Editorial

Claudin 18.2 in gastroesophageal adenocarcinoma: prevalence, biomarker associations, and implications for equity

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The therapeutic approaches in gastric adenocarcinoma (GA) and gastroesophageal adenocarcinoma (GEA) have shifted. With phase III evidence supporting the addition of zolbetuximab to first-line chemotherapy for human epidermal growth factor receptor 2 (HER2)-negative tumors with high claudin 18.2 (CLDN18.2) expression and the United States (U.S.) approval granted in October 2024, CLDN18.2 now sits alongside HER2, programmed cell death ligand 1 (PD-L1), and microsatellite instability (MSI) as a gatekeeper biomarker in frontline decision-making for advanced gastric/gastroesophageal junction (GEJ) cancer (1,2). Yet, the field still faces practical unknowns that matter at the bedside: how common is CLDN18.2 when measured with trial-aligned methods in real-world practice? Does expression vary across racial and ethnic groups seen in U.S. clinics? How does CLDN18.2 relate to other biomarkers clinicians already use? And more importantly does it carry independent prognostic weight?

In this paper, Wallam *et al.* (3) provide timely data that move those questions closer to actionable answers. After their institution implemented reflex CLDN18.2 testing in 2023, they retrospectively reviewed 75 consecutive patients with gastric, GEJ, or esophageal adenocarcinoma who underwent immunohistochemistry (IHC) testing of their tumor tissue with the Ventana CLDN18 (43-14A) RxDx assay. Positivity was defined exactly as in the phase III GLOW and SPOTLIGHT trials: moderate-to-strong (2–3+) staining in ≥75% of tumor cells. Using this strict, therapy-aligned threshold, CLDN18.2 positivity was 42.6% (20/47) for gastric cancers (GCs), 50.0% (7/14) in GEJ cancers, and 35.7% (5/14) in esophageal tumors; combining GC and GEJ, positivity was 44.3% (27/61), consistent with the percentage of patients found in the trials (1,2). That single figure is practice-relevant: when labs use the same assay and cutoff that determine eligibility for treatment, nearly half of "real-world" U.S. GA/GEA patients may qualify for CLDN18.2-directed therapy on biomarker grounds.

The cohort also reflects everyday U.S oncologists encounters (4,5). Primary sites were 62.7% gastric, 18.7% GEJ, and 18.7% esophageal; 32% were metastatic at diagnosis; and most tumors were high grade. Among the 47 gastric cases with Lauren classification, 57.5% were diffuse-type. Co-biomarker testing was comprehensive: 92% were mismatch repair (MMR)-proficient; 84% were HER2-negative; the mean PD-L1 combined positive score (CPS) was 9.1, with 80% CPS ≥1 and 52% CPS ≥5; Epstein-Barr virus (EBV) positivity was rare (two patients). In a 23-patient next-generation sequencing subset, TP53 alterations predominated (65.2%), and there was no clear gene-level association with CLDN18.2 status among a

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dozen queried genes with potential therapeutic relevance.

Two clinicogenomic associations stood out. First, CLDN18.2 positivity was significantly more common in female patients (P=0.002). Second, and most consequential for treatment planning, CLDN18.2 positivity was significantly associated with HER2-negative status (P=0.03). Together, these findings reinforce the practical framing of CLDN18.2 as an orthogonal antigenic target, one that is not merely a surrogate for known pathways, and that can open a targeted-therapy door precisely in the large segment of GA/GEA where HER2-directed options are unavailable. By contrast, CLDN18.2 showed no meaningful association with PD-L1, MMR, EBV, *Helicobacter pylori*, stage, grade, or Lauren type in this cohort, simplifying interpretation for clinicians: treat the marker as a predicate for eligibility, not as a shorthand for broader tumor biology as supported by other studies (6-8).

Importantly, Wallam *et al.* (3) add representation to a literature that has lacked it. Prior CLDN18.2 reports have come largely from ethnically homogeneous European or East Asian populations (9-11). Here, 20% of patients identified as Hispanic and 12% as Black. While subgroup sizes were modest and formal significance was not reached, the rate of CLDN18.2 positivity was numerically higher in Hispanic patients (53.3%) than in non-Hispanic patients (38.2%), with positivity of 50% in Asian, 44.4% in Black, and 37.8% in White patients. In a disease where incidence, stage at presentation, and outcomes already disproportionately burden racial and ethnic minorities, such an exploratory signal cannot be ignored. It should not be over-interpreted as evidence of differential treatment benefit which would require prospective evaluation in therapy-treated cohorts, but it does argue for intentional, reflex CLDN18.2 testing in clinics serving diverse populations so that eligibility for approved therapy is not missed.

Equally relevant are the negative results for survival. Across localized/locally advanced and metastatic settings, CLDN18.2 status did not associate with disease-free survival, progression-free survival on first-line therapy, or overall survival. Median DFS in the surgical subset was 27 months for CLDN18.2-positive tumors versus 19 months for CLDN18.2-negative tumors; median PFS on first-line treatment in metastatic disease was 9.8 *vs.* 9.5 months, respectively; and no significant overall-survival difference was detected. These findings align with most prior series and deliver the clinic message with clarity: do not use CLDN18.2 as a prognostic marker. Its value lies in its quality of being targetable rather than a determinant of natural history in the absence of targeted therapy (10).

