FIRST FACULTY OF MEDICINE
CHARLES UNIVERSITY IN PRAGUE

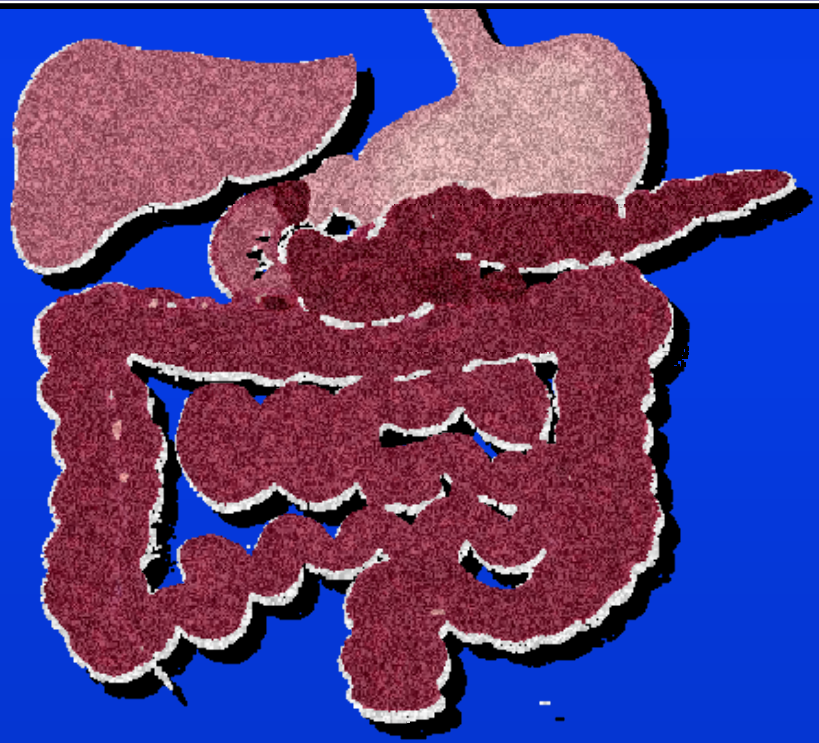
The role and importance of screening tests in gastrointestinal diseases

Kocna P., Vaníčková Z., Zima T.

12th EFCC Continuous Postgraduate Course in Clinical chemistry

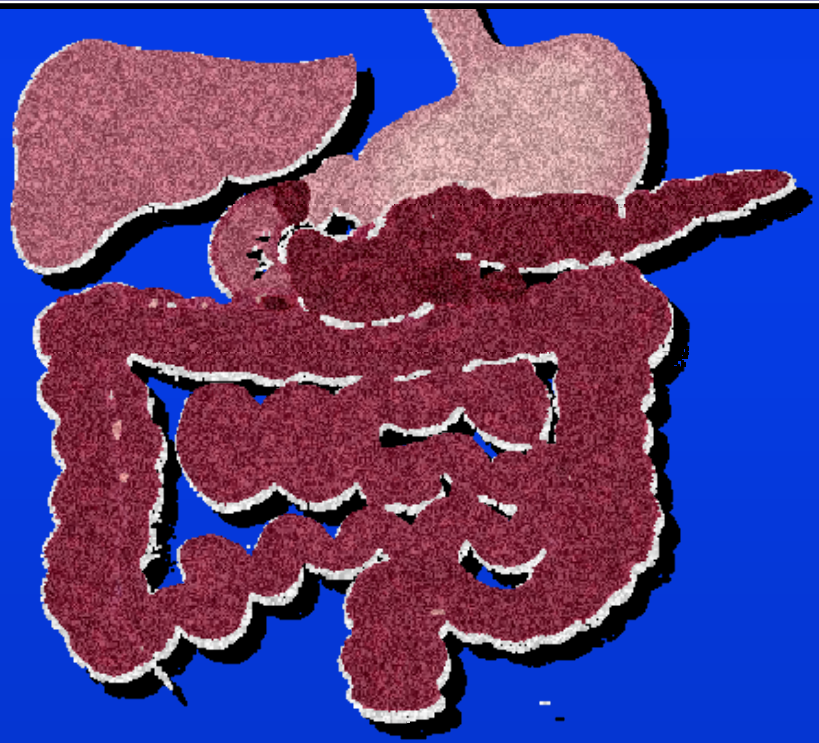
Dubrovnik, November 10, 2012

DISEASE SCREENING
COLORECTAL CANCER
COELIAC DISEASE
ATROPHIC GASTRITIS
INFLAMATORY BOWEL DISEASE



DISEASE SCREENING

COLORECTAL CANCER
COELIAC DISEASE
ATROPHIC GASTRITIS
INFLAMATORY BOWEL DISEASE



WHO defined criteria for disease screening

Criteria for disease screening

1. the condition screened for should be an important one
2. there should be an acceptable treatment for patients with the disease
3. the facilities for diagnosis and treatment should be available
4. there should be a recognised latent or early symptomatic stage
5. there should be a **suitable test or examination which has few false positives (specificity) and few false negatives (sensitivity)**
6. the test or examination **should be acceptable to the population**
7. the test should be **cheap/cost effective**

Screening - Wilson & Jungen (WHO, 1968)

Recommended laboratory methods for screening in gastroenterology

Gastrointestinal disease	Recommended screening test
Worldwide used screening	
Colorectal cancer	quantitative immunochemical Hb in stool
Coeliac disease	IgA atTG and IgG DGP plasma antibodies
Evaluated new screening	
Chronic atrophic gastritis Helicobacter pylori infection	plasma pepsinogen I/II ratio Helicobacter pylori antigen in stool
Inflammatory bowel disease	calprotectin in stool

Numbers of PubMed - Medline articles published in last 5 years with respect of reviews and screening

Year	Papers (all)	Review	Screening	Screening review
Colorectal cancer				
2011	9223	1308	5575	791
2010	9169	1368	6036	847
2009	8202	1222	5333	738
2008	7819	1209	5089	754
2007	7434	1323	4751	809

Numbers of PubMed - Medline articles published in last 5 years with respect of reviews and screening

Year	Papers (all)	Review	Screening	Screening review
Coeliac disease				
2011	862	150	509	95
2010	781	140	515	96
2009	802	154	512	94
2008	769	168	489	110
2007	701	130	473	90

Numbers of PubMed - Medline articles published in last 5 years with respect of reviews and screening

Year	Papers (all)	Review	Screening	Screening review
Atrophic gastritis				
2011	156	31	95	15
2010	159	20	107	6
2009	143	23	99	14
2008	151	23	111	16
2007	155	36	125	31

Numbers of PubMed - Medline articles published in last 5 years with respect of reviews and screening

Year	Papers (all)	Review	Screening	Screening review
Inflammatory bowel disease				
2011	2032	572	942	237
2010	1794	458	842	168
2009	1565	484	720	183
2008	1449	421	666	165
2007	1349	401	632	157

total number of papers - 54715

Reviews on screening of these 4 GE diseases with high risk of tumour development published in last 5 years

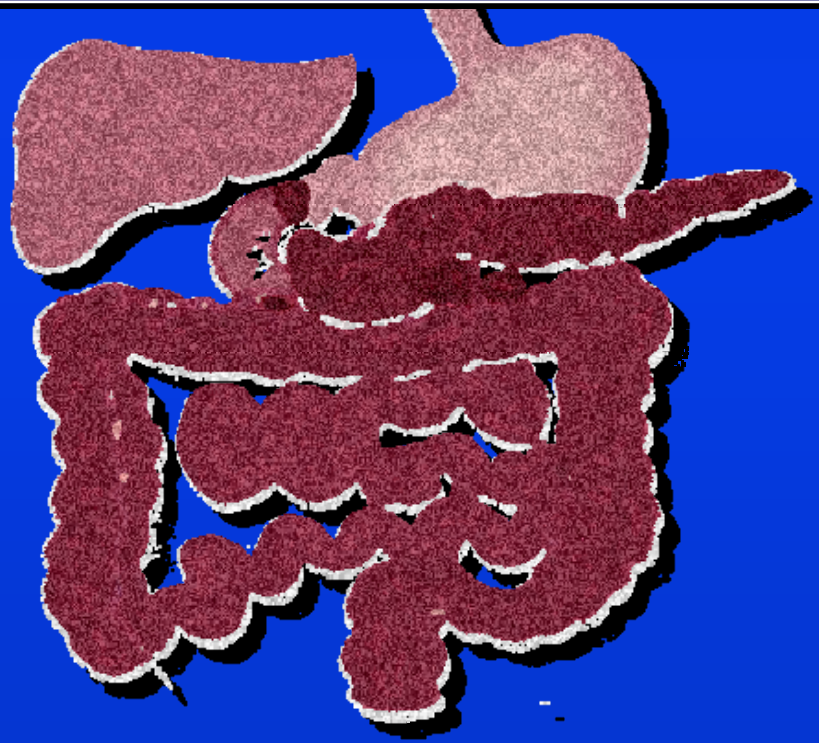
["Colorectal cancer" OR "Coeliac disease" OR "Atrophic gastritis" OR "Inflammatory bowel disease"] AND "Screening" AND "Review" AND "Published 2007 - 2011"

PubMed only 6000 journals

Google scholar all on the web 10 times more

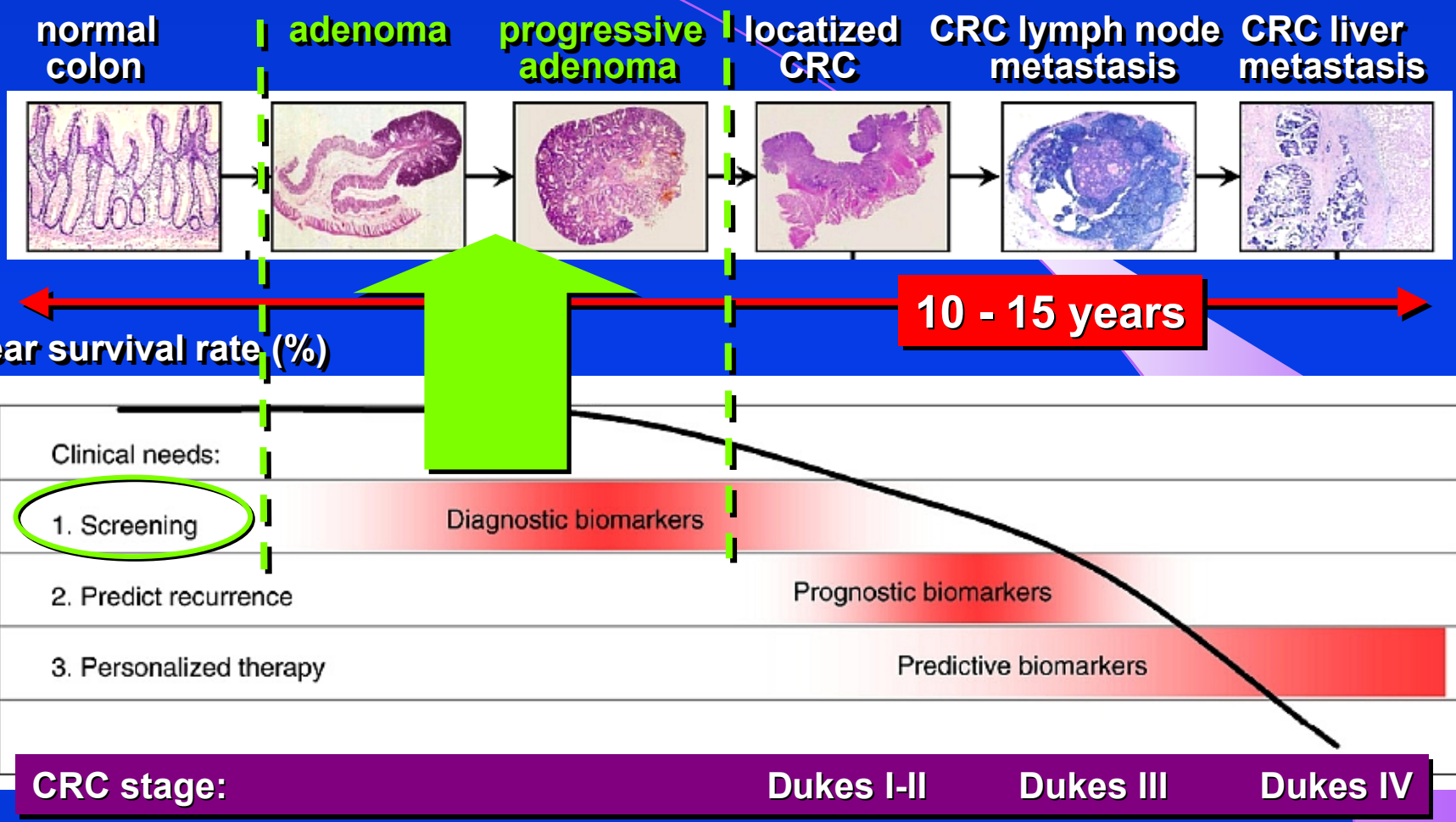
	NLM - PubMed	Google Scholar
Colorectal cancer	3939	42110
Coeliac disease	485	6850
Atrophic gastritis	82	1853
Inflammatory bowel disease	910	16680
	5416	**67493**

DISEASE SCREENING
COLORECTAL CANCER
COELIAC DISEASE
ATROPHIC GASTRITIS
INFLAMATORY BOWEL DISEASE



COLORECTAL CANCER - KEY MESSAGES

- ✓ Colorectal cancer often has no symptoms at early (and treatable) stages.
- ✓ The biggest risk factor for colorectal cancer is being age 50 or older.
- ✓ Colorectal cancer is the second most frequent malignant disease in Europe and US
- ✓ If everyone age 50 or older received regular screenings, almost two-thirds (60%) of colorectal cancer deaths could be prevented.
- ✓ There are different options recommended for colorectal cancer screening: choose one, and get it done.



