

Biomarkers for Gastric Cancer and Premalignant Gastric Conditions

Journal Review

Yoon JY, Li D, Shah SC. Gastroenterol Clin N Am 2026;55:55–72

CONTENTS

01 Background & Questions

02 Biomarker Landscape

03 HP · PG · AIG Markers

04 GIM · Genetic · Others

05 Early Detection

06 Challenges & Summary

Background: Gastric Cancer Burden

5th

전 세계 암 발생·사망 순위
(GLOBOCAN 2022)

40%↓

일본·한국 인구 기반
내시경 검진 후
GC-specific mortality 감소

37.%, 7.5%

5 year survival
for advanced stage GC

38%

미국 전체 5년 생존율
→ 대부분 진행기에 진단

Key message

- 고발생 국가의 **국가건강검진**은 사망률을 낮췄지만, 조직화된 검진은 일부 국가에 한정되어 있음
- 미국처럼 발생률이 낮거나 중간인 국가에서는 증상 발생 후 진단 → 낮은 생존율 = **missed opportunity**
- 누구에게 내시경을 할지 고르는 **risk stratification** 도구가 필요함

Why Biomarkers? Limits of Endoscopy-only Strategy

Upper endoscopy (gold standard)

장점

- Biopsy 가능
- advanced neoplasia **동시 절제** 가능

한계

- Resource-intensive
- Logistical barriers
- Procedural risk
- 저~중간 발생 국가(예: 미국)에서는 전 인구 검진보다 **targeted approach**가 필요

Current US guideline (2025)

AGA Clinical Practice Update

- 고위험군 targeted endoscopic screening
 - Select non-White racial/ethnic groups
 - Chronic HP + additional risk factors

ACG guideline

- Individualized basis 검진 고려
 - First degree relative of gastric cancer
 - 고발생국 출신 1세대 이민자

미국 고위험군에서 검진 효과 근거는 부족

Biomarker

- **Biological molecules that signal a normal/abnormal biological process**
 - Proteins: enzymes, hormones, antigens
 - Genetic signatures: mutation, amplification, translocation, methylation

Ideal biomarker

- **Highly sensitive & specific**
- **Cost-effective**
- **Reproducible**
- Serum 또는 내시경 검체에 적용 → benefit-to-harm/cost ratio 극대화

Scope of This Review: Two Key Questions

Q1

Can biomarkers be used for **GC risk stratification** to inform endoscopic screening or surveillance?

→ 내시경이 필요한 고위험군 선별

Q2

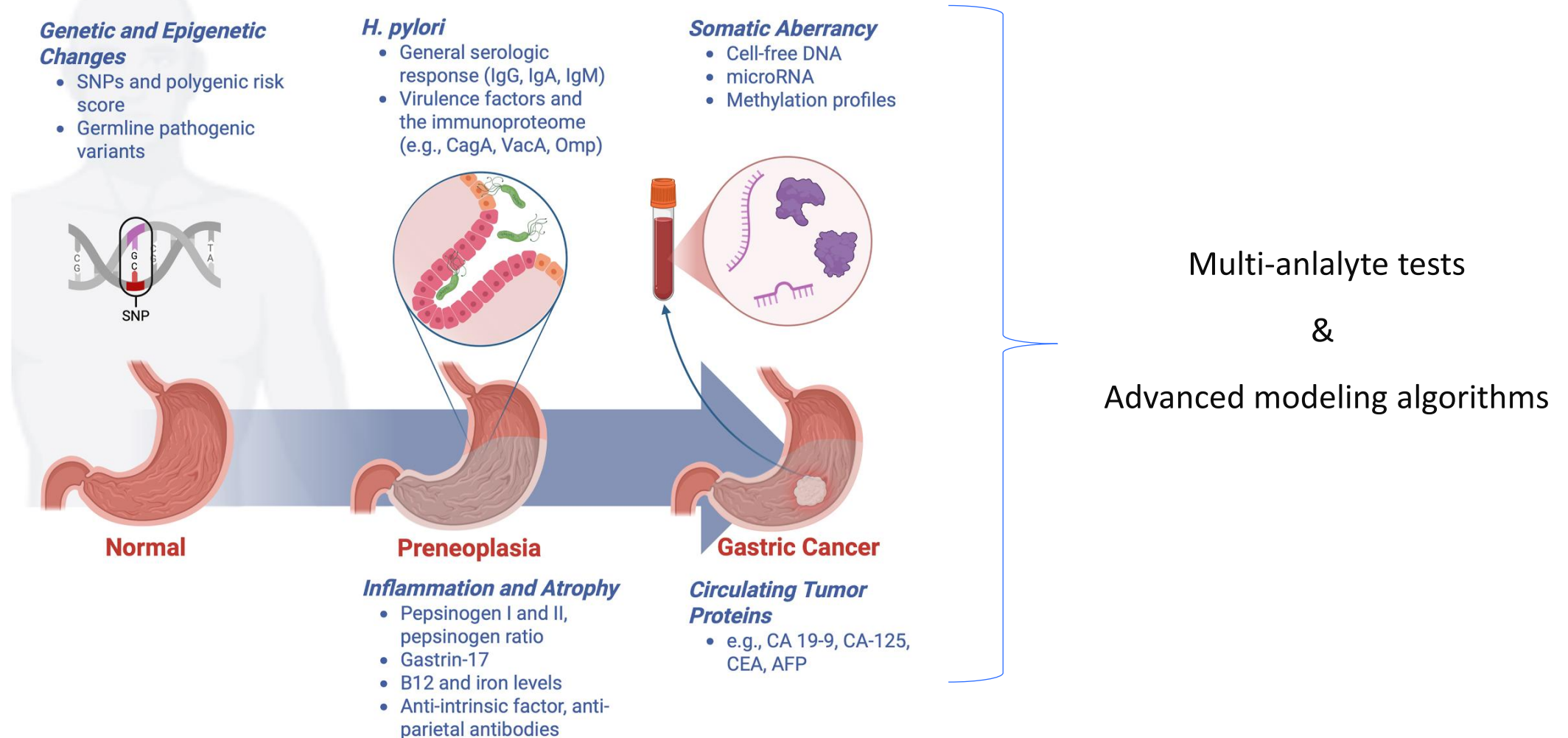
Can biomarkers accurately detect **gastric premalignant conditions and/or early GC**?

→ 전암 병변 · 조기 위암의 직접 검출

Caveat

- 대부분의 연구가 **subsite (cardia vs noncardia)** 또는 **histology (intestinal vs diffuse)** 별 test characteristics를 제시하지 않음
→ 본 리뷰는 GPMC와 gastric adenocarcinoma 전체를 좀 더 넓은 시야에서 검토

