

Development of Precision Medicine for Gastrointestinal Cancers

Utility of Liquid Biopsy in Genomic Analysis

October 6, 2020

National Cancer Center Japan

Japan Agency for Medical Research and Development

[Key points]

- This study demonstrates for the first time in the world that employing a blood test to detect genomic alterations (liquid biopsy) in screening of patients with gastrointestinal cancer shortens the turn-around time to return the test results and accelerates enrollment of patients to clinical trials, compared to conventional tissue biopsy.
- This is the first large-scale study that reports a comparison of the utility between tumor tissue biopsy and liquid biopsy for screening patients in clinical trials.
- Application of liquid biopsy as screening test^{*1} to many clinical trials is expected to broaden opportunities for more patients to receive the best medical care.

[Outline]

National Cancer Center (President: Hitoshi Nakagama, Tokyo, Japan) and Hospital East (Director: Atsushi Ohtsu, Chiba, Japan) demonstrated for the first time in the world that introducing a blood test to detect genomic alterations in patients with gastrointestinal cancer into screening for clinical trials achieves a shorter turn-around time to return the results, and expands patient enrollment in trials.

Liquid biopsy enables repeated testing of blood samples, eliminating the need for collecting tumor tissues. While conventional tissue collection is significantly invasive and sometimes leads to delays of treatment decisions, liquid biopsy would allow more patients to reach optimal therapeutic drugs with reduced burden to their bodies given its utility demonstrated in this study.

In this study, the turn-around time for receiving genomic analysis results, the enrollment rate in, and the drug efficacy in clinical trials were compared between the genomic analysis results from “GI-SCREEN-JAPAN (tumor tissue biopsy)”, which targets advanced gastrointestinal cancers, and those from “GOZILA study (liquid biopsy)”. The study revealed that liquid biopsy shortens turn-around time by approximately 22 days till obtaining results and raises patient enrollment to eligible clinical trials based on the genomic analysis results as compared with tissue biopsy.

This study was conducted by Dr. Takayuki Yoshino, Head of Gastrointestinal Oncology Group, Dr. Yoshiaki Nakamura, Translational Research Management Division, Clinical Research Support Office, and their colleagues as part of GI-SCREEN-JAPAN and GOZILA Study, and the study

results were published online (October 5 ,2020) in an American scientific journal “Nature Medicine”.

[Background]

A large number of clinical trials which utilize information about genomic alterations are conducted all over the world to establish cancer precision medicine². In these, tumor tissue biopsies have been used for identification of genomic alterations associated with the patient’s cancer characteristics. However, unavailability of tumor tissue in some patients and the relatively long timeframe requirement for analysis of tissue biopsies have impeded the acceleration of such trials.

On the other hand, liquid biopsy technologies have evolved rapidly in recent years. It has been suggested that liquid biopsy may resolve issues associated with conventional tumor tissue biopsy as liquid biopsy allows genomic profiling without tumor tissue samples, and also as the turn-around time to return test results is shorter. However, there had been no large-scale studies to date that compared the utility of tissue and liquid biopsies.

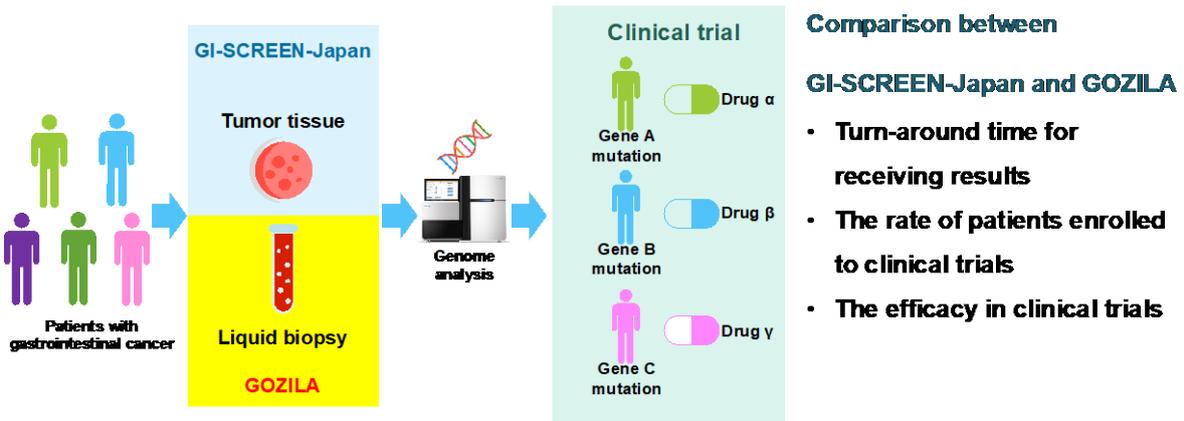
Given this situation, a large-scale comparative study was conducted by National Cancer Center Hospital East by utilizing the platform of a nation-wide industry-academia collaboration project “SCRUM-Japan”³.