The study's assay choices and reporting approach deserve emphasis because they point to a larger implementation theme: assay harmonization is an equity issue. Reported CLDN18.2 "positivity rates" in the literature span from approximately 10% to 87%, a spread driven less by biology than by differences in antibody clone, platform, scoring metric, and cutoffs used (e.g., percentage thresholds like ≥40% *vs.* ≥75% at 2–3+ intensity, or semi-quantitative systems like H-scores and immunoreactive scores). Wallam *et al.* (3) used the Ventana RxDx assay and the ≥75% at 2–3+ definition applied in registration-level trials which means that their positive/negative calls carry direct proven therapeutic implications. As institutions scale testing, pathology reports should mirror that standard: specify the assay/clone and platform, provide the percentage of tumor cells at each intensity level, and offer a clear binary interpretation tied to the trial-aligned cutoff. When tissue is scant, that detail can guide whether rebiopsy or retesting is justified; when results sit near threshold, it can guard against over- or under-calling eligibility.

The authors appropriately acknowledge limitations that also shape how programs should implement CLDN18.2 testing. Reflex CLDN18.2 staining began locally in 2023, yet follow-up in the dataset spans up to approximately 100 months, indicating that some earlier diagnoses were tested later via archival tissue or rebiopsy. That temporal asynchrony can introduce selection effects and complicate survival interpretation, but it also illustrates a practical point: retrospective reflex testing can still uncover patients who stand to benefit now; going forward, prospective reflex at diagnosis should be standard to avoid delays in therapy. Most CLDN18.2 assessments were performed on biopsies (70.7%), reflecting real-world tissue pathways but raising perennial concerns about intratumoral heterogeneity and sampling. Although the Ventana CLDN18 (43-14A) RxDx antibody binds both CLDN18.1 and CLDN18.2, CLDN18.1 is not physiologically expressed in gastroesophageal mucosa; therefore, staining in these tumors reflects CLDN18.2 and does not erroneously elevate positivity (12). Lastly, when pathology reports provided a range for percent positive cells, the analysis used the upper bound, a pragmatic choice but that could inflate positivity at the margin; to address these cases clinicians seeing "borderline" results should read the narrative report carefully and consider re-evaluation if clinical stakes are high.

What should clinicians, pathologists, and program leaders do now?

Embed CLDN18.2 in reflex testing for all newly diagnosed gastric/GEJ adenocarcinomas. Testing should launch at diagnosis, alongside HER2, PD-L1/CPS, and MMR/MSI (with EBV where relevant), with pathology turnaround times aligned so therapy selection is not delayed. When tissue is limited, prioritize assays that change first-line decisions. Standardize reporting to the therapy-aligned cutoff and include percent-by-intensity details to support nuanced decisions near the threshold.

Treat CLDN18.2 as predictive, not prognostic. Do not risk-stratify patients by CLDN18.2 status. Use the result to determine eligibility for zolbetuximab-based combinations (and forthcoming modalities) in HER2-negative disease, in concert with PD-L1 and MSI status and the clinical context.

Track equity metrics, not only positivity rates. The exploratory signal of higher CLDN18.2 positivity among Hispanic patients in this cohort, together with substantial rates among Black, Asian, and White patients, should prompt programs to monitor test completion, time to result, and time to treatment by race or ethnicity and by preferred language. Programs should also identify payer and logistical barriers that may selectively limit access to CLDN18.2-directed therapy. Implementation science, not descriptive biology alone, will determine whether this biomarker benefits every eligible patient.

Be ready for combination and sequencing questions. As other CLDN18.2-directed strategies (bispecific antibodies, antibody-drug conjugates, cellular therapies) mature, the field will need trials that interrogate additive or synergistic effects with PD-1 blockade, and that clarify sequencing for patients eligible for multiple targeted approaches (13). That agenda should include prospective, harmonized IHC with the therapy-aligned cutoff, rigorous capture of co-biomarkers, and planned analyses across diverse racial and ethnic groups.

Wallam *et al.* (3) ultimately remind us what matters most about CLDN18.2 in 2025. When tested with a therapy-aligned assay and cutoff, positivity is common in U.S. practice; it is more frequent in HER2-negative tumors; it appears more common in women; and it is not a prognostic marker of outcomes absent targeted therapy. The early signal toward higher positivity in Hispanic patients is hypothesis-generating and, given known disparities in GA/GEA incidence and stage at presentation, more than enough reason to ensure reflex testing and attentive implementation in diverse clinics. Getting CLDN18.2 right will be less about discovering new biology than about executing what we already know: harmonize assays, standardize reports, triage tissue wisely, and measure equity as a core quality metric. If we do, CLDN18.2 can deliver on its promise, not just in trials, but for the patients who need it most.

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