Selected biomarker targets for GC risk stratification and early detection

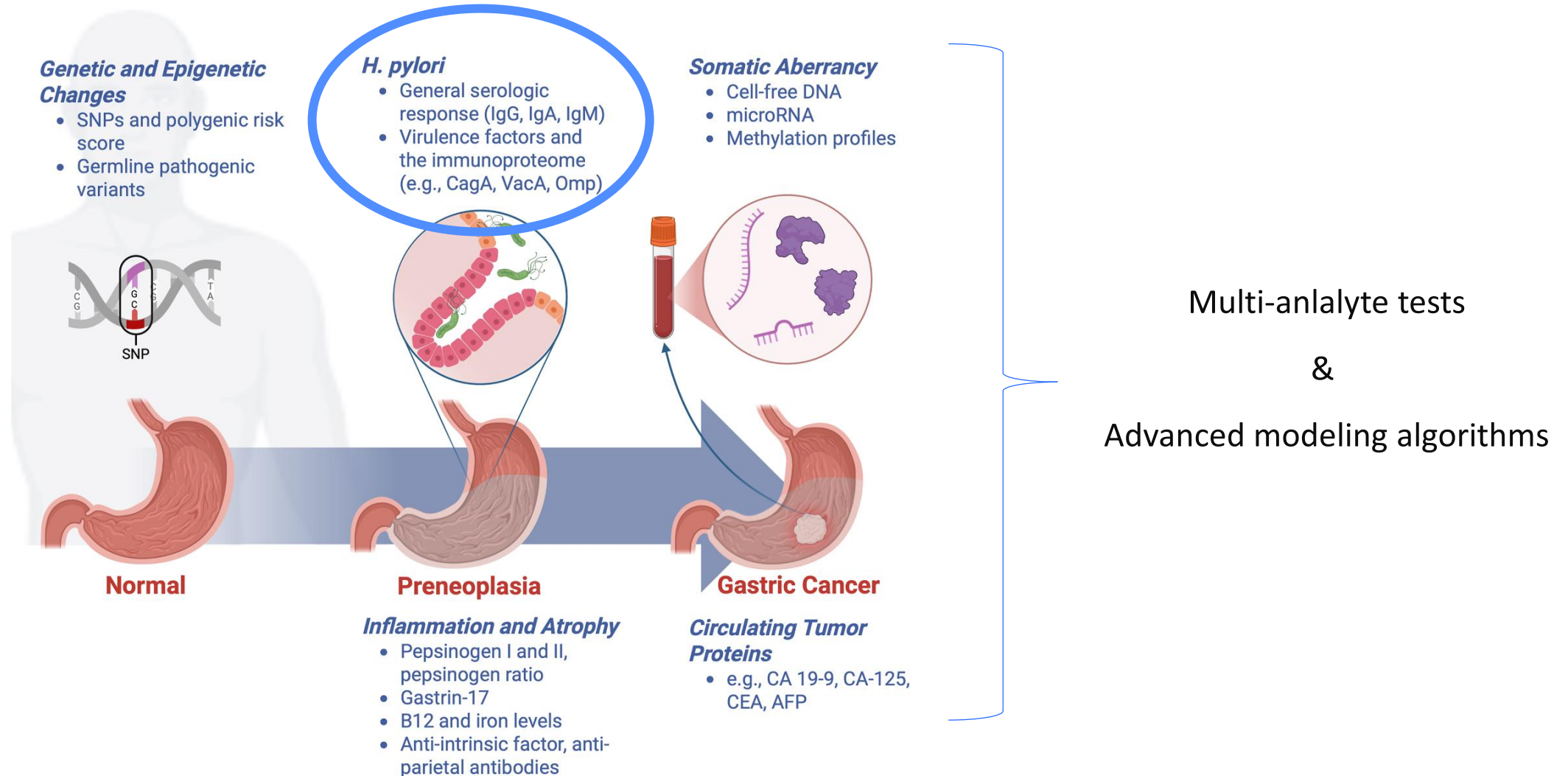


Part 1. Biomarkers for GC Risk Stratification

Q1. Who needs endoscopy?

HP-related · Pepsinogen · AIG · GIM · Genetic/Epigenetic · Others

Selected biomarker targets for GC risk stratification and early detection



Risk Factors & Rationale for Biomarker-based Stratification

H. pylori의 GC attributable risk

80–90%

더 높을 수도 있음

IARC **Group I** carcinogen
(GC & MALT lymphoma)

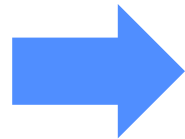
Additional modifiable risk factors

- **Diet:** high salt, preserved foods
- **Tobacco**
- **Heavy alcohol**
- 노출 차이 + host genetic diversity
→ 국가 간·국가 내 발생률 차이

US context

- 이민자·소수 인종군에 위험 집중 → targeted endoscopic screening의 대상
- 그러나 race, ethnicity, immigration status는 **social constructs**

Surrogate markers
(race · ethnicity · immigration)



Biomarkers characterizing the exposure profile (exposome)
or preneoplasia (e.g., molecular profiling)
→ risk assessment beyond surrogate markers

H. pylori: Correa Cascade & Virulence



Correa cascade — histologic progression to intestinal-type GC

HP 감염자(전 세계 인구의 절반) 중
GC로 진행되는 비율

<1–3%

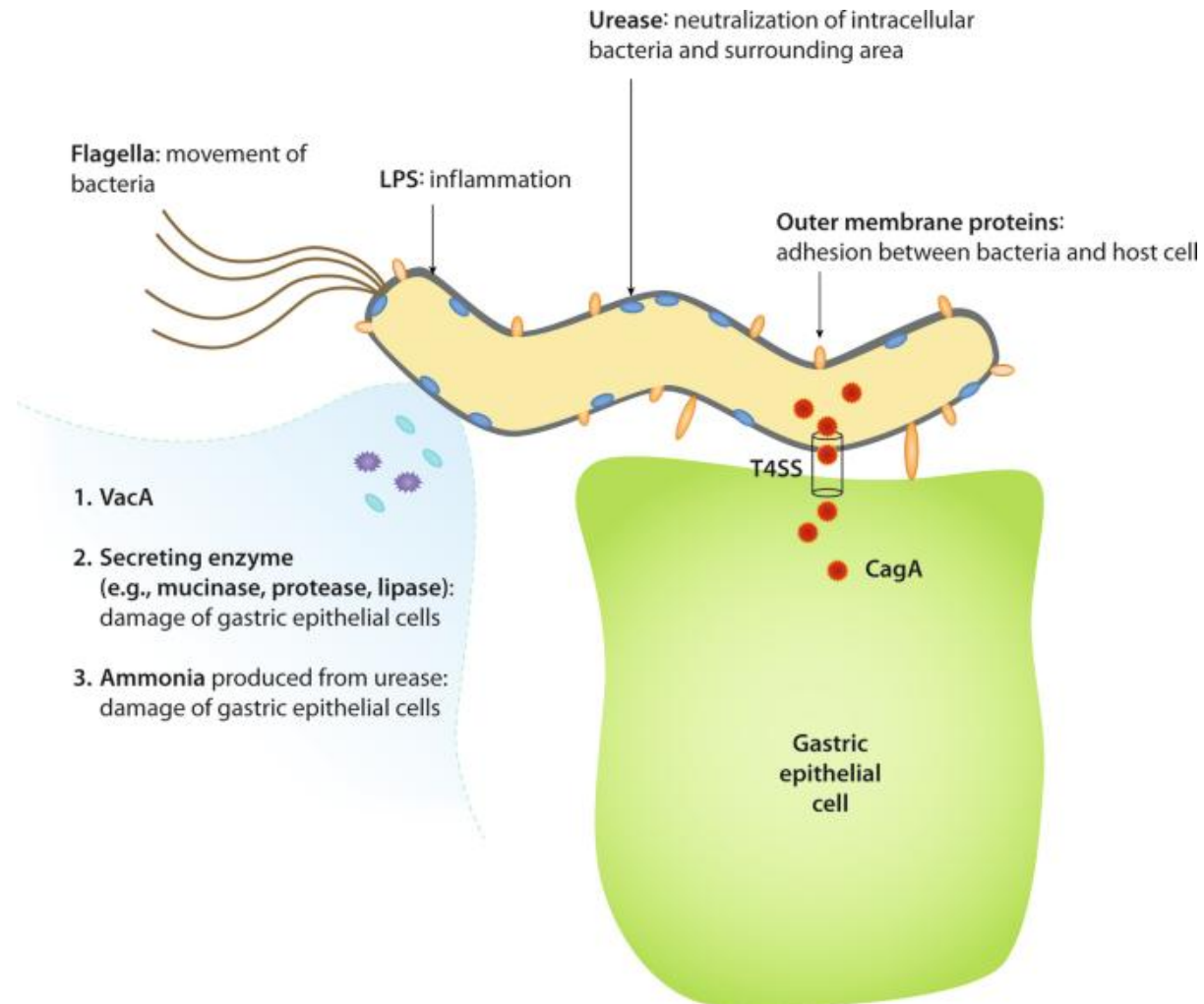
Virulence factors

- **CagA** (oncoprotein)
 - 상피세포 형태 변화 → motility/invasion
 - Apoptosis 교란
- **VacA**: immune cell function 저해
- **Immunoproteome** >1,500 proteins → 비침습 진단·층화 표적

