

EAP: Eesti Arstide Päevad, April 9, 2015

**Panel of Biomarkers
(GastroPanel®): the
First-Line Diagnostic Test for
Dyspeptic Symptoms and in
Screening for the
Risk of Gastric Cancer**

Prof. Kari Syrjänen, MD, PhD, FIAC
Chief Medical Director

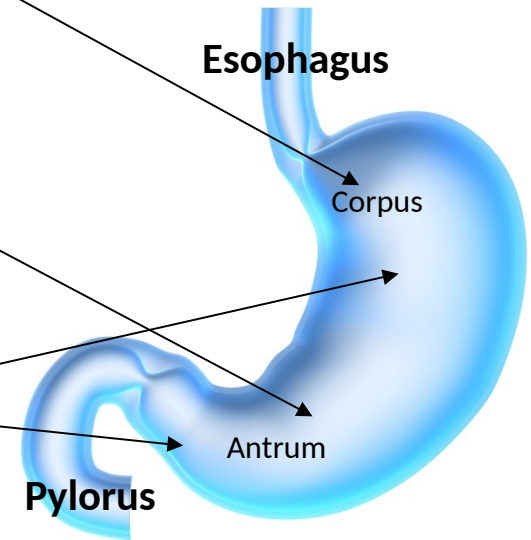


GastroPanel® test – a panel of 4 biomarkers

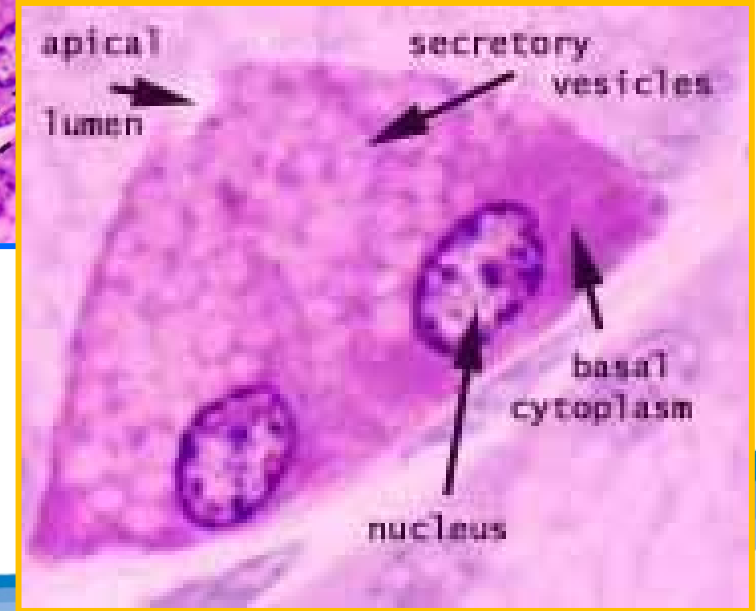
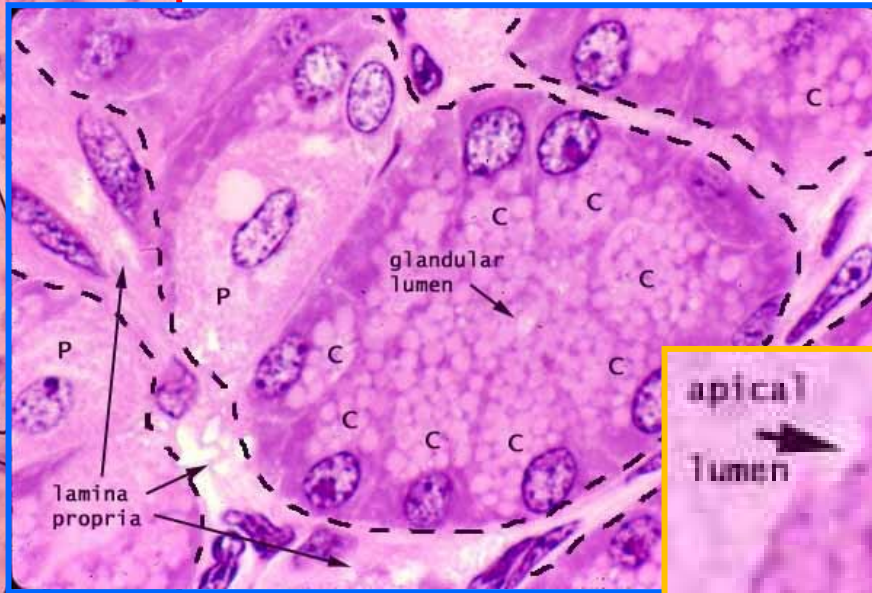
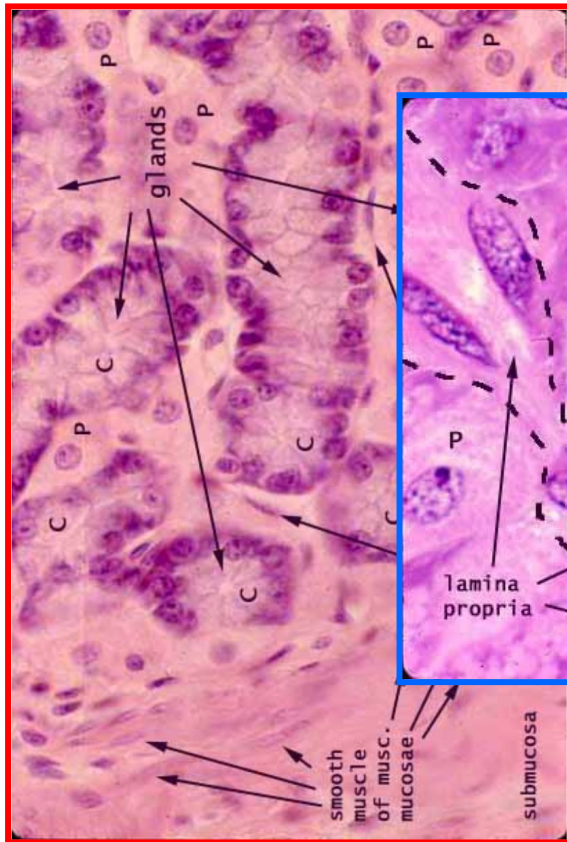
Pepsinogen I & II; Pepsinogen I/II ratio are biomarkers of gastric corpus

Amidated gastrin-17 is biomarker of antrum (G cells), together with Pepsinogen II

H. pylori IgG antibodies are markers of HP-associated gastritis (antrum & corpus)



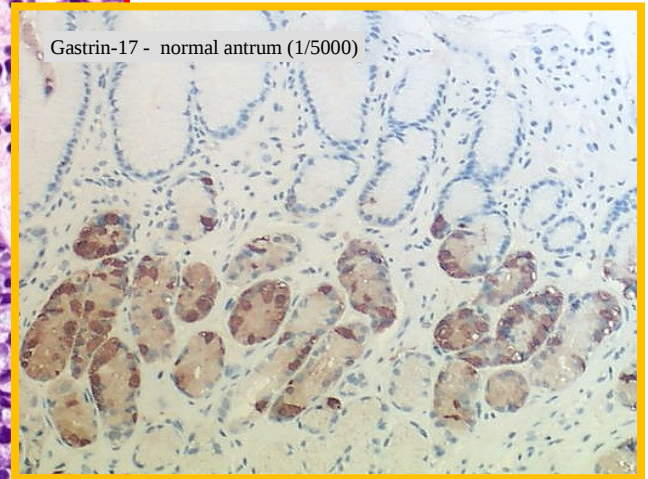
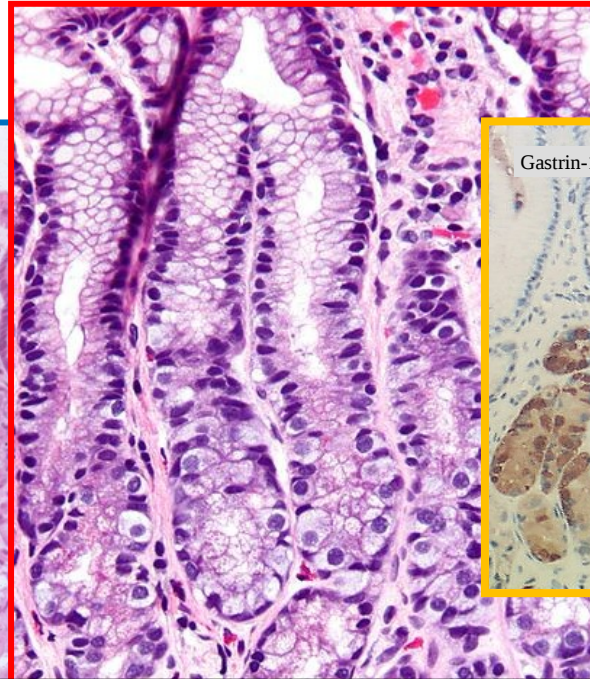
GastroPanel® test – based on stomach physiology



Pepsinogen I and II:

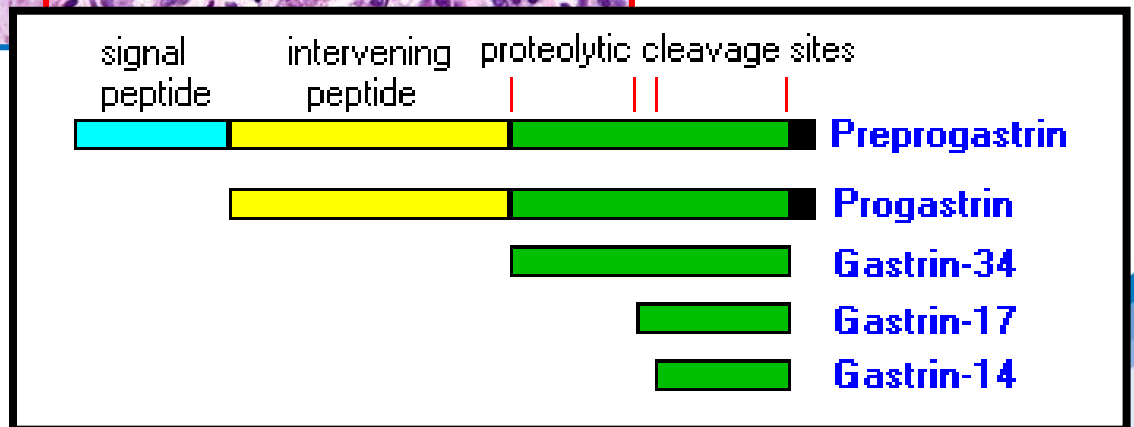
Chief cells (corpus)

