For Immediate Release

HKSH pioneers the use of Droplet Digital PCR for Minimal Residual Disease detection
Effectively monitors treatment efficacy and detects early signs of relapse in leukaemia patients

(6 October 2022, Hong Kong) Blood cancer is one of the top ten deadliest cancers in Hong Kong with thousands of new patients every year. There are three primary types of blood cancer, including leukaemia (in acute and chronic forms), lymphoma and myeloma. Among them, acute myeloid leukaemia (AML) is the most aggressive type that progresses quickly, usually develops over days or weeks at an exponential rate and deteriorates within a short span of time. The average survival rate in five years is only 30%. With today's advanced medical technology, blood cancer can be accurately diagnosed and analysed for the type of genetic mutation through molecular genetic testing in order to determine the best medical treatment.

Regular Minimal Residual Disease (MRD) monitoring in leukaemia patients is essential for defining the response to treatment, be it chemotherapy or targeted therapies, and determining the prognosis through tracking the mutated genes. The introduction of MRD monitoring transformed the disease management in hematological cancers. Significantly, MRD monitoring is covered under new international standards for evaluating therapeutic efficacy, detecting the risk of recurrence after treatment or guiding treatment regimens such as bone marrow transplantation. HKSH Medical Group (HKSH) is the first private medical institution in Hong Kong to use the most sophisticated pathological laboratory technology in MRD monitoring - Droplet Digital Polymerase Chain Reaction (ddPCR) - to track the status of leukaemia in affected patients.

The sensitivity and resolution of ddPCR is 100 times higher than conventional PCR methods, allowing physicians to get a more detailed picture of MRD status and confirm if a patient has achieved a cure or whether there is a chance of impending relapse. As of today, HKSH has used this technique to monitor 118 leukaemia patients with genetic alterations, of which 113 are AML patients, three are acute lymphoid leukaemia patients (ALL), and one patient each from chronic myeloid leukaemia (CML) and lymphoma.

Dr. Edmond MA, Director, Clinical Pathology & Molecular Pathology Division and Specialist in Haematology of Hong Kong Sanatorium & Hospital, said, "MRD is usually performed by cell analysis namely flow cytometry, or molecular analysis such as Next-generation Sequencing (NGS), Real-time Quantitative PCR (RQ-PCR), and Droplet Digital PCR (ddPCR). ddPCR achieves a high level of detection sensitivity, resolution, accuracy and specificity in measuring the quantity of the targeted mutated genes with a view to monitoring the status of MRD during treatment or at the post-remission stage. This technique is particularly pertinent to patients who harbor rare genetic translocation or mutation. Since the conventional cellular or molecular analysis may not be able to effectively track these rare genetic alterations, ddPCR assessment thus offers valuable clinical data in evaluating the depth of molecular response."

"Instead of using an off-the-shelf reagent, we customise unique assays corresponding to the type of mutated gene for individual patients, so we can accurately track and target the rare mutated genes in these patients. This is the gist of personalised medicine. The meticulously-designed assays that aim to guide individualised therapy for each patient are achievable through the extensive expertise and experience of our molecular pathology staff, which is the critical success factor in the process. In the past four years, HKSH has applied the ddPCR assay clinically to 118 patients, and we were able to target 79 genetic variants, of which 85% were mutations (including 67 types of genetic mutations) and the remaining 15% involved 12 fusion genes." Dr. MA elaborated.

The following three cases illustrate the clinical utility of ddPCR:

Case 1 - 58-year-old female with NPM1+ FLT3-ITD+ AML with normal chromosomes. She was in complete remission after chemotherapy. Because her NPM1 mutation was not a common type, we customised a ddPCR assay for MRD monitoring and found that the patient was MRD negative. The negative results sustained for over a year and thus her prognosis is relatively optimistic.

Case 2 - 53-year-old male with CML who carried the Philadelphia chromosome and BCR::ABL1 fusion gene, but his BCR breakpoint was rare and could not be measured by conventional quantitative PCR. After tailoring

a ddPCR assay to monitor MRD, we found that the patient did not respond well to the first generation CML targeted therapy drugs, and the fusion gene copy increased five-fold at the twelfth month due to acquired resistance to the first generation CML targeted drug. The patient was switched to a second generation CML targeted drug and responded well, achieving deep molecular response by the sixth month of treatment.