Why precision matters

- 고위험 HP phenotype
- 현재/과거 감염 여부
→ GPMC·GC 위험 정보
- Precision approach의 이점
 - Cost-effectiveness ↑
 - Antibiotic stewardship
 - 불필요한 치료 최소화

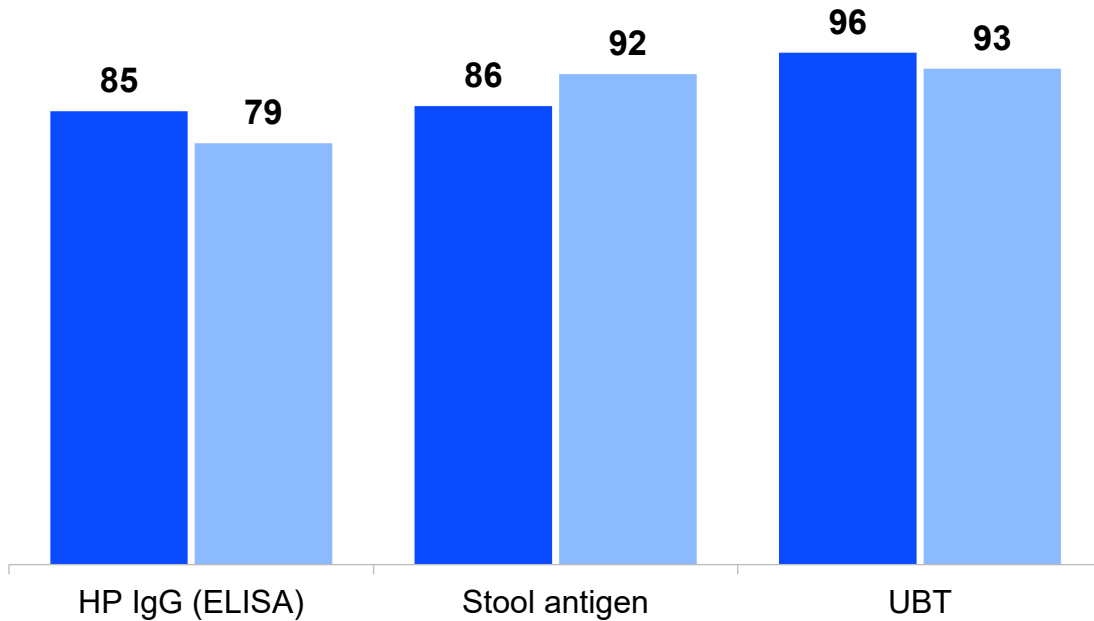
H. pylori: Correa Cascade & Virulence



HP Infection Tests: Serology vs Stool Ag vs UBT

Diagnostic accuracy for HP infection

■ Sensitivity (%) ■ Specificity (%)



IgM (현재/과거 감염 구분 시도): sensitivity **6.8%** → 부적합
Current vs prior infection을 구분하는 assay는 아직 임상예 없음

HP IgG (ELISA) GC risk (pooled OR)	3.01 (2.22–4.07)
Immunoblot / multiplex (CagA, VacA, UreA)	9.22 (3.12–27.21)
NPV of IgG test	97.4%
PPV of IgG test	22.8% (나이 들수록 ↓)

- Low PPV → **저유병률 환경(미국 대부분)**에서 사용 제한
- Advanced GPMC로 감염이 소실된 경우 **위음성** → 실제 위험 과소평가
- Assay·인구집단마다 성능이 달라 **local validation** 필요

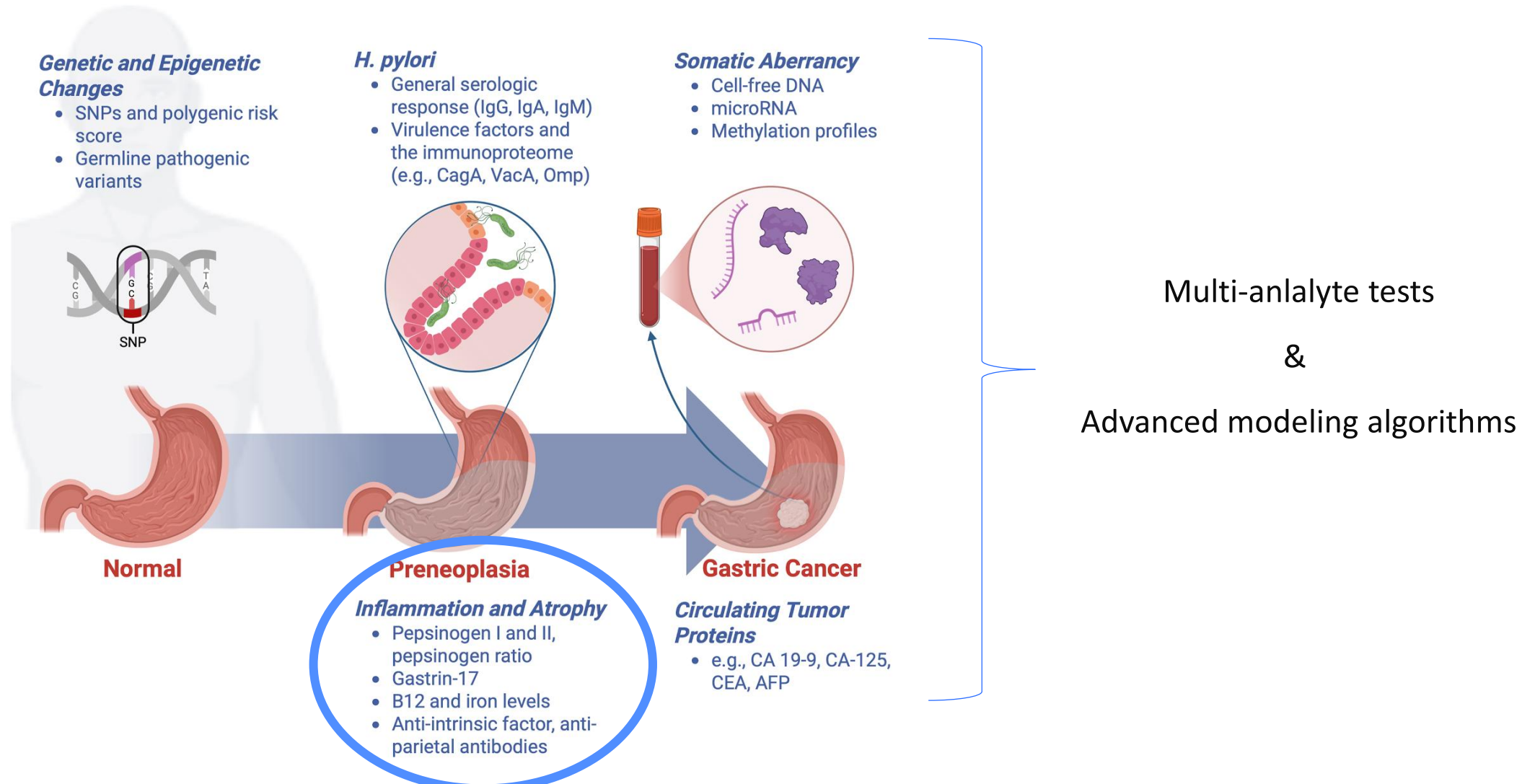
Multiplex Serology & HP Immunoproteome

Target / panel	Population	Outcome	Performance
≥2 of 4 virulence factors (VacA, GroEl, HcpC, HP1564)	US, predominantly African American	Active HP infection (vs UBT)	Sens 100% / Spec 90%
4-protein combination (Ggt, HslU, NapA, CagA)	Chile (50 GC / 50 controls)	GC vs controls	AUC 0.73
Omp + HP0305 seropositivity	Linqu, Shandong, China (N=1,402)	GPMC on endoscopy	OR 7.43 (5.59–9.88)
Omp, HP0305 + age, smoking, HP	Same cohort (classification model)	GPMC vs controls	AUC 0.75 (0.73–0.78)
11 IgG antibodies to HP proteins	Chile (50 GIM / 50 controls)	GIM vs controls	AUC 0.81 (0.75–0.87)

