DISCOVER HOW emerging biomarkers may play a crucial role in navigating the landscape of metastatic gastric cancer.

CLDN18.2 = Claudin18.2; FGFR2b = fibroblast growth factor receptor 2b; HER2 = human epidermal growth factor receptor 2; MSI = microsatellite instability; PD-L1 = programmed death-ligand 1.
Despite recent advances, there are still critical needs to address in gastric/gastroesophageal junction (G/GEJ) cancers. In the United States, approximately 6% of patients with metastatic gastric cancer (mGC) survive 5 years post diagnosis. In 2022, it is estimated that nearly 26,400 new cases of G/GEJ cancers will be diagnosed in the US, of which 62% will likely be advanced stage disease. In the US, patients with advanced disease at diagnosis will likely have a poor outcome, as less than 50% receive second-line therapy for mGC.
As novel biomarkers emerge, they reveal more opportunities to advance care for mG/GEJ cancer

**EMERGING BIOMARKERS**

help identify previously undefined subsets of mG/GEJ cancer patients:

- **CLDN18.2**, as a component of tight junctions, has a critical role in cell-to-cell epithelial adhesion and regulating selective barrier properties.\(^7\)\(^-\)\(^10\)

- **FGFR2b** is a splice variant of FGFR2, which triggers signaling pathways that intermediate diverse cellular behaviors and cellular processes, such as mitogenesis, differentiation, cell proliferation, angiogenesis, and invasion.\(^11\)\(^,\)\(^12\)

**ESTABLISHED BIOMARKERS**

are used to inform clinical decisions:

- **HER2** is associated with activation of downstream signaling that leads to uncontrolled cell-cycle progression, cell division and proliferation, motility, invasion, and adhesion.\(^13\)

- **MSI** is characterized by somatic alterations in microsatellite sequences that are associated with genomic instability.\(^11\)\(^,\)\(^14\)

- **PD-L1** can bind to the immune checkpoint receptor PD-1 (programmed death cell protein 1) which allows tumors to escape immune surveillance.\(^15\)

\(\text{CLDN18.2}=\) Claudin18.2; \(\text{FGFR2b}=\) fibroblast growth factor receptor 2b; \(\text{HER2}=\) human epidermal growth factor receptor 2; \(\text{MSI}=\) microsatellite instability; \(\text{PD-L1}=\) programmed death-ligand 1.
Emerging and established biomarkers can be detected by standard IHC staining methods.

**EMERGING BIOMARKERS**

- **CLDN18.2**: IHC
- **FGFR2b**: IHC, ctDNA

**ESTABLISHED BIOMARKERS**

- **PD-L1**: IHC
- **HER2**: IHC, ISH, NGS
- **MSI/MMR**: PCR, NGS/IHC

IHC=immunohistochemistry; ctDNA=circulating tumor DNA; ISH=in situ hybridization; NGS=next generation sequencing; PCR=polymerase chain reaction.

'*FGFR2b overexpression can be determined by IHC; FGFR2 gene amplification can be determined by ctDNA.

†Varying diagnostic assays.

‡Other ISH methods (FISH=fluorescent ISH; SISH=silver ISH; CISH=chromogenic ISH; DDISH=dual-color dual-hapten ISH).

**EMERGING BIOMARKERS**

Biomarker prevalence estimates from select studies are reported below. Prevalence data can vary among studies due to tumor heterogeneity, differences in patient population, clinical trial methodology, and diagnostic assays used.

**EMERGING BIOMARKERS**

- **CLDN18.2**: 36% (high expression)
- **FGFR2b**: 30% (positive)

**ESTABLISHED BIOMARKERS**

- **PD-L1**: 67-73% (CPS ≥1); 29-31% (CPS ≥5); 16-18% (CPS ≥10)
- **HER2**: 22% (positive)
- **MSI**: 4% (MSI-high)

CPS=combined positive score.

*2+/3+ IHC staining in ≥75% of tumor cells.

**SUMMARY**

Emerging biomarkers are highly prevalent among mG/GEJ biomarkers.
WELCOME TO
The Gastric Cancer Landscape
CLICK ON A BIOMARKER TO LEARN MORE
CLDN18.2
(Claudin 18.2)
CLDN18.2 is an emerging biomarker that may help you learn more about your patients with mG/GEJ cancer\textsuperscript{10,25}

Claudins are a family of transmembrane proteins\textsuperscript{7,26}

Claudins are present throughout the body, but CLDN18.2 is the dominant isoform in gastric tissue\textsuperscript{7,26}

**CLDN18.2 is typically buried in tight junctions, but preclinical studies have shown that it may become more accessible to antibodies as gastric tumors develop.**\textsuperscript{7,27,28}

**CLDN18.2 may be expressed when tumors develop in esophageal, pancreatic, lung, and ovarian tissues as well.**\textsuperscript{7}
Detecting the presence of CLDN18.2 identifies a previously undefined patient population

While approximately 70% of mG/GEJ cancers express CLDN18.2 (at any level), recent studies have shown approximately 36% of mG/GEJ patients are **CLDN18.2 positive** (high expression).[^20]

- **CLDN18.2+ (high expression)**
  - ~36%
  - ~70%

**CLDN18.2 EXPRESSION** (any expression level)

- High expression: 2+/3+ IHC staining in ≥75% of tumor cells[^20]
- Among mG/GEJ biomarkers, CLDN18.2+ is highly prevalent
- Detecting CLDN18.2 can be accomplished by standard IHC staining methods, as with many other biomarkers[^16]
When evaluating the relationship between CLDN18.2 and other biomarkers, data suggests there is **limited overlap**.

