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Parallel, not sequential: Why upfront multi-biomarker testing should define first-line gastric cancer care

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First-line treatment of unresectable or metastatic gastric adenocarcinoma now depends on HER2, programmed death-ligand 1 (PD-L1), mismatch repair/microsatellite instability (MMR/MSI), and CLDN18.2 results, and guidance recommends that results be available as soon as possible. Implementation, however, often remains fragmented: serial ordering consumes limited biopsy tissue and can force empiric treatment before the full biomarker profile is known. Chemotherapy should not be withheld while results are pending, but delays may postpone evidence-aligned treatment additions and complicate choices that registration trials evaluated from treatment initiation. We outline a resource-adaptive biomarker-first workflow based on coordinated upfront testing, pathology-led tissue allocation, central referral when local assays are unavailable, and assay-specific reporting. Testing should be parallel; treatment interpretation should remain evidence-structured and individualized when markers overlap. The immediate task is not to establish another biomarker list, but to make an accepted panel reliable across settings.

WHY DELAYED AND UNCOORDINATED TESTING REMAINS A TREATMENT PROBLEM

One endoscopic biopsy must now answer several treatment-defining questions. Serial ordering, HER2 first, PD-L1 later, CLDN18.2 only if tissue remains, repeatedly consumes sections, increases turnaround time, and can leave the final assays with the least representative material. Repeat biopsy is not always feasible, especially in patients with rapidly progressive disease. Coordinated upfront initiation is therefore a tissue-stewardship strategy as much as a laboratory scheduling choice.

ASCO advises against delaying clinically necessary chemotherapy while results are pending.[1] Starting a chemotherapy backbone and adding a biomarker-directed agent when results return may be pragmatic, but it does not reproduce the registration-trial strategy of initiating the complete regimen from cycle 1. Delayed testing forces reliance on empiric regimen selection, postpones evidence-aligned additions, and narrows the basis for shared decision-making.

Real-world practice lags this therapeutic landscape. In the SAPHIR registry, local testing was documented in 78.6% of cases for HER2, 31.3% for PD-L1, and 15.6% for MSI; central retesting also identified discordance with local results, including 12.4% for HER2 and 22.4% for PD-L1.[2] These gaps show why a biomarker-first perspective must focus on implementation: the right result must come from the right specimen early enough to inform care.

Unplanned serial testing also amplifies assay limitations. PD-L1 CPS and CLDN18.2 depend on morphology, sampling, and threshold-based interpretation; neither is replaced by a generic sequencing panel. When assays compete for dwindling material, pre-analytic choices become part of treatment planning.

THE BASELINE PANEL IS DEFINED; IMPLEMENTATION IS NOT

The core baseline panel is now HER2, PD-L1 CPS, MMR/MSI, and CLDN18.2.[1,3] HER2 defines the anti-HER2 backbone, PD-L1 informs the expected benefit and regional use of immunotherapy, MMR/MSI identifies a biologically distinct immune-sensitive subgroup, and CLDN18.2 identifies eligibility for zolbetuximab in HER2-negative disease.[1,4-8] All can redirect initial management, so their assessment should be planned before the block is depleted.

Here, parallel means coordinated upfront initiation of the complete core panel on the initial specimen; Epstein-Barr virus (EBV) testing and broad next-generation sequencing (NGS) can be layered on for trial matching. Table 1 translates this into a specimen-to-decision matrix.

A RESOURCE-ADAPTIVE BIOMARKER-FIRST WORKFLOW

A pathology-led workflow should adapt to tissue and local resources. At diagnosis, the pathologist should select the most representative block, plan batched sections, conserve unstained slides, and initiate all locally available core assays together. Where assays are unavailable locally, predefined hub-and-spoke referral preserves parallel ordering. In the rare severely tissue-limited case, one Canadian consensus recommends prioritizing HER2 and MMR/MSI and obtaining additional tissue for PD-L1 and CLDN18.2.[3] High-throughput testing may complement MSI or broader genomic assessment, but it cannot substitute for PD-L1 CPS or CLDN18.2 immunohistochemistry (IHC). Parallel ordering does not require same-day staining or one local laboratory; it requires that the complete testing plan be triggered at diagnosis and that material not be consumed by reactive recuts.

For co-positive tumors, testing should remain parallel and treatment interpretation should be evidence-structured and case-by-case. HER2-positive, PD-L1 CPS ≥1 disease is directly informed by KEYNOTE-811.[6] For HER2-negative disease with both PD-L1 and CLDN18.2 positivity, ASCO recommends case-by-case shared decision-making based on PD-L1 level, symptoms, toxicity, comorbidity, and patient preference; a 2026 Chinese consensus offers a regional CPS-stratified framework.[1,9] MSI-H/dMMR supports immunotherapy-based management within the complete biomarker profile, and HER2/CLDN18.2 co-expression lies outside SPOTLIGHT/GLOW eligibility.[5,7,8] Combining checkpoint and CLDN18.2-directed therapy requires randomized evaluation (NCT06901531). When evidence-supported options remain in equipoise, trial enrollment should be prioritized.

WHAT STILL NEEDS TO BE STANDARDIZED AND PROVED

Validating the health-system value of parallel testing requires prospective implementation studies. Such studies should measure baseline profile completeness, tissue exhaustion, turnaround time, repeat biopsy, treatment modification after results, and cost per actionable profile, providing a direct evaluation of the workflow.

