PRACTICE CASE STUDY

PREDICTIVE BIOMARKER TESTING IN GASTRIC & GEJ CANCER: A PAN-CANADIAN CONSENSUS

THEMES

- Biomarker testing
- Precision medicine
- Early diagnosis
- Gastric cancer
- Gastroesophageal adenocarcinoma

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OVERVIEW

Gastroesophageal cancers are tumours of the stomach, esophagus, and gastroesophageal junction (GEJ), characterized by high global incidence[1] and persistently poor 5-year survival.

Adenocarcinoma is the predominant subtype, representing approximately 95% of all gastroesophageal cancer cases.[1]

Recent advancements in targeted therapies and immunotherapies have enhanced treatment options, but their effectiveness relies on predictive biomarker testing. Predictive biomarkers, the mainstay of precision medicine,[2] identify patients who are most likely to benefit from a given therapeutic intervention and provide information about how a patient will respond to a treatment. Predictive biomarkers can be targets for therapy and be used to optimize therapy decisions. **Predictive biomarker testing therefore plays a crucial role in the accurate and timely diagnosis of gastric and gastroesophageal junction (G/GEJ) adenocarcinomas**[3] by guiding personalized treatment strategies in patients with locally advanced, unresectable, or metastatic G/GEJ adenocarcinoma.[4]

This paper summarizes a case study for the development of consensus recommendations for the implementation of predictive biomarkers in clinical care. The creation of pan-Canadian recommendations on the role of predictive biomarker testing for gastric (G) and gastroesophageal junction (GEJ) adenocarcinoma represents a landmark effort **to standardize and enhance cancer diagnosis and treatment.**[4] This initiative, driven by a multidisciplinary working group of pathologists, oncologists, and patient advocates, provides a unified framework for diagnostic decision-making that is tailored to the Canadian healthcare system. The purpose of the framework is to ensure timely, accurate, and actionable diagnostic information for oncologists.

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THE PROCESS FOR CANADIAN CONSENSUS RECOMMENDATIONS

The consensus was developed through a structured process involving two key meetings of the expert working group (see Figure 1).

Figure 1. Steps in Developing Canadian Consensus Recommendations

Step 1: Formation of Multidisciplinary Working Group
Initial group: 8 pathologists, 1 oncologist. Expanded for in-person meeting (30 Oct 2023) to 9 pathologists and 3 oncologists. Representatives from 4 major provinces ensure pan-Canadian relevance.
Step 2: Virtual Meeting #1
Focused on scope, methodology, and initial literature review. 321 records retrieved; 94 articles reviewed for CLDN18 IHC testing.
Step 3: Drafting Recommendations
Steering committee (3 pathologists, 1 oncologist) created draft recommendations using NCCN, ESMO, ASCO guidelines and targeted literature searches.
Step 4: In-Person Consensus Meeting
Held in Toronto on 30 Oct 2023. Expanded group revised draft recommendations through detailed discussions.
Step 5: Working Group Review
Revised recommendations circulated to the working group for further review and input.
Step 6: External Panel Review
7 pathologists and 4 oncologists reviewed recommendations for clarity and implementation challenges. Feedback incorporated.
Step 7: Patient Advocate Review
Patient advocates provided insights to ensure recommendations align with patient-centered care goals.
Step 8: Final Recommendations
Consensus recommendations finalized for CLDN18 IHC and biomarker testing in G/GEJ adenocarcinoma.

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Initially, a literature review was conducted to assess evidence for CLDN18 IHC testing, as well as established biomarkers like HER2, MMR/MSI, and PD-L1.[5] The group's recommendations were informed by guidelines from the National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO), and the Canadian Association of Pathologists (CAP), and recently published best practices for managing patients with unresectable metastatic gastric and gastroesophageal junction cancer in Canada.[6]

Draft recommendations were then refined during a second meeting, incorporating feedback from an external pan-Canadian panel of oncologists and pathologists. This iterative process ensured that the recommendations were both evidence-based and adaptable to the logistical realities of Canadian laboratories. The working group also outlined pre-analytic, analytic, and post-analytic considerations essential for effective predictive biomarker testing in G/GEJ adenocarcinoma. Implementing these recommendations will ensure that medical oncologists receive accurate and timely biomarker results to inform treatment decisions effectively.