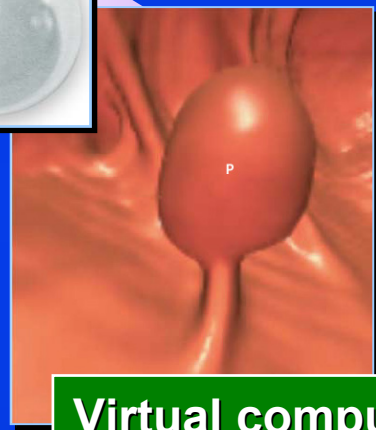
Proteomics of colorectal cancer: overview of discovery studies and identification of commonly identified cancer-associated proteins and candidate CRC serum markers. Jimenez CR, Knol JC, Meijer GA, Fijneman RJ. - J Proteomics. 2010;73:1873-1895

CRC SCREENING METHODS

FOBT/FIT tests

Capsule endoscopy

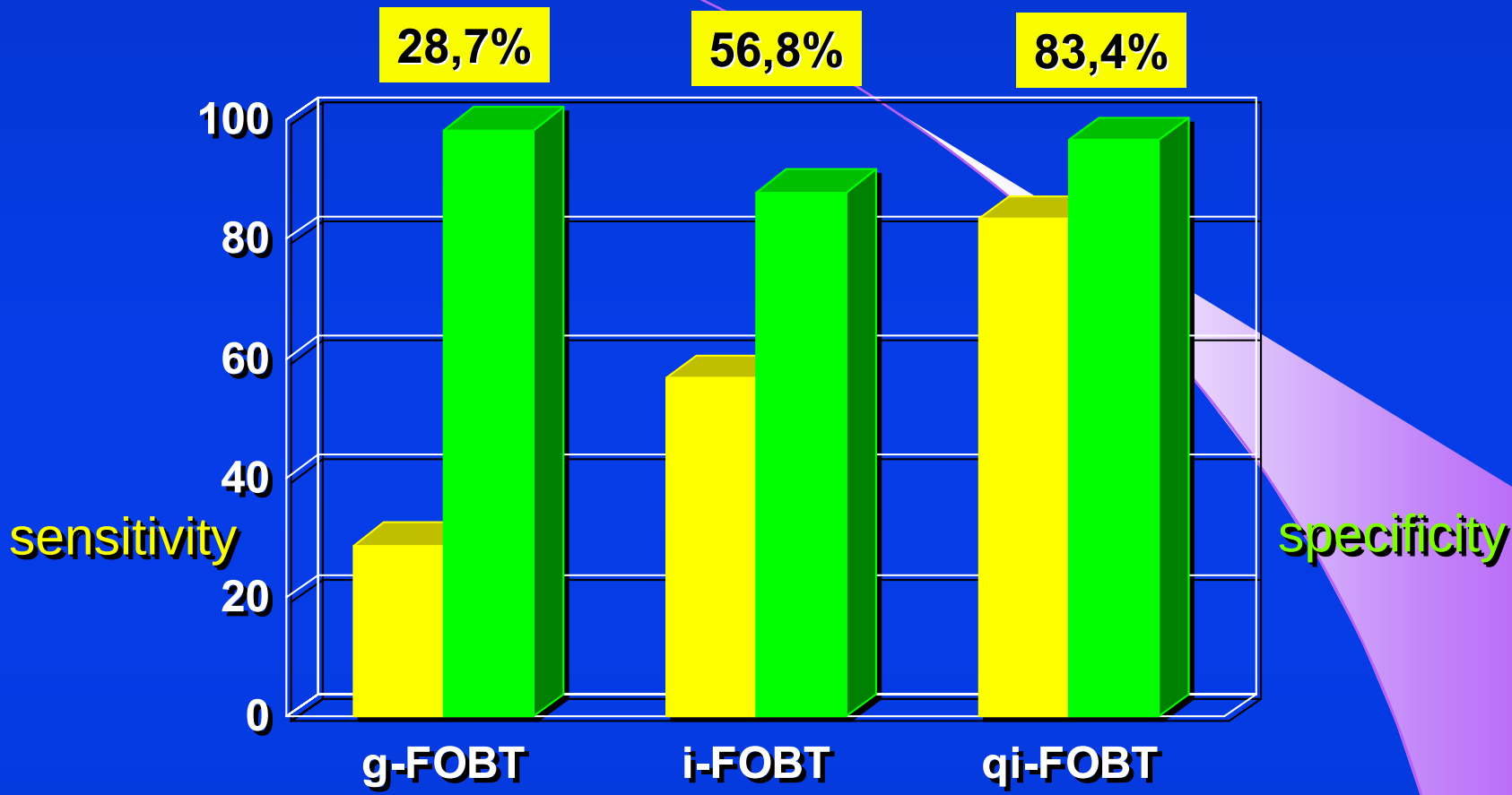
Screening colonoscopy



Virtual computer colonoscopy

DNA chips CRC markers

Automated analysis fecal Hb



Quantitative immunochemical - qiFOBT are **3x more** reliable to guaiac FOBT

Colorectal Cancer Screening and Diagnosis Guidelines Seminar - April 2011
prof.Stephen Halloran - NHS criticized qualitative FOBTs:
No Automation - Operator Variability - Can't adjust positivity

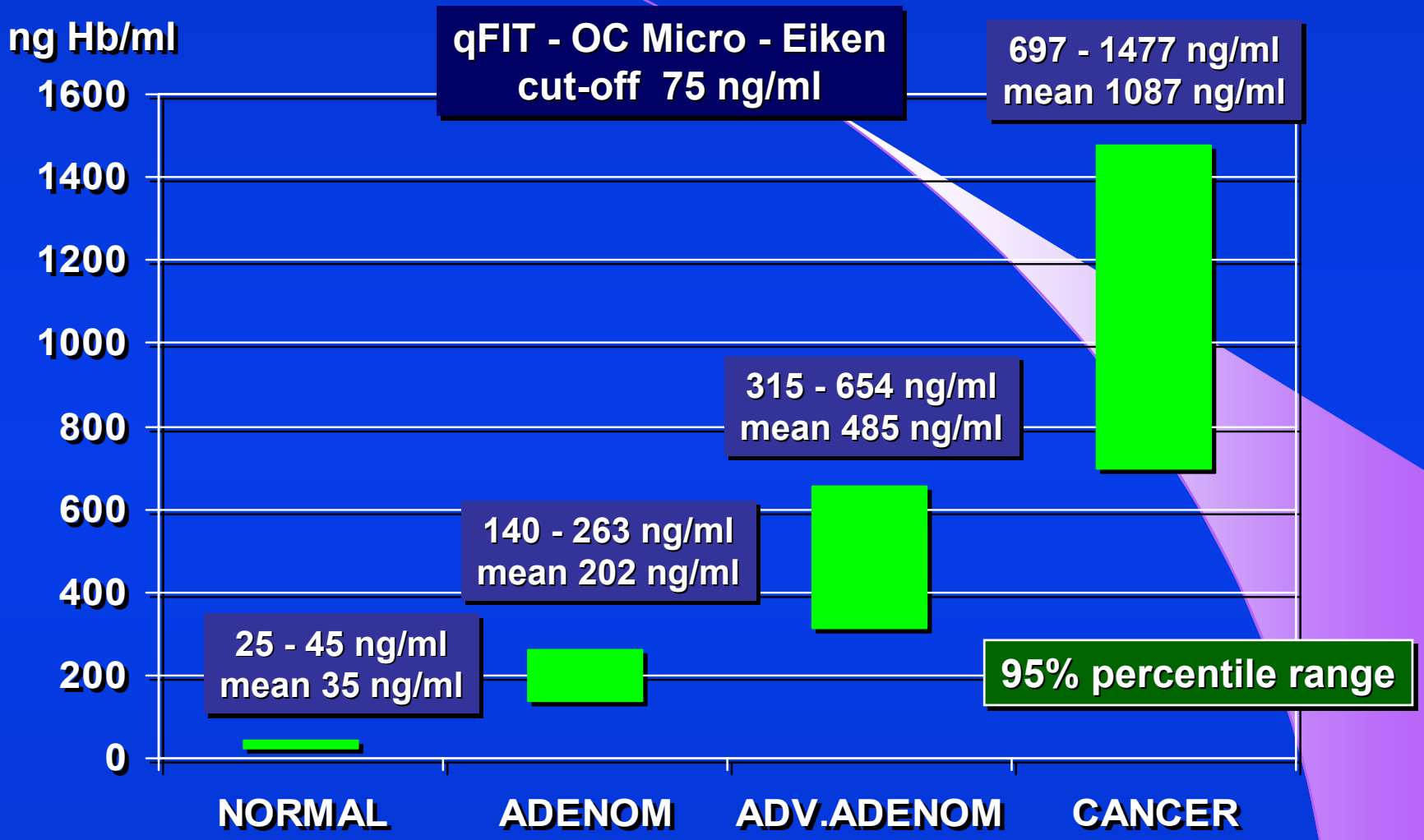
QUANTITATIVE IMMUNOCHEMICAL TESTS - qFIT IN EUROPE

Recommendations for a colorectal cancer screening programme in Ireland - **12/2008**
The National Cancer Screening Service Board, Ireland
The Board's recommendation that the immunochemical faecal occult blood test (iFOBt) which operates on an **automated testing platform**.

Immunochemical faecal occult blood tests - Evaluation report - **November 2009**
Centre for Evidence-based Purchasing of the NHS Purchasing and Supply Agency.
The **OC-Sensor / DIANA analyser** is well designed and is the most suitable system for the **English bowel cancer screening programme.**

A national colorectal cancer screening programme, **November 17, 2009**
The Health Council of the Netherlands
The Committee recommends iFOBT-based screening (**OC-Sensor**, one faecal sample) once every two years for men and women between fifty-five and seventy-five years old.

Faecal occult blood test-based screening programme with high compliance for colonoscopy has a strong clinical impact on colorectal cancer. British Journal of Surgery **2009 May**
Parente F. on behalf of the **Lecco Colorectal Cancer Screening Group**
Immunochemical faecal tests (HM-Jack, Kiowa; Japan) were processed by a single central laboratory using an **automated reading technique**; the positivity cut-off was 100 ng/ml.