GastroPanel® test – based on stomach physiology

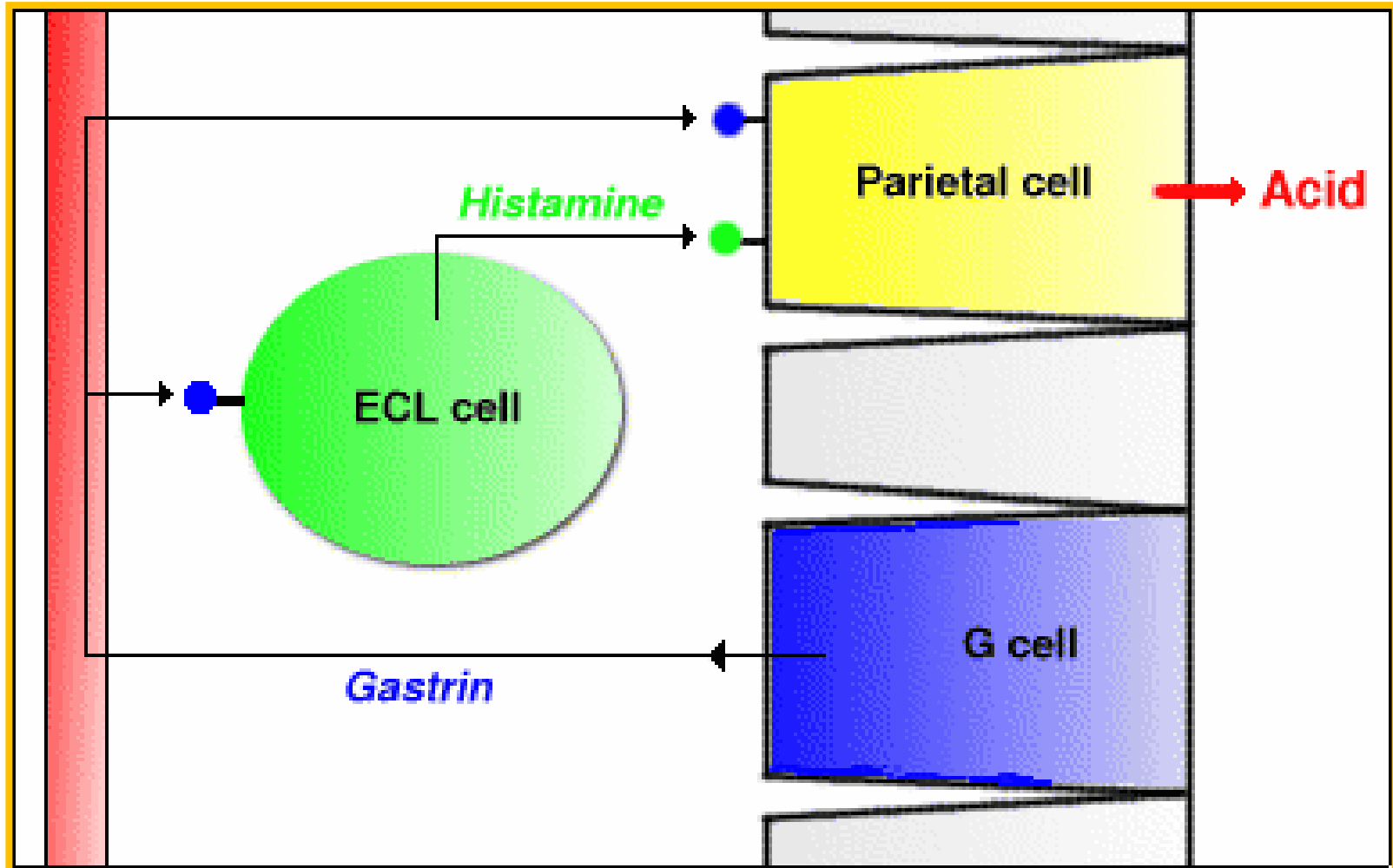


Gastrin-17:

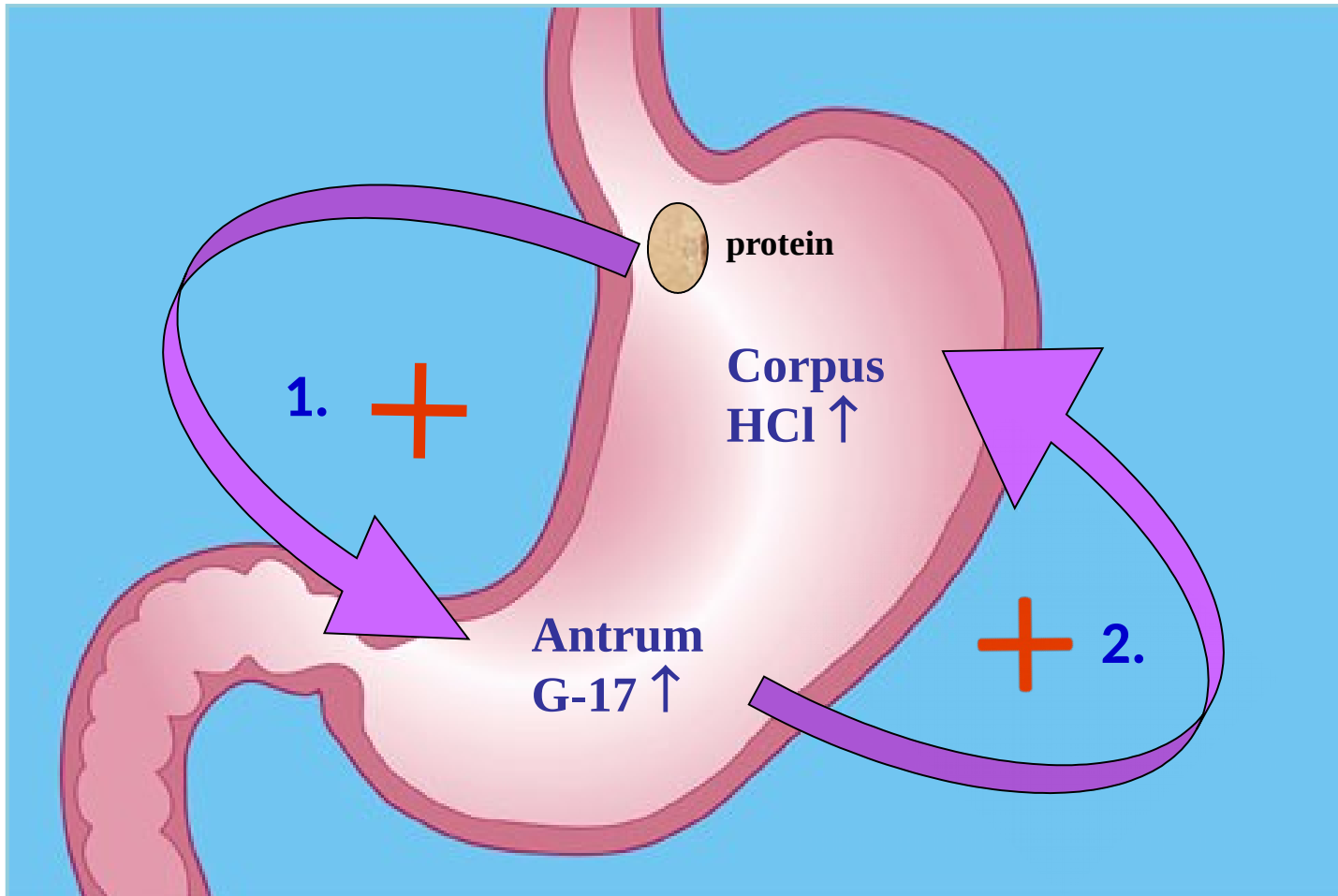
G-cells (antrum)



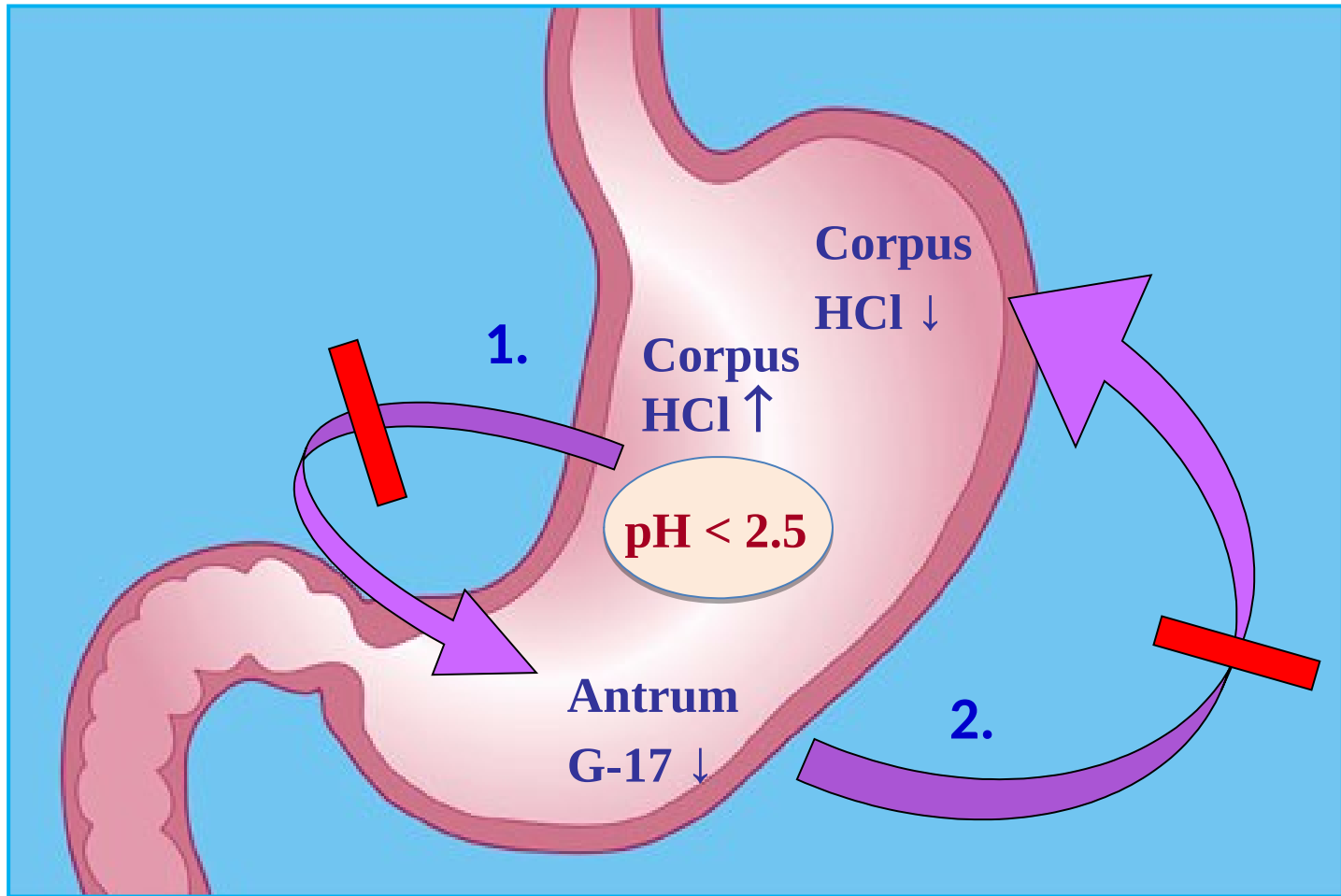
GastroPanel® test – based on stomach physiology



Positive feedback mechanism (1)



Negative feedback mechanism (2)



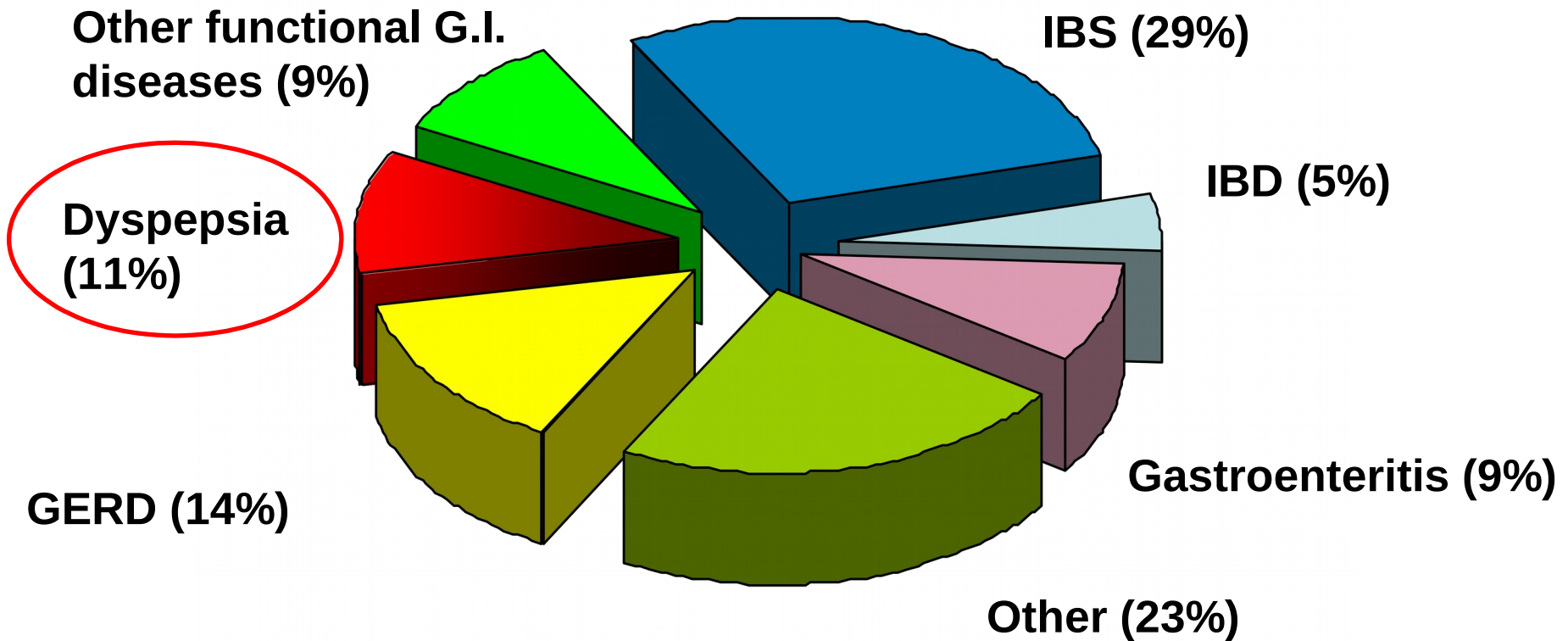
GastroPanel® test – two principal uses

- The First-Line Diagnostic Test for Patients with Dyspeptic Complaints
- For Screening of the Subjects at Increased Risk for Gastric Cancer