Regional heterogeneity of GC-associated HP antigens

- Europe: **CagA, GroEL**만 연관 vs East Asia: + **HP0305, HyaA, NapA, Omp, VacA**
- 노출·HP serotype·host genetics 차이 반영 → **target population validation** 필수, 아직 **commercially unavailable**

Selected biomarker targets for GC risk stratification and early detection



Serum Pepsinogen (PG I, PG II, PG I/II Ratio)

Principle & cutoffs

- PG: **gastric mucosal status** 반영
- ↓ PG I:II ratio = HP gastritis가 **antrum** → **corpus**로 진행

Standard cutoffs

- PG I ≤70 ng/mL &
- PG I:II ratio ≤3
- 동아시아에서 개발, Portugal 등에서 검증
- 최적 threshold는 인구집단마다 다를 수 있음

Meta-analysis: 31 studies (1,520 GC; 2,265 AG; mostly Asia)

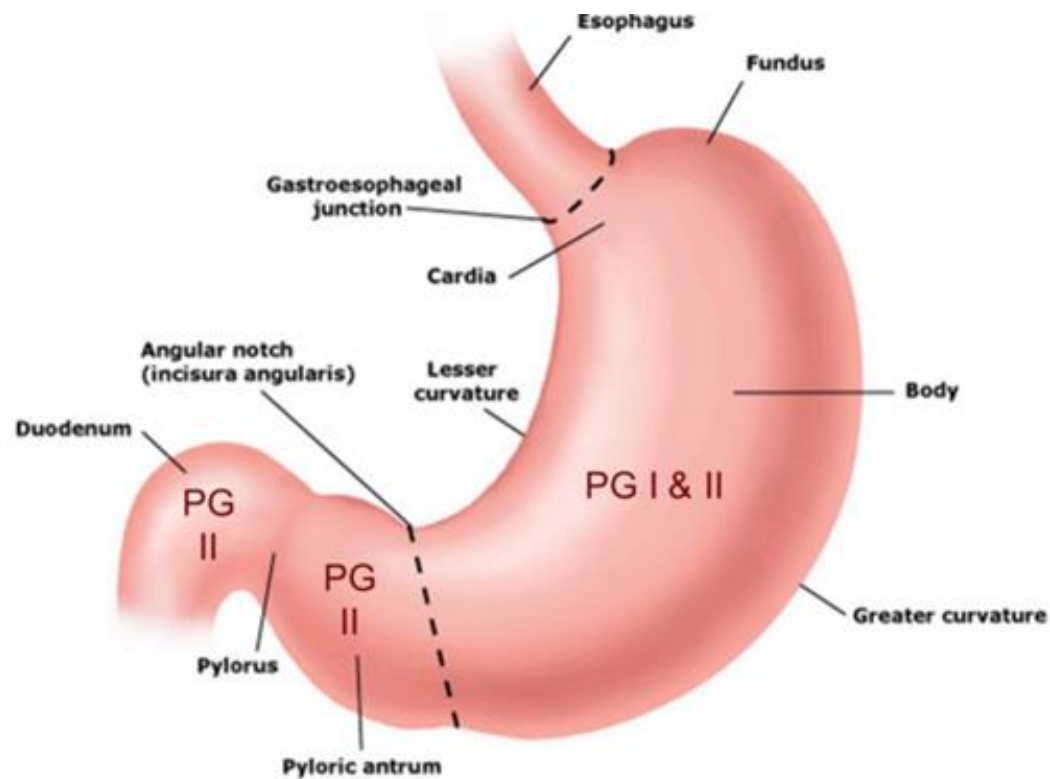
Target	Sensitivity	Specificity	AUC
Gastric cancer	0.69 (0.60–0.76)	0.73 (0.62–0.82)	0.76
Atrophic gastritis	0.69 (0.55–0.80)	0.88 (0.77–0.94)	0.85

한계: high heterogeneity · publication bias · 동아시아 외 일반화 제한

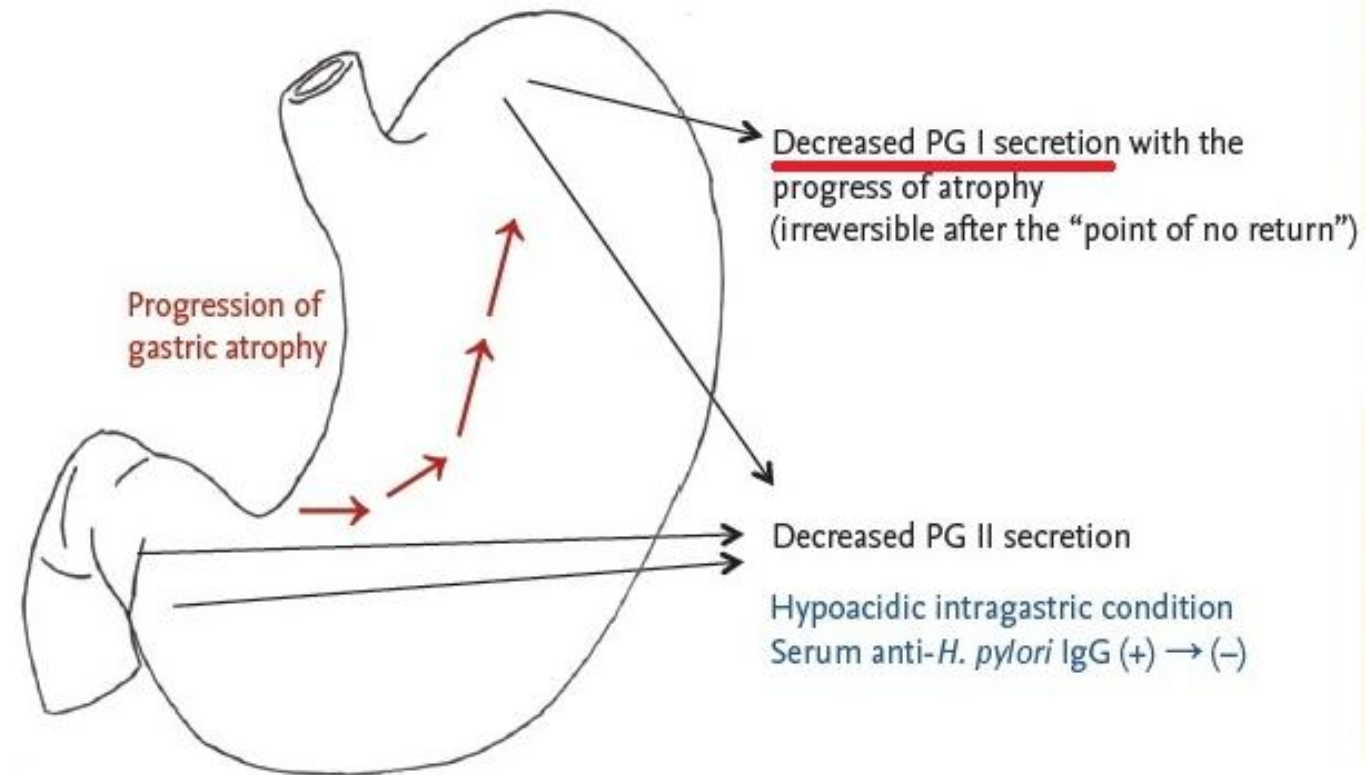
US data

- PLCO nested case-control** (105 GC / 209 controls): OR **10.6** (4.3–26.2)
- HP·가족력·흡연 보정 후
 - Standard cutoffs: sens **0.34–0.44** / spec 0.92–0.94
 - Alternative (PG ratio ≤5.2, HP IgG ≥17.5 U/mL): sens 0.88 / spec 0.51
- Multiethnic high-risk cohort** (N=135): GPMC sens **15–47%**, spec 78–95%;
- + HP IgG/G-17도 AUC <0.7