A Quantitative Immunochemical Fecal Occult Blood Test for Colorectal Neoplasia
Levi Z.,Rozen P.,Hazazi R.,Vilkin A.,Waked A.,Maoz E.,Birkenfeld S.,Leshno M.,Niv Y.
Ann Intern Med. 2007;146:244-255

CRC - SCREENING - DUTCH STUDY 2008

iFOBT - OC Micro - Eiken
cut-off 100 ng/ml

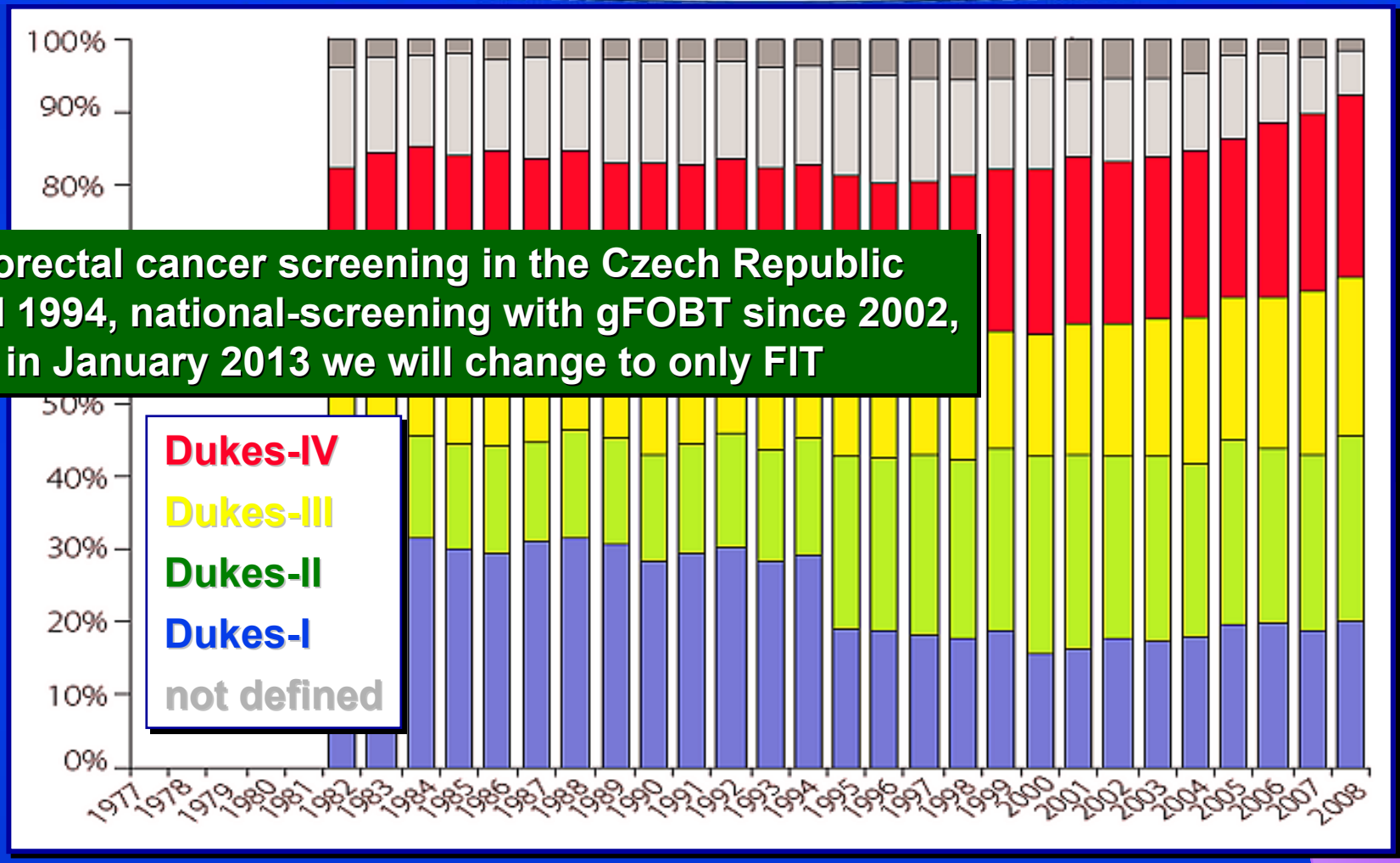
	20 623 SAMPLES RANDOMIZATION	
	g-FOBT	i-FOBT
INVIATION	10 301	10 322
PARTICIPATION	4 836	6 157
POSITIVE FOB TEST	117	339
EXAMINATION	103	280
POLYPS AND CANCER	80	218
ADV.ADENOMAS AND CANCER	57	145
COLORECTAL CANCER	11	24

Comparison Of Guaiac And Immunochemical Fecal Occult Blood Tests For Colorectal Cancer In A Screening Population - Gastroenterology (2008)
van Rossum, L.G., van Rijn, A.F., Laheij, R.J., van Oijen, M.G., Fockens, P., van Krieken, H.H., Verbeek, A.L., Jansen, J.B., Dekker, E., Random

WHAT IS CURRENT KNOWLEDGE

- ✓ The quantitative immunochemical fecal occult blood test (qFIT) has shown better performance characteristics than the standard guaiac-based fecal occult blood test (GT) for detecting advanced colorectal neoplasms (ACRNs) in high-risk population.
- ✓ This paper confirmed with better evidence the observations of others that qFIT has a higher sensitivity for detecting ACRNs than GT, and has an acceptable specificity that significantly reduces the need for colonoscopic evaluation in the screened population.

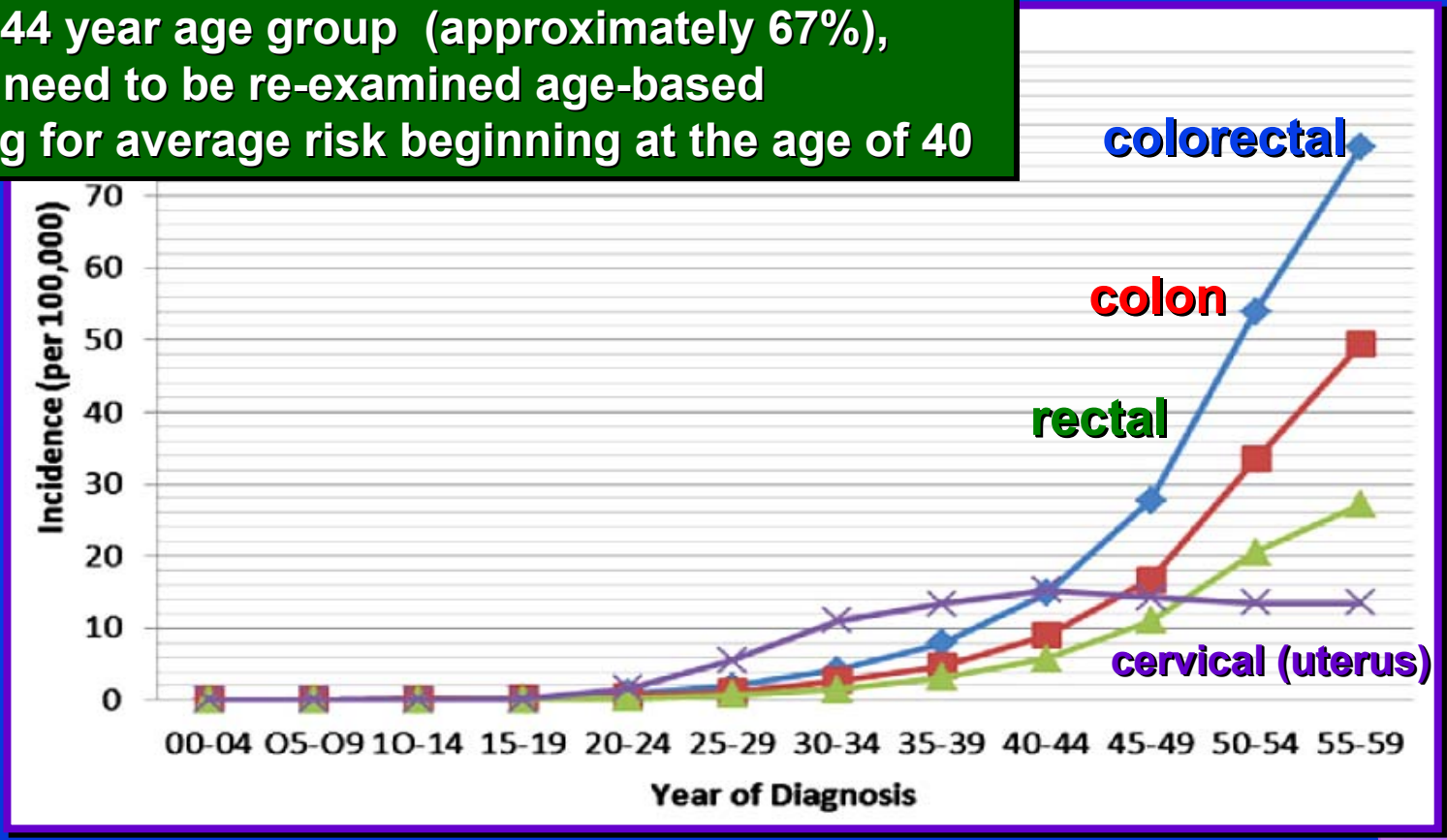
Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening - Park DI, Ryu S, Kim YH, Lee SH, Lee CK, Eun CS, Han DS. Am J Gastroenterol. 2010;105(9): 2017-2025



Colorectal cancer screening in the Czech Republic started 1994, national-screening with gFOBT since 2002, in January 2013 we will change to only FIT

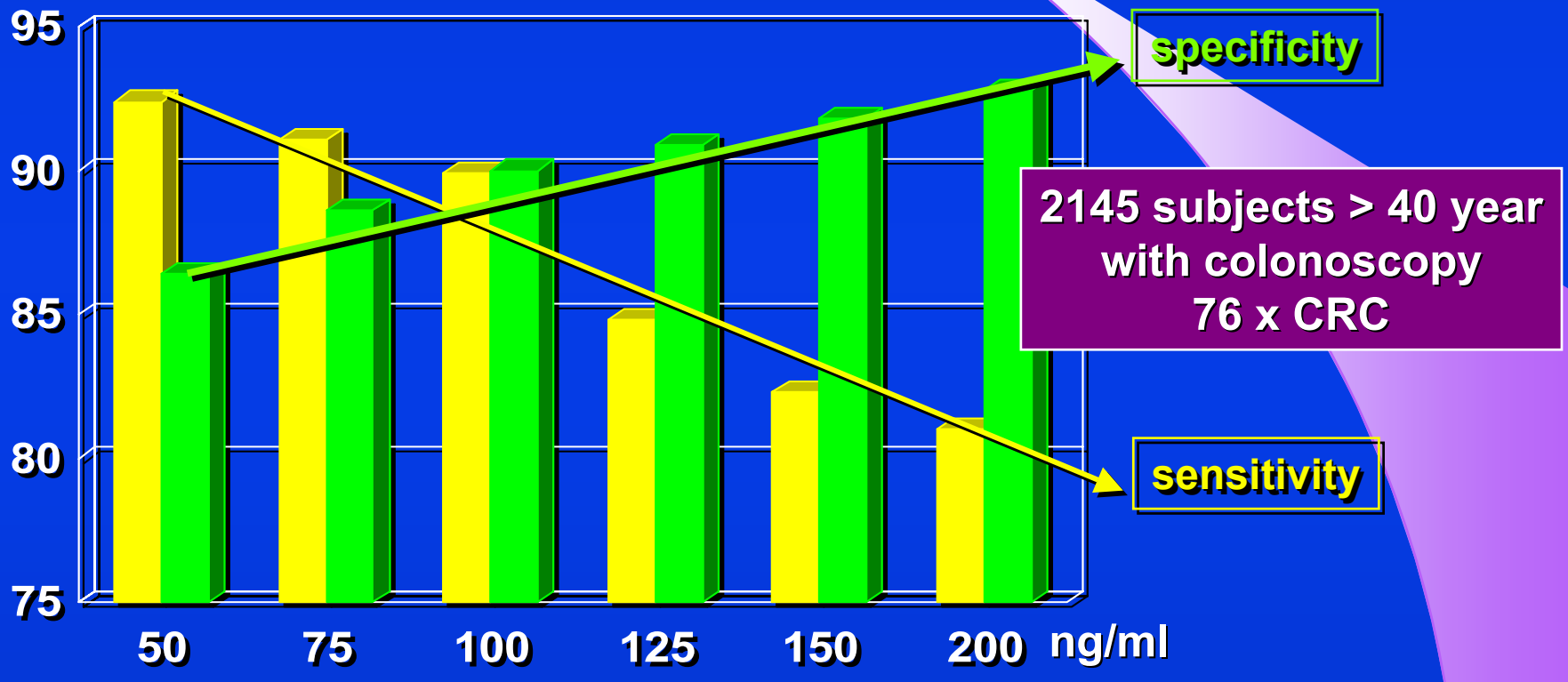
Epidemiology, etiology, screening and diagnosis of colorectal cancer, including the therapeutic procedures in colon and rectum. Suchánek Š., Vepřeková G., Májek O., Dušek L., Zavoral M. - Onkologie 2011; 5(5): 261–265

Colorectal cancer in the young continues to increase, with the most dramatic increase in the 40 to 44 year age group (approximately 67%), need to be re-examined age-based screening for average risk beginning at the age of 40



Is it time to lower the recommended screening age for colorectal cancer?
Davis DM, Marcet JE, Frattini JC, Prather AD, Mateka JJ, Nfonsam VN.
J Am Coll Surg. 2011; 213(3): 352-361

Optimization of qFIT cut-off, for indication to colonoscopy:
Indicate as much as possible, all pathology - with 15% healthy subjects ?
NOT indicate healthy subjects, but decrease sensitivity about 15% ?



