

Towards Precision Diagnostics in GI Cancers:

Do LIQUID BIOPSIES present a strong case for making inroads into the clinic?

Key Emerging Perspectives

Comparative utility of ctDNA vs. Tumor Tissue Sequencing: What performs better?¹

Combined analyses of two nationwide Cancer Genome Screening Projects in Japan provide important insights for **advocating the use of ctDNA Genotyping in advanced GI cancers**. The analyses highlighted that compared to tissue-based testing, **plasma genotyping**

- **significantly reduces turn around time (TAT)**
- **is associated with rapid enrollment to matched trials**
- **demonstrates similar efficacy as that of tissue-based analysis**

The utility of plasma vs. tissue sequencing for trial enrollment of patients with advanced GI cancer was analyzed by NGS in the **GOZILA and SCRUM-Japan GI-SCREEN Combined analyses**, respectively.

Test results were generated in 5,029 of 5,743 pts (88%) in GI-SCREEN and 1,089 of 1,103 pts (99%) in GOZILA. Median TAT was 35 days (GI-SCREEN) and 12 days (GOZILA). **Proportion of enrolling matched clinical trials in GOZILA was significantly higher (60 pts, 5.4%) than in GI-SCREEN (126 pts, 2.2%).** The ORR and PFS were not significantly differentiated (ORR: 17.5 vs. 16.7%, p=1.00; mPFS: 2.8 vs. 2.0 mo, p=0.24).

Encouraging results from a blood-based (cfDNA methylation sequencing) multicancer screening study for early cancer detection²

With 99% specificity and a highly accurate **tissue of origin (TOO)** localization, the latest update from **CCGA, GRAIL study** suggests that **a single noninvasive blood test for cfDNA methylation testing could be a practical method of detecting and localizing GI and numerous other cancers.**

Circulating Cell-free Genome Atlas (CCGA), study from GRAIL (NCT02889978):

Methylation sequencing of plasma cfDNA from individuals with >20 GI cancers (all stages, newly diagnosed) and without cancer, demonstrated 82% detection across all GI cancers at a >99% pre-set specificity. The overall predicted **TOO accuracy was 92%** among the samples for which TOO was predicted. Moreover, **accurate (92%) localization of cancer** to specific regions of the GI tract was also achieved.

GERMLINE Testing in pancreatic Ca (PC) – is the landscape changing?^{3,4}

Systematized workflows for GC evaluation not reliant on active referral, led to **markedly higher uptake of MGT (Multi-gene Germline Testing) and mutation carrier identification in PC**. This was highlighted in a **Systematic Hereditary PC Risk Assessment study (NCT03060720)** at Dana-Farber Cancer Institute.

Clinical implementation of routine GC/MGT in PC patients is feasible and results in the **detection of mutations that are actionable for PC patients and at-risk family members.**

To this end, a minimally invasive liquid biopsy (mostly performed on total peripheral blood in PC)/cfDNA assays could immensely help improvise the diagnostic paradigm of PC.

NCT03060720: An analysis of clinical and germline data of PC patients undergoing GC and MGT helped understand the implications of universal implementation of germline testing in PC. Of the 1,305 new patients seen, 318 (25.1%) underwent GC and 29 (9.1%; 2.2% of all PC patients seen) were found to carry germline PC susceptibility gene mutations on MGT.

Mutation carrier identification rates almost doubled from 0.79 mutation carriers/month (1.6% of all new PC patients seen) to 1.75 mutation carriers/month (3.5% of all new PC patients seen) (2017-2019) after the institutional clinical workflow change (in 2018).

Sources:

1. Nakamura et al. Utility of circulating tumor DNA (ctDNA) versus tumor tissue clinical sequencing for enrolling patients (Pts) with advanced gastrointestinal (GI) cancer to matched clinical trials: SCRUM-Japan GI-SCREEN and GOZILA Combined Analysis.
2. Wolpin et al. Performance of a blood-based test for the detection of multiple cancer types.
3. Yurgelun et al. Implementation of systematic genetic counseling (GC) and multigene germline testing (MGT) for pancreatic cancer (PC) patients (pts).
4. Eduardo Vilar-Sanchez. Germline Panels: How do they help us?