Prevalence of G.I. diseases in the primary care

9% of all visits in primary care are for G.I. symptoms




GastroPanel® - dyspepsia

- Dyspepsia is not a specific symptom; dg not possible by symptoms alone
- Affects some 20-40% of the population
- Most common findings:
 - Dyspepsia or GERD
 - Functional dyspepsia
 - Gastritis
 - Helicobacter pylori infection



THE DIAGNOSTIC DILEMMA



Hp
INFECTION
SYMPTOMS?

GERD
or
DYSPEPSIA?

FUNCTIONAL
DYSPEPSIA?



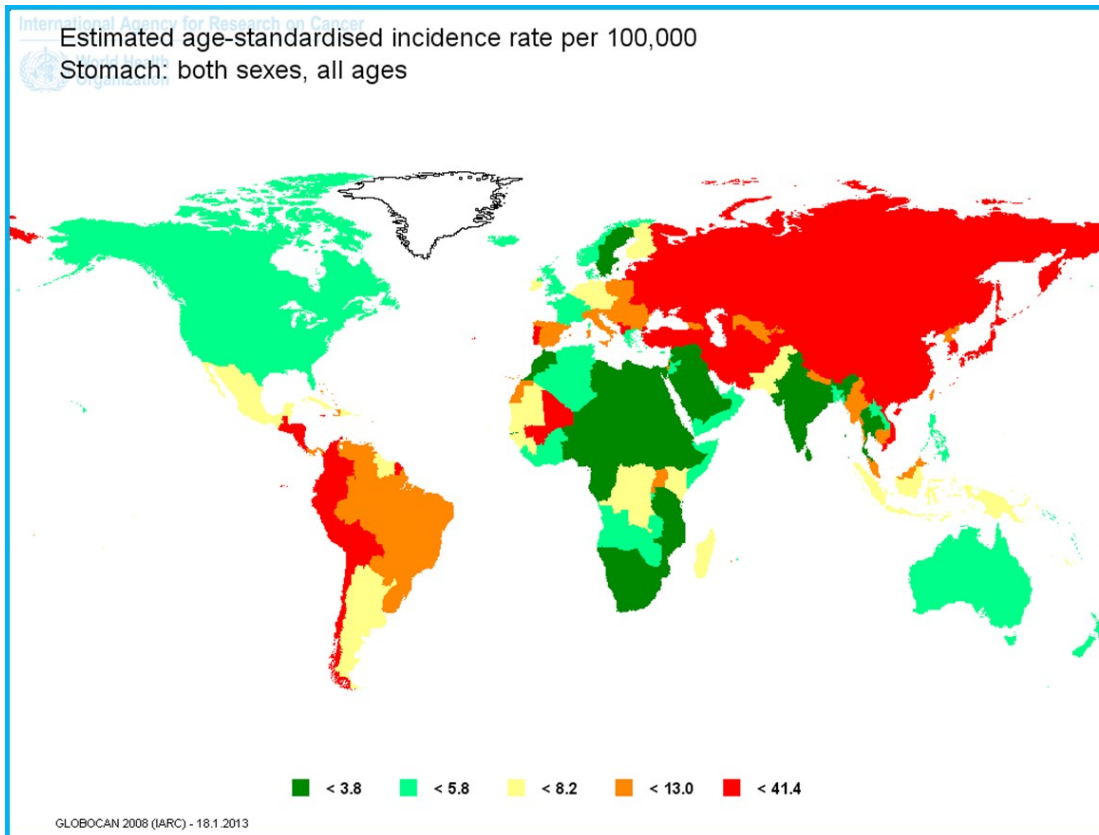
GastroPanel



GASTRITIS
SYMPTOMS?



GastroPanel® – risk factors of gastric cancer



Helicobacter pylori
infection:

OR=3.0–13.3

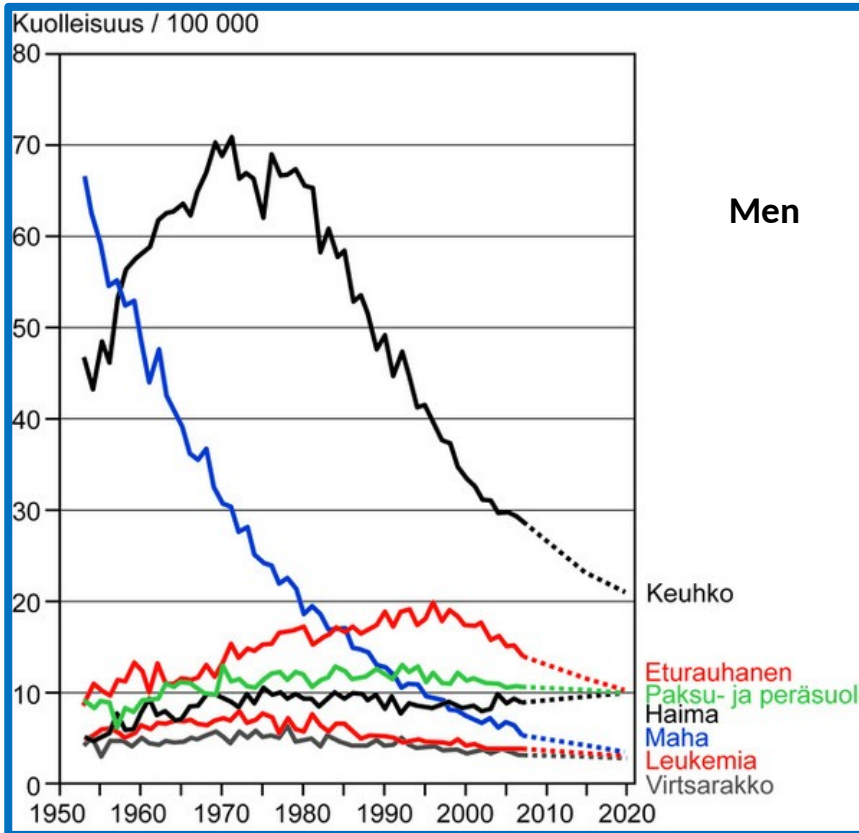
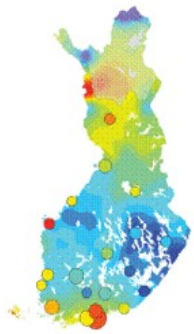
Atrophic gastritis:

OR= up to 90

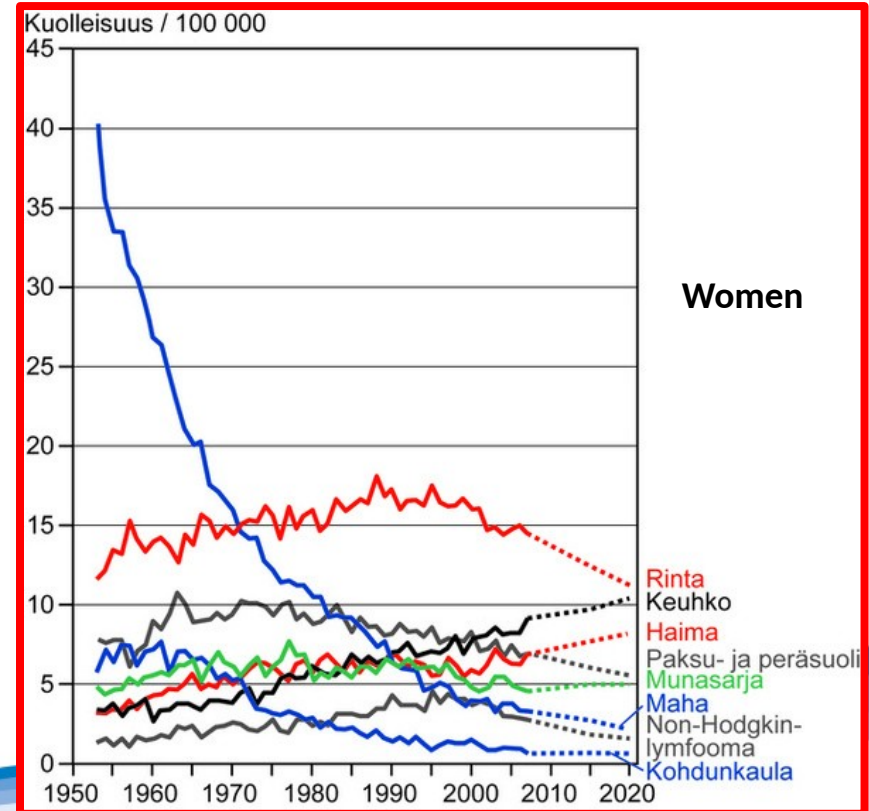


Ref: smoking and lung cancer: OR=12
HPV16 and cervical cancer: OR>400

Gastric cancer – trends in Finland



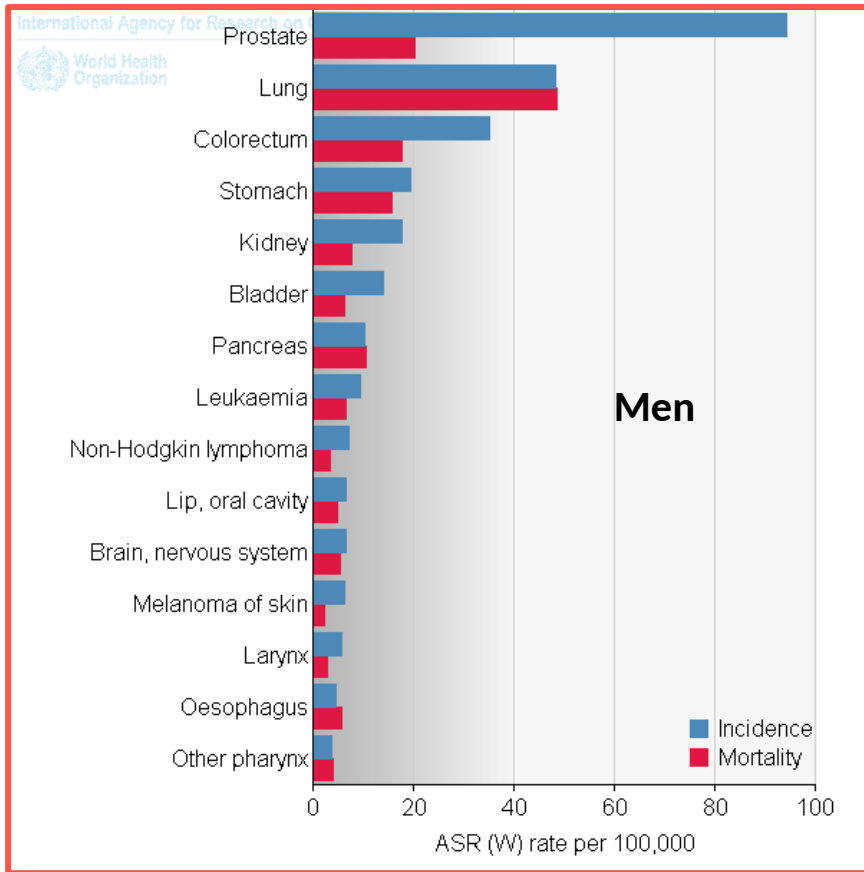
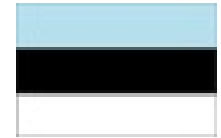
N=273; 2.1%; 3.9/100.000
N=209; 3.9% 2.8/100.000