Serum Pepsinogen (PG I, PG II, PG I/II Ratio)



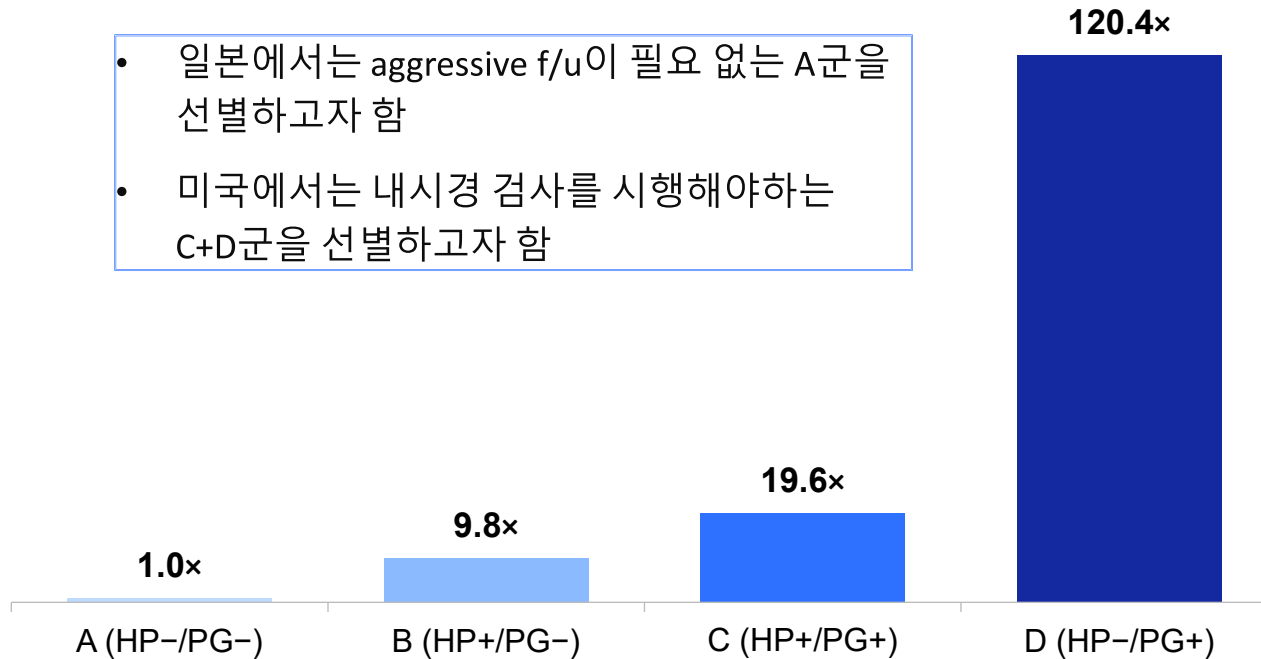
Stomach with chronic inactive *H. pylori* infection



ABC(D) Method & GastroPanel

ABC(D) method, Japan: GC risk over 8 years

- 일본에서는 aggressive f/u이 필요 없는 A군을 선별하고자 함
- 미국에서는 내시경 검사를 시행해야하는 C+D군을 선별하고자 함



US PLCO: **PG+ 군(C, D)**만 GC 위험 증가, 효과 크기는 더 작음 (OR **9.3**, 3.4–25.2)
 PG+ = standard cutoff 기준 위축 양성

GastroPanel (Biohit, Finland)

- Commercial ELISA panel: **PG I, PG II, gastrin-17, HP IgG**
- Dyspepsia 평가 / atrophic gastritis

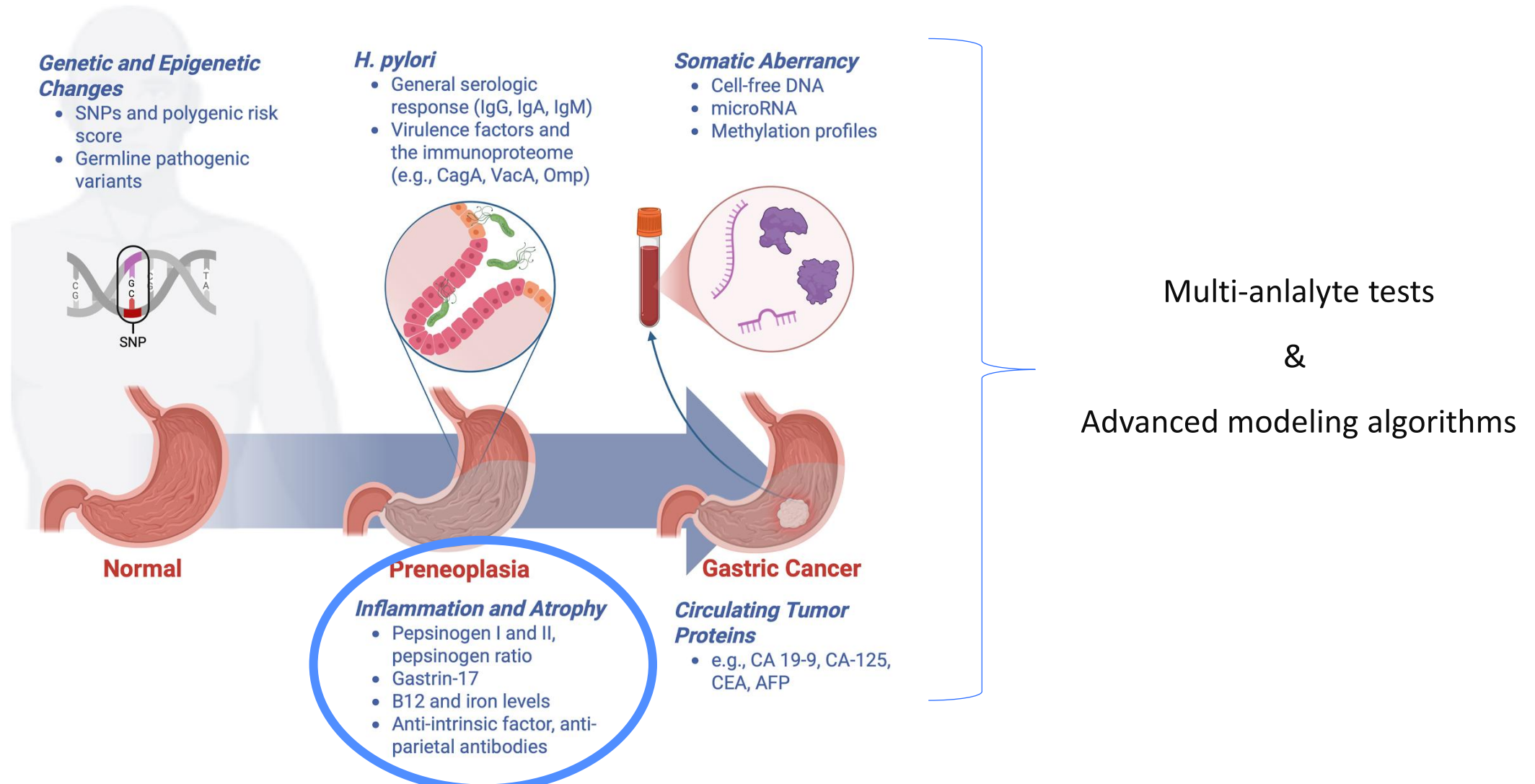
Meta-analysis (27 studies, Asia & Europe, N=8,654)

- AG: sens **0.70** (0.64–0.76), spec **0.94** (0.90–0.95)