Higher Fecal Immunochemical Test Cutoff Levels
Terhaar sive Droste JS et al. Cancer Epidemiol Biomarkers Prev. 2011; 20(2)

OPTIMIZATION OF CUT-OFF VALUE FOR qFIT

Value defined by manufacturer (Eiken): **100 ng/ml**

Dutch study - GE specialization: **75 ng/ml**

Cutoff value determines the performance of a semi-quantitative immunochemical faecal occult blood test in a colorectal cancer screening programme. van Rossum LG, van Rijn AF et al. Br J Cancer. 2009;101:1274

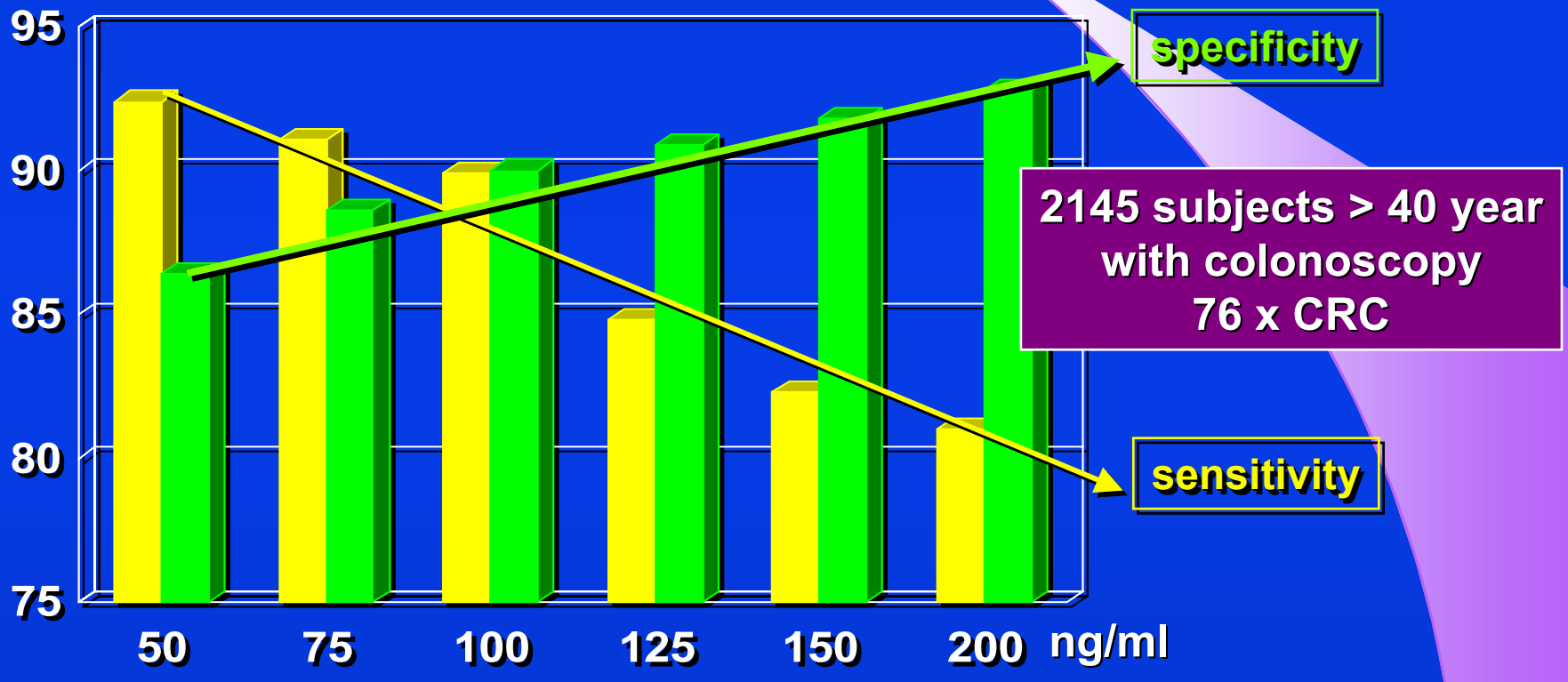
Pilot study in the Czech Republic: **75 ng/ml**

Improvements in colorectal cancer screening programmes – quantitative immunochemical faecal occult blood testing . Kovářová J.T., Zavoral M., Zima T., Žák A., Kocna P. et al. Biomed Pap 2012, 156:143

Dutch study - economical: **50 ng/ml**

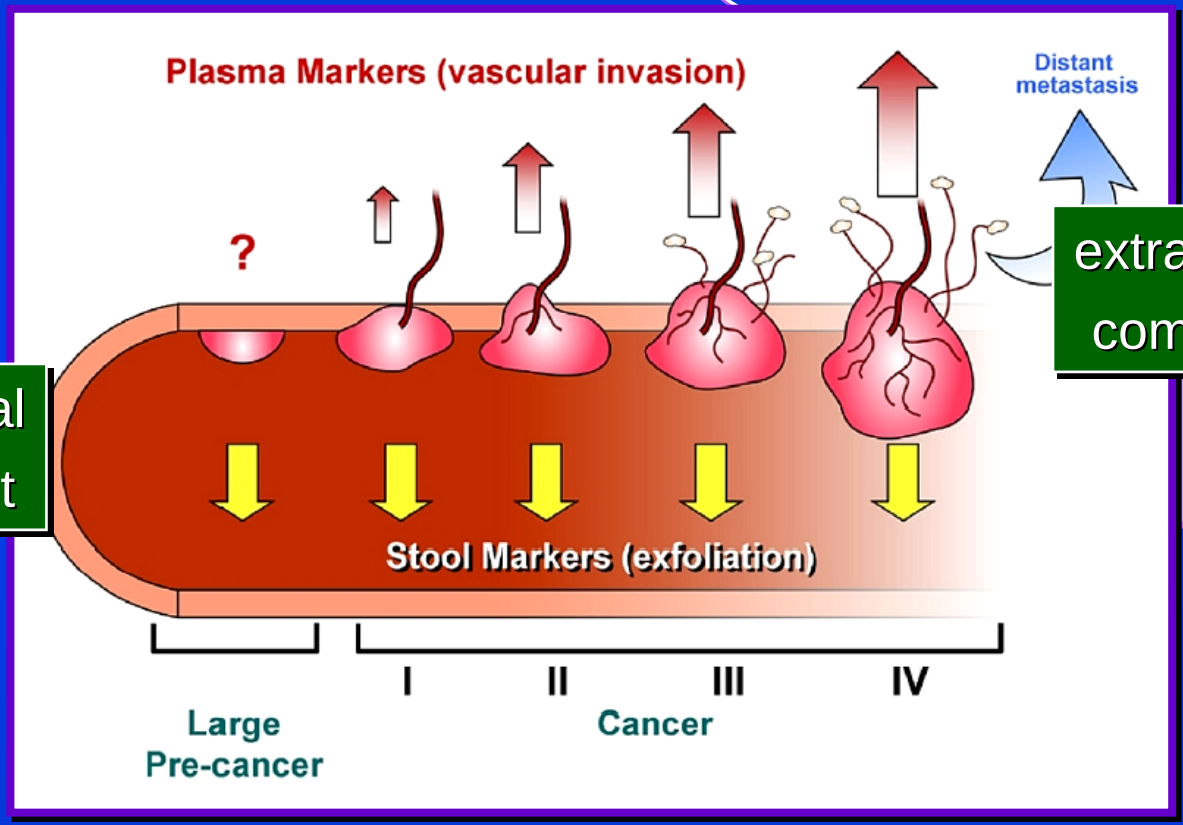
Cost-effectiveness analysis of a quantitative immunochemical test for colorectal cancer screening. Wilschut JA, Hol L, Dekker E et al. Gastroenterology. 2011;141:1648

Optimization of qFIT cut-off, for indication to colonoscopy:
Indicate as much as possible, all pathology - with 15% healthy subjects ?
NOT indicate healthy subjects, but decrease sensitivity about 15% ?



Higher Fecal Immunochemical Test Cutoff Levels
Terhaar sive Droste JS et al. Cancer Epidemiol Biomarkers Prev. 2011; 20(2)

NEW CRC MARKERS - FECAL OR SERUM

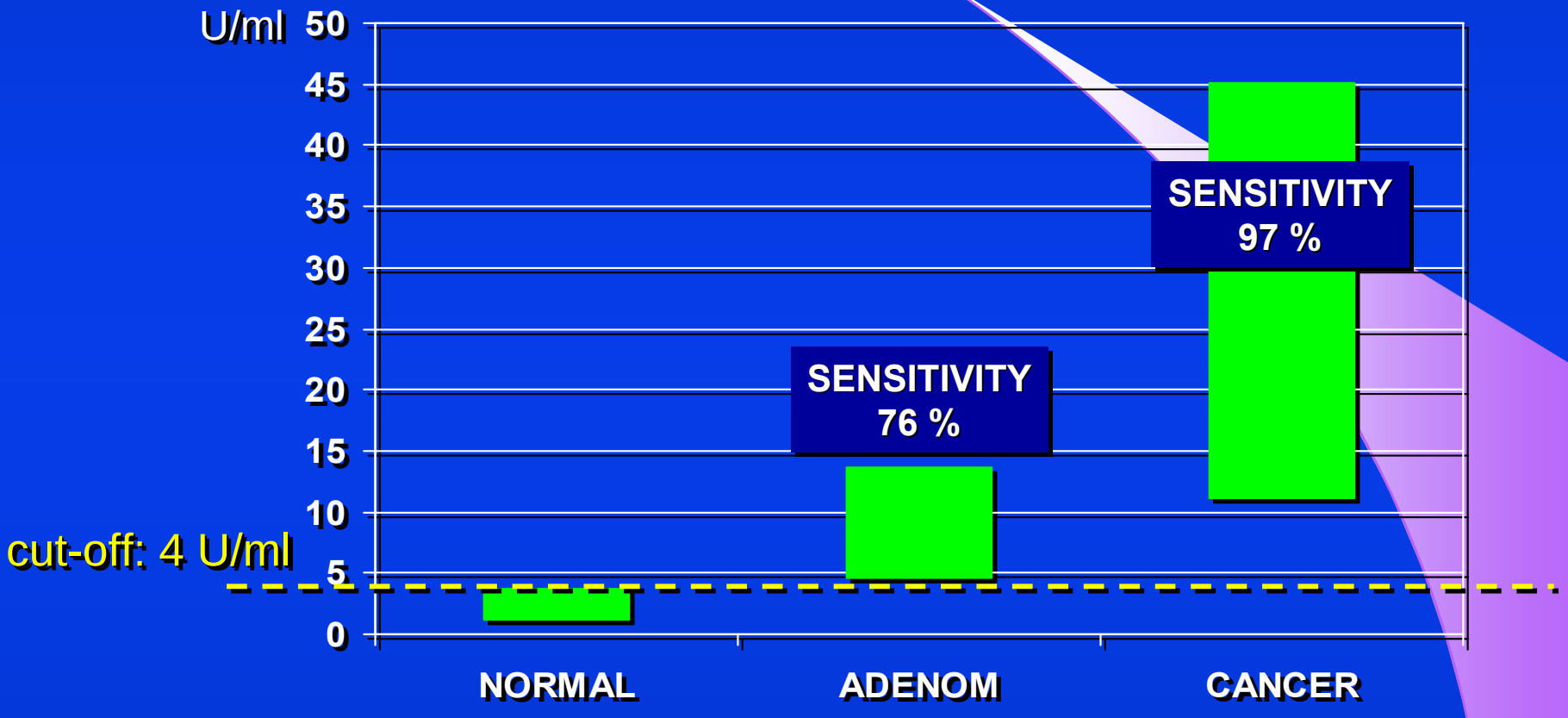


intra-intestinal compartment

extra-intestinal compartment

The stool DNA test is more accurate than the plasma septin 9 test in detecting colorectal neoplasia. Ahlquist DA, Taylor WR, Mahoney DW.et al. Clin Gastroenterol Hepatol. 2012; 10(3): 272-277