OUTCOMES

Key recommendations from the expert working group emphasize the importance of reflex testing for several biomarkers at the time of initial diagnosis of G/GEJ adenocarcinoma in order to determine the best treatment pathway for this specific cancer type, including:

- HER2
- Mismatch repair (MMR)
- Microsatellite instability (MSI)
- CLDN18
- PD-L1

Furthermore, emerging therapies, such as CLDN18.2 monoclonal antibody therapy, necessitate the implementation of new biomarker tests in laboratories. Additionally, testing for NTRK fusions may be included as a reflex test or requested by the treating clinician when third-line therapy is being considered.[4]

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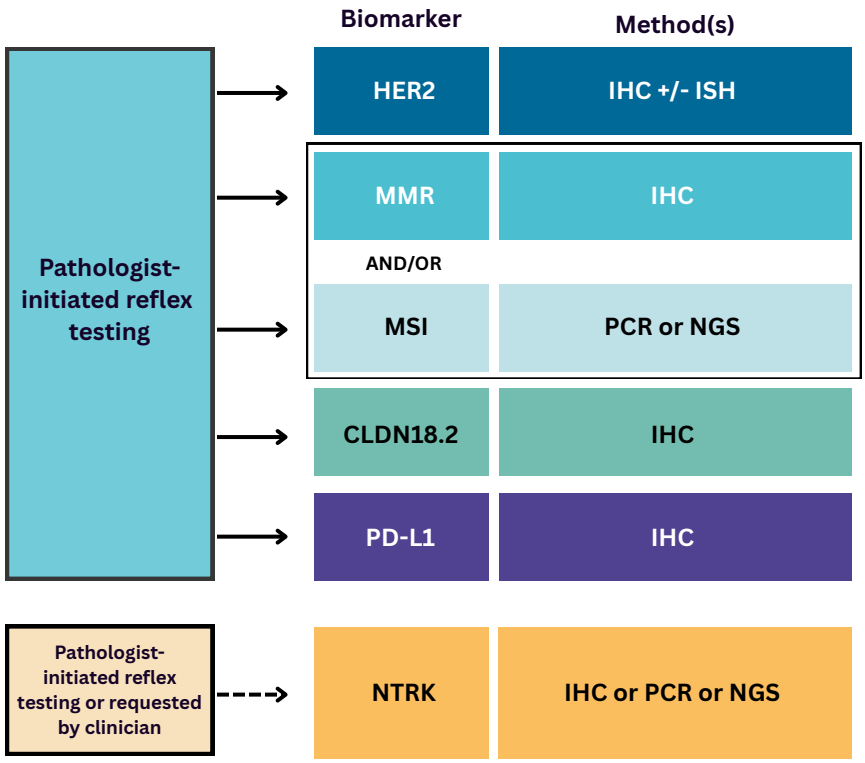
Although NTRK fusions and CLDN18 are distinct molecular markers, they exemplify the paradigm of **precision oncology**, where specific genetic or protein alterations guide therapy. Both markers emphasize the importance of molecular diagnostics in identifying actionable targets, particularly in cancers with limited treatment options.

Development of these recommendations aimed to integrate emerging therapies, such as CLDN18.2 monoclonal antibody therapy, and **standardize the diagnostic processes across Canadian laboratories**. By reflexively **initiating biomarker testing at diagnosis**, oncologists can have the necessary information readily available for patients, particularly in the advanced stages of the disease, when treatment needs to be rapidly initiated.

Figure 2. Predictive biomarker testing for patients with gastric or gastroesophageal junction adeno-carcinoma[4]



By aligning with emerging therapies, such as CLDN18.2-targeted treatments, and integrating international best practices, the consensus aims to address the growing complexity of predictive biomarker testing.

Additional recommendations pertained to important pre-analytic, analytic, and post-analytic test considerations for predictive biomarker testing in G/GEJ adenocarcinoma.[4]

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FRAMEWORK USED TO ESTABLISH CONSENSUS

Pre-analytic, analytic, and post-analytic considerations were thoroughly reviewed to ensure the reliability and efficiency of recommended predictive testing protocols. For example, proper sample handling, validation protocols, and the selection of controls for immunohistochemistry (IHC) assays are essential to ensuring accurate results. The working group also underscored the role of molecular pathology reports in providing oncologists with actionable data, streamlining clinical workflows, and enhancing multidisciplinary treatment planning. Furthermore, reflex testing was highlighted as critical for reducing delays in treatment, supporting the efficient use of laboratory resources, and achieving cost-effectiveness.