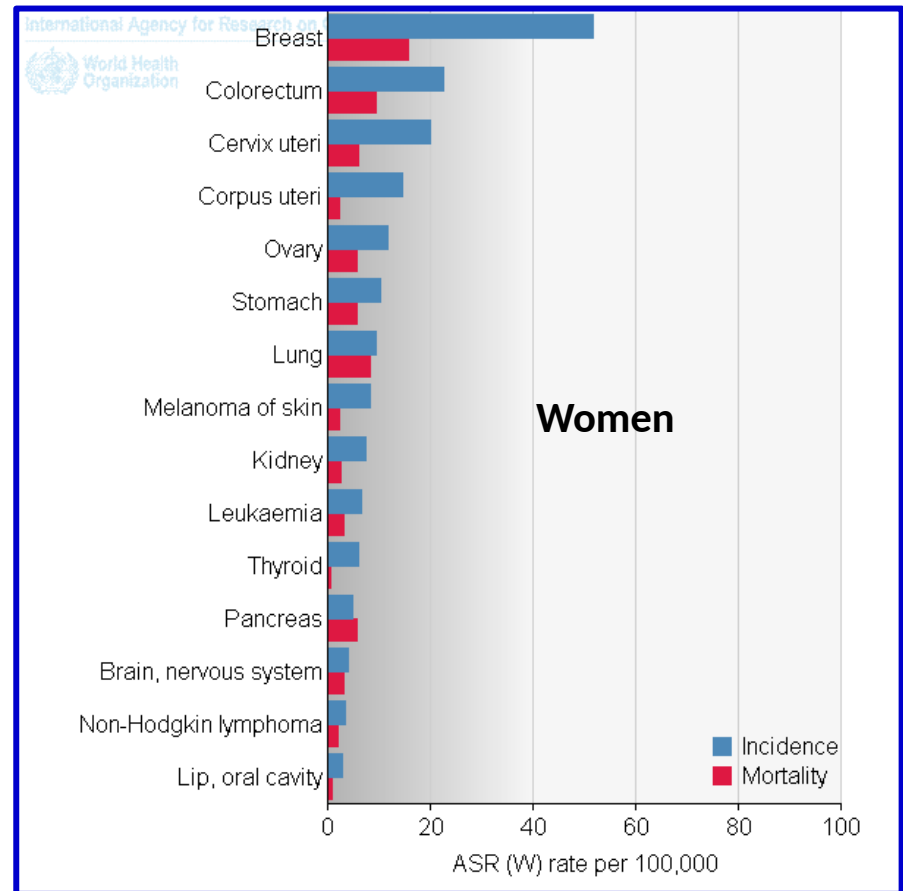
N=368; 2.4%; 6.7/100.000
N=270; 4.4%; 4.8/100.000



Gastric cancer – Estonian perspective



N=174; 6.0%; 10.3/100.000
N=121; 7.3%; 5.8/100.000



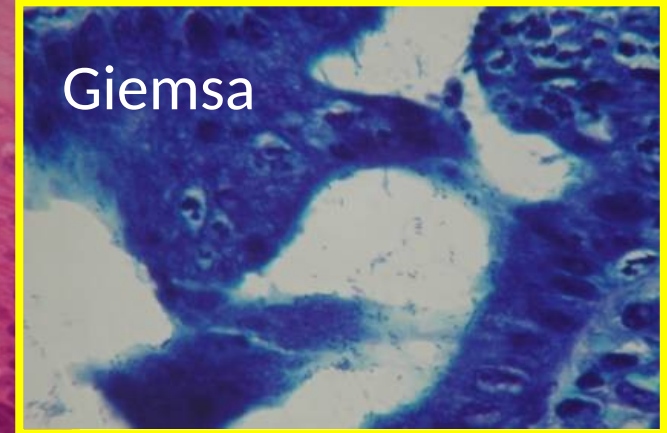
N=196; 6.1%; 19.5/100.000
N=165; 8.4%; 15.8/100.000



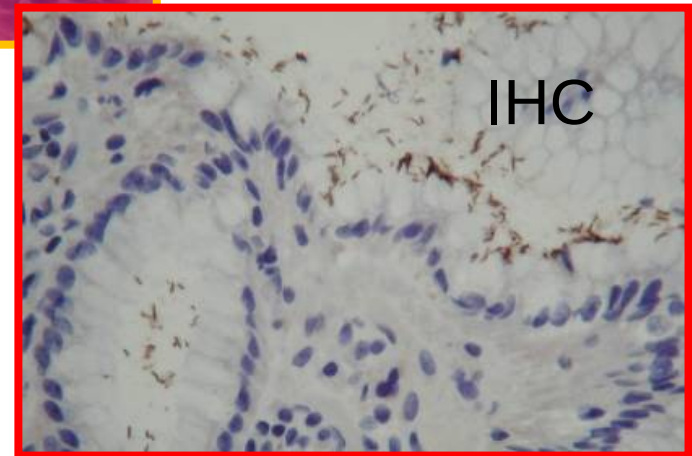
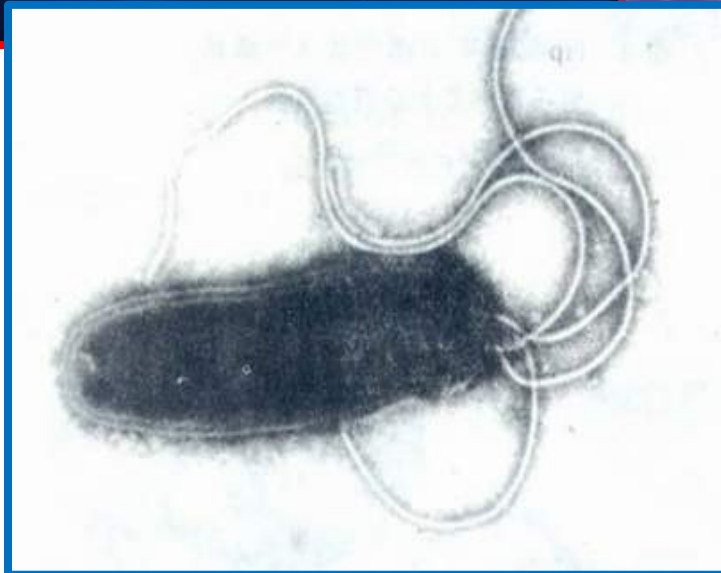
Gastric cancer – *Helicobacter pylori*



H&E



Giemsa



IHC



Helicobacter pylori to GC

H. pylori -infection

(Class I carcinogen)

↓
Acute gastritis

↓
Chronic gastritis

↓
Atrophic gastritis

Severe atrophic gastritis

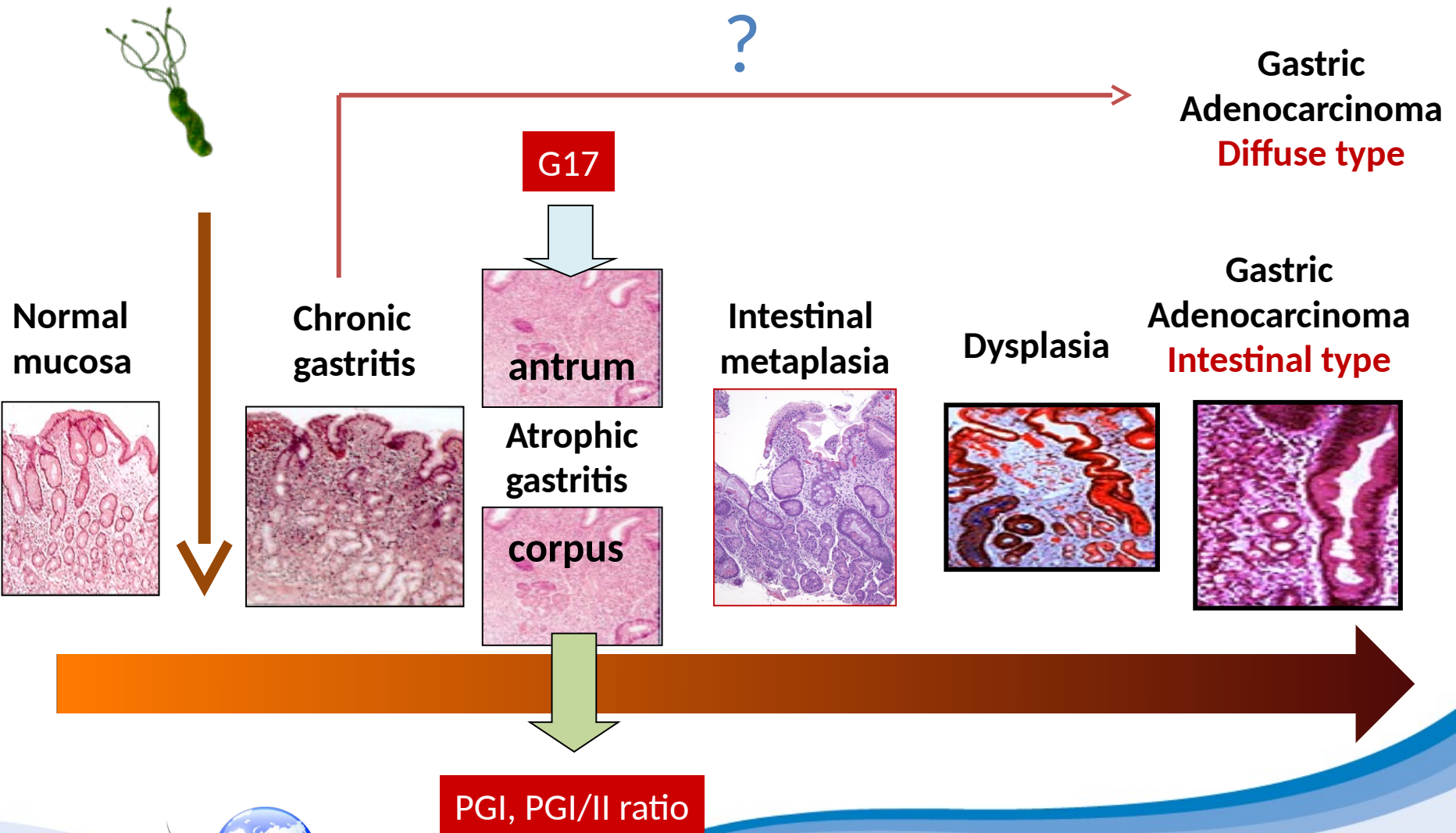
↓
Gastric cancer

↓
Peptic ulcer

→ MALT lymphoma



“Correa’s cascade”