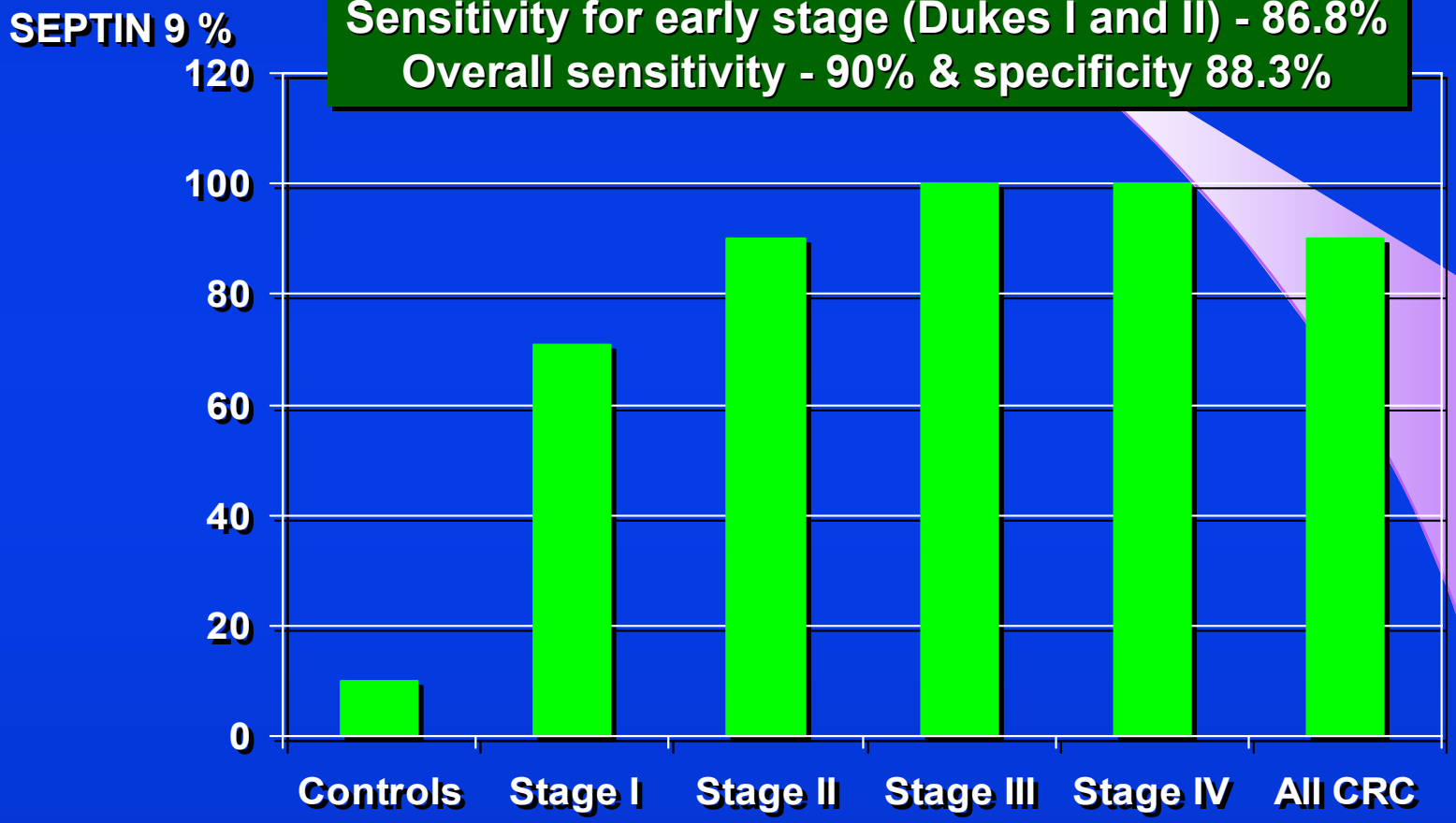
FAECAL PYRUVATE KINASE ISOENZYME TYPE M2-PK MARKER - STOOL



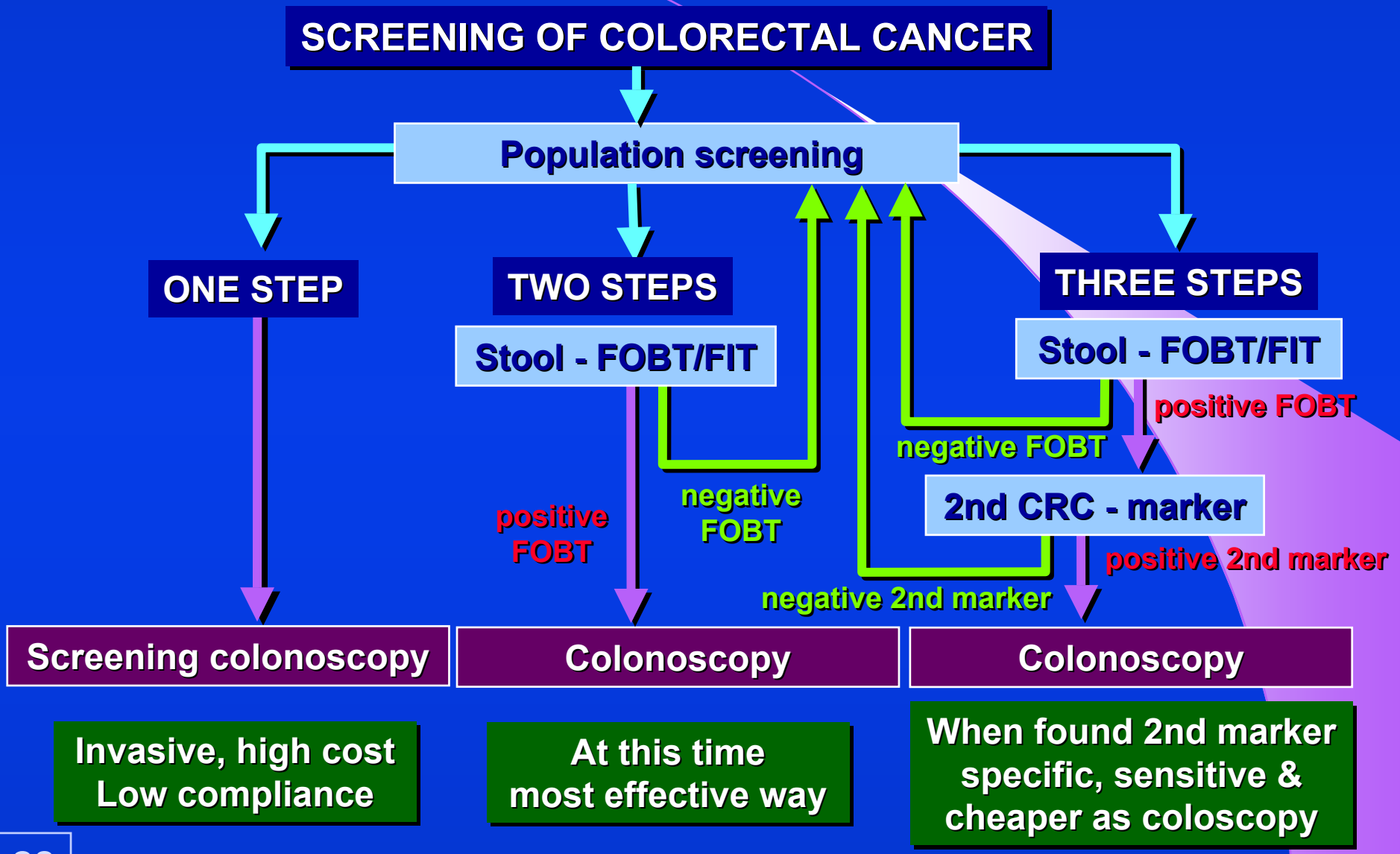
Faecal pyruvate kinase isoenzyme type M2 for colorectal cancer screening: A meta-analysis - Tonus C., Sellinger M., Koss K., Neupert G. World J Gastroenterol 2012 August 14; 18(30): 4004-4011

SEPTIN 9 METHYLATED DNA - SERUM

Sensitivity for early stage (Dukes I and II) - 86.8%
Overall sensitivity - 90% & specificity 88.3%



Septin 9 methylated DNA is a sensitive and specific blood test for colorectal cancer. Warren JD. et al. - BMC Med. 2011, 4; 133

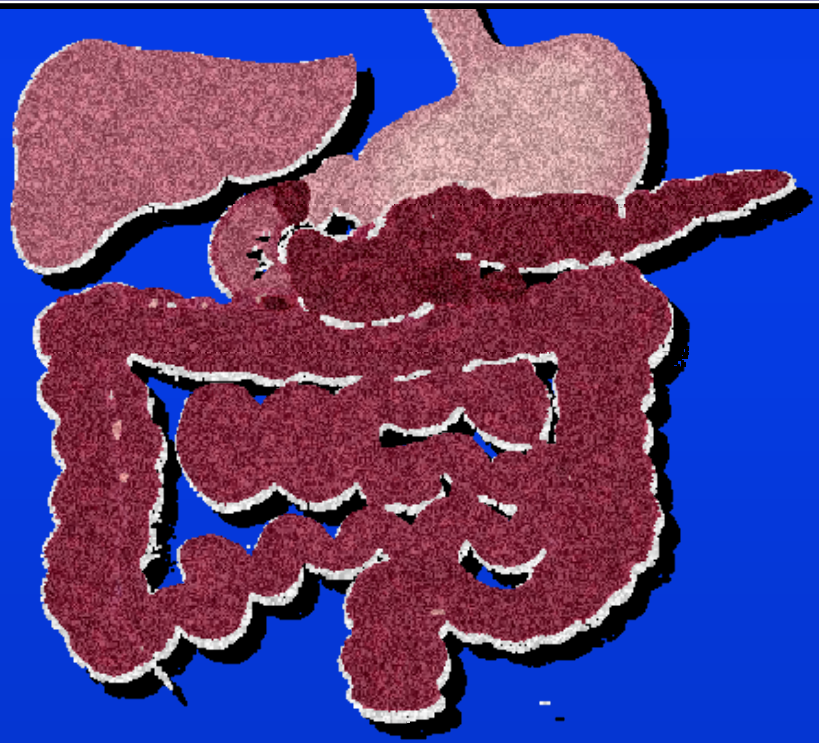

SCREENING OF COLORECTAL CANCER
Population screening
ONE STEP
TWO STEPS
THREE STEPS
Stool - FOBT/FIT
Stool - FOBT/FIT
positive FOBT
negative FOBT
2nd CRC - marker
positive FOBT
negative FOBT
positive 2nd marker
negative 2nd marker
Screening colonoscopy
Colonoscopy
Colonoscopy
Invasive, high cost
Low compliance
At this time
most effective way
When found 2nd marker
specific, sensitive &
cheaper as coloscopy

SCREENING OF COLORECTAL CANCER

WHAT COULD BE CHANGED - WHAT COULD BE DISCUSSED:

- ✓ There are different options for colorectal cancer screening: choose one, and get it done. No more valid ?
- ✓ We have to change to only standardized quantitative FIT method
- ✓ We have to change any type of screenings to population - screening
- ✓ We have to optimize cut-off value according to GE - oncology - and economics
- ✓ Is it time to lower the recommended screening age ?
- ✓ Could other, new, 2nd markers in stool and serum increase screening effectivity ?
- ✓ May we change CRC screening from one/two step to three ?

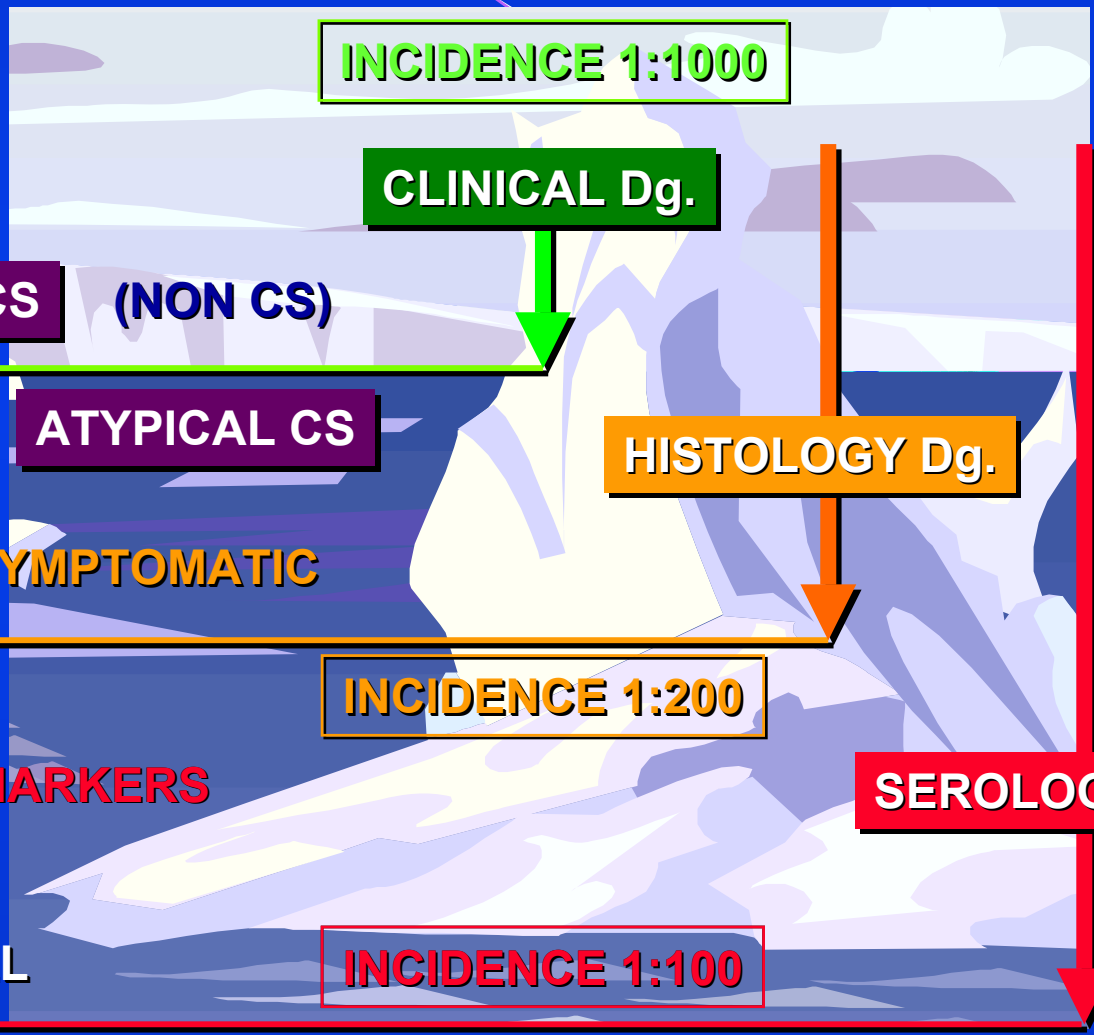
DISEASE SCREENING
COLORECTAL CANCER
COELIAC DISEASE
ATROPHIC GASTRITIS
INFLAMATORY BOWEL DISEASE



COELIAC DISEASE - KEY MESSAGES

- ✓ Coeliac disease is a common disorder affecting 1% of the European population.
- ✓ Coeliac disease is underdiagnosed even in European countries with high knowledge of the variable clinical picture of the disease.
- ✓ The prevalence of coeliac disease varies markedly in different European countries.

