**Review**

# Improvement of patient care using cancer genomic profiling: SCRUM-/CIRCULATE-Japan experience

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**Abstract:** We launched SCRUM-Japan platform for the cancer genome profiling (CGP) test screening followed by the enrollment to genomically-matched clinical trials in 2015. More than 30,000 tissue-based and 10,000 liquid-based CGP tests have already been performed for enrolling to a total of 127 industry-/investigator-initiated registration trials, which resulted in regulatory approvals of 12 new agents with 14 indications in Japan. Using the clinical-genomic database, a new driver gene was recently discovered with dramatic response by genomically-matched agent. Our comparative study with tissue-based CGPs revealed more usefulness of liquid biopsy in terms of less invasive manner, shorter turn-round time, and higher enrollment rate for matched treatments than tissue-based in gastrointestinal cancers. For detecting minimal/molecular residual disease (MRD) after surgery, post-surgical monitoring with tumor-informed liquid biopsy assay in association with two randomized control trials have also started in 2020 (CIRCULATE-Japan). The observational cohort study showed obvious efficacy of the MRD monitoring for predicting recurrence, leading to change clinical practice in patient selection who should receive adjuvant therapy in the near future.

**Keywords:** cancer genome medicine, comprehensive cancer genome profiling, liquid biopsy, precision medicine

## Introduction

Cancer comprehensive genomic profiling (CGP) tests have recently been implemented in oncology daily practice, particularly for patients with advanced solid tumors. However, there still remain major barriers to achieve meaningful CGP-based precision oncology: most of the actionable targets are present only in a small fraction of patients and the number of effective agents matched to actionable targets is still limited. To overcome these barriers, large-scale CGP screening platform followed by a large number of genomically-matched clinical trials are desirable. Thus, we launched a nationwide CGP screening platform accompanying matched clinical trials with the aim of regulatory approval, named SCRUM-Japan, as an academia-industry collaboration starting in 2015.

Historically, a previous platform was started in lung cancer (the LC-SCRUM project) in 2013 aiming to recruit patients with non-small cell lung cancer patients harboring a *RET* and *ROS1* fusion gene.[1)] In 2014, the multicenter GI-SCREEN project was started for patients with gastrointestinal (GI) cancers. With the development of a comprehensive multigene screening panel, and the two groups were integrated and we launched a nationwide genome screening platform named SCRUM-Japan in collaboration with more than 200 hospitals and 10 pharmaceutical companies (18 at present) in 2015. The aims of this project are to deliver new effective agents with regulatory approval prioritized for cancer patients and to accelerate innovative precision oncology. The GI-SCREEN group firstly targeted patients with GI cancers, followed by MONSTAR-SCREEN with expansion into all adult solid tumors, except for lung cancer, since 2019.[2)] The aims of SCRUM-Japan are to accelerate patient accrual in

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| Region | Japan | | | | Asia Pacific |
|---|---|---|---|---|---|
| Study | LC-SCRUM-Asia | LC-SCRUM-TRY | LC-SCRUM-Advantage/MRD | LC-SCRUM-Support | LC-SCRUM-AP |
| Histology | NSCLC | NSCLC | NSCLC | NSCLC | NSCLC |
| Target population | Untreated, advanced stage | Treated, advanced stage | Operable, early stage | Every patient enrolled into LC-SCRUM | Untreated, advanced stage |
| Gene analysis | • Amoy multiple PCR<br>• OPA by NGS<br>• Amoy Master Panel<br>• RNA sequence | • OPA by NGS<br>• MET FISH | • Amoy multiple PCR<br>• OPA by NGS<br>• PD-L1 IHC<br>• Liquid biopsy<br>• MRD monitoring | (Not gene analysis)<br>LC-SCRUM office provides ongoing clinical trial information to patients by email | • Amoy multiple PCR<br>• NGS Panel |
| Objective | Genomic screening | Identification of acquired resistance | Genomic screening | Information on clinical trials | Genomic screening |
| Status | 2013-Ongoing | 2020-Ongoing | Ongoing (2022/8/29 start) | 2021-Ongoing | Ongoing (2022/10/31 start) |

NEW NEW Support!!

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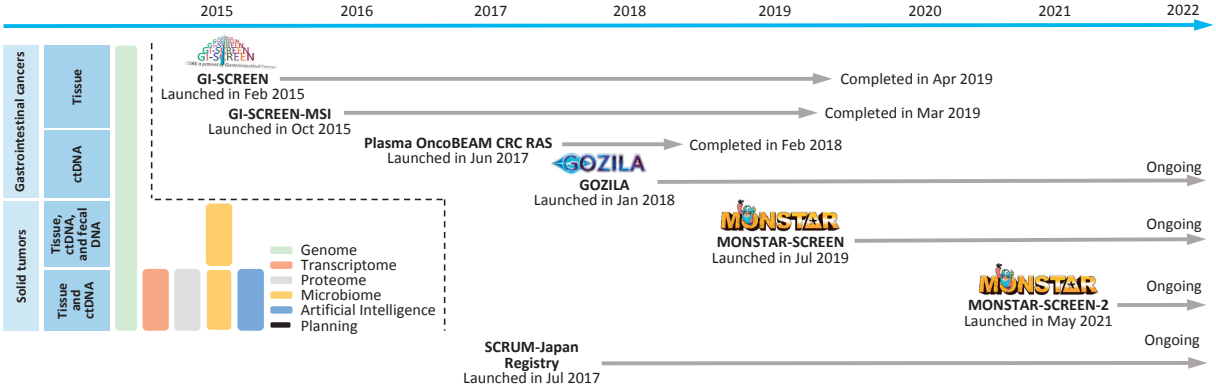


Fig. 1. (a) Studies conducted in SCRUM-Japan/LC-SCRUM-Asia/AP. (b) Study timelines of SCRUM-Japan/GI- and MONSTAR-SCREEN. (Cancer Sci. (2021) **112**, 4425–4432 (Ref. 2))

industry-/investigator-initiated clinical trials registered on the platform and to introduce worldwide cutting-edge technology of multi-omics analyses including not only tissue-based but also liquid-based CGP tests in order to promote innovative precision oncology (Fig. 1).