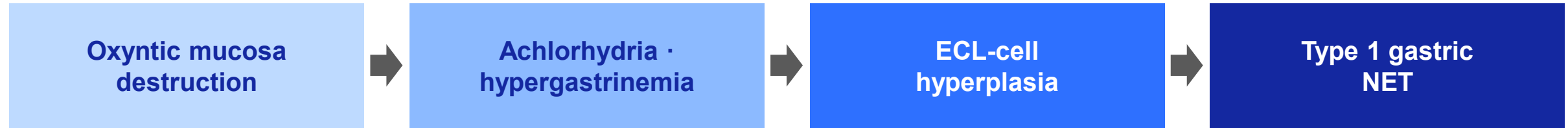
Prospective UK study (N=324, HP+ 21.6%)

- Updated Sydney System과 **91%** 일치 (0.88–0.94)
- → 비침습적 risk stratification 도구로서 가능성

Selected biomarker targets for GC risk stratification and early detection



Autoimmune Gastritis (AIG) & Gastric Cancer Risk



Primary neoplastic pathway of AIG

7×

Pernicious anemia
(late-stage manifestation)
GC risk

RR 11.05

Metaplastic AIG
(8 observational studies)
95% CI 6.39–19.11

But... confounding by HP

- AIG 중증도 다양, HP confounder 고려 불충분
- HP 노출을 고려한 연구: **HP-naïve AIG에서는 GC 연관 없음**
(N=211, median f/u 7.5 yr — 규모·기간 제한)
- AIG vs HP-related metaplasia: 조직학·면역형광(GKN3, MUC6, GIF)·전사체 모두 **구분 불가**
- 공통 GC-related marker: **ANPEP/CD13**

→ AIG 자체의 선암 위험은 **HP 교란**을 고려해 해석해야 함

AIG Biomarkers: Antiparietal cell antibody & Antiintrinsic factor antibody

	Anti-PCA	Anti-IFA
Sensitivity (AIG)	70–80%	30–60%
Specificity	Lower	>95%
Pitfalls	HP gastritis·타 자가면역 양성; advanced AIG 위음성	진행된 AIG에서 출현
GC association	HP-seronegative women OR 5.52 (3.16–9.64)	—

Combination & staging

- PCA + IFA + B12 + ChromograninA + Hb
→ AIG 진단 sens **85.7%** / spec **83.7%** (Italy, N=100)
- AIG stage 3: gastrin-17 ↑, PCA 양성률은 stage와 무관 (N=282)
- IFA·PCA 수치는 **GC 위험과 직접 연관 없음**

Clinical implications

- European & US guidelines: **새로 진단된 pernicious anemia** → **endoscopic GC screening** 제안 (surveillance 권고는 데이터 추가 필요)
- 위축 마커(↓PG I, ↓PG ratio) 적용 가능하나, AIG는 **corpus-dominant** → HP 위축과 cutoff가 다름

Tissue-based Biomarkers for Gastric Intestinal Metaplasia

1.6%

GIM의 10년 GC risk
(clinical/histologic stratification 무관)

Higher-risk GIM	RR (95% CI)
Extensive (corpus)	2.1 (1.0–4.4)
Incomplete type	3.3 (2.0–5.6)

내시경·병리 의존 → 비용·접근성 한계, 덜 침습적인 층화법 필요

US practice

- AG보다 **interobserver variability** ↓
- 병리 보고가 더 보편적

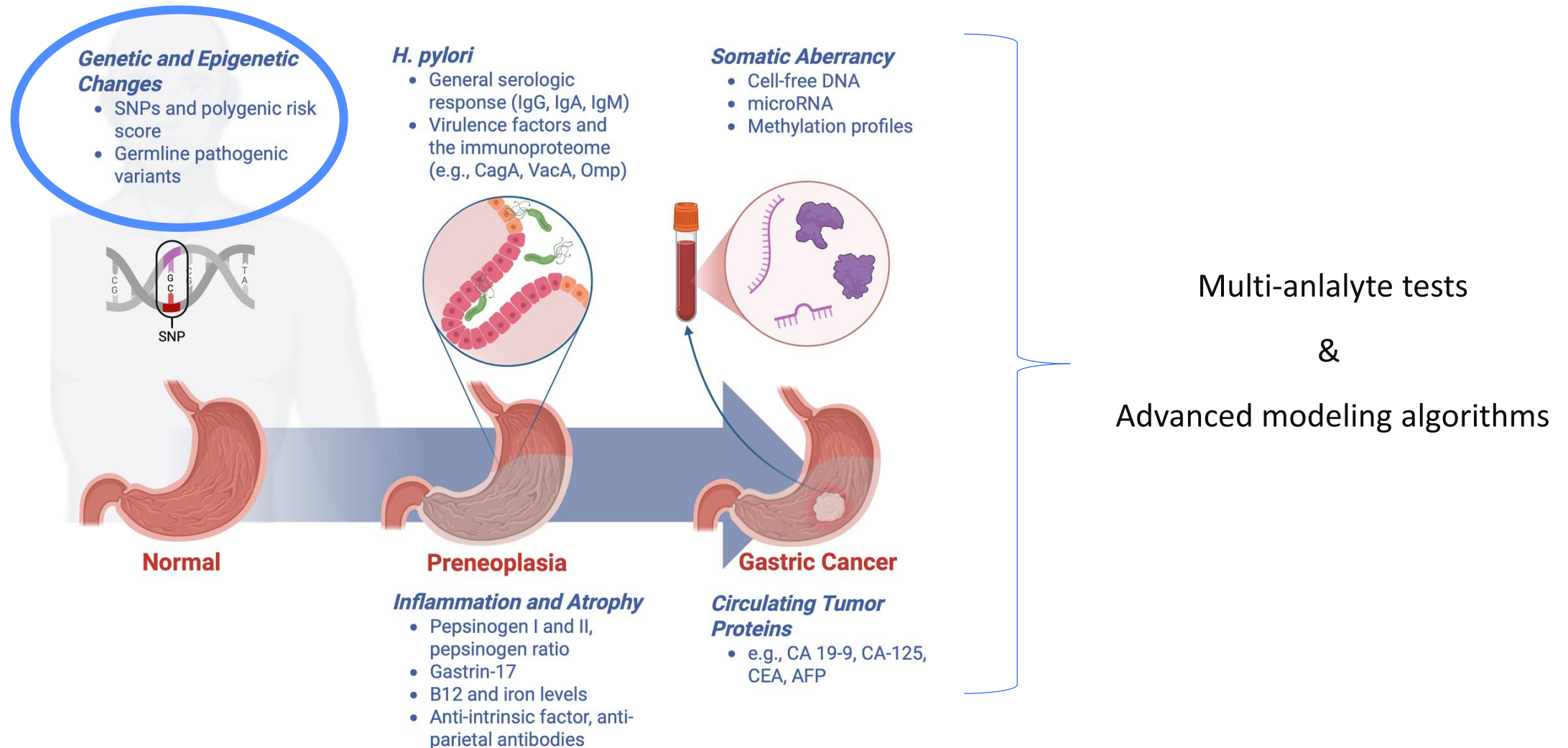
GCEP (large Asian biobank)

- Chromosomal alterations, shortened telomeres → **dysplasia/GC**
- Normal-like epigenome → **regression**
- **Active HP 포함** → HP-induced 변화와 구분 어려움; 서구 인구 검증 필요

Gastric Precancerous Conditions Study

- Multiethnic, **HP-negative** cohort
- **26-gene signature** (incl. CDH17, KRAS) for advanced GIM (**OLGIM III–IV**)
- Metaplastic glands·intestinal-type GC에 국한, 정상 점막에는 없음

Selected biomarker targets for GC risk stratification and early detection



Genetic & Epigenetic Alterations

Germline pathogenic variants

- 10% familial clustering
- Hereditary syndrome **<3%**
 - APC, ATM, BRCA1/2, CDH1, MLH1, MSH2, MSH6, PALB2
- **HR genes** (BRCA1/2, PALB2, ATM) PV + HP
 - **synergistic** GC risk