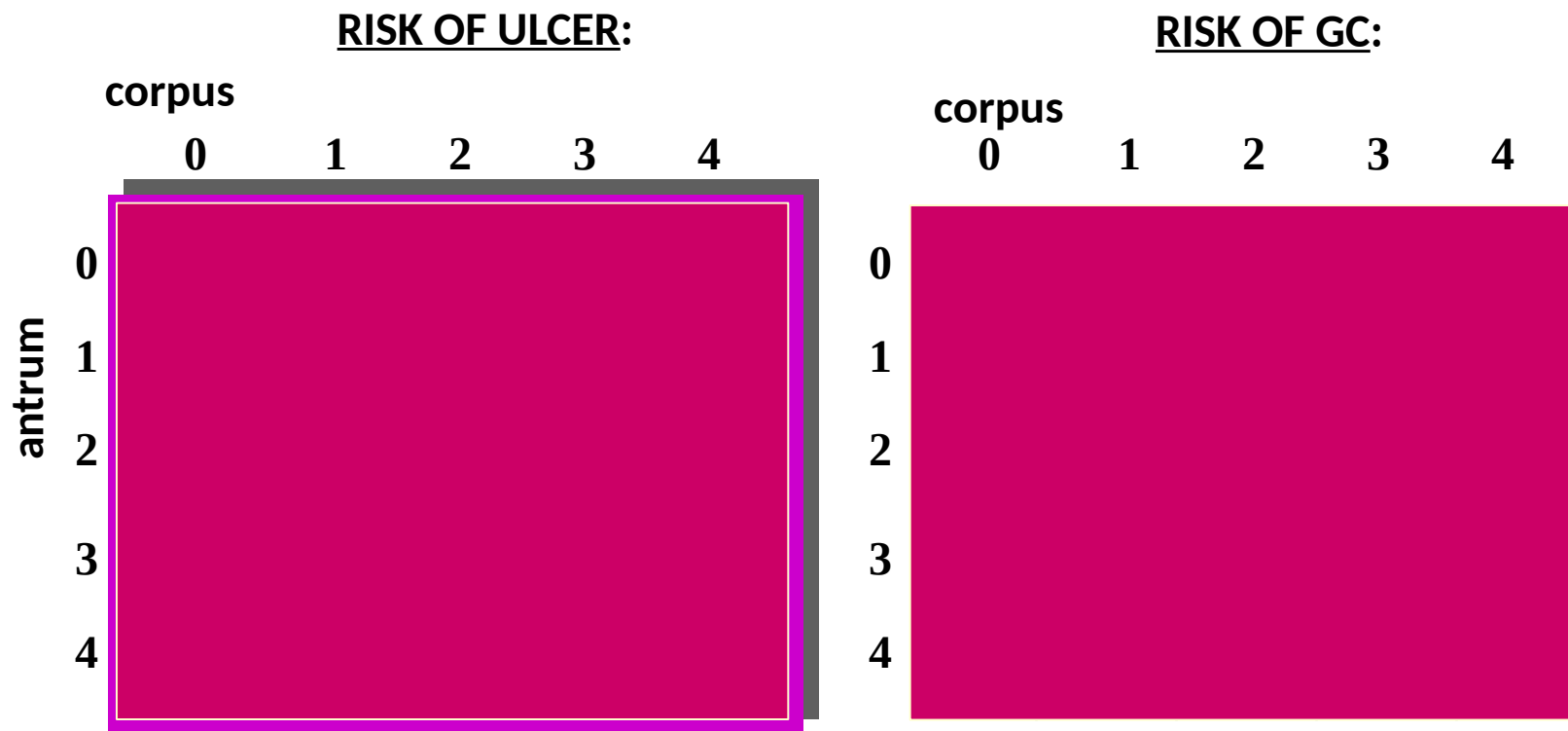


HP and AG - two diseases, one diagnostic test

GastroPanel: WHY? and HOW?



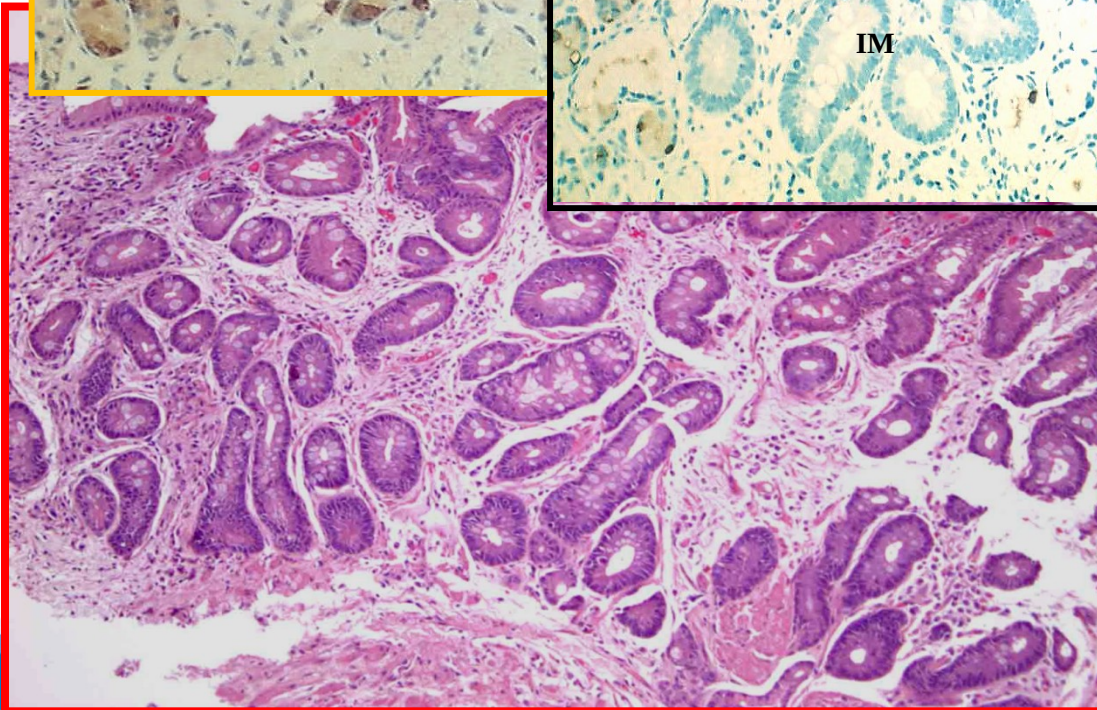
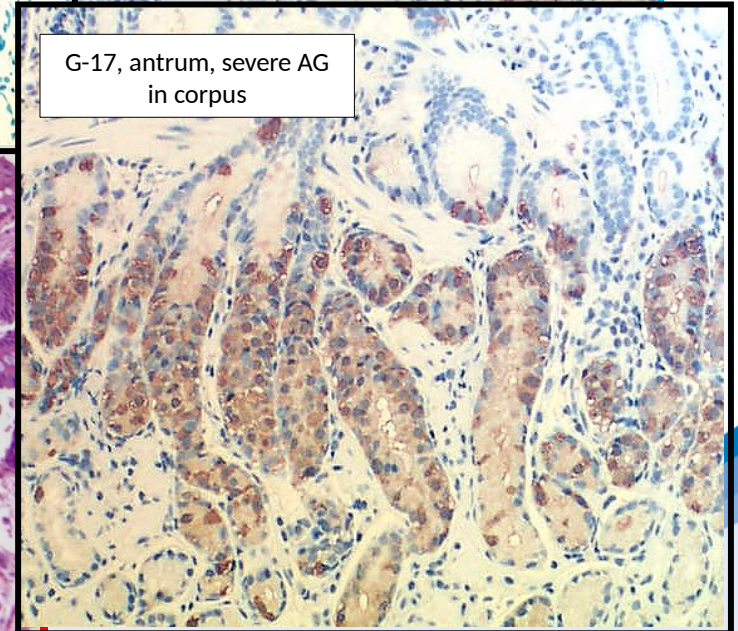
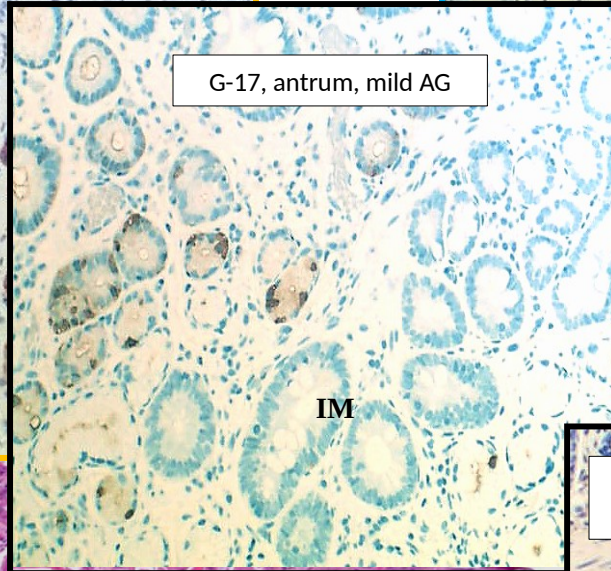
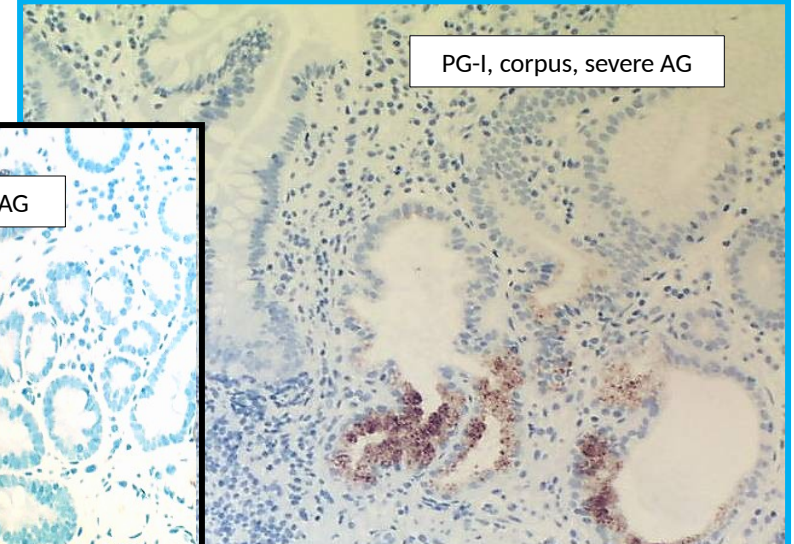
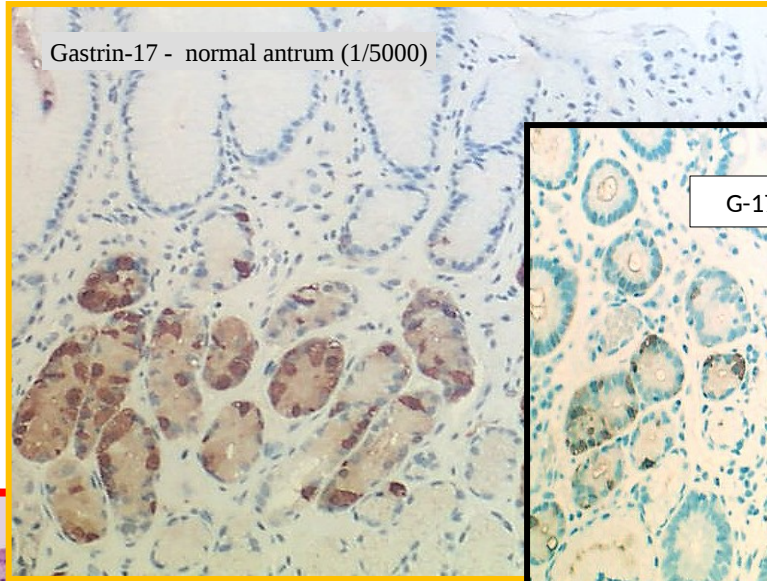
Phenotype of gastritis - risk for GC is different



