The Evolving Biomarker Landscape in GI Cancers

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Types and Roles of Biomarkers

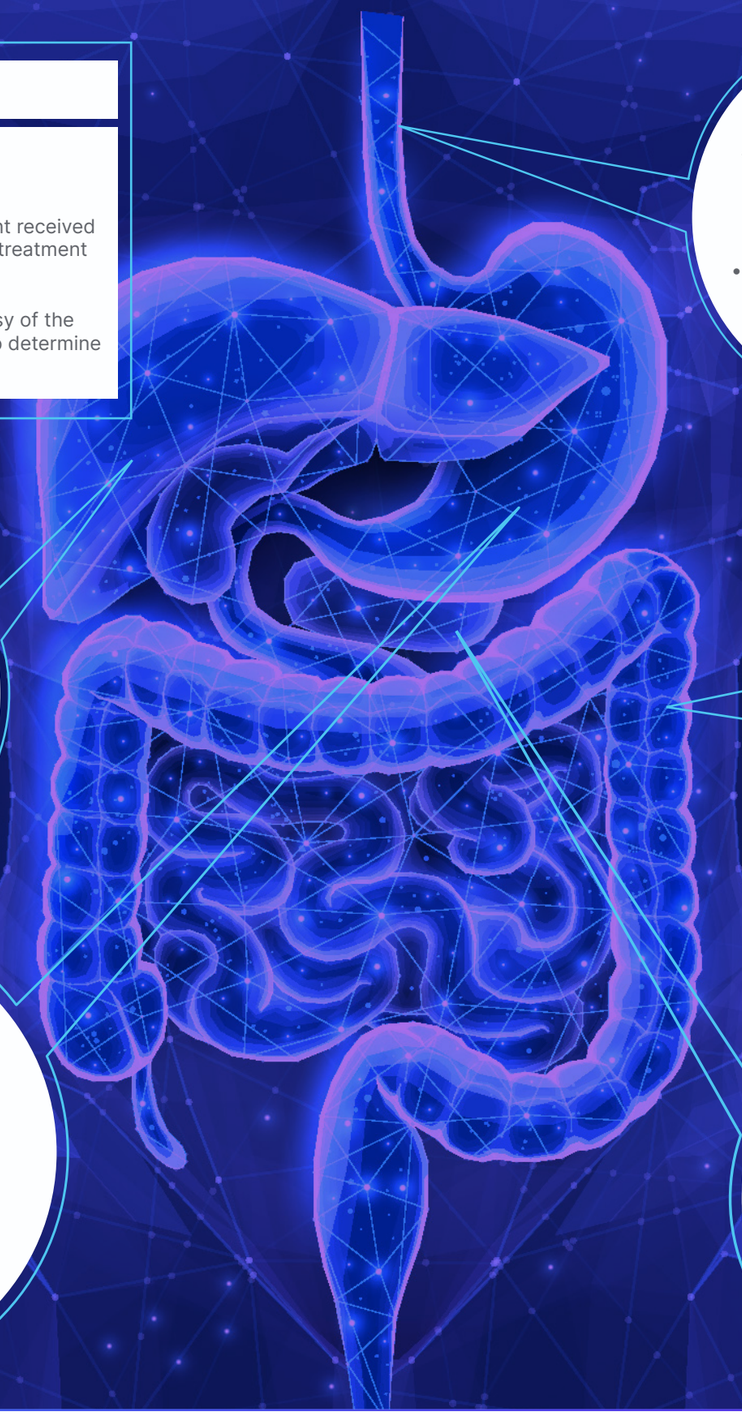
There are various ways biomarkers can be used:

1. Diagnostic - aid in disease detection
2. Prognostic - help determine clinical outcome, regardless of treatment received
3. Predictive - determine the potential benefit or lack of response to a treatment
4. Monitoring - assess the effect of a certain treatment[2]

Biomarker testing is usually performed by taking a blood sample or biopsy of the tumour and sending it to a pathology laboratory, where tests are done to determine abnormalities in DNA, RNA, hormones, or proteins.[3]

Prevalence of Gastrointestinal Cancers

- The main types of GI cancers are cancers of the oesophagus, stomach, colon and rectum, liver, and pancreas.[1]
- In 2022, there were over **4,000,000** new cases and **3,000,000** deaths from the five GI cancers, accounting for **23.9%**, and **33.2%** of all new cancer cases and deaths worldwide, respectively.[1]



Oesophageal cancer:[4]

- Predictive biomarkers to determine the potential treatment response for EAC are **HER2**, **MSI-H**, and **PD-L1**.
- Diagnostic and prognostic biomarkers include **HER2**, and **PD-L1**.[5]

Hepatocellular carcinoma:[12]

- The most common serum protein marker is AFP.
- The cut-off for AFP in diagnosing HCC is generally 20 ng/mL. However, the sensitivity is around 60%.

Colorectal cancer:[6]

- Elevated levels of CEA post-surgery could indicate recurrence of the cancer.
- Approximately 40-50% of colorectal cancer patients have a ***KRAS*** mutation.[7]
- The most common ***KRAS*** mutations are **G12V**, **G12D**, **G13D**, and **G12A**.
- A ***BRAF*** mutation is found in 10% of colorectal cancer patients, the most common mutation being V600E.
- Other common biomarkers include **MSI-H** and **HER2/ERBB2**, which both act as prognostic and predictive biomarkers.[8]

Stomach cancer:[10-11]

- Predictive biomarkers include **PDL-1, CLDN18.2** and **MET**.
- In a 2024 US study of gastric and gastroesophageal junction adenocarcinomas, 44.4% of tumours were CLDN18.2-positive overall, with 51.4% positivity specifically in gastric adenocarwcinomas.[10]
- A **PD-L1 CPS** of 1% or higher is seen in over 80%; however, this can vary with different populations.[11].

Pancreatic cancer:[13]

- ***KRAS*** codon 12 mutations are the most common genetic alterations in PDAC, occurring in over 90% of cases.[13]
- Other common genetic alterations include ***TP53***, ***CDKN2A***, and ***SMAD4***.[13]

Innovations in Detection Technologies

Circulating Nucleic Acids:

- ctDNA is emerging as a promising non-invasive approach for cancer detection.
- A 2024 study showed ctDNA profiling improved therapy matching, survival, and assessment of tumor heterogeneity.[14]

Microbiome-Based Biomarkers:

- A 2023 study showed that gut microbiome and metabolite changes, including *Flavonifractor plautii* enrichment and altered bile acid, choline, and tryptophan metabolism, distinguished early-onset colorectal cancer from controls.[15]

Breath Analysis:

- A 2022 study showed that analysing VOCs in exhaled breath can noninvasively detect advanced adenomas and colorectal cancer in screening populations, achieving about 77–80% sensitivity and 70% specificity, thus potentially improving colorectal cancer screening accuracy in the future.[16]

Abbreviations

AFP: alpha-fetoprotein; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; CLDN18.2: claudin 18.2; ctDNA: circulating tumour; CPS: Combined Positive Score; DNA; dMMR: mismatch repair deficiency; DPD: dihydropyridine dehydrogenase enzyme; EAC: oesophageal adenocarcinoma; ERBB2: Erb-B2 receptor tyrosine kinase 2; GC-MS: gas chromatography mass spectrometry; GI: gastrointestinal; HCC: hepatocellular carcinoma; HDI: high development index; HER2: human epidermal growth factor receptor 2; MSI-H: microsatellite instability; PALB2: partner and localiser of BRCA2; PD-L1: programmed death ligand 1; VEGFR2: vascular endothelial growth factor receptor 2; VOC: volatile organic compounds.

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