2-hit hypothesis

- HP (CagA) → Double Strand Breaks → error-prone repair (NHEJ, MMEJ) → gross chromosomal rearrangement

Polygenic risk score (PRS)

- Genomewide association studies lower-penetrance loci: **ANKRD50, PTGER4** (Chinese & European)
- Chinese cohort:
 - **Eradication은 high-PRS군에서만 GC 위험 감소**
- Discrimination 불충분: AUC **0.56–0.78** (East Asian, European)
- 대상 인구에서 평가 필요

DNA methylation

- Methylation burden:
 - ✓ HP gastritis에서 ↑
 - ✓ advanced GPMC로 갈수록 ↑
- WNT, p53 등 cancer-related pathway 영향 가능
- Japanese cohort: **miR-124a-3, EMX1, NKX6-1**
 - Highest vs low burden: **HR 3.0** (1.58–5.72)
- 다양한 인구 검증 필요, 상용화 전

Additional Serologic Markers

EBV serology	Trefoil factors (TFF)	HE-4 + PG	Body iron stores
anti-BALF2 · anti-LF2 · anti-BORF2	Goblet cell 분비, GC·GPMC에서 ↑	Atrophic gastritis 검출	EPIC (EURGAST) study
AUC 0.81–0.85	PPV 0.828	Sens 85.2%	Low iron ↔ GC
- EBV-associated GC (~10%) vs EBV- GC 구분 - EBV ubiquity → 조기 발견엔 부적합 - PD-L1 ↑ → ICI 반응 예측 가능성	- PG + TFF: PPV 0.828 / NPV 0.878 - PG alone: PPV 0.608 / NPV 0.874 - Limited validation	- PG alone sens 55.6% Specificity 감소 - Limited validation	심한 AG → achlorhydria → 철 흡수 저하 가능성

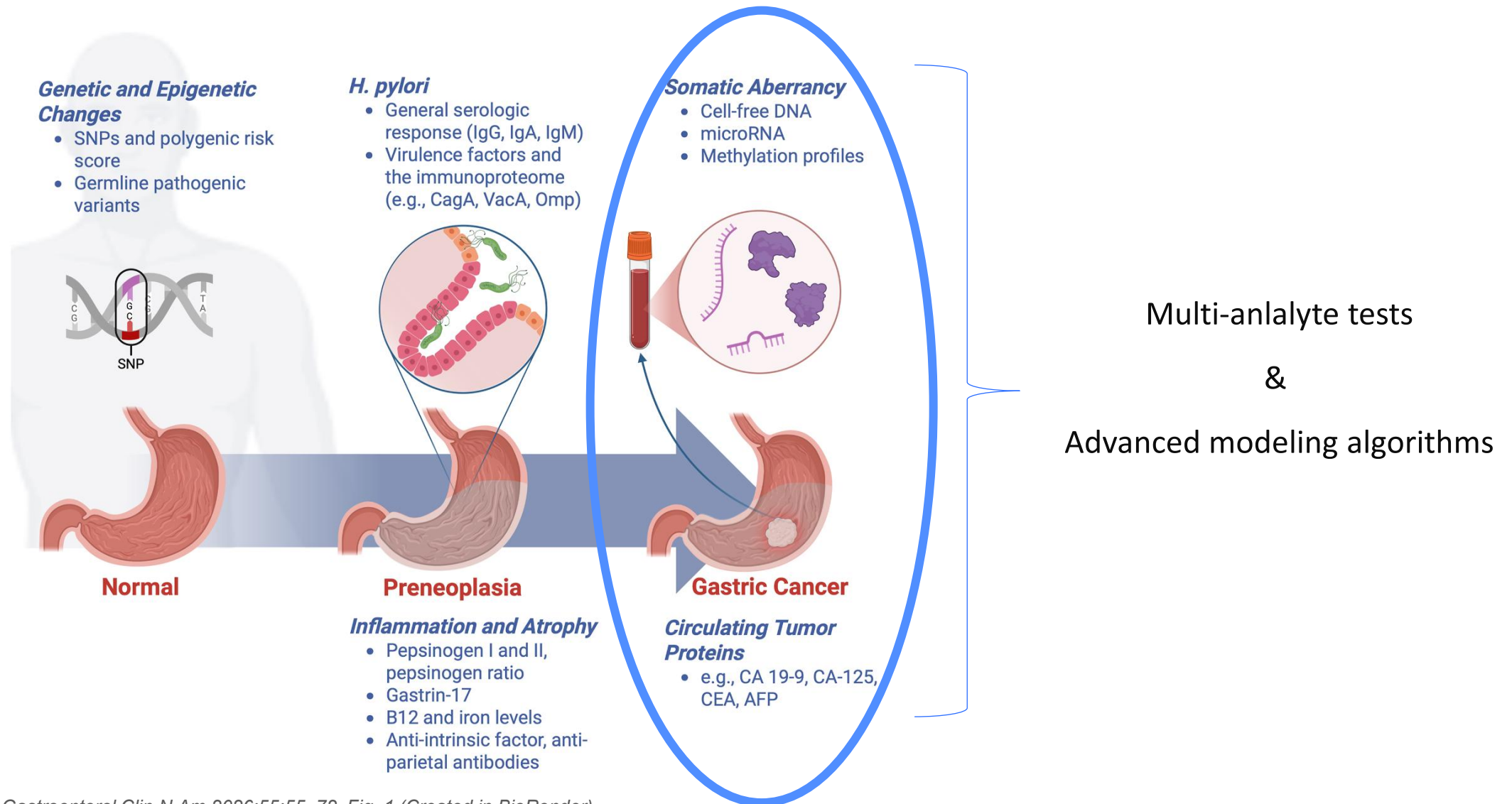
→ These markers show **limited promise to date**

Part 2. Biomarkers for Early Detection of GC

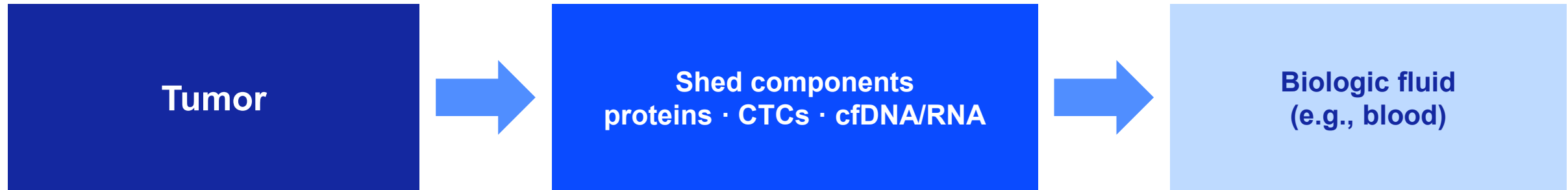
Q2. Can we detect early GC in blood?