Figure 3. Pre-Analytic, Analytic & Post-Analytic Workflow for Biomarker Testing

TESTING ALGORITHM

All patients with G/GEJ adenocarcinoma should be tested at diagnosis for the following panel of biomarkers: HER2, MMR deficiency/MSI, CLDN18 expression, and PD-L1 expression.

Optimally, testing for all predictive biomarkers should be carried out reflexively in the same laboratory, concurrently, if possible.

NTRK fusions appear rare in G/GEJ adenocarcinomas. Depending on laboratory preference, the test may be included as part of reflex testing or may be requested at the discretion of the treating oncologist when third-line therapy or beyond is being considered.

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PRE-ANALYTIC CONSIDERATIONS

The accuracy of biomarker testing relies heavily on proper sample collection, handling, and processing. The working group emphasized the need for high-quality specimens with adequate tumour cellularity.

Testing of primary tumour tissue specimens is preferred, but testing of metastatic tumour specimens is also reasonable. Most clinical studies have used primary tumour specimens for biomarker testing, as there is reasonable concordance between biomarker results from primary and metastatic tumour specimens. Specimens used for testing should have adequate tumour cellularity, and this may guide which specimen to use. Cell blocks from specimens that have been in cytology/alcohol-based fixatives should only be used if adequate validation has been performed.

For biopsy specimens, multiple biopsy fragments (at least six) are recommended for assessment of predictive biomarkers as there is known intratumoural heterogeneity for predictive biomarkers in GC. However, this does not limit testing of cases with minimal tumours present if the minimum number of tumour cells are present (for example, minimum considered to be 100 for PD-L1 testing).

Optimally, testing should be carried out on one block that is representative of the tumour, with adequate cellularity. As noted in the guidelines from the College of American Pathologists, the American Society for Clinical Pathology, and the American Society of Clinical Oncology as well as PD-L1 testing guidelines from the Canadian Association of Pathologists, more than one block may be selected if different morphologic patterns are present, or if the minimum number of tumour cells is insufficient in one block.

If specimens are being sent out for molecular testing, they should be sent to the testing laboratory as quickly as possible using a courier service, preferable with a travel time of less than 3 days.

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ANALYTIC CONSIDERATIONS

Immunohistochemistry (IHC) remains the cornerstone of biomarker testing in G/GEJ adenocarcinoma, supported by molecular methods like PCR or next-generation sequencing (NGS) for confirmatory testing. The group outlined the **importance of validating laboratory-developed tests (LDTs)** against clinically validated reference standards to ensure consistent results.

On-slide controls with positive tissue, negative tissue, and limit of detection (system level control) tissue should be used for all IHC predictive biomarker tests. Tissues to be used as controls should align with recommendations from the individual test kits. For CLDN18 IHC, the recommended control is gastric mucosa containing intestinal metaplasia. An additional control of a positive tumour specimen may also be used.

Biomarker testing should be performed by a licensed, accredited laboratory and reported by pathologists trained to read the specific biomarker(s) being tested. Testing should be performed using either of the following:

- A clinically validated commercial companion diagnostic assay following appropriate verification in accordance with the manufacturer's requirements.
- A laboratory-developed test that is validated in accordance with fit-for-purpose principles against a clinically validated reference standard (e.g., a companion diagnostic assay as described above).
- Considering the multiple antibodies available for PD-L1, if the laboratory is not going to be using the standard PD-L1 pharmDx companion diagnostic kit with antibody clone 22C3 for assessment of patients for consideration of pembrolizumab therapy, then during validation of any laboratory-developed PD-L1 test, results must be compared to results from the companion diagnostic kit.[6] If the laboratory is planning on validating only one PD-L1 antibody (either 28-8 or 22C3) when results from both might be needed depending on the treatment being considered, the laboratory should validate the antibody in use against the other antibody, which may require support from a laboratory that has the well-validated alternative antibody.

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POST-ANALYTIC CONSIDERATIONS

The group recommended that all biomarker results be compiled into a single synoptic report within 10 working days of requisition. This format supports clear communication with oncologists and ensures that all actionable data are readily available for treatment planning. An addendum with the compiled biomarker results should be added to the original diagnostic report when predictive biomarker testing is completed. Multidisciplinary tumour boards were also identified as critical forums for interpreting complex biomarker profiles.