Liquid biopsies, particularly for circulating tumor DNA (ctDNA), have become a novel tool for precision oncology, with applications for target screening and monitoring during drug therapy in advanced cancers. Recently, this technology has been indicated for the detection of minimal/molecular residual disease (MRD) during perioperative treatment, which may aid in patient selection to receiving adjuvant chemotherapy (ACT). In this regard, we launched another multilayer testing platform, named CIRCULATE-Japan, in 2020 to evaluate the clinical utility of liquid-based CGP tests focusing on MRD detection.[3)]

## SCRUM-Japan: An overview

During the early period of SCRUM-Japan, most efforts were put towards patient screening in genomically-matched trials with tissue-based CGP panels

Table 1. No. of IND registration trials registered on the SCRUM-Japan platform

| Trial type | Organ | No. of target genes | SIT | IIT | Total |
|---|---|---|---|---|---|
| Umbrella | Lung cancer | 11 | 25 | 15 | 40 |
| | Other solid tumors | 8 | 6 | 7 | 13 |
| Basket | Solid tumors | 15 | 25 | 7 | 32 |
| Total | | 34 | 56 | 29 | 85 |

such as "Oncomine Comprehensive Assay" (OCA: Thermo Fisher Scientific) and "FoundationOne CDX" (Foundation Medicine). Then, ctDNA screening with "Guardant 360" (Guardant Health) was introduced in 2018. As of March 2023, a total of 56 industry-initiated (mostly as part of multiregional trials) and 29 investigator-initiated trials have been registered in the SCRUM-Japan patient referring system, which has enabled more than 1,300 patients in total to be accrued into genomically-matched trials. Of the 30 trials for which primary outcomes have been reported, 20 new agents with 24 indications have received regulatory approval for medical re-imbursement in Japan so far (Table 1).

The number of known driver genes are remarkably different between lung cancer and other solid tumors and an implementation of CGP tests into daily practice in Japan in 2019; therefore, different approaches were adopted in each study group. The LC-SRCUM group developed a small panel with a short turnaround time, which makes precision oncology easily accessible. On the other hand, the GI-SCREEN group reorganized from being GI cancer specific to all adult solid tumors except lung cancer toward the development of tumor agnostic indication, named MONSTAR-SCREEN.

## Achievements of LC-SCRUM-Japan/ Asia-Pacific

LC-SCRUM-Japan first started as a nationwide *RET* and *ROS1* fusion gene screening study in collaboration with around 200 hospitals. Between February 2013 and March 2015, a total of 19 patients with *RET* fusion-positive non-small cell lung cancer (NSCLC) were accrued into an investigator-initiated phase II trial (LURET study: UMIN-CTR 000010095).[4] Among 17 eligible patients included in the primary analysis, nine (53% [95% CI 28–77]) achieved an objective response, which met the primary endpoint. Final survival results of this study also showed favorable survival with median progression-free survival (PFS) of 6.5 months and median overall survival (OS) of 13.5 months.[5] A CGP panel with OCA was introduced into the group in 2015, and more than 17,000 patients have been already screened, resulting in a total of 552 patients for any of the genotype-matched trials as of August 2022. These efforts contributed to the regulatory approval of new agents in Japan such as crizotinib for *ROS1* fusion, dabrafenib and trametinib for *BRAF* V600E, entrectinib for *NTRK* and *ROS1* fusion, tepotinib/ cabozantinib for *MET14* skipping. selpercatinib for *RET* fusion positive and sotorasib for *KRAS* G12C mutation positive NSCLC.

Since March 2019, the screening platform was expanded to 6 institutions in Taiwan, which led to a change in name to LC-SCRUM-Asia. In parallel with the expansion, another project named LC-IRICA-China was launched in collaboration with LC-SCRUM-Asia. Using the LC-SCRUM large clinicogenomic data set with a total of 10,023 patients with NSCLC, the prevalence of *KRAS* G12C mutation, recently becoming a new target of sotorasib, was analyzed. In this study, *KRAS* mutations were detected in 1,258 patients (14%), including G12C in 376 (4.0%), G12D in 289 (3.1%) and G12V in 251 (2.7%). The results revealed remarkably lower frequency of *KRAS* G12C (4.0%) mutation than in a Caucasian population (14%).[6] The platform was further expanded to Asia-Pacific region, including Thailand and Malaysia as LC-SCRUM-AP, which was launched in October 2022, as an independent but parallel organization (Fig. 2).

Although many driver genes have been discovered in NSCLC, such drivers are not found in approximately 25–40% of patients. For molecular screening in LC-SCRUM-Asia, DNA and RNA were extracted from fresh and frozen tissues or from formalin-fixed paraffin-embedded (FFPE) samples. We attempted whole transcriptome sequencing using the remained samples for discovering new driver gene in 75 samples negative for known oncogenic driver and finally identified an in-frame fusion transcript of *CLIP1* on chromosome 12q24 and *LTK* on chromosome 15q15 in one patient.[7] Then transforming potential of *CLIP1-LTK* was investigated in transfected NIH3T3 cells followed by detection of robust phosphorylation in CLIP1-LTK-expressing cells but much weaker phosphorylation when cells were transfected with wild-type LTK. Because *LTK* and *ALK* share nearly 80% identity in their respective kinase domains, 7-FDA-approved ALK inhibitors were