Liquid biopsy · miRNA · cfDNA methylation · lncRNA · MCD tests

Selected biomarker targets for GC risk stratification and early detection



Liquid Biopsy: Principle & Pitfalls



Pitfall: necrosis-dependent release

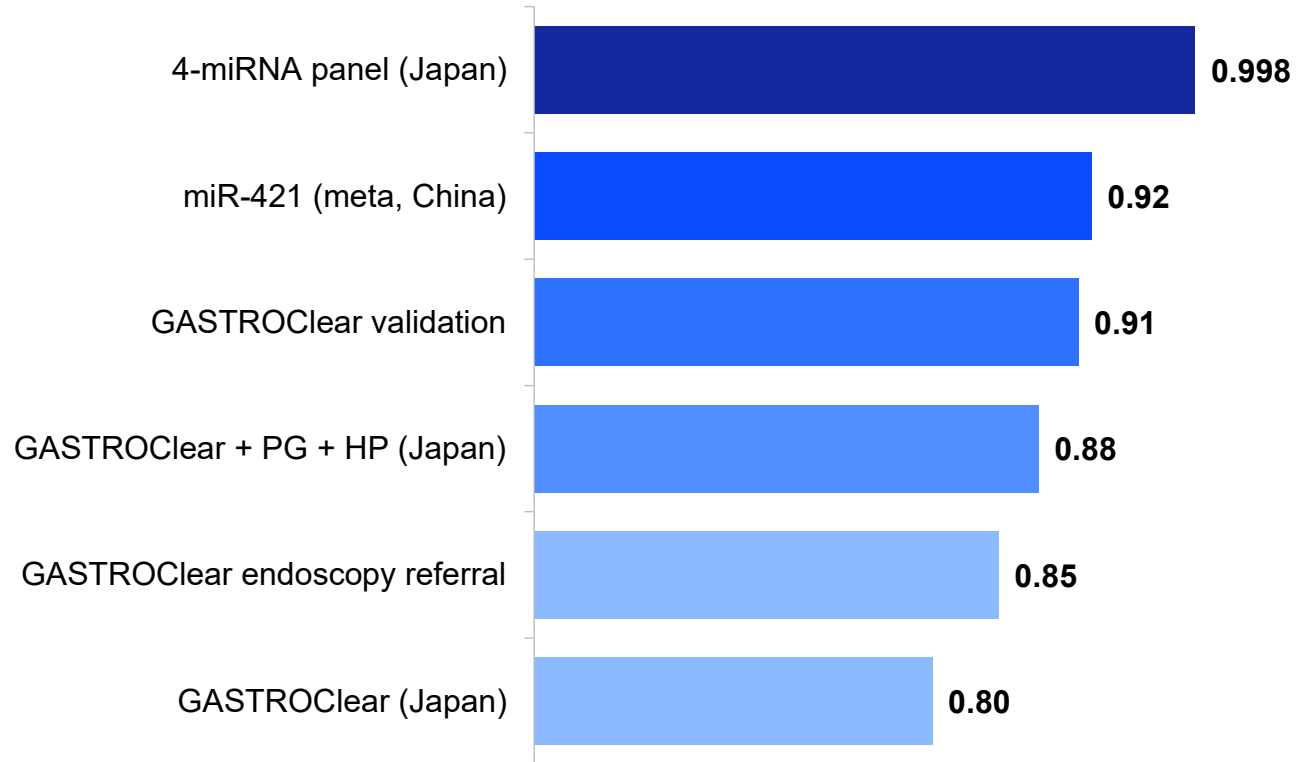
- Tumor necrosis가 marker를 방출
→ **advanced cancer**에서 더 민감·특이
- 조기 발견 성능은 **early disease** 비율이 높은 코호트에서 평가해야 함
- Standalone proteins (**CEA, CA19-9, AFP, CA-125**): GC에서 성능 낮음 → multi-analyte test의 구성 요소로 활용

Why microRNA?

- Tumor cell이 **non-necrotic mechanism**으로 방출
→ 조기 GC 검출에 유망
- Combination assays 개발 중:
circulating RNA + miRNA + DNA methylation

MicroRNA Panels for Early GC Detection

Reported AUC for (early) GC detection



※ 서로 다른 코호트의 값으로 직접 비교 불가 (x축 0.5부터 표시)

GASTROClear® (MiRXES; 12-miRNA)

- Stage I–II GC 대상, **Singapore에서 상용화**
- Validation: sens 0.86 / spec 0.85
- Endoscopy referral: sens 0.87 / spec **0.68**
- Japan (stage I 58%): sens 0.71 / spec 0.75
→ + PG·HP: spec 0.87
- Cost-effective: Singaporean Chinese men 50–75 yr (**NNS 489**)
- US **FDA Breakthrough Device** designation
- 4-miRNA panel (Japan): sens 0.996 / spec 0.953, prospective study ongoing

Circulating Methylated DNA & Extracellular IncRNA

Reprimo cfDNA (methylated Reprimo)

- Reprimo: tumor suppressor gene

GC vs normal/GPMC

- Sens **65%** (53.5–75.3) / Spec **75.9%** (73.2–78.5)
- RPRM+ → HGD/early GC **OR 3.9** (1.53–9.93)

+ PG I:II ratio (Chile)

- HGD/early GC: sens **78%** (54.4–94.0) / spec 63.0% (52.3–72.9)
- Validation needed; moderate specificity

GCInc1 (EV-derived IncRNA)

- Extracellular vesicle 유래 long noncoding RNA

Stage I–II GC 검출

- AUC **0.94** (0.91–0.97)

CEA · CA72-4 · CA19-9 음성 증례에서

- Early GC vs GPMC: AUC **0.89** (0.86–0.92)
- Investigational; 아직 임상 사용 전

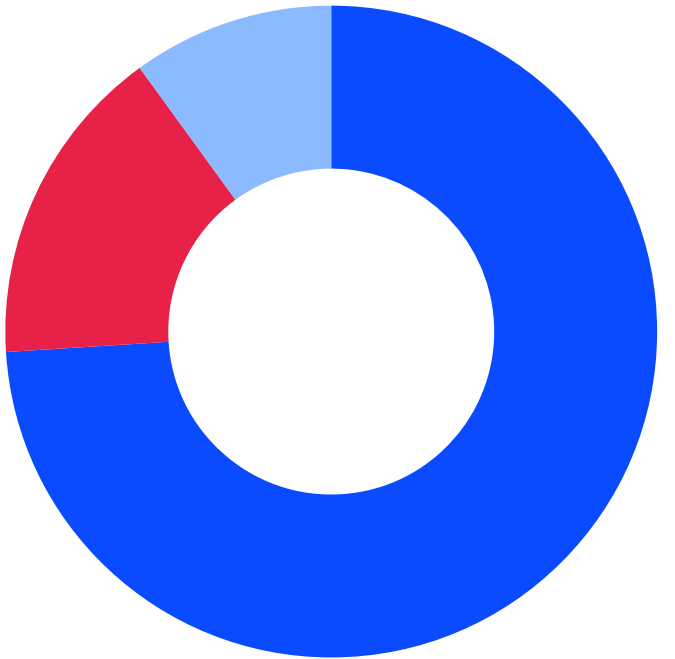
Part 3. Challenges & Future Directions

What stands between biomarkers and practice?

Histology · Regional HP heterogeneity · Representation · Implementation

Challenges & Future Directions

GC by histology (US)



■ Intestinal 74% ■ Diffuse 16% ■ Other 10%

연구는 HP 관련 **intestinal-type**에 집중
diffuse·기타 유형은 blind spot 가능

1

Histology & subsite

Histology·anatomic subsite별 평가 연구가 드물(통계적 검정력 부족)
→ 모든 GC에 적용 가능한지 불확실

2

Regional HP heterogeneity

HP 유병률·genome이 다인종 국가 내 하위집단 간에도 다름
US **CagA+ Black 82% vs NHW 36%** ($P<.0001$)

3

Validation & representation

고발생 지역(동아시아·남미) 중심 데이터
→ 저발생·다양한 인구에서 **추가 검증** 필요, 고위험군의 trial 참여 확보

4

Implementation

Overall effectiveness, screening interval, **cost burden**
downstream impact의 신중한 평가

Take-home Messages

1

GC는 예방 가능한 주요 암 사망 원인이나, 조직화된 검진은 일부 국가에 한정되고 내시경은 실행 장벽이 있음

2

Biomarker 활용 목적은 두 가지: ① 내시경이 필요한 **고위험군 선별** ② **advanced GPMC-early GC 검출**

3

Targets

HP (serology, virulence), mucosal atrophy (PG, G-17), AIG antibodies, GIM signatures, genetic/epigenetic, liquid biopsy

4

현재까지 **단독(standalone)**으로 실제 도입 수준의 성능을 보인 마커는 없음
→ **multi-marker panel + advanced modeling**으로 정확도 개선 중

5

target population validation, 정확도·재현성 개선, cost-effectiveness, accessibility, downstream effect

Thank you

Questions & Discussion