STRENGTHS

COMPREHENSIVE MULTIDISCIPLINARY COLLABORATION

The recommendations were crafted through the combined expertise of pathologists, oncologists, and patient advocates to ensure they are both clinically relevant and practical across a variety of healthcare settings.

DETAILED GUIDELINES ACROSS ALL TESTING PHASES

The case study provides clear and thorough guidance for the pre-analytic, analytic, and post-analytic stages of biomarker testing. These detailed protocols for specimen handling, assay validation, and result reporting promote accuracy and consistency in clinical practice.

PROACTIVE INTEGRATION OF EMERGING BIOMARKERS

Reflex testing means automatic testing in the lab initiated by the pathologist without a specific request from an oncologist; it ensures that all necessary pathology data are available when advanced therapy options are being considered. Reflex testing is particularly crucial in gastric and GEJ adenocarcinoma, as these cancers are frequently diagnosed in advanced stages due to asymptomatic early progression. Reflex testing at the diagnostic stage enables oncologists to reduce treatment delays and provide patients with timely access to targeted therapies, including immunotherapies and monoclonal antibody therapies like zolbetuximab, which targets CLDN18.2-positive tumors. By addressing the incorporation of CLDN18.2 testing to align with novel therapies, the recommendations demonstrate a forward-thinking approach that anticipates and adapts to advances in treatment options.

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LESSONS LEARNED

Systemic inequities significantly impact patients' access to genomic medicine in Canada.[6] Additional challenges—including standardization, validation, regulatory approval, and cost-effectiveness—must be addressed to promote more equitable access.[8] Limited laboratory infrastructure and trained personnel remain major barriers to implementing reflex testing across all centres. The key lesson is to prioritize workforce development and invest in future infrastructure to meet these needs.[9] Finally, reliance on external laboratories for testing often results in delays that impact timely and/or accurate decision-making. Therefore, future clinical practice should involve developing in-house testing capabilities to reduce turnaround times and improve patient care.[4]

Overall, the following insights may guide biomarker testing in the near future:

- The expert working group cannot directly resolve national disparities with additional funding or staff, but it can help smaller laboratories validate biomarker testing to support more equitable access across Canada. Its recommendations may also inform future requests to funding agencies.

- Smaller laboratories will struggle to find sufficient in-house cases to validate CLDN18.2 IHC and will require collaboration, which the working group can help facilitate.

- Reflex testing protocols are already standardized for many biomarkers and tumour types; however, continued provincial funding is essential, as lack of funding discourages reflex testing and leads to centers waiting for requests instead.

- In the future, AI may assist in biomarker assessment; however, its use in pathology remains at an early stage. Implementing these technologies would also introduce additional costs, for which laboratories currently receive no dedicated funding.

- Regarding the inclusion of new biomarkers in reflex testing, FGFR2b will be a new biomarker with targeted therapy.

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FUTURE DIRECTIONS

Although implementing these consensus recommendations poses challenges, such as limited resources and the need for specialized training for laboratory staff, pathologists, and clinicians, they offer a valid framework for addressing current gaps and to effectively navigate introduction of new processes. For example, pathologist training is important to ensure accuracy and consistency in the reporting of biomarker results.[9] Promoting standardization, engaging stakeholders, and integrating innovative technologies, such as artificial intelligence into diagnostic workflows, can also overcome future obstacles.

The integration of artificial intelligence (AI) and machine learning algorithms into digital pathology platforms shows significant potential for improving diagnostic accuracy and efficiency in predictive biomarker testing.[10] Furthermore, AI-based methods may play a transformative role in translational medicine and clinical practice, particularly by predicting gene mutations from routine histopathology slides. Given the ongoing challenges in achieving comprehensive genomic testing and profiling,[11] complementary approaches may offer supplementary means to enhance reliability and support clinical applicability. Evidence suggests that AI driven methodologies might provide simultaneous assessment of pathological and genomic features, offering a more integrated and comprehensive diagnostic perspective.[10]

Collaboration among researchers, healthcare providers, regulatory bodies, policymakers, and patients will be essential to navigate the complexities of integrating biomarker-based approaches into evidence-based standardized cancer care. These efforts will not only enhance patient outcomes, but also contribute to more efficient resource utilization within the healthcare system. These recommendations thereby support a strategic plan for positioning Canada as a leader in oncology care by ensuring equitable and high-quality access to predictive biomarker testing.[6,12]

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