

# New study of primary liver cancer calls for strategies targeting heterogeneous tumors

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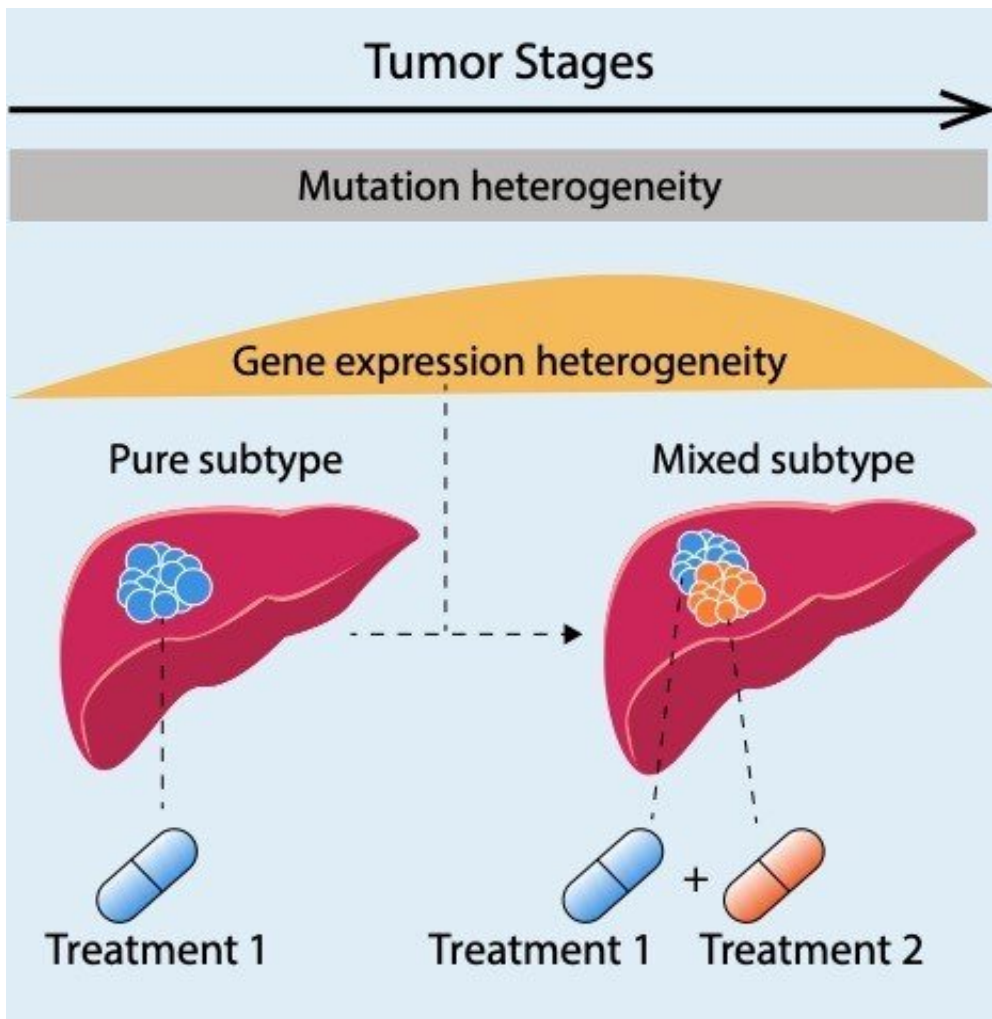


Figure 1: Hepatocellular carcinomas (HCC) diversify during tumour evolution, leading to multiple co-existing subtypes in a significant proportion of HCC that will require combination systemic therapies to treat the disease. Credit: A\*STAR's Genome Institute of Singapore

Clinicians, scientists from the National Cancer Center Singapore (NCCS) and institutional collaborators have described a dynamic genomic landscape of tumor heterogeneity in hepatocellular carcinoma (HCC). This research comes from one of the largest prospective cohorts for HCC known as the Precision Medicine in Liver Cancer across Asia-Pacific Network (PLANet) study. These novel findings from PLANet were recently published in the journal *National Science Review (NSR)*.

HCC is the seventh most common [cancer](#) worldwide, but the fourth leading cause of cancer death globally due to its high mortality rate. Strikingly, a disproportionate 80 percent of the disease burden is shouldered by Asian populations. Despite much effort, there is currently no validated predictive biomarker for systemic therapies in HCC and treatment efficacy remains poor.

The PLANet study was initiated to enroll a prospective HCC patient cohort working with the Asia-Pacific Hepatocellular Carcinoma (AHCC) Trials Group across multiple Asian countries. Specifically, PLANet aims to understand molecular diversities within a tumor known as intra-tumor heterogeneity (ITH), as well as how clinicians can use this understanding to guide patient stratification and treatment in HCC. In 2017, the group discovered that HCC has a wide range of genetic ITH across patients.

## **The study and its findings**

The current study is based on a cohort of 67 patients from four Asian countries from the PLANet study and is the first study of ITH across multi-omic data layers (genome, transcriptome, immunome) in HCC. Researchers found variations in different regions of the same tumor for both genetic (DNA mutation) and transcriptomic (RNA expression) profiles. In particular, they found that the level of such variations differs across patients and over 30 percent of patients show a high

transcriptomic ITH where a single tumor could contain multiple transcriptomic subtypes.

The dynamic, evolutionary process in HCC helps to explain the poor response to systemic therapy in HCC, where therapies addressing only a single group of molecular targets are insufficient. Using the PLANet cohort, the authors demonstrated that a combination therapies can potentially address the high ITH to increase treatment response rates for HCC. Discoveries from this research provide a novel scientific rationale for the development of innovative therapies for HCC. In the next phase, the group will focus on how to improve [liver cancer](#) treatment outcomes by targeting this dynamically evolving heterogeneity.

The PLANet study has also provided researchers and clinicians an atlas to assess the evolutionary history of liver cancer. Such genomic information will provide a solid basis for understanding how individual patients might respond differently to drug treatments, thus enabling a precision medicine approach to treat patients differently in the future. Data from this study is now publicly available via the Singapore Oncology Data Portal (OncoSG) which allows integration, visualization, analyses, and sharing of cancer genomics datasets generated in Singapore.

Dr. Zhai Weiwei, a former principal investigator at GIS who co-led this work, noted, "This study depicted the first full landscape of tumor heterogeneity in HCC, providing a solid basis harnessing tumor evolution for patient prognosis and treatment."

Professor Pierce Chow, senior author of the study, the overall principal investigator of PLANet and senior consultant, Department of Hepato-Pancreato-Biliary/Transplant Surgery, Division of Surgery and Surgical Oncology at SGH and NCCS said, "I have been treating HCC for more than 20 years and have conducted multi-national clinical trials in this

cancer, but HCC remains a very challenging malignancy. Significant scientific breakthroughs are required to further improve patient outcomes and our current findings provide an important step in this direction."

**More information:** Weiwei Zhai et al, Dynamic phenotypic heterogeneity and the evolution of multiple RNA subtypes in Hepatocellular Carcinoma: the PLANET study, *National Science Review* (2021). [DOI: 10.1093/nsr/nwab192](https://doi.org/10.1093/nsr/nwab192)

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