine for Chinese in 1887, was renamed the Hong Kong College of Medicine in 1907 and became the premier founding Faculty when the University was established in 1911. From its modest beginnings, the Faculty has grown to become the largest faculty of the University. The Faculty is comprised of 16 departments and units, School of Biomedical Sciences, School of Chinese Medicine, School of Clinical Medicine, School of Nursing, School of Public Health and a number of strategic centres of research excellence. For more information about LKS Faculty of Medicine, please visit www.med.hku.hk.

About Hong Kong Hereditary Breast Cancer Family Registry

Established in 2007, Hong Kong Hereditary Breast Cancer Family Registry (The Registry) is the only and first-ever charitable organisation dedicated to help the high-risk families who have hereditary risk of breast, ovarian and prostate cancer due to BRCA gene mutations. It also aims to advance and standardise clinical care by formulating preventative measures through data collection, research, public education, counselling and supportive care services in reducing the incidence of hereditary cancers in Chinese population. The Registry now has the largest database and biobank of hereditary breast cancers specimens in Chinese which would facilitate better understanding research of the disease locally and worldwide.

Photo caption:
Professor Ava KWONG, Clinical Professor of the Department of Surgery, School of Clinical Medicine, HKUMed, Chairman of the Hong Kong Hereditary Breast Cancer Family Registry and Honorary Consultant in Breast Surgery and Specialist in General Surgery of Hong Kong Sanatorium & Hospital (right), and Dr Edmond MA, Director, Clinical Pathology & Molecular Pathology Division and Specialist in Haematology of Hong Kong Sanatorium & Hospital (left), shared the germline mutation landscape of hereditary breast and ovarian cancers in Hong Kong.



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Hong Kong Hereditary Breast Cancer Family Registry 香港遺傳性乳癌家族資料庫

Appendix

Outputs of Collaborative Research Studies by HKSH, HKUMed and the Registry (Non-exhaustive List)

Year	Research Topic	Publication
2023	Molecular characteristic of Asian male BRCA related cancers	Breast Cancer Res Treat. 2023; 198(2): 391 - 400.
	Effect on germline mutation rate in a high risk Chinese breast cancer cohort after compliance with The National Comprehensive Cancer Network (NCCN) 2023 v.1 testing criteria	Cancers (Basel). 2023; 15(9): 2635
2022	Germline mutations in Chinese ovarian cancer with or without breast cancer	Mol Genet Genomic Med. 2022;e1940
	How does re-classification of variant of unknown significance (VUS) impact the management of patients at risk for hereditary breast cancer?	BMC Med Genomics. 2022;15(1):122
2021	Rapid breakpoint mapping of a novel germline PALB2 duplication by PCR-free-long-read sequencing informs interpretation of its pathogenicity	JCO Precision Oncology 2021; 5:1044-1047
	Germline PALB2 mutation in high-risk Chinese breast and/or ovarian cancer patients.	Cancers (Basel) 2021; 13:4195-211
2020	Germline mutation in 1,338 BRCA-negative Chinese hereditary breast and/or ovarian cancer patients: clinical testing with a multigene test panel	J Mol Diagn. 2020;22(4):544-554
	Somatic mutation profiling in BRCA-negative breast and ovarian cancer patients by multigene panel sequencing	Am J Cancer Res. 2020; 10(9):2919-2932
	Mutation screening of germline TP53 mutations in high-risk Chinese breast cancer patients	BMC Cancer 20, 1053 (2020)