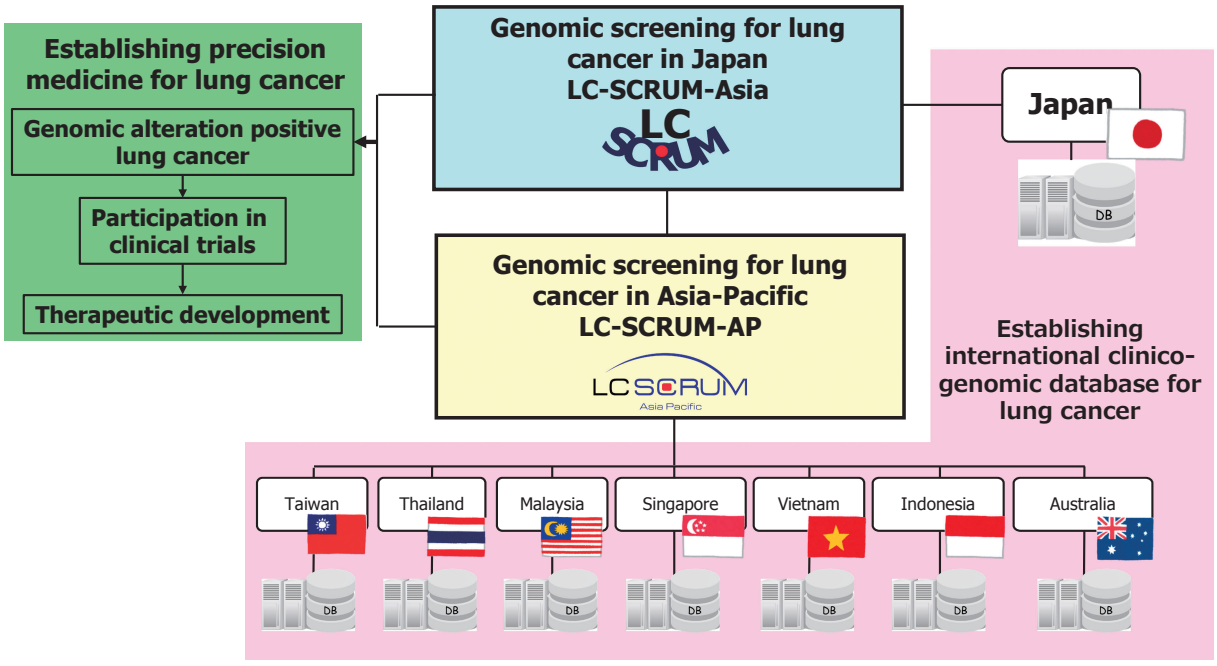


Fig. 2. Outline of LC-SCRUM-AP.

screened in transfected mice, in which lorlatinib showed the highest efficacy. After off-label use was approved by National Cancer Center Hospital East review board, lorlatinib was administered to a patient harboring *CLIP1-LTK* fusion gene who had received robust standard of care treatment, which resulted in a rapid and dramatic response seen in follow-up CT and PET imaging (Fig. 3). Following treatment success, a new investigator-initiated trial with lorlatinib for *LTK* fusion-positive NSCLC was recently initiated.

Another study was conducted to determine adequate predictive markers for immune checkpoint inhibitors in NSCLC.[8] PD-L1 expression using four IHC assays (22C3, 28-8, SP263, SP142), tumor mutation burden (TMB) by whole-exome sequencing and oncogenic driver alterations were also analyzed comprehensively in a total of 1,017 patients with NSCLC. The results of 22C3 and 28-8 for PD-L1 expression showed acceptable concordance ($k = 0.89$; 95% confidence interval [CI], 0.87–0.92) with similar clinical outcome prediction for ICIs. Patients with both high PD-L1 expression and high TMB showed a good response to ICIs with a response rate of 64% and median PFS of 9.0 months despite the small population, which showed the possible utility of these combined assays.

Liquid biopsy using plasma cell-free DNA (cfDNA) collected with a Streck Cell-Free DNA BCT (Streck Corporate, NE) tube for the Guardant 360 panel was also investigated as a comparative study with a tissue-based CGP panel. Paired blood and tissue samples were obtained in 1,062/1,112 enrolled patients with NSCLC.[9] Oncogenic alteration was detected by plasma cfDNA sequencing and tissue assay in 455 (42.8%) and 537 (50.5%) patients, respectively. Oncogenic drivers were positive for plasma cfDNA and negative for tissue due to unsuccessful genomic analysis from poor-quality tissue samples (70%) and were negative for plasma cfDNA and positive for tissue because of the low sensitivity of cfDNA analysis (61%). However, in patients with positive oncogenic drivers by plasma cfDNA sequencing but negative by tissue assay, the response rate of genotype-matched therapy was 85% and median PFS was 12.7 months. These results suggested that cfDNA can be an alternative when tissue assays are unavailable or insufficient for DNA and RNA analyses.

### Achievements of GI-/MONSTAR-SCREEN

The GI-SCREEN was launched as a multi-institutional collaborative study with 26 core centers in Japan (UMIN000016343, UMIN000016344) using