[Research methods and achievements]

National Cancer Center launched a nation-wide industry-academia collaboration project “SCRUM-Japan” and has conducted “GI-SCREEN-JAPAN (currently MONSTAR-SCREEN)” since February 2014. GI-SCREEN-Japan is a nation-wide cancer genome screening project wherein NCC cooperates with major cancer specialty hospitals and university hospitals in Japan to deliver therapeutic drugs to advanced gastrointestinal cancer patients. In January 2018, NCC launched GOZILA study, a screening project in collaboration with Guardant Health Inc. (USA), in which blood samples of patients with advanced gastrointestinal tumors are analyzed by liquid biopsy (Guardant360® Assay) utilizing the platform of GI-SCREEN-Japan.

In this study, we compared 5743 patients enrolled in GI-SCREEN-Japan (tumor tissue biopsy) from February 2015 to April 2019 (4 years and 2 months) and 1787 patients enrolled in GOZILA Study (liquid biopsy) from January 2018 to August 2019 (1 year and 7 months) (Figure 1).

Figure 1 Study outline

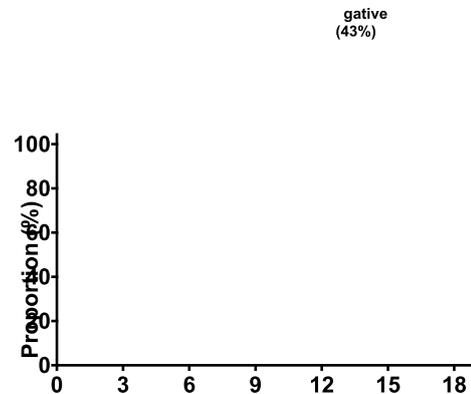


◆ Comparison results (GI-SCREEN-Japan vs. GOZILA Study) (Figure2)

- Project enrollment to sample arrival (median: 14 days vs 4 days, $P < 0.0001$)
- Sample arrival to return of test results to patients (median: 19 days vs. 7 days, $P < 0.0001$)
- Patients with actionable genomic alterations identified (54% vs. 57%)
- Patients enrolled in clinical trials of drugs matching detected genomic alterations (4.1% vs. 9.5%, $P < 0.0001$)
- Patients whose tumors responded in clinical trials (16.7% vs. 20.0%, $P = 0.69$)
- Progression-free survival in clinical trials (median: 2.8 months vs. 2.4 months, $P = 0.70$)