In a real-world mono-institutional study, CLDN18.2+ (high expression) samples were also positive for the following biomarkers:\(^{20}\):  

<table>
<thead>
<tr>
<th>Biomarker 1</th>
<th>Overlap</th>
<th>Biomarker 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLDN18.2</td>
<td>15%</td>
<td>HER2</td>
</tr>
<tr>
<td>CLDN18.2</td>
<td>26%</td>
<td>PD-L1 (CPS ≥1)</td>
</tr>
<tr>
<td>CLDN18.2</td>
<td>18%</td>
<td>PD-L1 (CPS ≥5)</td>
</tr>
<tr>
<td>CLDN18.2</td>
<td>13%</td>
<td>dMMR</td>
</tr>
</tbody>
</table>

*Study population was limited to 350 Caucasian patients with mG/GEJ cancer, of which 117 patients had high expression of CLDN18.2. FGFR2b was not evaluated in this study.

**CLDN18.2** is expressed in both **diffuse-type tumors and intestinal-type tumors.**\(^{16}\)

- Tumors with diffuse histology, as seen in the US and other Western countries, are associated with a poorer prognosis than those with intestinal histology.\(^{29}\)
FGFR2b
(fibroblast growth factor receptor 2b)
FGFR2b is an emerging biomarker that introduces another way to identify a subset of patients with mG/GEJ cancer\textsuperscript{12}

FGFR signaling contributes to tumor progression by enhancing angiogenesis and proliferation\textsuperscript{11}

- FGFR2 (fibroblast growth factor receptor 2) is a receptor tyrosine kinase that has a role in normal cell development\textsuperscript{15}
- The splice variant FGFR2b is also expressed in various other types of epithelial cells where tumors may begin to grow (including pancreatic, breast, endometrial, cervical, lung, and colorectal cancers)\textsuperscript{30,31}
- FGFR2b may be associated with higher T stage (size of the tumor and any spread into nearby tissue) and higher N stage (extent of nodal metastases)\textsuperscript{12,32}

**FGFR2b positivity can be observed in 30\% of mG/GEJ cancers.**\textsuperscript{21}

Detected **FGFR2b** can be done with the **following tests**.\textsuperscript{17}

- FGFR2b overexpression by IHC
- FGFR2 gene amplification by ctDNA
HER2 was the first biomarker used to guide clinical decisions in mG/GEJ cancer

HER2 (human epidermal growth factor receptor 2) is a receptor-tyrosine kinase that is overexpressed and/or amplified in mG/GEJ cancer

HER2 is a proto-oncogene that is involved in signaling pathways, which leads to cell growth and differentiation.

- Studies have shown HER2 is present in several cancers, including colorectal, ovarian, prostate, lung, gastric, and gastroesophageal tumors
- When HER2 is overexpressed and/or amplified, it can lead to uncontrolled cell growth and tumorigenesis
  - However, the mechanisms that lead to gene amplification remain largely unknown
HER2 positivity has been reported in 22% of advanced G/GEJ cancers.¹³

Detection of HER2 may be done with **IHC, ISH methods, and NGS**, and is generally more associated with the **intestinal type**. ⁴,¹³,¹⁸

- Guidelines recommend starting with IHC and following with ISH methods only when expression is 2+ (equivocal)⁴
  - ISH methods include fluorescent in situ hybridization (FISH), silver in situ hybridization (SISH), chromogenic in situ hybridization (CISH), and dual-color dual-hapten in situ hybridization (DDISH)⁴,¹³
- Positive (3+) or negative (0 or 1+) IHC results do not require further testing via ISH⁴

¹HIC/ISH should be considered first, followed by additional NGS testing as appropriate.⁴
MSI
(microsatellite instability)
MSI is an established biomarker that can be found in a broad range of solid tumor types, including mG/GEJ cancer\textsuperscript{14}

MSI is associated with \textit{genomic instability and increased susceptibility to tumor development}\textsuperscript{11}

Microsatellites are \textit{repeated sequences} of nucleotides in DNA.\textsuperscript{14}