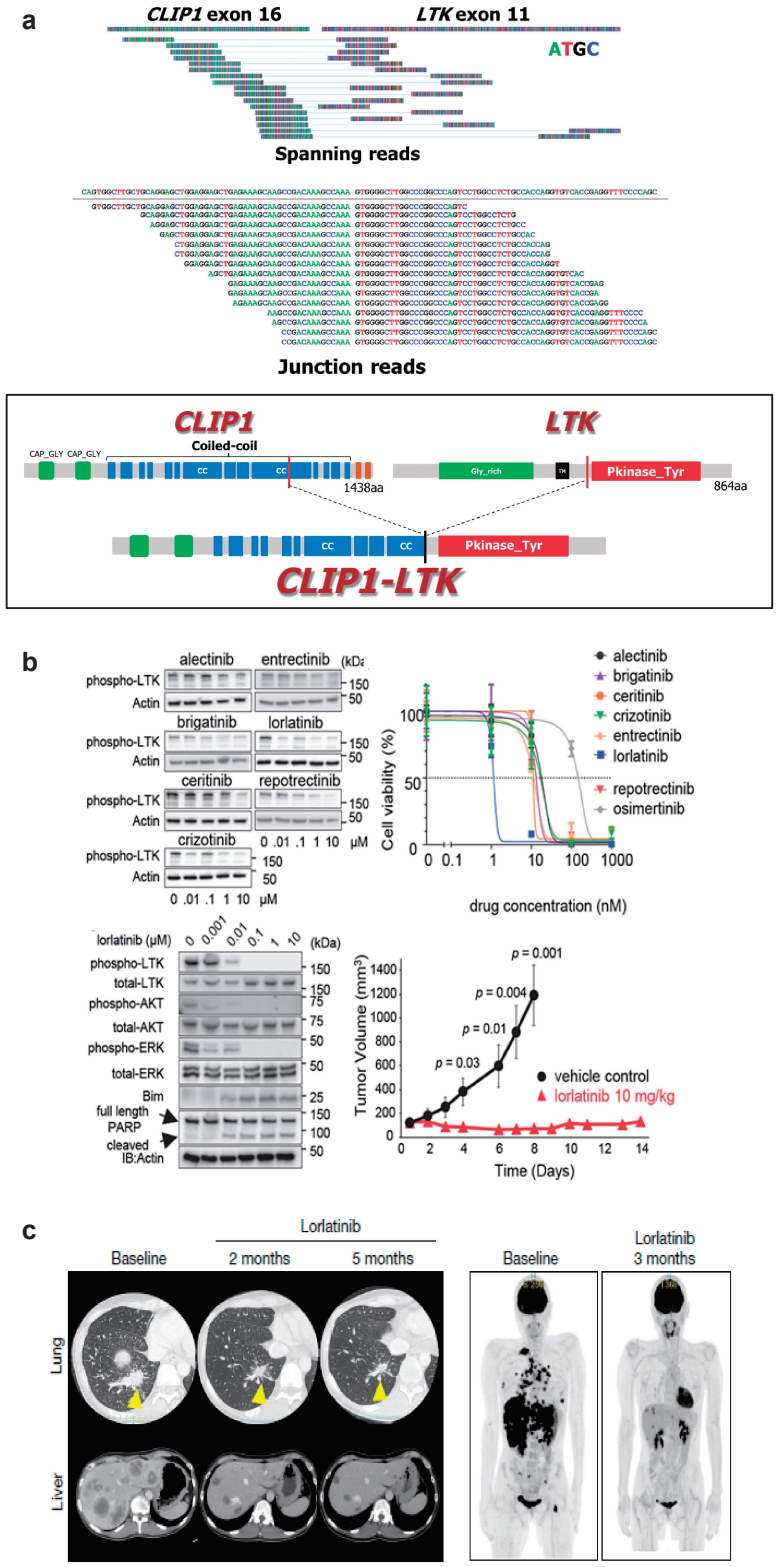


Fig. 3. Discovery of new driver genes in LC-SCRUM-Asia. (a) Discovery of a new driver gene: *CLIP1-LTK* fusion gene. (b) Screening for *CLIP1-LTK* inhibitors. (c) Time course of patients with *CLIP1-LTK* fusion genes treated with lorlatinib. (Nature (2021) **600**, 319–323 (Ref. 7))

a tissue-based CGP panel. During the period between February 2015 and April 2019, a total of 5,743 patients with advanced GI cancers including colorectal (n = 2,791), gastric (n = 1,141), esophageal (n = 369), pancreatic (n = 652), biliary tract (n = 416), liver (n = 67), small intestine (n = 93), appendiceal (n = 47), anal canal cancers (n = 13), GI stromal tumors (n = 79), and neuroendocrine tumors (n = 75). The landscape of genomic alterations was comparable to that reported in other profiling studies in Western countries appearing as a "long-tail" distribution in a considerable number of gene alterations. An international study with Memorial Sloan Kettering Cancer Center and Massachusetts General Hospital was conducted to validate a proposed classification of *BRAF* non-V600E mutation in kinase activity in patients with colorectal cancers (CRC). In this study, mutations outside of the V600 amino acid in *BRAF* were divided into class 2 and class 3: BRAF class 2 mutants are activating and RAS independent; they dimerize and signal without RAS activation. Class 3 BRAF mutants exhibit low kinase activity or are kinase-dead but activate the MAPK pathway through enhanced RAS binding and subsequent RAS-dependent CRAF activation. Internationally integrated analyses revealed the patients with class 2 mutations were less likely to respond anti-epidermal growth factor receptor (EGFR) therapy than those with class 3 mutations across ethnicities.[10] Another international collaborative study with U.S. and Korean investigators established an international harmonization of diagnostic criteria that integrated data based on immunohistochemistry (IHC), fluorescence *in situ* hybridization, and different CGP tests for HER2-positive metastatic CRC.[11]

ctDNA screening was introduced since January 2018 involving 31 core hospitals in the GI-SCREEN network. As of February 2023, more than 5,000 patients have been screened using ctDNA. We conducted a comparative study on the clinical utility between tissue-based CGP and ctDNA screening in patients with advanced GI cancers.[12] In this study, 5,621 patients receiving tissue-based and 1,687 patients with ctDNA screening were compared in terms of detection rate of actionable gene alterations, turnaround time, enrollment rate in clinical trials, and their outcomes. The CGP between the ctDNA-based and tissue-based revealed similar detection rate of actionable genes. The sample unavailability rate was 0.3% *vs.* 1.5%, the failure rate was 0.1% *vs.* 10.6%, the median sample acquisition duration was 4 *vs.* 14 days, and the median test duration was 7 *vs.* 19 days in ctDNA-based *vs.* tissue-based CGP, respectively. As a whole, ctDNA genotyping led to a statistically significant increase in enrolment into genomically-matched clinical trials (9.5% *vs.* 4.1% of patients; $P < 0.0001$) without compromising treatment efficacy in clinical trials (response rate of 20.0% *vs.* 16.7%; median PFS, 2.4 *vs.* 2.8 months) (Fig. 4). These results suggested the clinical utility of ctDNA tests in patients with advanced GI cancers.

On the tissue-based and ctDNA screening platform, a total of 12 investigator-initiated trials with molecular targeting agents consisted of 6 tumor-specific umbrella type and 6 tumor-agnostic basket type trials were conducted for genomically-matched patients.[13] In parallel with these trials, regulatory-grade registry data were captured for the development of an external control comparing each single-arm trial. A phase II combination trial (UMIN000027887) of pertuzumab and trastuzumab in patients with HER2-positive CRC (TRIUMPH study) showed efficacy with the objective response rate (ORR) of 30% in 27 tissue-positive and 28% in 25 ctDNA-positive patients.[14] The trial data were compared with 14 extracted patient data sets from the SCRUM-Japan registry, showing no objective response, in the review process of the Pharmaceuticals and Medical Devices Agency (PMDA), by which regulatory approval was achieved in 2022 (Fig. 5).