ICEBERG HYPOTHESIS OF COELIAC INCIDENCE



CLINICAL CS

TRANSIENT CS (NON CS)

ATYPICAL CS

SILENT CS

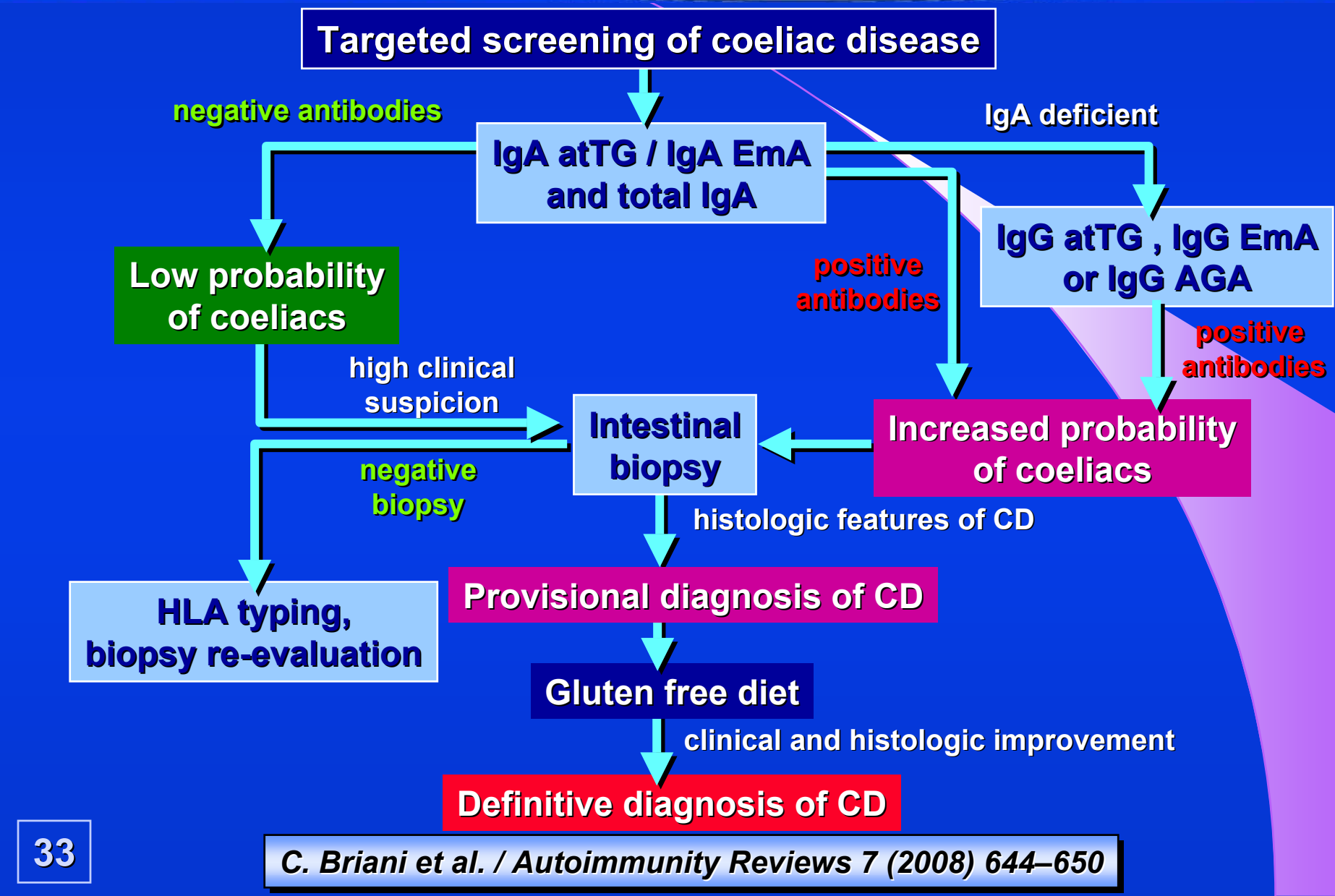
MUCOSAL DEFECT, ASYMPTOMATIC

LATENT CS

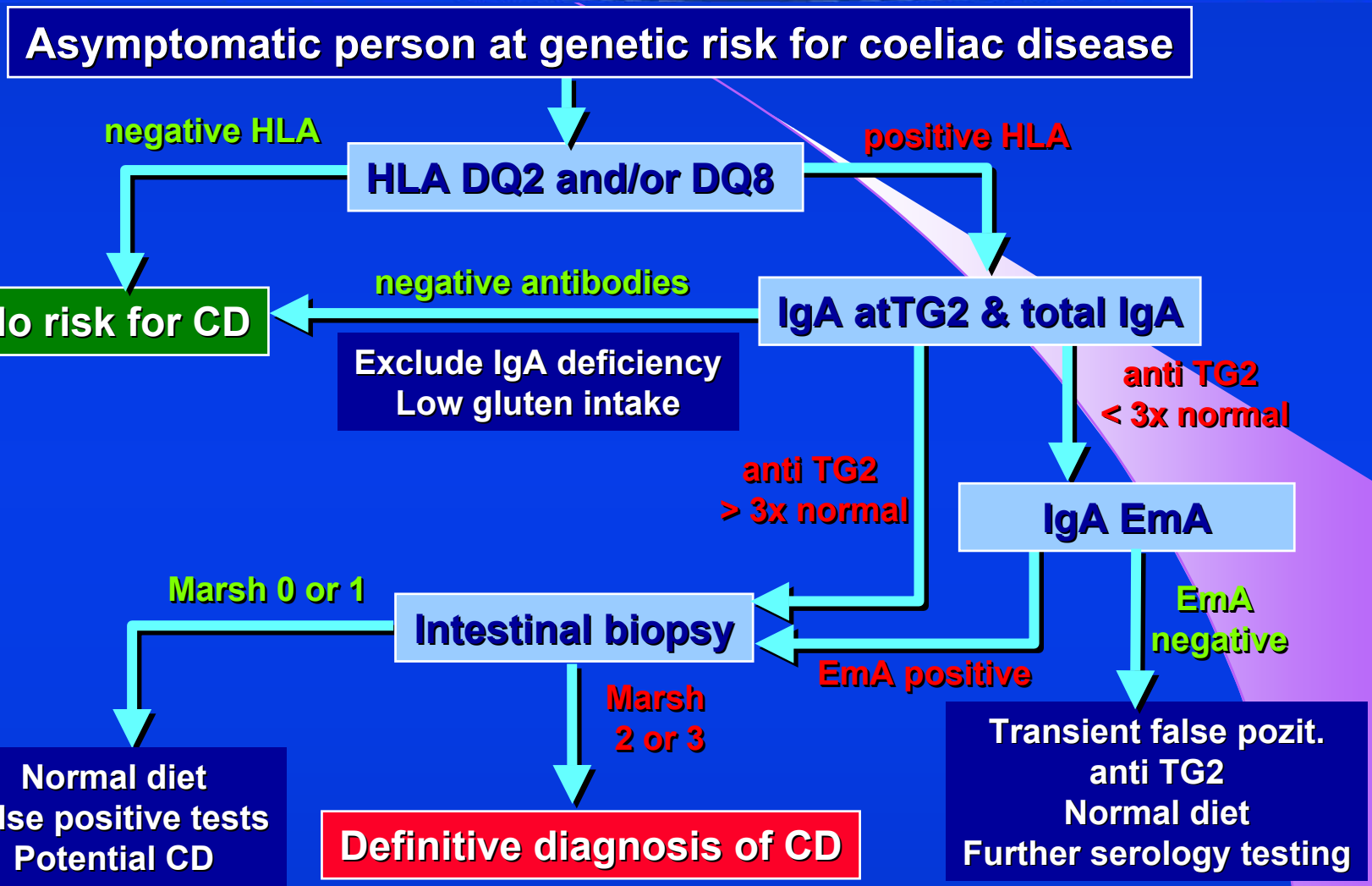
NORMAL MUSOCA, + MARKERS

POTENTIAL CS

HLA DQw2, ↑IEL, ↑ γ/δ IEL

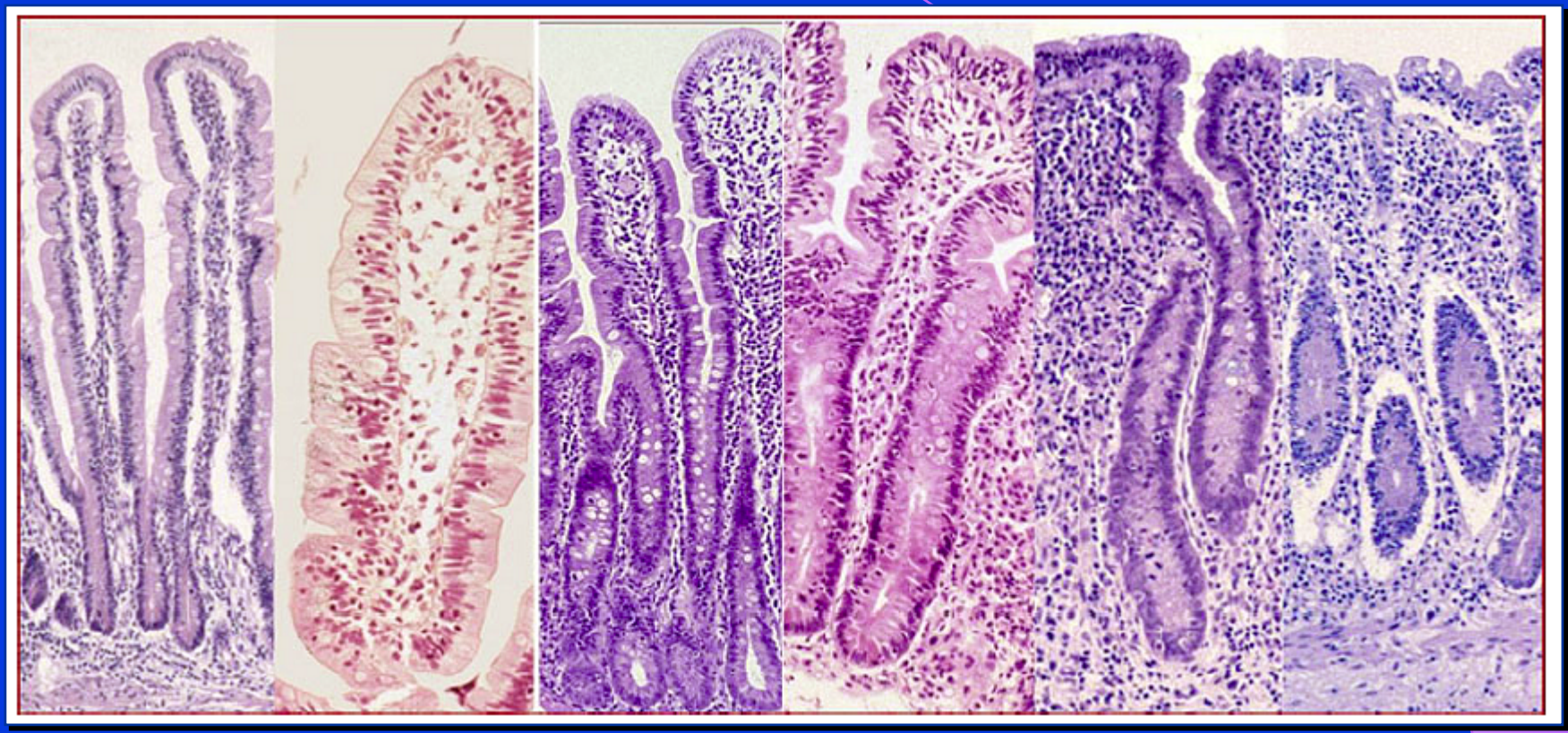


C. Briani et al. / Autoimmunity Reviews 7 (2008) 644–650



New ESPGHAN guidelines for the diagnosis of Coeliac Disease in Children and Adolescents - Steffen Husby, Odense University Hospital, Denmark