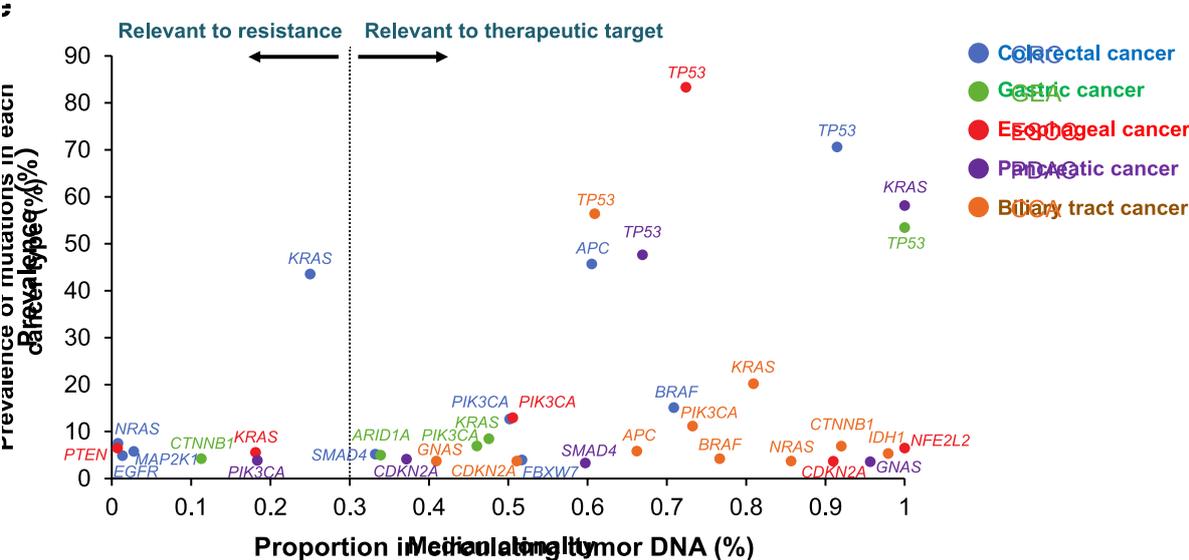
Figure 2 Comparison results of GI-SCREEN-Japan (tumor tissue biopsy) and GOZILA Study (liquid biopsy)

Enrollment to sample arrival: 4 days Sample arrival to return of test results: 7 days



In addition, genomic profiling⁴ by liquid biopsy in GOZILA study revealed useful biomarkers and several novel driver gene⁵ mutations including *NFE2L2* mutation in esophageal squamous cell carcinoma, *GNAS* mutation in pancreatic cancer and *CTNNB1* mutation in biliary tract cancer, potential candidates of therapeutic targets.

Figure 3 The profile of cancer genomic alterations in GOZILA Study



[the Future]

Based on the results of this study, utilizing liquid biopsy as screening test in clinical trials is expected to deliver optimal treatments to many patients. In addition, the discovery of new driver gene mutations will potentially instigate clinical development of drugs for them. Indeed, several investigator-initiated trials have already been launched based on liquid biopsy results in GOZILA study. National Cancer Center Hospital East will continue to further establish genomic medicine using liquid biopsy to deliver optimal therapies to as many patients as possible.

[Research Paper]

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 Title: Clinical Utility of Circulating Tumor DNA Sequencing in Advanced Gastrointestinal Cancer: SCRUM-Japan GI-SCREEN and GOZILA Studies
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[Glossary]

***1 Screening test**

In screening tests for clinical trials, patients are tested and interviewed to check whether they meet eligibility requirements. Items include height, weight, body temperature, blood pressure, blood collection, respiratory examination, electro-cardiogram, CT scan and interview.

***2 Cancer precision medicine**

Medical treatments adapting to constitutions and medical conditions of individuals by identifying cancer-associated gene alterations by simultaneous testing of multiple genes.

*3 SCRUM-Japan (Cancer Genome Screening Project for Individualized Medicine in Japan)

An industry-academia collaborative cancer genome screening project integrated both LC-SCRUM-Japan (currently LC-SCRUM-Asia) for patients with lung cancer started in 2013 and GI-SCREEN-Japan (currently MONSTAR-SCREEN) for patients with gastro-intestinal cancer started in 2014. The project aims at screening genomic alterations in patients with solid tumors, over 10,000 patients with advanced solid cancer have participated in this study since its launch in February 2015. Outcomes of this study include regulatory approvals of 8 new drugs and 9 in vitro diagnostics. With participation of over 200 medical institutions and 17 pharmaceutical and diagnostics companies, academia, hospitals and industries are developing drugs and diagnostics together that match genetic alterations of cancer patients in Japan.

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https://www.ncc.go.jp/jp/information/pr_release/2018/0313/index.html

*4 Profiling

An inspection to check multiple genes in one assay using a tumor tissue sample.

*5 Driver genes

Genes that play direct and important roles in carcinogenesis and cancer development, such as oncogenes and tumor suppressor genes.

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