- Microsatellite instability (MSI) represents phenotypic evidence that the DNA mismatch repair (MMR) system is not functioning normally\textsuperscript{14}
- This loss prevents normal repair and correction of DNA, allowing mismatches to occur\textsuperscript{14}
- The MMR proteins are the most frequently mutated genes in cancer\textsuperscript{14}
- Tumors with ≥30% expression of unstable microsatellites are referred to as MSI-high (MSI-H), while tumors with 10-29% expression are considered MSI-low\textsuperscript{11}
- MSI is found most often in colorectal cancer, gastric cancer, and endometrial cancer, but it may also be found in many other types of cancer\textsuperscript{14}
MSI-H has been reported in 4% of mG/GEJ cancers.\textsuperscript{24}

Detection of MSI is typically assessed with \textit{various methods}.\textsuperscript{4}

- MSI gene expression can be detected via PCR-based molecular testing and NGS
- MMR protein expression can be analyzed via IHC
PD-L1
(programmed death-ligand 1)
Among biomarkers in mG/GEJ cancer, PD-L1 is one of the more recent to be utilized in clinical decision-making\(^3_4\).

**PD-L1 (programmed death-ligand 1)** is a transmembrane protein that may be expressed on various tumor cells and/or immune cells\(^3_5\).

- When bound to PD-1, PD-L1 acts as a T-cell inhibitory molecule, leading to immune cell evasion and subsequent tumor cell survival\(^3_5\).
- PD-L1 expression has been detected in various tumors, including lung, colon, ovarian, and gastric cancers\(^3_6\).
- However, the cellular process of expression may not always be the same throughout the body\(^1_9\).
  - Various studies have shown discordant levels of PD-L1 in the primary tumor vs metastatic lesions\(^1_9\).
Prevalence of PD-L1 has been reported for several positivity thresholds throughout various studies: 67-73% CPS ≥1, 29-31% CPS ≥5, and 16-18% CPS ≥10.22,23*†

- The variations in prevalence may be due to several factors, such as tumor heterogeneity and clinical trial methodology (including differences in patient population, staining techniques, scoring algorithms, and diagnostic assays)19,37
- Expression levels may also vary during disease progression, as PD-L1 is impacted by changes in immune response19

PD-L1 expression is detected using IHC.4
Initial diagnostic panels that include biomarker testing may help provide a more comprehensive patient profile and lead to more informed clinical decisions.

NCCN Clinical Practice Guidelines in Oncology for Gastric Cancer (NCCN Guidelines®) support using biomarkers to help map the path forward for patients.¹

- Biomarker testing has an important role in the diagnosis, classification, and molecular characterization of GC
- The implementation of molecular testing has had a significant impact on clinical practice and patient care

The NCCN Guidelines® recommend:

- Testing for all established biomarkers (HER2, MSI, PD-L1) at diagnosis if metastatic cancer is documented or suspected
- The use of IHC/FISH/targeted PCR should be considered first, followed by additional NGS testing
Biomarker testing provides more insight into mG/GEJ cancer as more biomarkers are discovered

**Standard IHC staining methods can detect a wide range of emerging and established biomarkers**

- IHC can detect CLDN18.2, FGFR2b, PD-L1, HER2, MMR
- Other testing methods often focus on specific biomarkers (ctDNA for FGFR2, ISH/NGS for HER2, and PCR/NGS for MSI)

*IHC/ISH should be considered first, followed by additional NGS testing as appropriate.*

In various clinical trials, biomarker testing has revealed a high prevalence of emerging biomarkers

- 36% of mG/GEJ patients were CLDN18.2 positive (high expression)
- 30% of mG/GEJ cancers observed FGFR2b positivity

Prevalence of established biomarkers have been reported throughout various studies as:

- HER2 positivity in 22% of advanced G/GEJ cancers
- MSI-H in 4% of mG/GEJ cancers
- PD-L1 at several positivity thresholds: 67-73% CPS ≥1, 29-31% CPS ≥5, and 16-18% CPS ≥10

As biomarker research continues, it expands our view of the patient population, reveals more information about the mG/GEJ cancer landscape, and helps inform clinical decisions.
REFERENCES


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Over 1 million new cases of G/GEJ cancers were diagnosed worldwide in 2020, making it the 5th most diagnosed cancer.\(^5\)

An estimated 769,000 people died worldwide in 2020 due to G/GEJ cancers, making it the 4th most deadly cancer.\(^5\)

In 2018, the global overall 5-year survival rate was approximately $\leq 10\%$ in mGC.\(^6\)
CLDN18.2 is an emerging biomarker that may help you learn more about the disease.

CLDN18.2 may be expressed when tumors develop in esophageal, pancreatic, lung, and ovarian tissues as well.?
FGFR2b is an emerging biomarker that introduces another way to treat cancer.
HER2 was the first biomarker used to guide clinical decisions in cancer treatment.
MSI is an established biomarker that can be found in a broad range of tumors, particularly in colorectal cancer. It is characterized by microsatellite instability, leading to an increased number of mutations in the genome. MSI testing is crucial for identifying patients who may benefit from treatment with immune checkpoint inhibitors.
Among biomarkers in mC/GEMI cancer, PD-L1 is one of the main candidates.