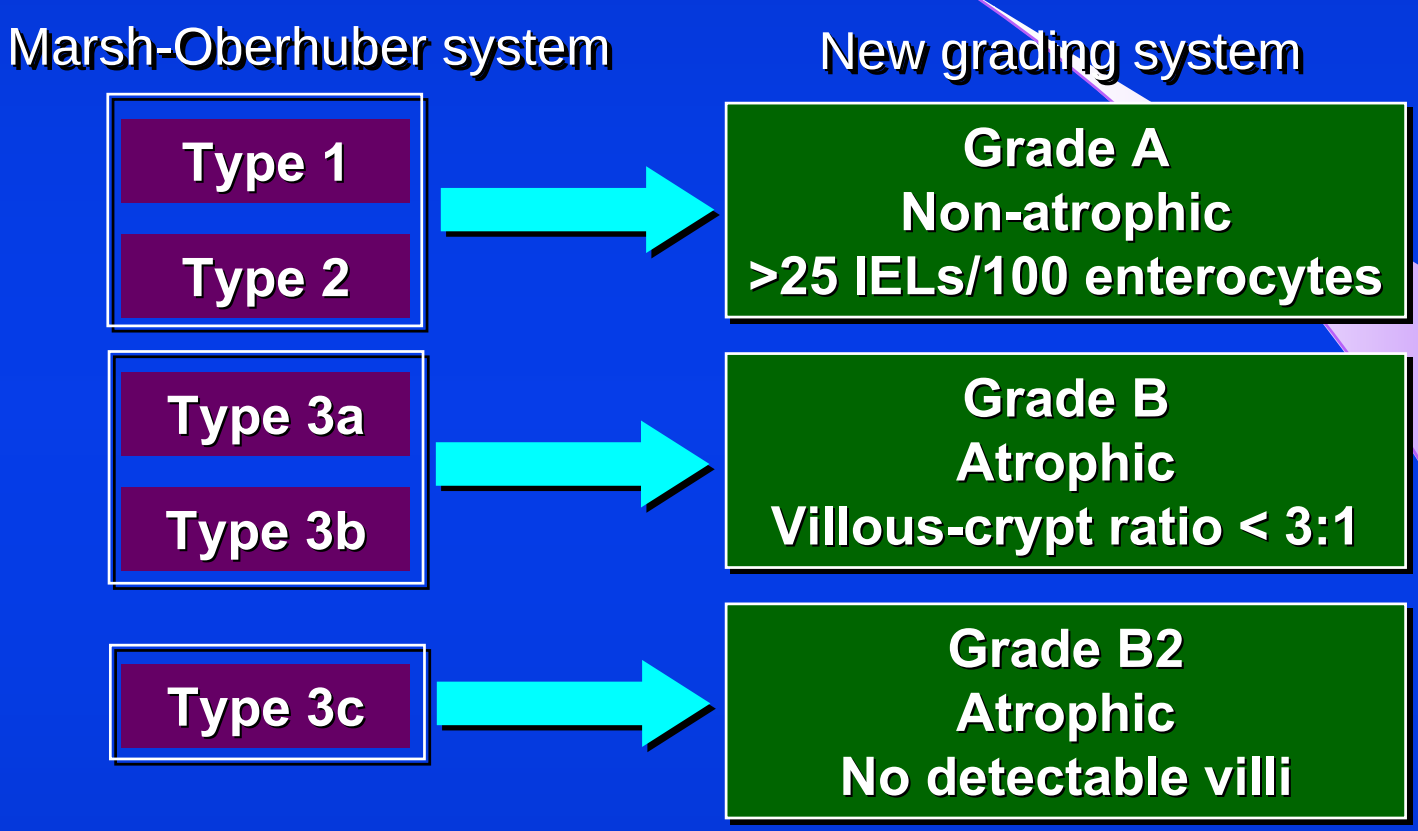
INTESTINAL BIOPSY IN THE COELIAC DISEASE DIAGNOSTICS



Marsh 0 Marsh 1 Marsh 2 Marsh 3a Marsh 3b Marsh 3c

Clinical practice - Coeliac disease - Eur J Pediatr. - online March 2012
C. M. Frank Kneepkens & B. Mary E. von Blomberg

INTESTINAL BIOPSY - NEW GRADING SYSTEM



Recent advances in coeliac disease. Armstrong MJ, Robins GG, Howdle PD. Curr Opin Gastroenterol. 2009; 25(2): 100-109

ACTUAL PROTOCOL
ANTIBODIES DETERMINATION
(EVIDENCE - BASED)

IgA atTG

+ IgA EmA

INCREASE OF IgA atTG SPECIFICITY

+ IgG atTG

COELIAC DETECTION WITH IgA DEFFICIENCY

+ IgA AGA

COELIAC DETECTION IN CHILDRENS < 2 YR

PERSPECTIVE PROTOCOL
ANTIBODIES DETERMINATION
(WORKING HYPOTHESIS)

IgA atTG

+ IgG DGP

INCREASE OF IgA atTG SPECIFICITY
COELIAC DETECTION WITH IgA DEFFICIENCY
COELIAC DETECTION IN CHILDRENS < 2 YR

Old and new serological tests for celiac disease screening.
Volta U., Fabbri A., Parisi C. et al. Expert Rev. Gastroenterol. Hepatol. 2010, 4(1)

INCREASED PREVALENCE OF CD IN CHILDREN WITH

Type 1 diabetes	2-12 %
Down's syndrome	5-12 %
Autoimmune thyroid disease	to 7 %
Turner syndrome	2-5 %
Williams' syndrome	to 9 %
IgA deficiency	2-8 %
Autoimmune liver disease	12-13 %
First degree relatives with CD	10-20 %

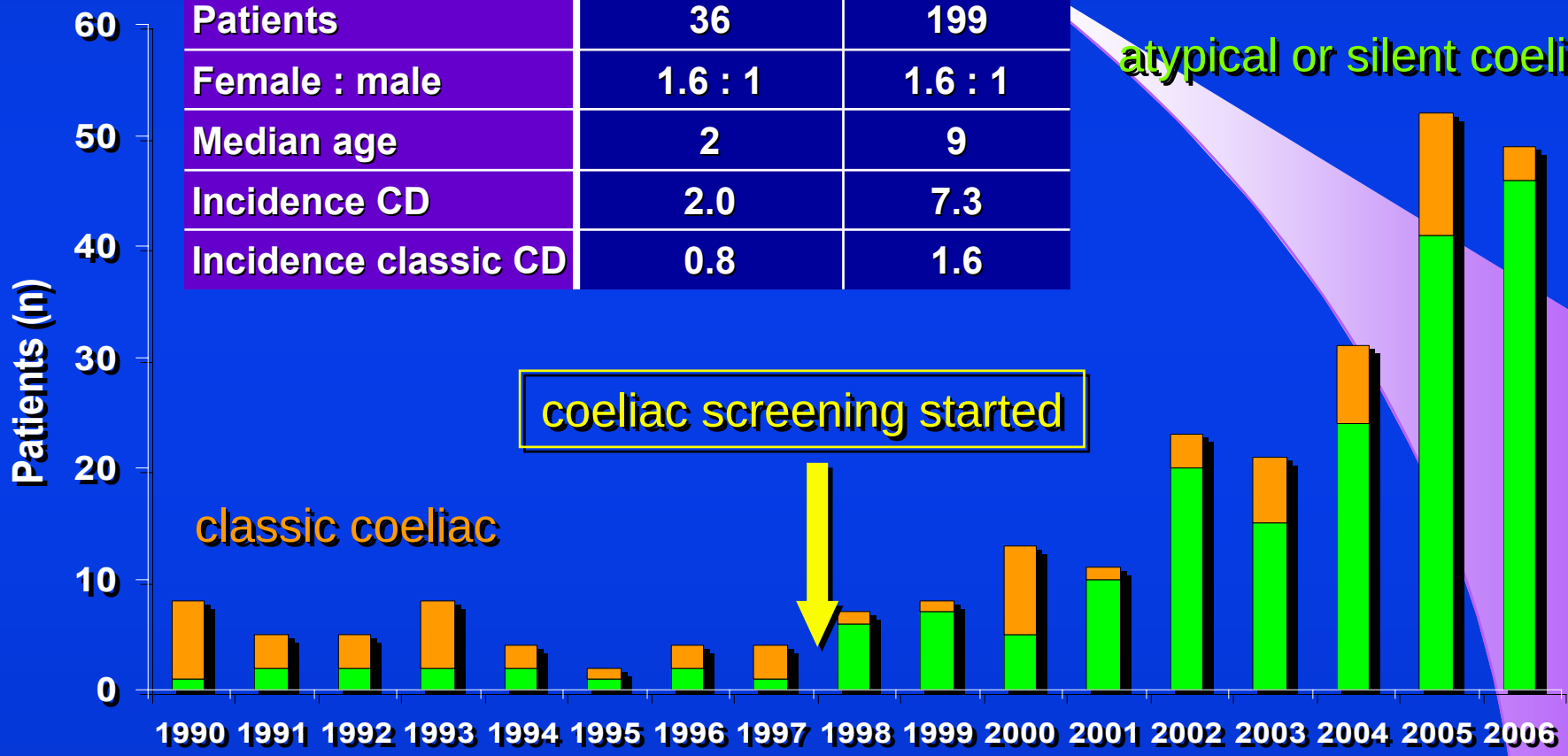
New ESPGHAN guidelines for the diagnosis of Coeliac Disease in Children and Adolescents
Steffen Husby - Odense University Hospital, Denmark

TARGETED SCREENING OF COELIAC DISEASE IN CZECH REPUBLIC

Associated symptoms and signs	Associated diseases and syndromes
Dermatitis herpetiformis	Type 1 diabetes
Osteoporosis, unexplained fractures	Autoimmune thyroiditis
Chronic diarrhoea with abdominal distension	Autoimmune liver disease
Anemia	Systemic lupus erythematosus
Chronic fatigue syndrome	Primary biliary cirrhosis
Polyneuropathy	Primary sclerosing cholangitis
Cerebellar ataxia, epilepsy	Sjögren syndrome
Spont. abortion and fetal growth retardation	Alopecia areata
Growth retardation, pubertal delay	IgA nephropathy
Involuntary weight loss	IgA deficiency
Unexplained anaemia (iron, folic acid)	
Dental enamel hypoplasia	
Recurrent aphthous stomatitis	
Hypertransaminasemia	

Children Diagnosed with Coeliac Disease at Alberta Childrens' Hospital

	Pre-screening	Screening
Patients	36	199
Female : male	1.6 : 1	1.6 : 1
Median age	2	9
Incidence CD	2.0	7.3
Incidence classic CD	0.8	1.6



Celiac Disease in Children:The Calgary Clinic Data
Calgary Celiac Disease Conference, 2008 - J. Decker Butzner

SCREENING OF CD MEETS THE SIX WHO CRITERIA

- ✓ Early detection could be difficult on a clinical basis
- ✓ Available tests (atTG) are highly sensitive and specific, not expansive, with good compliance
- ✓ Treatment of the disease is available, and if not recognized, the disease could result in severe complications difficult to manage

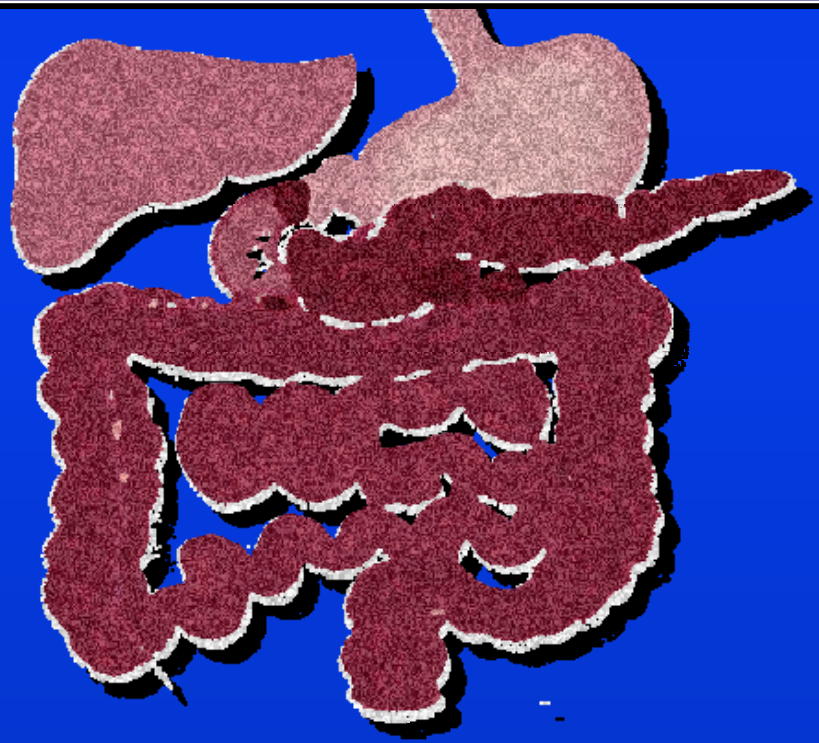
CD reduces life expectancy because of a higher risk of malignancies such as:

Small-bowel lymphoma, small-bowel adenocarcinoma, esophageal carcinoma, ulcerative jejunitis, refractory CD, enteropathy-associated T-cell lymphoma.