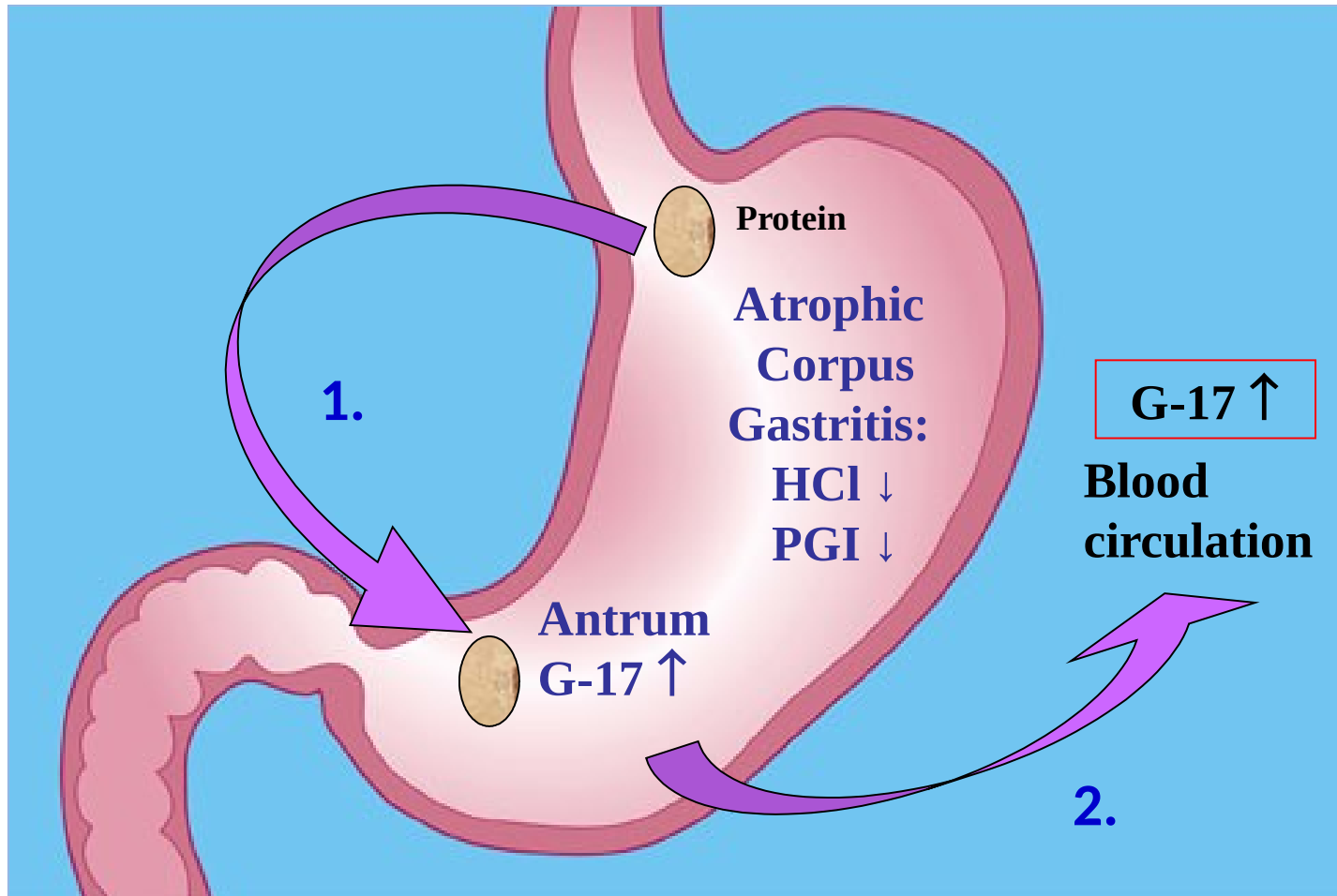
0=normal; 1=non-atrophic gastritis; 2=mild AG, 3=moderate AG; 4=severe AG



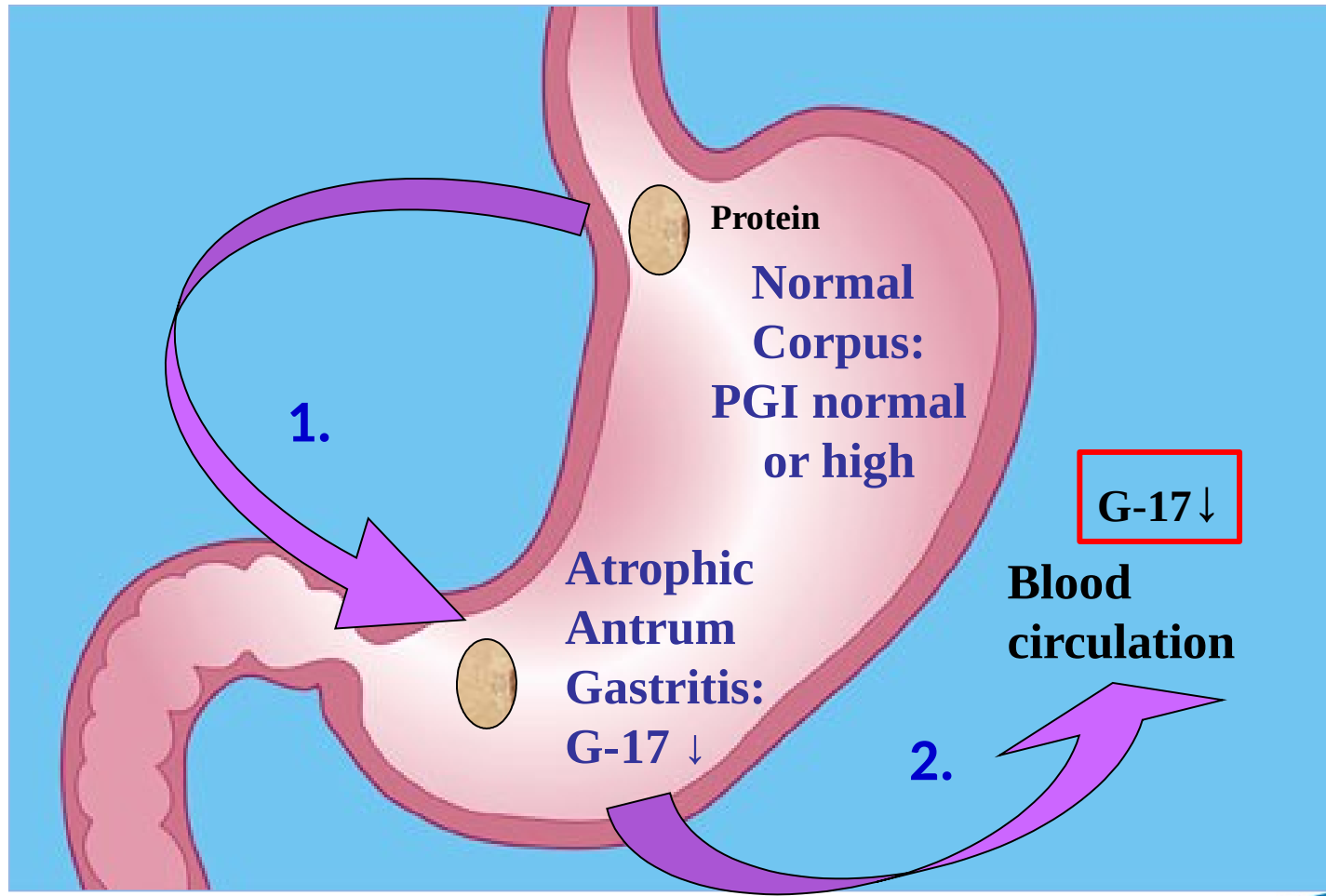
Phenotype of gastritis – defined by biomarker expression profiles



Atrophic gastritis (AG) in the corpus



Atrophic gastritis (AG) in the antrum



GastroPanel® – results reported by GastroSoft®

GastroPanel report

5.11.2012

Patient Data

Name	Carl Gastritis (#1)
Date of birth	121256-1213
Age	53
Eradicated	No
Use of PPI	Continuously
Acidic symptoms	No
Use of NSAIDs	No

Assay Data

Collected	12.2.2010
Analyzed	12.2.2010
Pepsinogen I (PGI)	112,0 µg/l
Pepsinogen II (PGII)	8,0 µg/l
PGI/PGII	14,0
Gastrin 17B	1,1 pmol/l
<i>H. pylori</i> antibodies (HPAB)	6,0 EIU

reference range:

30 - 160 µg/l
3 - 15 µg/l
3 - 20
< 7 pmol/l
< 30 EIU

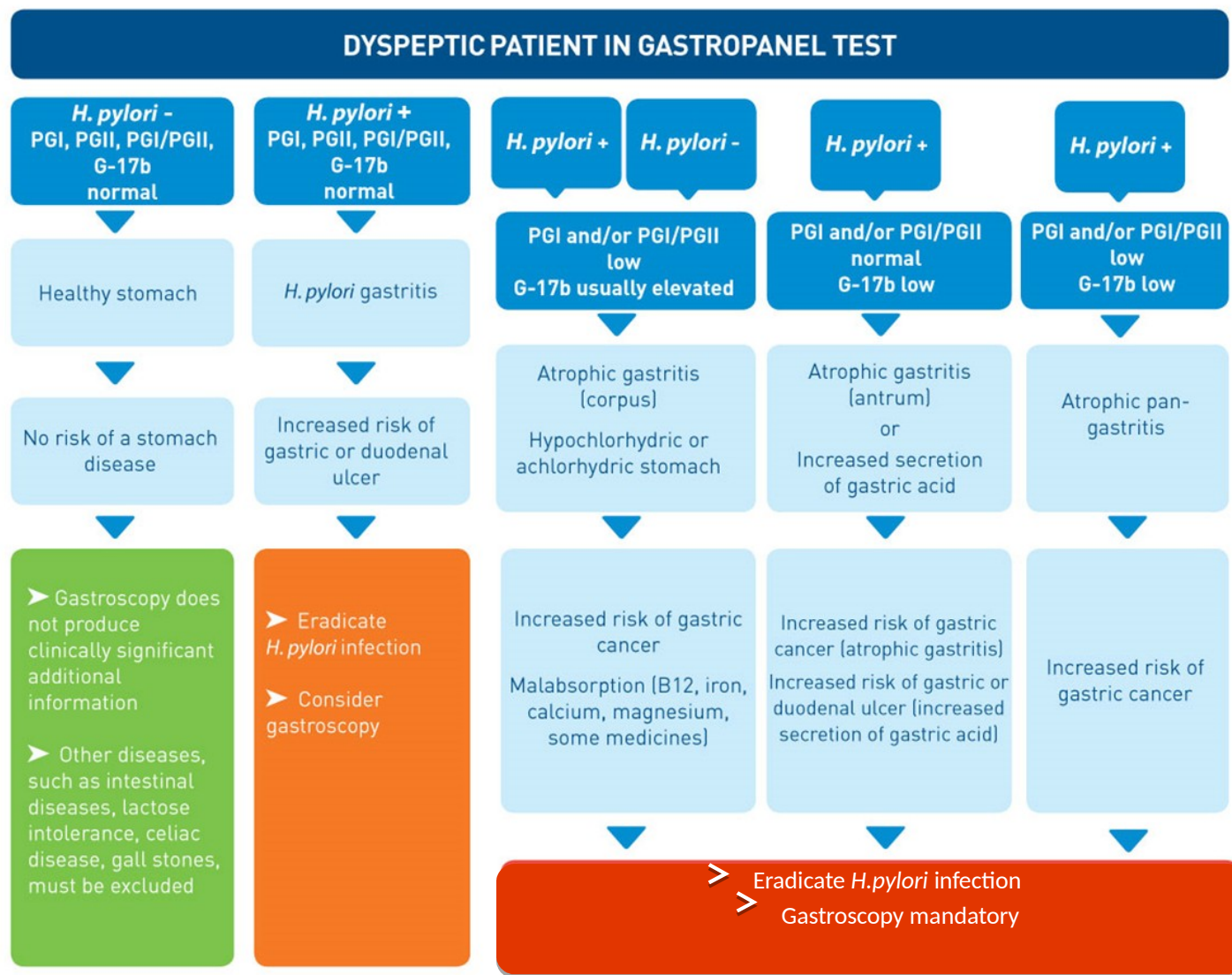
Interpretation

The results indicate that there is neither *Helicobacter pylori* infection, nor atrophic gastritis (loss of gastric glandular cells).

Acid secretion in the stomach is normal.



GastroPanel® - the diagnostic algorithm



GastroPanel® – three categories of risk

“Healthy”, normal stomach mucosa:

No

risk of gastric cancer or ulcer

Non-atrophic *H.pylori* (Hp+) gastritis:

High ulcer risk, low cancer risk.

