Table SI. Structured search framework and evidence boundaries.

Source/date	Core concept block	Illustrative search logic	Use in the present review
PubMed/MEDLINE; last updated 1 July 2026	Exposure and eradication	('Helicobacter pylori' OR H. pylori) AND (eradication OR post-eradication OR metachronous).	Residual-risk premise and paired post-eradication evidence.
PubMed/MEDLINE	Precursor conditions	(gastric atrophy OR intestinal metaplasia OR dysplasia OR precancer*) AND (immune OR microenvironment OR surveillance).	Direct infection/precursor tissue evidence.
PubMed/MEDLINE	High-dimensional tissue methods	(single-cell OR scRNA-seq OR spatial transcriptom* OR TCR OR multiplex immunohistochemistry) AND stomach/gastric.	Cell states, neighborhoods and candidate measurements.
Web of Science Core Collection	Topic/title replication	Equivalent exposure, precursor, immune, eradication and spatial-omics blocks.	Citation expansion and retrieval of related indexed studies.
Citation tracking	Sentinel guidelines and mechanistic studies	Forward and backward reference tracking.	Foundational staging, metaplasia biology and newly published linked evidence.
Eligibility principles	Priority and boundaries	Human mucosa, paired eradication, precursor omics, trials, systematic reviews and guidelines prioritized; animals, organoids, gastric cancer and cross-cancer studies used only as indirect mechanisms.	Prevents tumor-stage evidence from being presented as direct precursor proof.

This structured search supported a narrative review and was not used to claim systematic-review completeness or to generate a PRISMA flow diagram. H. pylori, Helicobacter pylori.

Table SII. Direct post-eradication human evidence: Study-level interpretation and evidence ceiling.

First author/s, year	Population and design	Paired/longitudinal measurement	Main human finding	What the study supports	Evidence ceiling	(Refs.)
Ihan *et al*, 1999	24 patients with duodenal ulcer; post-eradication follow-up.	Gastric mucosal T-cell CD25 and IFN-γ at 3 and 12 months.	Both measures declined after eradication.	Reversibility of selected infection-dependent cellular immune activation.	Not a precursor cohort; limited immune compartments; no epithelial-field comparison or cancer outcome.	(53)
Tsai *et al*, 2006	Randomized placebo-controlled preneoplasia trial; 54 gastric biopsies analyzed by microarray.	Baseline and one-year gastric gene-expression profiling.	Eradication produced measurable molecular reprogramming.	Human molecular responsiveness of preneoplastic mucosa after eradication.	Biopsy-level molecular analysis rather than 54 patients; gene-expression change is not direct immune function; no incident outcome validation.	(76)
Hung *et al*, 2009	65 patients with gastric intestinal metaplasia after successful eradication.	Histologic IM trajectory and β-catenin-related measurements; mean follow-up 33.9 months.	44 patients (67.7%) had persistent IM; persistence was associated with higher baseline nuclear β-catenin.	Heterogeneous epithelial recovery and a measurable structural/molecular correlate.	Epithelial mechanism rather than immune persistence; no external replication or cancer endpoint.	(15)
Sung *et al*, 2020	Randomized eradication-versus-placebo cohort; 102 before/after eradication biopsy pairs and 100 before/after placebo biopsy pairs (404 gastric biopsies total).	16S rRNA sequencing at baseline and 1 year.	Microbial communities shifted after eradication; distinct taxa accompanied persistent inflammation, atrophy or intestinal metaplasia.	Non-uniform human microbial recovery and a competing/modifying explanation.	Microbiome association is not proof of persistent immune function or independent prognostic value.	(35)
Kodama *et al*, 2021	172 eradicated patients; prospective annual histology for up to 17 years.	Serial antral and corpus atrophy and IM scores.	Atrophy improved; IM showed no significant long-term change at either site.	Long-term dissociation between inflammatory/atrophic improvement and structural IM persistence.	No direct immune measurement; no head-to-head epithelial-field or immune model; outcome linkage limited.	(16)
Kim *et al*, 2025	36 metachronous-neoplasia cases and 36 matched controls after endoscopic resection.	Longitudinal histologic and CD8-associated gastric mucosal measurements after eradication.	Trajectories differed according to subsequent metachronous neoplasia.	Outcome-linked tissue heterogeneity in a clinically enriched cohort.	Previous neoplasia limits generalizability; CD8-related measurements are tissue proxies rather than direct functional assays.	(54)

Song *et al*, 2026	35 patients with gastric cancer undergoing endoscopic therapy and longitudinal follow-up; 14 successfully eradicated, 3 recurrent after eradication, 11 non-eradicated and 7 H. pylori-negative.	Repeated gastric corpus mucosal microbiota sampling over at least two time points.	Eradication produced significant community-level remodeling.	Additional human longitudinal evidence for non-uniform microbial recovery.	Established cancer population and microbial endpoint; low directness to precursor-stage immune persistence.	(36)

This table separates direct human observations by population, biological layer and inferential limit. The studies are complementary but do not form a single continuous proof chain from persistent immune function to incident gastric cancer in the primary-prevention population. The most defensible current conclusion is layer-specific, heterogeneous recovery after eradication. Direct evidence for a persistent, functionally defined immune-associated state that independently predicts incident gastric cancer in individuals without previous gastric neoplasia remains absent. H. pylori, Helicobacter pylori.

Table SIII. Measurements, evidence limits and longitudinal tests.

Module	Representative measurements	Direct evidence boundary	Key longitudinal test
Exposure	Active/previous H. pylori, eradication date, reinfection, antibiotics and proton-pump inhibitor use.	Clinical and epidemiologic; exposure misclassification remains common.	Confirm eradication and exclude reinfection at each tissue time point.
Myeloid and antigen-presenting cells	HLA-II and antigen-presentation modules, phagocytic programs, myeloid states and spatial location.	Direct infection-stage evidence; most named macrophage-CAF networks are cancer-stage.	Test persistence and functional relevance after controlling for histology and inflammation.
T-cell surveillance	CD8-associated tissue features, TCR clonality, regulatory/effector balance and functional readouts.	Limited paired human evidence (36,37); conventional immunohistochemistry is not equivalent to function.	Assess paired early, intermediate and later trajectories linked to prespecified outcomes; exact intervals require empirical confirmation.
Metaplastic epithelium	Extent/subtype of metaplasia, spatial epithelial programs, methylation or clone burden.	A strong competing structural and epithelial explanation.	Test whether immune information remains after epithelial-field variables are included.
Stroma and extracellular matrix	Fibroblast activation, extracellular-matrix organization and immune-stromal proximity.	Predominantly tumor-stage indirect evidence.	Require direct precursor spatial validation and reproducibility across biopsy sites.
Microbiome	Community composition and functional potential.	Associative and confounded by drugs, diet and geography.	Treat as a modifier; require independent and reproducible value before clinical use.

This supplementary table expands the operational measurement framework referenced in the main manuscript. No single marker is expected to be sufficient; any candidate panel requires longitudinal derivation, functional support and independent replication. H. pylori, Helicobacter pylori.