In 2019, the MONSTAR-SCREEN project was launched with a target of expansion to all adult solid tumors except lung cancers in collaboration with 31 core hospitals. We monitored genomic alterations using FoundationOne Liquid CDx (Foundation Medicine) in addition to tissue-based CGP analyses, which target alterations in 324 genes as well as complex biomarkers, such as microsatellite instability (MSI), blood tumor mutational burden (bTMB), and tumor fraction, to assess the landscape of genomic evolution throughout systemic therapy (UMIN000036749) in a total of 2,200 patients with various solid tumors. In the bTMB analysis, the frequency of tissue TMB-H ($\geq$10) tumors was higher than that of bTMB-H ($\geq$10) tumors (19% *vs.* 13%), although the prevalence of bTMB-H by cancer type was correlated with the prevalence of elevated tissue TMB.[15] The detection of bTMB-H and MSI-H in liquid biopsies was associated with elevated ctDNA levels, potentially indicating a more aggressive pathobiology in samples positive for these biomarkers. The fecal microbiome was also analyzed before and after systemic therapy by 16S ribosomal

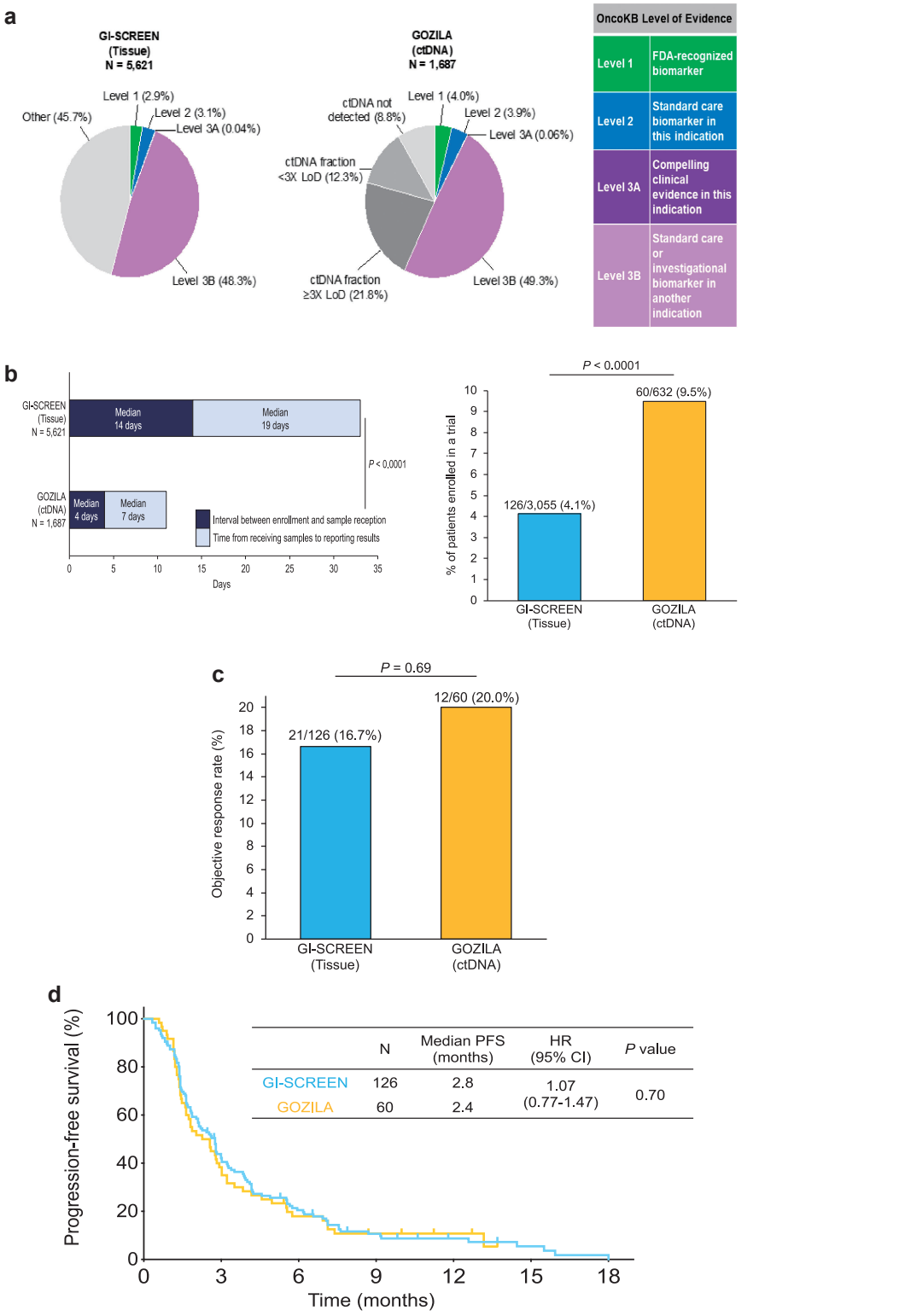


Fig. 4. A comparative study between tissue- and liquid-based CGP in GI cancers. (a) Actionable gene alterations by onco KB evidence level. (b) Turnaround time and trial enrollment rates in each modality. (c) Objective response rate in enrolled patients in genomically-matched trials. (d) Progression-free survival by each modality in enrolled patients in genomically-matched trials. (Nat. Med. (2020) **26**, 1859–1864 (Ref. 12))