Atrophic gastritis (Hp+ or Hp-):

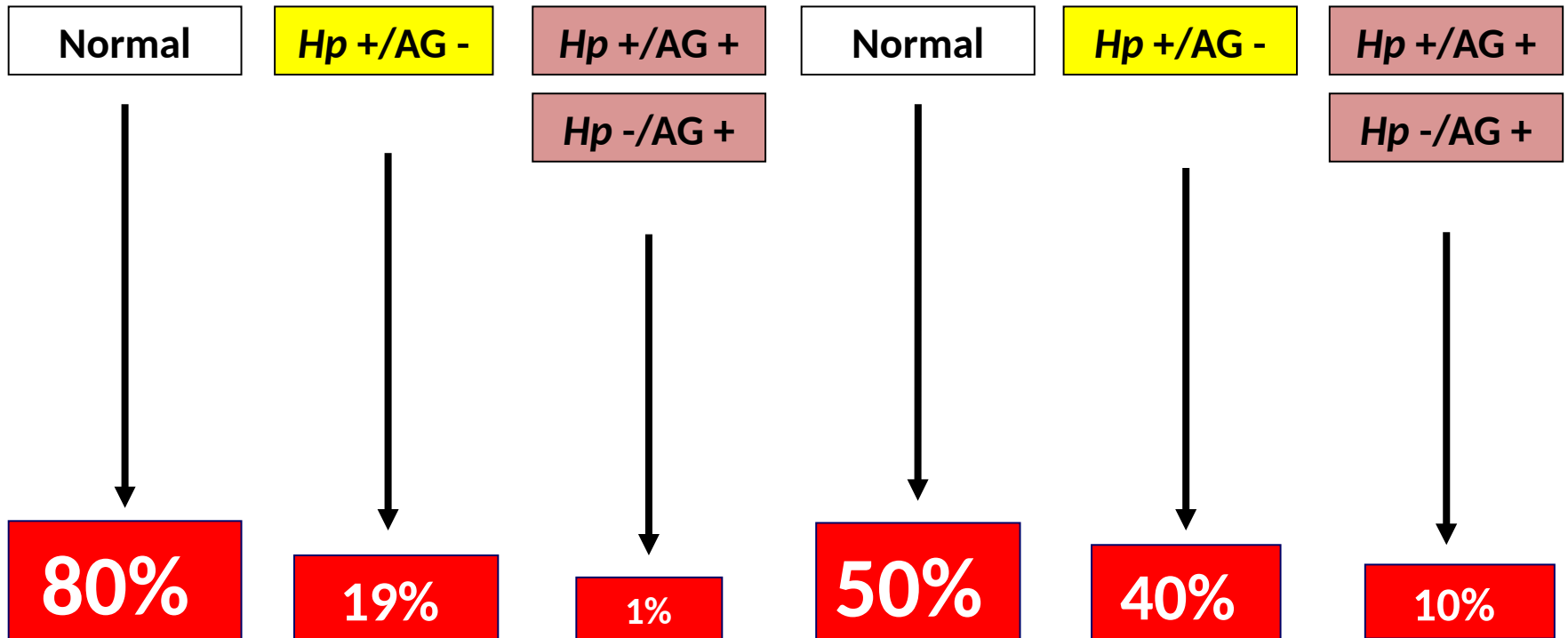
High cancer risk, low ulcer risk. High risk of mal-absorption of vitamin B12, calcium, iron, magnesium and zinc. Stomach is acid-free and colonized with bacteria and fungi. Carcinogenic acetaldehyde appears in stomach.



GastroPanel® - subject allocation to triage (population)

Patients under 45 years of age

Patients above 45 years of age



Hp=Helicobacter pylori; AG=atrophic gastritis

How common is atrophic gastritis?

Population – based study on 1,000 adult (20-80 years) subjects in Northern Sweden (Kalixanda*). Prevalence of advanced (**moderate or severe**) atrophic corpus gastritis.

GastroPanel® biomarker test

Age group; yrs	Prevalence; %
20 - 49	1.3
50 - 59	4.1
60 - 69	11.4
70 - 80	17.8

*Storskrubb et al Scand J Gastroenterol 2008.



GastroPanel® – three approaches of management

“Healthy”, normal stomach mucosa:

No need for prompt gastroscopy.

Non-atrophic *H.pylori* (Hp+) gastritis:

Patient and physician may decide of further treatment and examinations. Consider eradication of *H.pylori*!

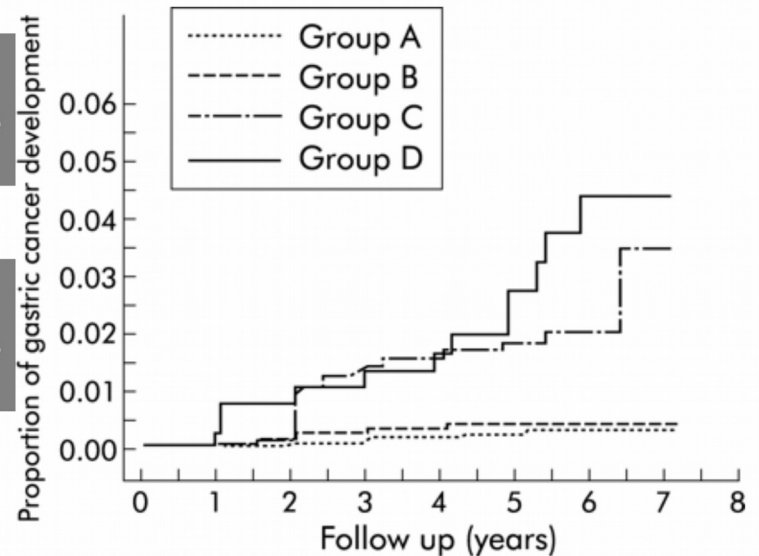
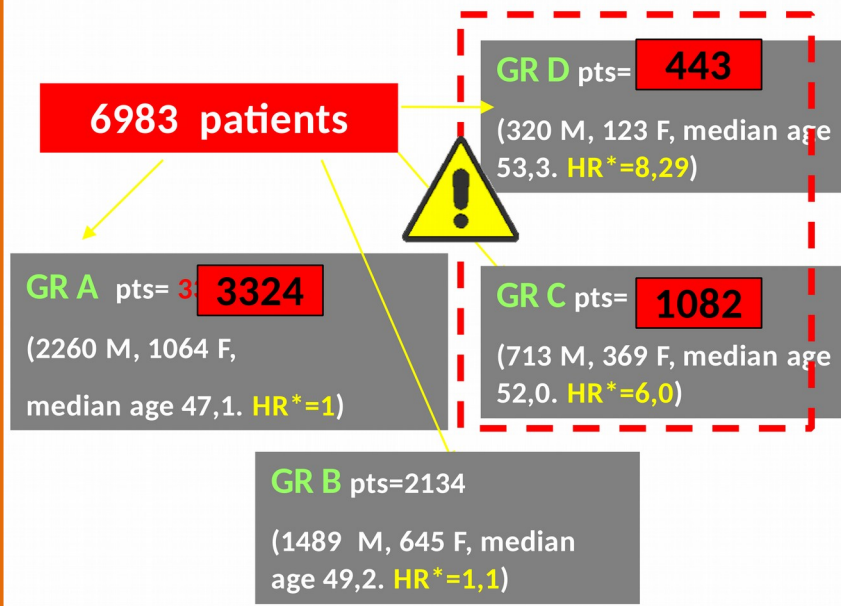
Atrophic gastritis (Hp+ or Hp-):

Gastroscopy is mandatory. Eradication of *H.pylori* is necessary if bacteria present.



PGI, PGI/II Ratio, HpAb (IgG) and Gastric Cancer

Development of Gastric Cancer as related to PGI levels and HP infection



No. at risk

Group A	3324	3217	2997	2743	2448	1950	950
Group B	2134	2071	1904	1726	1537	1229	579
Group C	1084	1050	950	866	761	610	298
Group D	443	420	384	345	305	237	105

	A	B	C	D
Pepsinogen index	N	N	↓	↓
IgG anti-Hp	-	+	+	-

↓ = sPGI < 70 ng/ml and PGI/PGII ratio < 3,0 ng/ml
 N = all other cases

(HR* = Hazard Ratio)

Follow-up 4,7 years

Watabe et al. Gut 2005; 54: 764-68



GastroPanel® – AUC for PGI (AGC_{ms} cut-off)

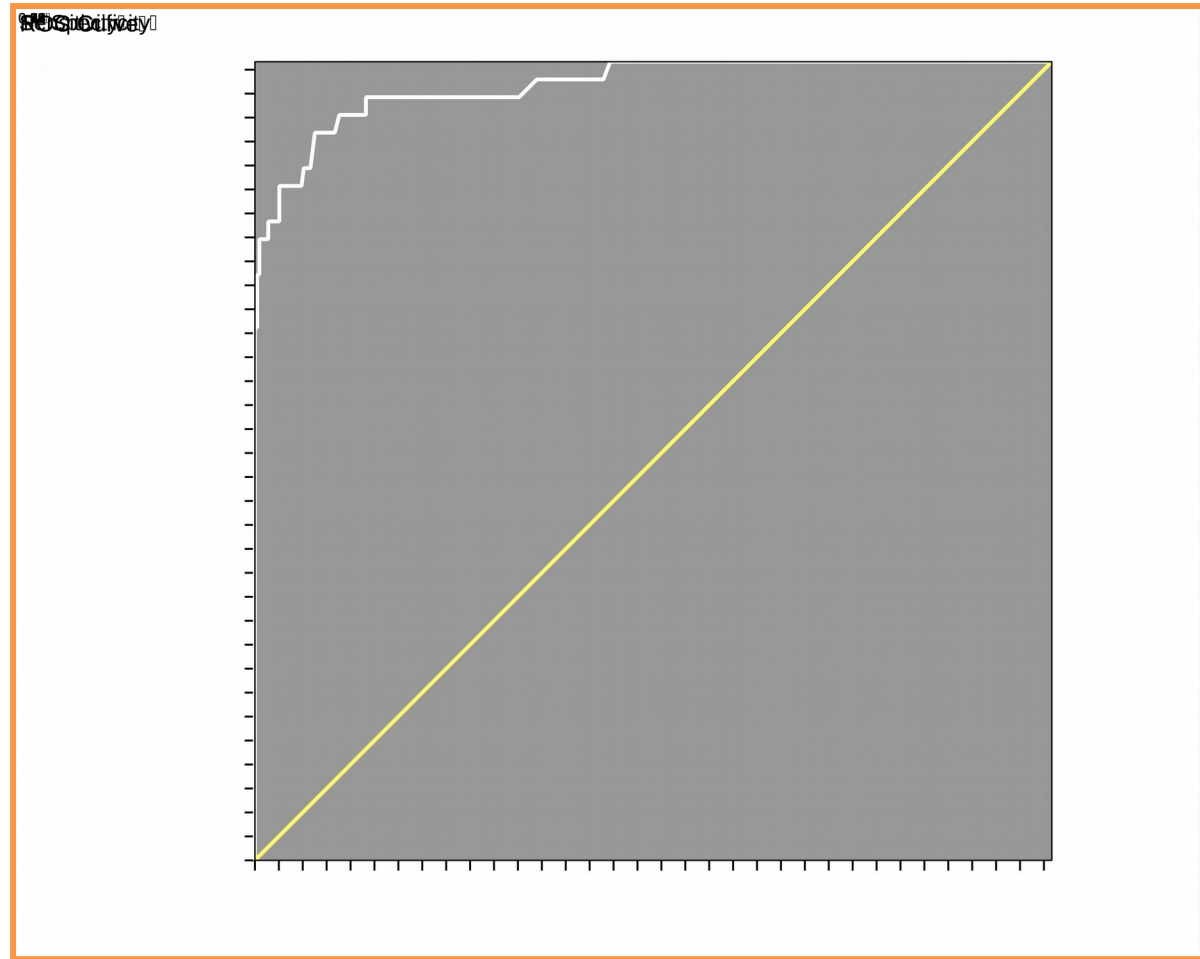
AUC: 0.970; 95%CI 0.945-0.996

SE: 80.0% (65.4% 90.4%)

