RECENT ADVANCEMENTS OF LIQUID BIOPSY IN PRECISION MEDICINE

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"The future is already here – it's just not evenly distributed."

- William Gibson,
The Economist, Dec 4th, 2013

In the last decade, we've seen the field of liquid biopsy, particularly cell-free DNA (cfDNA), progress from the early clinical proof-of-concept phase to the late clinical application stage. Just like any other type of technological advancements that emerge and peak at the right time and the right place, so is liquid biopsy. With the first discovery of cfDNA in human blood by Mandel and Metais in 1948, it went through intermittent investigations until late 2000s to early 2010s, when next generation sequencing (NGS) and sensitivity PCR technologies such as digital PCR (dPCR) became commercially available, the discovery and development momentum finally started to pick up. So far, there are at least two successful applications of cfDNA that have become part of standard of care in many clinics: i) noninvasive prenatal testing (NIPT) for fetal aneuploidy detection; ii) tumor genotyping for treatment decision making.

To make those clinical applications commercially successful, it cannot leave biology behind. On one hand, we've seen NGS and dPCR enable a deeper understanding of the biology associated with cfDNA, such as why it is even viable in the circulation (e.g. due to histone protein and transcription factor protection), the tissue origins, the DNA fragment length distributions, and its presence in different types of biofluids besides blood. On the other hand, the accumulated biological knowledge accelerates the applications of cfDNA in novel clinical research, which catalyzes the development of new cfDNA related products. For example, liver contributes to the most of cfDNA derived from distant organs in a healthy state. This finding has prompted research using cfDNA to study liver-associated diseases such as hepatocellular carcinoma. Another example showcasing how biology and technology go hand in hand is using microsatellite instability (MSI) as a predictive biomarker for the immune checkpoint PD-1 inhibitor (ICI). The concept and clinical evidence that microsatellite instability high state would lead to an increased tumor mutation burden and thus neoantigen presentation, rendering tumors to the immune checkpoint inhibition is a breakthrough. Detecting MSI through cfDNA in cancer patients, which has recently been developed and validated by a liquid biopsy company (Guardant Health, Inc), provides patients access to the ICI when tumor biopsy is not readily available.

Moving forward, we will continue to see more therapeutics developed to target tumor genetic alterations, either in a tumor tissue type-specific manner or an agnostic way. With increased tools in the oncology toolkit, more tumor genetic biomarkers will appear in the diagnostic testing menus for liquid biopsy, complementary to tumor tissue testing, not necessarily a complete replacement.

But prescribing the right kind of therapeutics targeting patient tumor's underlying biology is just one piece of puzzles the physicians are trying to solve on the journey of patients' care. There are unmet needs at multiple timepoints of a patient's journey where liquid biopsy could make an impact. It can start when an asymptomatic person is being diagnosed with cancer (so called early detection), or when physicians need to decide whether to continue treatment or stop, or when survivors are monitored in order to know whether the cancers are relapsed. Although each presents unique challenges, the common theme faced here is low signal-to-noise ratios: with small tumor burdens, the genetic information floating in the blood could be minimal. The field is tackling this challenge through multiple different angles: i) developing sensitivity sequencing technologies/softwares to reduce technical PCR errors while increasing the fidelity of mutation identification (e.g. through adding unique barcodes to DNA libraries and error correction algorithms); ii) customizing a testing panel to target individual patient's pre-existing tumor genomics (not applicable to early detection); iii) combining with non-mutation related liquid molecular information, such as DNA methylation status, immune cell populations, along with machine learning approach (largely experimental for early detection).

In summary, we are at an exciting era of bringing scientific and technological advancements in liquid biopsy to medicine. It takes stakeholders in every domain to realize the ultimate goal of improving patient care. Are you ready to be a part of the evolution?

Disclosure: I have no conflict of interest. The opinions presented here are my own and do not represent my employer's.

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Qing Kang-Fortner, Ph.D., has been in her current role as a Senior Scientist in Translational Medicine at Syros Pharmaceuticals, Inc. since March 2018, where she serves as the project lead and clinical biomarker lead for the ongoing two clinical trials. Previously she served as a Scientist at Progenity, Inc. from May 2017 to March 2018, where she was responsible for research and development activities associated with oncology and liver disease biomarker discovery and validation, with a focus of utilizing next generation sequencing based technologies to develop diagnostic tests that influence clinical decisions. Prior to joining Progenity she was a research fellow in Dr. Muneesh Tewari's laboratory at the University of Michigan, where she led a multidisciplinary team to study circulating tumor DNA both in blood and urine as a non-invasive approach to detect and monitor cancer patients and also served as a group member of Cancer Moonshot Blood Profiling Atlas Program. She received a B. E. in Bioengineering from China Pharmaceutical University and a Ph.D. in Molecular Biology and Genetics from Indiana University Bloomington.

Liquid Biopsy - The Technology Hype Cycle