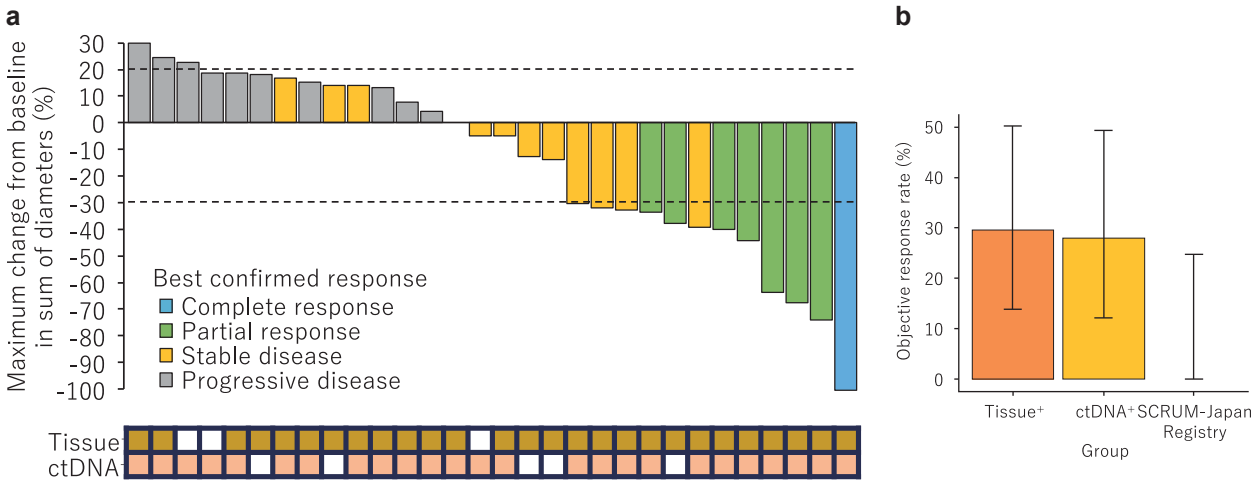


Fig. 5. Results of the TRIUMPH trial. (a) Waterfall plot for efficacy in each patient. (b) Objective response rate in comparison with registry data. (Nat. Med. (2021) **27**, 1899–1903 (Ref. 14))

RNA sequencing. Most of the analyses with clinical outcomes are now under investigation, which will be published elsewhere in the near future.

Various abnormalities occur in cancer cells not only highlighted in DNA changes alone but also in RNA and protein expression, which can be a drug target. Additionally, recent success including antibody-drug conjugates, radionuclide therapy agents, and bispecific antibodies make us consider the importance of multi-omics analysis with artificial intelligence (AI)/machine learning (ML) in addition to DNA sequencing. In May 2021, we launched MONSTAR-SCREEN-2, a nationwide multilayered molecular profiling study with AI/ML based on the SCRUM-Japan platform (UMIN000043899). In this study, a target sample size of 2,750 patients with solid tumors are being enrolled, and whole-exome and whole-transcriptome sequencing of tumor tissue and plasma samples were performed for comprehensive molecular multi-omics profiling using assays developed by Caris Life Sciences Ltd. Tumor tissue samples were also used for multiplex IHC analysis to assess the TME, as well as IHC testing for HER2 and PD-L1. Patient accrual is still on-going.

### Achievements of CIRCULATE-Japan

ctDNA has a potential clinical utility not only in screening and monitoring for targeted therapy but also in detecting MRD during perioperative treatment in solid tumors. For the latter purpose, the CIRCULATE-Japan project was launched in 2020 for patients with resectable CRC. We adopted the Signatera assay™ (Natera, Inc) for MRD monitoring as a custom-built ctDNA monitoring assay for MRD detection (bespoke, mPCR-NGS) that tracks 16 patient-specific somatic single-nucleotide variants in the patient's plasma, according to variants identified via whole-exome sequencing of the tumor tissue. The project consists of three parts (Fig. 6). The GALAXY study is a registry-based prospective observational study for patients with stage II–IV CRC who can undergo complete surgical resections. The tumor-informed Signatera assay is used to monitor post-surgical recurrence at 4, 12, 24, 36, 48, 72, and 96 weeks after surgery. The target sample size of the GALAXY study is 6,300. The VEGA trial is a randomized phase III study with a target sample size of 1,000 patients designed to evaluate whether postoperative surgery alone is non-inferior to standard adjuvant capecitabine plus oxaliplatin (CAPOX) therapy. The third part, ALTAIR (JapicCTI-205363 and NCT04457297) is a randomized, double-blind, phase III study with a target sample size of 240 that is designed to test the superiority of trifluridine/tipiracil (FTD/TPI) compared with placebo in patients with radically resected CRC who show ctDNA-positive status without any sign of radiological recurrence at any time after curative resection with or without following standard ACT.

We have recently published the first report on the GALAXY study in patients enrolled as of April 2021, including 1,039 patients and a median follow-up period of 16.74 months.[16] Postsurgical ctDNA positivity (at 4 weeks after surgery) was associated

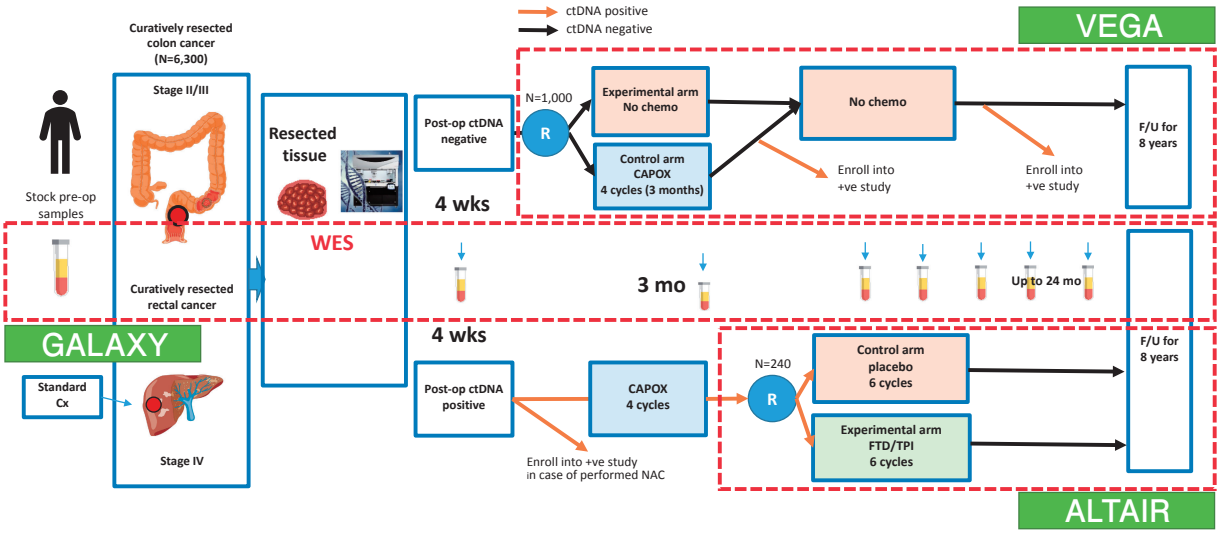


Fig. 6. Overview of CIRCULATE-Japan. (Cancer Sci. (2021) **112**, 2915–2920 (Ref. 3))