SP: 98.1% (96.0% 99.2%)

PPV: 83.7% (69.3% 93.2%)

NPV: 97.5% (95.3% 98.9%)



GastroPanel® – AUC for PGI/PGII ratio (AGC_{ms} cut-off)

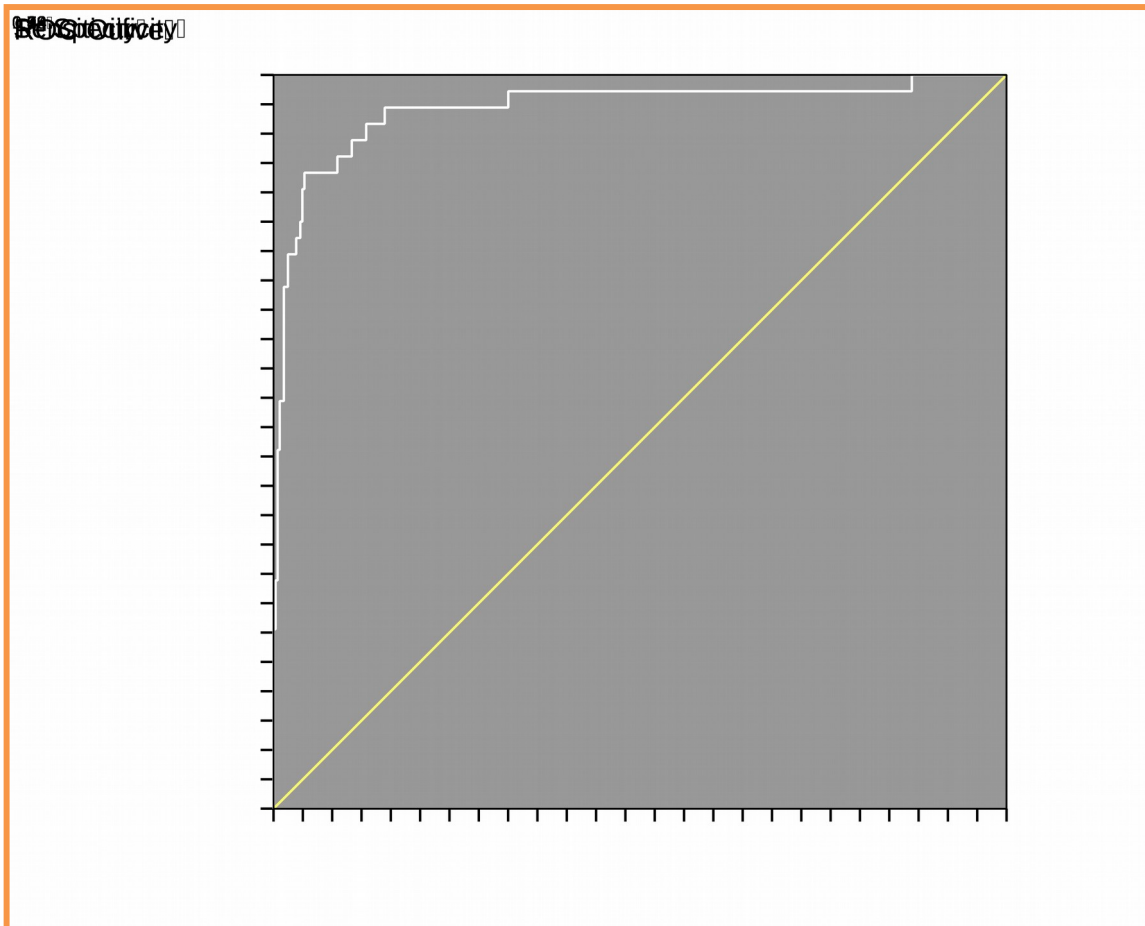
AUC: 0.954; 95%CI 0.913-0.995

SE: 75.6% (60.5% 87.1%)

SP: 98.0% (96.0% 99.2%)

PPV: 82.9% (67.9% 92.8%)

NPV: 96.9% (94.6% 98.5%)



**Rational use of GastroPanel® testing
will induce substantial savings in
health care costs**



GastroPanel® – opportunity for substantial cost savings



Gastroscopy
vs.
GastroPanel



Diagnostic Test

Cost/test (€) Total Cost (€)

(a) Gastroscopy + histology (n=1000):	400	400 000
(b) GastroPanel® test for all:	90	90 000
(c) Gastroscopy for 400 GP+ subjects*	400	160 000

Cost savings: a-(b+c):

* 1000 subjects, with GastroPanel+ rate 40%
(includes Hp+ and AG+ cases)

GastroPanel[®] : modelling the cost savings

BIOHIT HealthCare

Innovating for Health

Nordic Health Care Group

Fredrik Herse; Riikka-Leena Leskelä;
Pyry Niemelä



Two GastroPanel Models: different purpose of use

- Two models were designed to analyze the potential savings in health care costs to be achieved by applying GastroPanel test in screening of asymptomatic people or dyspeptic patients:

1) A hybrid cost-efficiency/budget impact model for GastroPanel screening (**GastroPanel Screening Model**)

2) A budget impact model (**Municipality Model**)

■ The GastroPanel screening model:

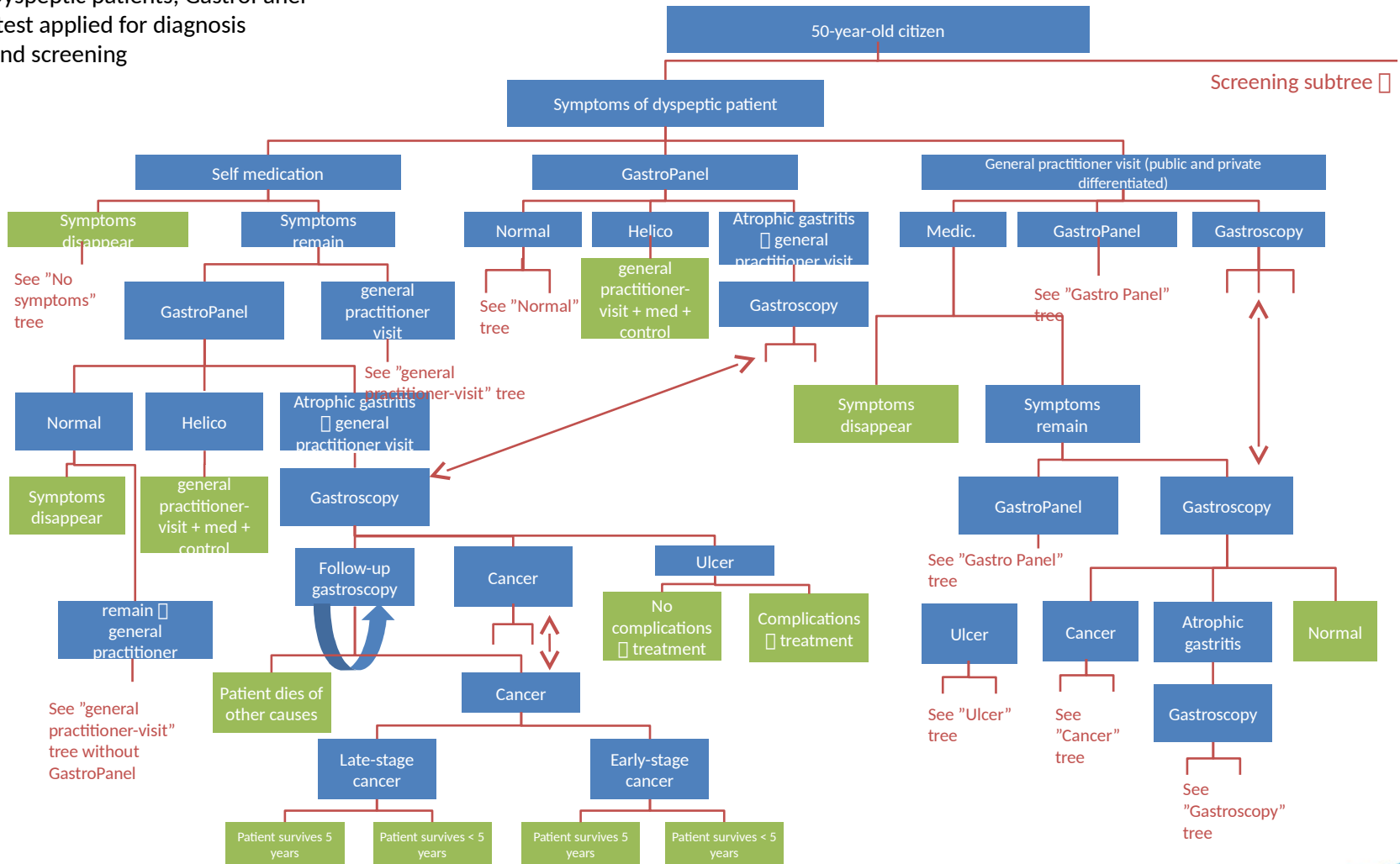
- considers the use of GastroPanel both in the diagnosis of dyspeptic patients and in screening of asymptomatic people in a specified age group.
- all inputs in the model (costs and probabilities) depend on the country in question and on age of the target patients.
- inputs can be tailored according to different countries and different age groups.

■ The budget impact model:

- (the municipality model), analyzes the short-term cost impact of adopting GastroPanel as a diagnostic tool but not implemented in a screening setting
- The budget impact model is also based on a decision tree, with all of its parameters adjustable according to individual needs

Decision tree - an example

Dyspeptic patients, GastroPanel
-test applied for diagnosis
and screening



Direct and Indirect Costs – Definitions

Direct Costs

- All costs that incur in the care process and which somebody has to pay
- Direct medical costs:
 - Cost of healthcare service: visit to a doctor or nurse, hospitalization, procedure, rehabilitation
 - Cost of diagnostics
 - Cost of medication
 - Cost of technology and devices (e.g. self-testing devices)
- Direct non-medical costs:
 - Cost of transportation to hospital or health center
 - Personal aide / care giving
 - House modifications

Direct and Indirect Costs – Definitions

Indirect Costs

- Costs that are not directly related to the care event itself
- Are born by someone in the society, for example
 - Cost of lost labor input due to sick leave
 - Cost of lost labor input due to premature death
 - Cost from reduced ability to work (usually hard to quantify)

Basic Scenario vs. GastroPanel Scenario in Population-Based Screening

Population	5,426,674		
Age group	67,833		
Number of age groups screened	1		
Findings(number of patients in age groups)	Baseline	GastroPanel	
Helico diagnoses/eradications	3,353	31,140	
Atrophic gastritis diagnoses	176	1,588	
Ulcer without complications	6,136	795	
Ulcer with complications	323	237	
Late stage cancer diagnoses during lifetime	601	151	
Early stage cancer diagnoses during lifetime	63	148	
Number of GastroPanels in screening purpose	0	53,724	
Direct costs	Baseline	GastroPanel	Savings
Expected lifetime values - costs per capita	1,153 €	660 €	494 €
Age group lifetime costs for Gastroscopy vs GastroPanel	78,231,035 €	44,750,245 €	33,480,790 €
Total direct savings	33,480,790 €		
Indirect costs	Baseline	GastroPanel	Savings
Expected lifetime values - costs per capita	810 €	447 €	363 €
Age-group lifetime costs for Gastroscopy vs GastroPanel	54,943,374 €	30,311,314 €	24,632,060 €
Total indirect savings	24,632,060 €		
TOTAL SAVINGS:	58,112,850 €		



GastroPanel® - recommended by international experts

DYSPEPTIC PATIENT IN GASTROPANEL TEST



Agréus, Kuipers, Kupcinskas, Malfertheiner, DiMario, Leja, Mahachai, Mahachai, Niv, van Oijen, Perez-Perez, Rugge, Ronkainen, Salaspuro, Sipponen, Sugano, Sung. Rationale in diagnosis and screening of atrophic gastritis with stomach-specific plasma biomarkers.

Scand J

Gastroenterol 2012;47:136-147.

- Eradicate *H. pylori* infection
- Gastroscopy necessary





Thank you very much
for your attention!