Case 3 - 58-year-old male with NPM1+ FLT3-ITD+ AML with normal chromosomes and a common type A NPM1 gene mutation. He was in complete remission after chemotherapy and underwent a haploidentical bone marrow transplant. Unfortunately, one year after transplantation, detectable MRD was found by ddPCR, and a series of treatments were performed under the guidance of MRD results. Despite attainment of transient MRD negativity, the MRD started to rise again and frank relapse of the blood cancer occurred.

Dr. Raymond LIANG, Director, Comprehensive Oncology Centre and Specialist in Haematology & Haematological Oncology of Hong Kong Sanatorium & Hospital, said, "Tumor cells are very resilient and are able to circumvent corresponding treatment drugs. These abnormal cells can quickly evolve and replicate once the patient's immune system becomes dysfunctional, losing its ability to attack them. AML is a cancer with a high recurrence rate, indicating a high probability of recurrence within five years of the first diagnosis. Given the presence of rare genetic variants or fusion genes in some patient cases, the treatment for these cases becomes increasingly complex. So even after a course of treatment and the concerned patients are in remission, we still need to closely monitor the MRD level to ensure continual treatment efficacy. Accurate detection of MRD helps us to 'catch' the very small amount of residual tumor cells and intervene in their growth as soon as possible. ddPCR can provide us with highly precise quantitative data that supports whether the patient is in full remission or not. We can then predict the prognosis and relapse, and determine whether a bone marrow transplant is needed."

"The prolonged COVID-19 pandemic can increase the level of uncertainty faced by leukaemia patients, especially for cases who are eligible for bone marrow transplantation. The plan for bone marrow transplantation has to be deferred when the leukaemia patient or the bone marrow donor got infected with COVID-19. The pandemic may also affect the schedule of bone marrow or stem cell transfer from abroad, which may delay bone marrow transplantation procedure for patients," added Dr. LIANG. He anticipates a wide adoption of ddPCR assay as doctors can obtain the necessary detailed information on MRD for clinical decisions from the ddPCR test results, which provide important guidance on the dosage and dosing of chemotherapy and targeted therapy. As for bone marrow transplantation, he said the risk and timing of transplantation can also be reflected through ddPCR analysis. If MRD drops to a desired level before transplantation, the risk of recurrence after transplantation can be greatly reduced.

HKSH has accumulated invaluable experience in ddPCR in the past few years to support the design of leukaemia therapeutic approaches and prognosis prediction with highly accurate and scientific insights. In the future, HKSH will investigate the use of ddPCR for hematological tumors (lymphoma) and the detection of other solid tumour cancers, such as liver, breast and prostate cancers, under the auspices of liquid biopsy.

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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 in 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".

About Hong Kong Sanatorium & Hospital
Established in 1922, Hong Kong Sanatorium & Hospital is one of the leading private hospitals in Hong Kong. With the motto "Quality in Service Excellence in Care", the Hospital is committed to serving the public as well as promoting medical education and research.

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Photo caption:

1. Dr. Edmond MA, Director, Clinical Pathology & Molecular Pathology Division and Specialist in Haematology of Hong Kong Sanatorium & Hospital says HKSH customises unique assays corresponding to the type of mutated gene for individual patients instead of using an off-the-shelf test reagent in ddPCR application. The meticulously-designed assays aim to guide individualised therapy for each patient to accurately track and target the rare mutated genes in these patients.

2. Dr. Raymond LIANG, Director, Comprehensive Oncology Centre and Specialist in Haematology & Haematological Oncology of Hong Kong Sanatorium & Hospital anticipates a wide adoption of ddPCR assay as doctors can obtain the necessary detailed information on MRD for clinical decisions from the ddPCR test results, which provide important guidance on the dosage and dosing of chemotherapy and targeted therapy.

3. Dr. Raymond LIANG (left) and Dr. Edmond MA work closely together to design the most suitable treatment strategies for patients with the application of ddPCR.

4. HKSH pioneers the use of the most sophisticated pathological laboratory technology in MRD monitoring - Digital Droplet Polymerase Chain Reaction (ddPCR), which sensitivity and resolution is 100 times higher than conventional PCR methods, allowing physicians to get a more detailed picture of MRD status and confirm if a patient has achieved a cure or whether there is a chance of impending relapse.