Standardization is particularly important for CLDN18.2. Reports should name the assay and platform, state the therapeutic cutoff, quantify moderate-to-strong membranous staining, identify the specimen site, and comment on adequacy or heterogeneity. The FDA review of the VENTANA CLDN18 (43-14A) assay found high controlled-reader agreement but lower agreement at one external site, underscoring that reproducibility depends on training and context.[10] Laboratories should use therapy-matched validated assays, competency assessment, and second review for near-cutoff or markedly heterogeneous cases. Near-cutoff reports should retain the continuous percentage alongside the binary label, and discordance between sampling sites should prompt review or repeat sampling when clinically feasible. External quality assessment and cross-platform bridging are priorities for future adoption.

CONCLUSION

Parallel testing coordinates the initial specimen so that HER2, PD-L1 CPS, MMR/MSI, and CLDN18.2 results become available early and can be interpreted together. It accommodates clinically necessary chemotherapy, assay-specific technologies, and individualized treatment interpretation. A resource-

Table 1. Specimen-to-decision implementation matrix for the core reflex biomarker panel

Decision node	Assay and tissue plan	Minimum report	First-line implication	Quality safeguard
HER2	IHC on a representative viable-tumor block; reflex ISH for IHC 2+; batch sections with the other core assays and reserve unstained slides.	IHC score (0/1+/2+/3+), antibody clone/platform, specimen site and adequacy; for IHC 2+, ISH method, amplification status, and ratio/copy-number result.	Defines the anti-HER2 backbone; with PD-L1 CPS ≥1, supports pembrolizumab plus trastuzumab and chemotherapy where approved.[6]	Document viable invasive tumor and heterogeneity; resolve equivocal or discordant IHC-ISH results before treatment; generic NGS does not establish HER2 status.
PD-L1	PD-L1 IHC with CPS assessment in viable tumor and associated immune cells; retain material for CLDN18.2 and record the assay-specific clone/platform.	Numeric CPS, clone/platform, specimen site, tumor adequacy, therapeutic threshold, and any indeterminate limitation; do not report a binary label alone.	CPS level and regional labeling inform the role of a PD-1 inhibitor with chemotherapy; in HER2-positive CPS ≥1 disease, interpret with the trastuzumab-based route.[1,4,6]	CPS is morphology- and sampling-dependent; flag low cellularity, necrosis, heterogeneity, or near-threshold values and use second review when appropriate; NGS does not substitute for CPS.
MMR/MSI	MMR IHC for MLH1, MSH2, MSH6, and PMS2 or a validated MSI method; broader NGS may be layered for biologic characterization or trial matching.	Each MMR protein as retained/lost or the MSI category, method/platform, control status, tumor adequacy, and any indeterminate result.	dMMR/MSI-H supports immunotherapy-based management and may alter the first-line route; interpret within the complete HER2, PD-L1, and CLDN18.2 profile.[1,5]	Use internal controls and representative viable tumor; resolve discordant or indeterminate IHC/MSI findings with an orthogonal validated method when feasible.
CLDN18.2	Therapy-matched IHC on representative viable tumor; document the specimen site; use the VENTANA 43-14A CDx or a locally approved, analytically bridged equivalent.	Percentage of viable tumor cells with moderate-to-strong membranous staining, intensity, clone/platform, cutoff, specimen site, adequacy, heterogeneity, and continuous percentage alongside the binary label.	For the 43-14A CDx, ≥75% moderate-to-strong staining in HER2-negative disease gates zolbetuximab where approved; PD-L1 co-positivity requires case-by-case interpretation.[1,7-10]	Use competency-based second review for near-cutoff or markedly heterogeneous cases; consider another block or repeat sampling when feasible; use external quality assessment and cross-platform bridging; NGS does not establish eligibility.
Panel-level workflow	At diagnosis, select a representative block, batch sections, conserve unstained slides, trigger all four core assays, and use a predefined hub-and-spoke referral pathway where needed.[1,3,9]	One integrated report lists specimen/site, method/platform, result, therapeutic cutoff, adequacy/heterogeneity, and pending or failed status for every marker.	Use the complete profile for evidence-aligned first-line selection; start clinically necessary chemotherapy while results are pending and add or adjust biomarker-directed therapy when supported and feasible.[1]	Audit profile completeness, turnaround time, tissue exhaustion, repeat biopsy, local-central discordance, and near-cutoff second review; assess cost per complete actionable profile, not assay price alone.
Co-positive profile	Cross-reference all four results in one decision record; no additional assay substitutes for integrated interpretation.	State the marker combination, assay confidence, regional label, and applicable evidence pathway; separate directly supported routes from combinations in equipoise.	KEYNOTE-811 directly informs HER2-positive/CPS ≥1 disease; SPOTLIGHT/GLOW enrolled CLDN18.2-positive/HER2-negative disease; other combinations remain case-by-case, with NCT06901531 evaluating checkpoint plus CLDN18.2-directed therapy.[1,6-8]	Document symptoms, toxicity, comorbidity, patient preference, trial availability, and the rationale for the selected route; do not impose a rigid global hierarchy when comparative evidence is absent.

CPS: combined positive score; IHC: immunohistochemistry; ISH: in situ hybridization; MMR: mismatch repair; MSI: microsatellite instability; NGS: next-generation sequencing. Parallel testing denotes coordinated initiation of all four core assays on the initial specimen. Continuous values and assay metadata should be retained. Co-positive profiles require evidence-structured, case-by-case interpretation.

adaptive workflow can coordinate local testing, referral, tissue triage, and quality control while acknowledging evidence gaps in co-positive disease and CLDN18.2 scoring. The practical shift is therefore from drug-first to workflow-first thinking: guidelines now identify the relevant biomarkers, and implementation must ensure that limited tissue yields a complete, reliable profile before avoidable uncertainty accumulates.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

AI tools were used to assist with language refinement. The authors take full responsibility for the content of the publication.

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DECLARATION OF INTERESTS

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ETHICAL STATEMENT AND PATIENT CONSENT

Not applicable.