with higher recurrence risk (hazard ratio [HR] 10.0, $P < 0.0001$) and was the most significant prognostic factor associated with recurrence risk in patients with stage II or III CRC (HR 10.82, $P < 0.001$). The subset analysis revealed that postsurgical ctDNA positivity identified patients with stage II or III CRC who derived benefit from the standard ACT (HR 6.59, $P < 0.0001$). Furthermore, patients with high-risk stage II or stage III disease and ctDNA-positive status 4 weeks after surgery derived significant benefit from ACT (adjusted HR 6.59, 95% CI 3.53–12.3, $P < 0.0001$). On the contrary, in ctDNA-negative patients, after accounting for potentially confounding factors, no statistically significant benefit from ACT was observed (adjusted HR 1.71, 95% CI 0.80–3.7, $P = 0.16$): 18-month DFS of 94.9% (95% CI 91.0–97.2%) and 91.5% (95% CI 87.6–94.2%) was observed for the ACT group and the no-ACT group, respectively (Fig. 7). Throughout the study, a total of 8,374 genes were selected from 1,039 patients. The most frequently selected genes were *TP53* (25.6%) and *APC* (17.5%), and more than 50% of genes were unique to each patient, suggesting large variability in the mutational landscape of CRC outside of known hotspot regions.

## Current status and issues in clinical development of precision oncology

CGP testing has been rapidly introduced into daily practice world-wide. However, the number of patients receiving the test followed by genotype-matched therapy is still limited to around 3–10% not only in Japan but also in the United States. Although several issues including cost, reimbursement for off-label use, difficulties in accessing trial sites are known, one of the major issues is that the number of effective targeted agents are still limited compared with the increasing number of tested genes and detected actionable gene alterations. There are high hurdles in clinical development of new agents: the frequency of driver genes is very low, which make it unrealistic to conduct randomized controlled trials and also making drug discovery less of an incentive for industry due to the very small market size. Particularly in Japan, off-label and compassionate use are uncommon, and regulatory approval for extended indications is basically required for a patient's access to a matched therapy. Although resource issues remain, regulatory-grade registry data used in the review process of the TRIUMPH study as an external control may support resolutions for these dilemma. In the early period of constructing the regulatory-grade SCRUM registry, we received the PMDA consultation for registry holders on the concept of planning and improving quality and ensuring the reliability. Then, we determined to collect prospectively captured high-quality clinical data, which made it possible for us to submit a quality-assured external control finally classified as "evaluation material".[17] This attempt with registry-based real-world data might be the first using control data defined as not "reference data" but "evaluation data" in a new agent evaluation and approval process. The SCRUM-Japan platform with its

