

### Results of Early-stage Liver Cancer Detection in At-risk Individuals Using Liquid Biopsy Published in PNAS

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Highlights:

- Genetron Health (Beijing) Co. Ltd and National Cancer Center/ Cancer Hospital, Chinese Academy of Medical Sciences published the promising results of their liver cancer early screening study using cell free DNA and protein biomarkers.
- This product for screening HCC in at-risk populations, will be further validated and then available for use.
- This methodology is expected to be applied in early screening of other cancer types.

March 12th, 2019, Beijing – Today, Proceedings of the National Academy of Sciences (PNAS) published the results of a pilot study for early detection of liver cancer in a cohort of HBV carriers, who are at risk for developing this disease. This screening technology, known as HCCscreen, relies on detecting a combination of tumor-specific mutations in cell free DNA (cfDNA) and protein markers. This work was a collaborative effort between National Cancer Center/ Cancer Hospital, Chinese Academy of Medical Sciences and Genetron Health (Beijing) Co. Ltd (Genetron). Based on these promising results, assays such as this, after rigorous clinical validation, could be developed into an application for the detection of early-stage liver cancer.

The HCCscreen assay developed in the study uses both specific mutation profiles from plasma cfDNA along with protein biomarkers. The combination of these markers enabled excellent performance of the assay in a cohort of asymptomatic HBV carriers. A total of 331 HBV carriers (with normal alpha-fetoprotein levels and normal ultrasound) were tested using HCCscreen. Among them, 24 subjects were identified as positive and 307 (out of 331) as negative. Furthermore, four out of the 24 individuals with a positive HCCscreen test were later diagnosed as having early stage liver cancer (less than 3 cm) within 6-8 months. The early detection with HCCscreen allows earlier intervention with surgery, which significantly increases the likelihood of cure. On the other hand, none of HCCscreen-negative individuals were diagnosed clinically with liver cancer in the same follow-up period. Therefore, at the time point, this result demonstrated a 17% positive predictive value, a 100% sensitivity and a 94% specificity in this cohort.

One of HCCscreen's core technologies is Mutation Capsule, invented by Genetron, which enables the accurate detection of hot spot mutations, indels and hepatitis B virus (HBV) integrations commonly present in HCC tumors. Besides the biomarkers described in this study, this assay can be further optimized to detect more genetic alterations, such as copy number variations. The optimized assay has been validated in additional cohorts with >93% sensitivity and >98% specificity.

Mr. Sizhen Wang, co-founder and CEO of Genetron, emphasized: "Some developed countries have achieved extraordinary performance in reducing morbidity and mortality of some cancer types, such as colorectal cancer in the United States and gastric cancer in Japan, which need to thank the efficient early screening of the cancers. Genetron is working diligently and would like to launch the product for early screening of liver cancer, therefore, to reduce mortality of liver cancer patients. The similar technology can be adapted and developed to screen other types of cancers after clinical validation, and we are dedicated to providing effective technologies for the early detection of cancer in high-risk populations, as well as in general populations."

With a noninvasive blood test, the liquid biopsy technology can provide important diagnostic indicators for asymptomatic HBV carriers. The research team is currently conducting a larger scale clinical trial to further improve and validate the method.

#### Background

Liquid biopsy using plasma cell free DNA (cfDNA) mutation profiles has made great progress in recent years, and promising results have been demonstrated in early screening of multiple cancer types.

Patients identified by HCCscreen as being positive for tumor-specific markers in this prospective study were mostly asymptomatic as they had very early stage liver cancer. Compared to the differentiation of healthy individuals and hospitalized cancer patients in retrospective studies, it could be more challenging to distinguish asymptomatic early-stage HCC patients from at-risk individuals, however, the prospective studies could be important to set up the algorithm and threshold with favorable performance in the screening of early HCC, as the screening of HCC most likely happens in the context of high-risk individuals in clinical practice.

#### About Cancer Hospital, Chinese Academy of Medical Sciences

The Cancer Hospital of CAMS was founded in 1958, and is the home of the China National Cancer Clinical Medical Research Center, the National Standardized Cancer Diagnosis and Treatment Quality Control Center, and the State Food and Drug Administration certified National Drug Clinical Research Center. It integrates medical education and research and is the authority for the nation's basic research and clinical diagnosis and treatment of cancer. The hospital is in the forefront of the multidisciplinary and standardized comprehensive treatment of various tumors in China. The annual outpatient visits are more than 840,000, and the annual operations is more than 20,000.

The hospital has extensive academic influence internationally and cooperates with the WHO International Agency for Research on Cancer (IARC), the National Institutes of Health (NIH), the National Cancer Institute (NCI), and the MD Anderson Cancer Center. It has signed strategic cooperation agreements with internationally renowned cancer research and treatment institutions such as Mayo Clinic, University of California, Los Angeles

(UCLA), and the UK Cancer Institute (CRUK).

#### About PNAS

Proceedings of the National Academy of Sciences of the United States of America (PNAS) is one of the world's most-cited and comprehensive multidisciplinary scientific journals, which strives to publish only the highest quality scientific research, and papers undergo rigorous peer review and approval by an NAS member before publication. PNAS publishes cutting-edge research, science news, Commentaries, Perspectives, Colloquium Papers, Reviews, and actions of the NAS. The journal's content spans the biological, physical, and social sciences and is global in scope.