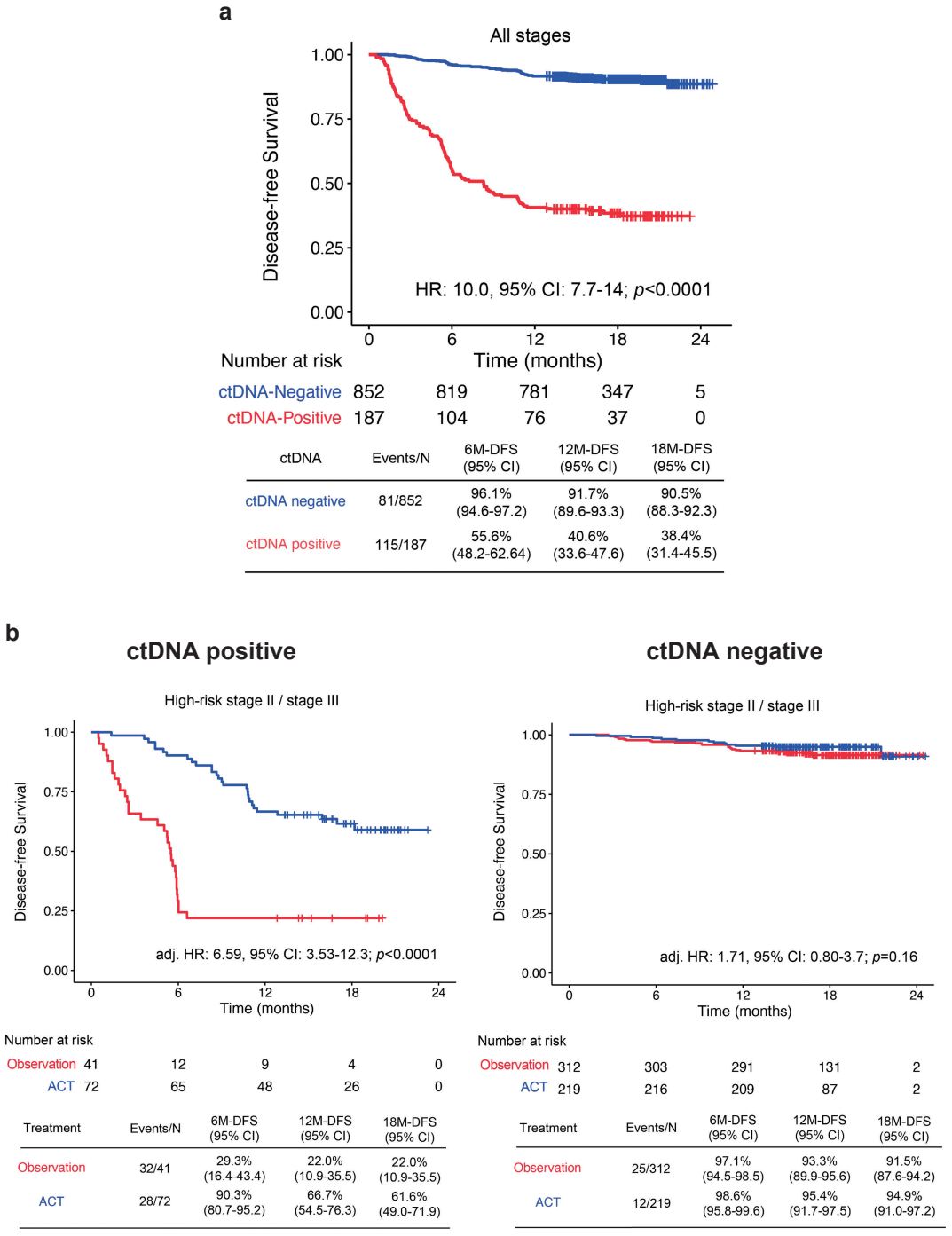


Fig. 7. Results of the VEGA study in CIRCULATE-Japan. (a) Post-operative 4-week ctDNA status and disease-free survival. (b) Post-operative 4-week ctDNA status and response to adjuvant chemotherapy. (Nat. Med. (2023) **29**, 127–134 (Ref. 16))

registry has contributed to regulatory approval by facilitating trial enrollment and partly by reducing the cost of clinical trials in Japan.

## Utilization of clinical and genomic/multi-omics data for new target and drug discovery

Data on more than 40,000 patients have already

been accrued with clinico-genomic data into SCRUM-/CIRCULATE-Japan database including more than 1,200 patients enrolled into any of the IND registration trials. These data with a large number of remaining samples have been utilized in clinical and basic research, which yielded more than 60 publications in peer-reviewed journals. One of the major research areas is to discover therapeutic targets, including resistance mechanism including evidence from serial liquid biopsies, as mentioned above. In this regard, the discovery of the *CLIP1-LTK* fusion gene in NSCLC is a significant success case, which was followed by a significant response with a matched agent after drug screening of approved ALK inhibitors. Although this seems to be a desirable story, it seems very hard to make an original new agent for a new fusion gene because of the very low frequency of 0.4% in NSCLC. On the other hand, several successes of new modalities such as antibody-drug conjugates, radionuclides targeting membranous proteins have recently been reported with significant clinical impact. The TME, including the immune response network and cancer-associated fibroblasts, is also becoming more important as a therapeutic target. In addition, recent progress in drug design has been able to make major drug non-targetable proteins such KRAS into drug targets, as seen in several reports of new agents such as sotorasib and adagrasib for *KRAS* G12C mutant NSCLC, CRC, and pancreatic cancer.[18)–20)] These changes in drug discovery and development required not only genome analyses but also multi-omics analyses including the TME, which led us to conduct the ongoing multi-omics project, MONSTAR-SCREEN-2. In this project, huge amounts of clinical and multi-omics data on solid tumors are being stored in a supercomputer for AI/ML analysis. This infrastructure in academia-industry collaborations is anticipated to lead to new drug discoveries and further developments in precision medicine.

## Current status and issues in liquid biopsy in precision oncology

With recent progress in capture and analytical technology, liquid biopsies have been implemented in oncology daily practice. This liquid-based profiling has several advantages such as easy accessibility to samples and shorter turnaround time than tissue-based profiling tests, including monitoring for resistance during treatment, whereas lower sensitivities and specificity than tissue-based approaches have also been pointed out. There are remarkable differences in concordance rate between tissue- and liquid-based profiling among organs, particularly lower rates in lung cancer and relatively higher rates in GI cancers in the SCRUM project. Several reasons can be raised, including differences in shedding rates from tumor tissues and frequencies of fusion driver genes between lung and GI cancers. Liquid biopsy may, at least, compensate for inadequate tissue-based profiling due to lower accessibility. Rapid technology progress in liquid biopsies has been able to detect transcriptional changes, which may overcome the weakness in detecting fusion genes. This new technology has already been indicated in the MONSTAR-2 study and the efficacy of this new technology will be clarified in the near future.

Another important area utilizing liquid biopsies is MRD detection during perioperative treatment. Although longer follow-up and on-going confirmatory trial results are needed, the GALAXY study with a tumor-informed assay in stage I–IV CRC revealed a high predictive value for cancer recurrence. An Australian study group has recently reported significant, practice-changing results from a randomized controlled phase II trial.[21)] Patients with stage II CRC were randomly allocated in a 2:1 ratio to have treatment decisions guided either by tumor-informed ctDNA assay results for adjuvant chemotherapy or standard clinicopathological features. This trial met its primary efficacy endpoint of 2-year recurrence-free survival: non-inferiority of the ctDNA-guided group with standard management and a significantly lower percentage of patients who received adjuvant chemotherapy in the ctDNA-guided group. These results encouraged oncologists to use ctDNA in treatment decisions for adjuvant chemotherapy, particularly in CRC. Whether these approaches are useful in other tumors, and the tumor-informed ctDNA assay should be mandatory or can be replaced by plasma-only assay are the next question to be elucidated in future studies. Further important information will be derived from GALAXY registry data, which stores whole exome profiling with precise clinicopathological information for more than 5,000 enrolled patients. With longer follow-up times, certain predictive markers for recurrence by genome profiling may be revealed, which may lead to individualized genomically-matched perioperative treatments.

## Conclusion

The SCRUM-/CIRCULATE-Japan platforms

have contributed the efficient clinical development of targeted therapies, which have resulted in timely new agent approvals and adequate precision oncology. Additionally, large databases consisting of cutting-edge multi-omics and clinical data including patient outcomes have been utilized for the discovery of new targets and resistance mechanisms and yielding innovative evidence in precision oncology. Challenges will continue with introducing newly developed analytical methods and longer follow-up periods for capturing clinical outcome data for the purpose of developing/providing new active agents and optimal treatments for patients with cancer.

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## Profile

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