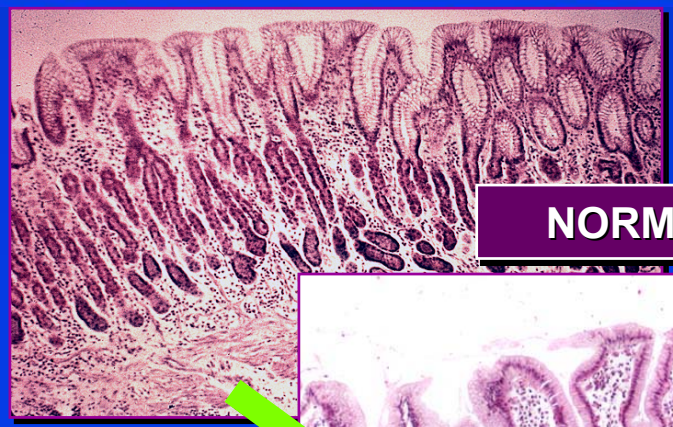
TREATED CD ON GLUTEN-FREE DIET SIGNIFICANTLY

- ✓ Reduce risk of malignancies
- ✓ Have a beneficial effect on preservation of β-cell function in IDDM
- ✓ Change diabetes onset in IDDM children
- ✓ Will have a positive effect on autoimmune diseases
- ✓ Generally will improve subject health

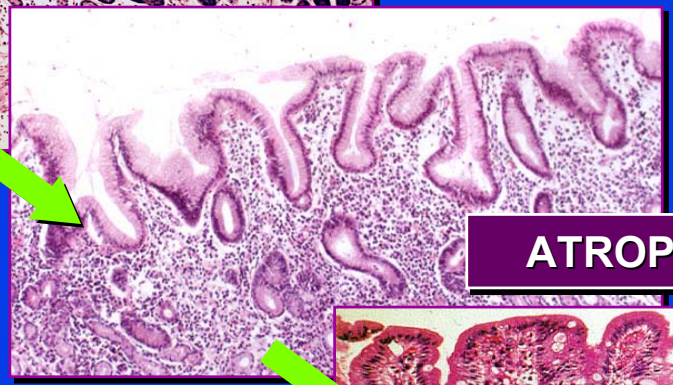
DISEASE SCREENING
COLORECTAL CANCER
COELIAC DISEASE
ATROPHIC GASTRITIS
INFLAMATORY BOWEL DISEASE



GASTRITIS - CARCINOMA SEQUENCES

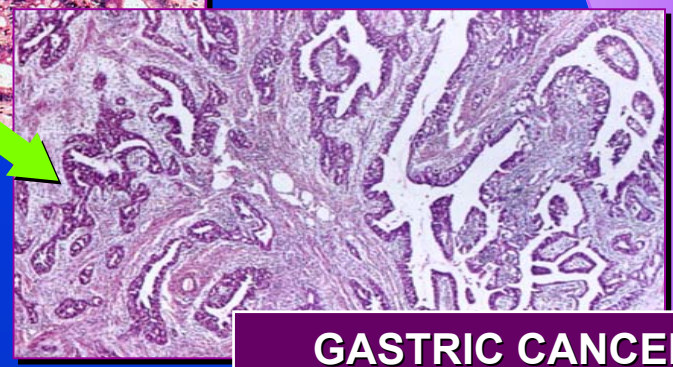


NORMAL MUCOSA



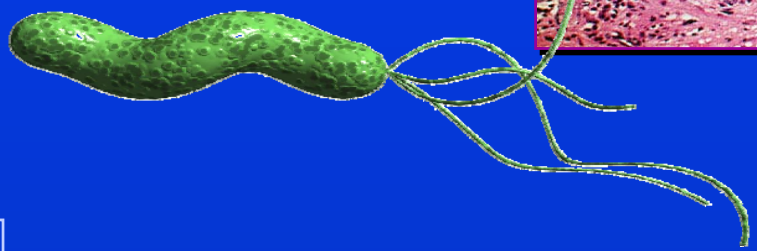
ATROPHIC GASTRITIS

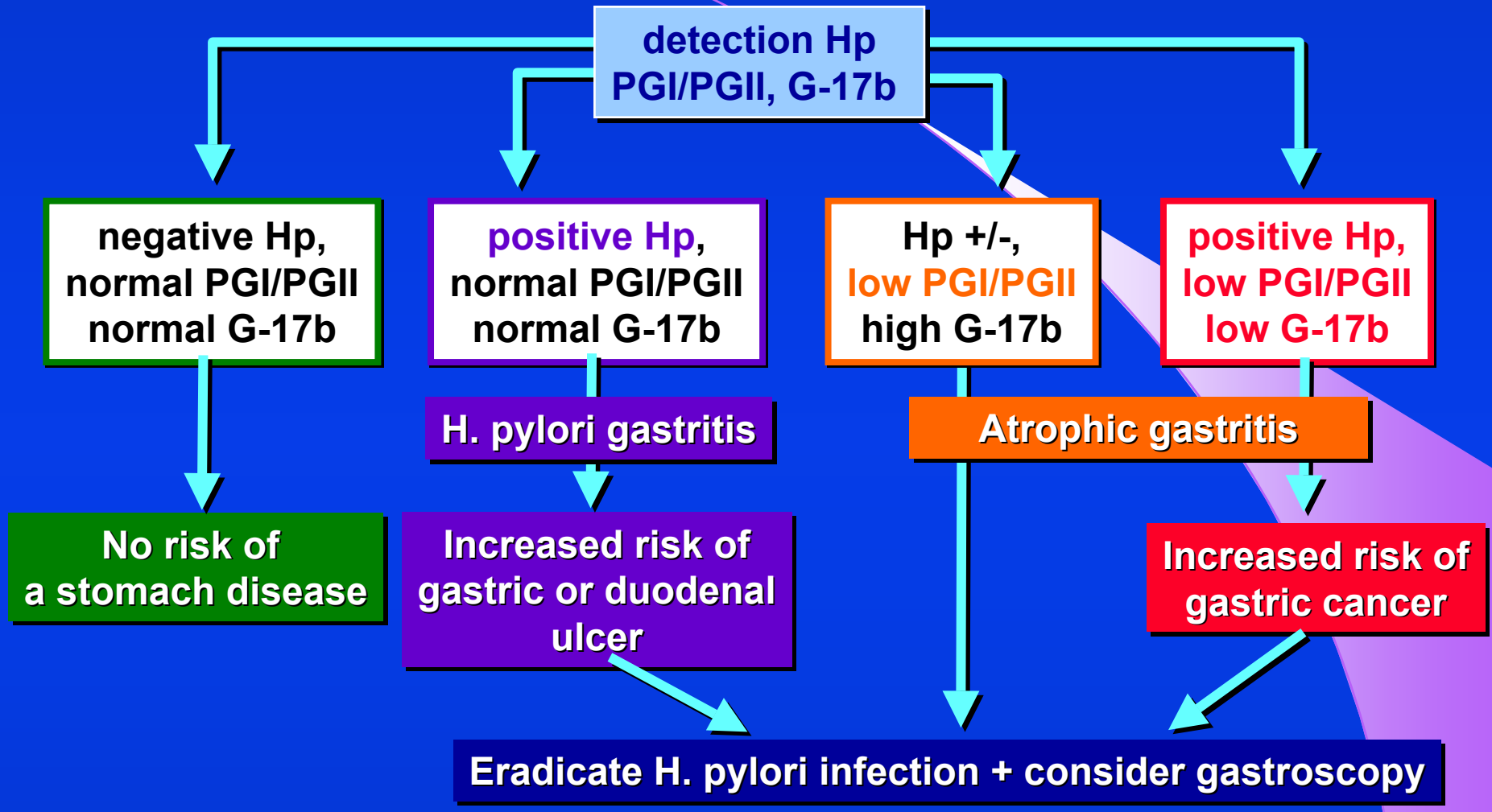
INTESTINAL METAPLASIA



GASTRIC CANCER

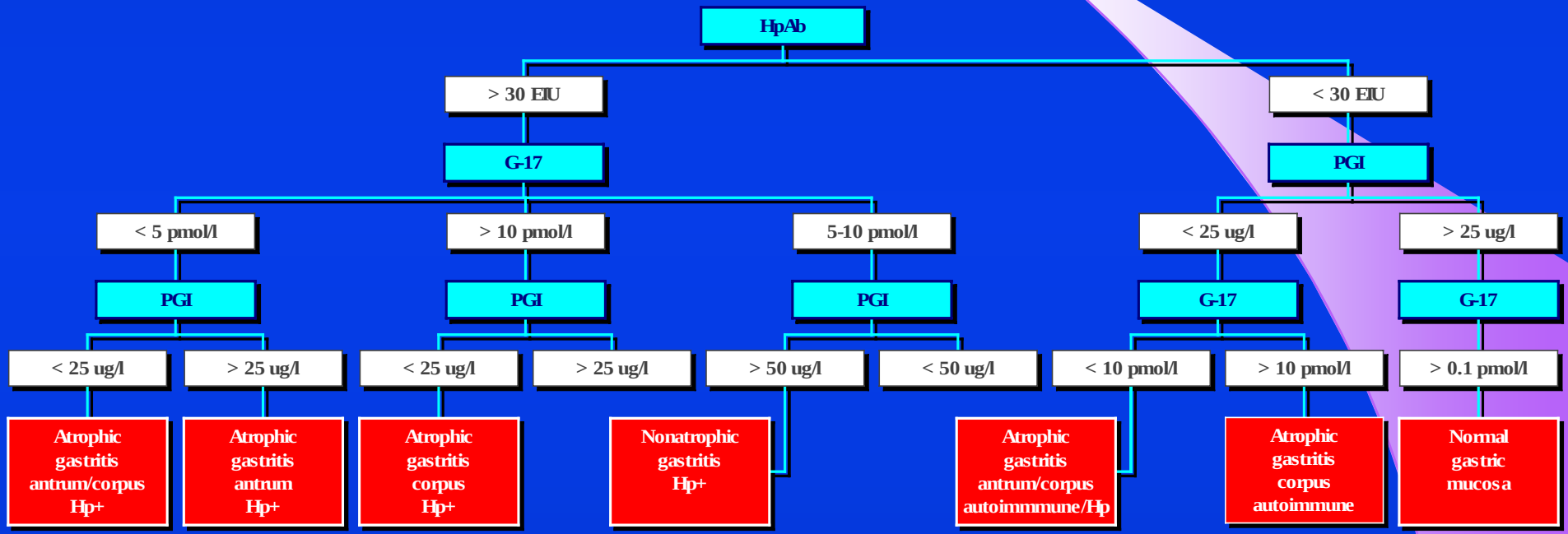
Hp - IARC 1994
1.class cancerogen





Rationale in diagnosis and screening of atrophic gastritis with stomach-specific plasma biomarkers. Agréus L, Kuipers EJ, Kupcinskas L, Malfertheiner P, et al. Scand J Gastroenterol. 2012; 47(2):136-147

PGI, Pepsinogen I, ELISA
PGII, Pepsinogen II, ELISA
G-17, Gastrin 17, ELISA
HpAb, Hp antibodies IgG, ELISA



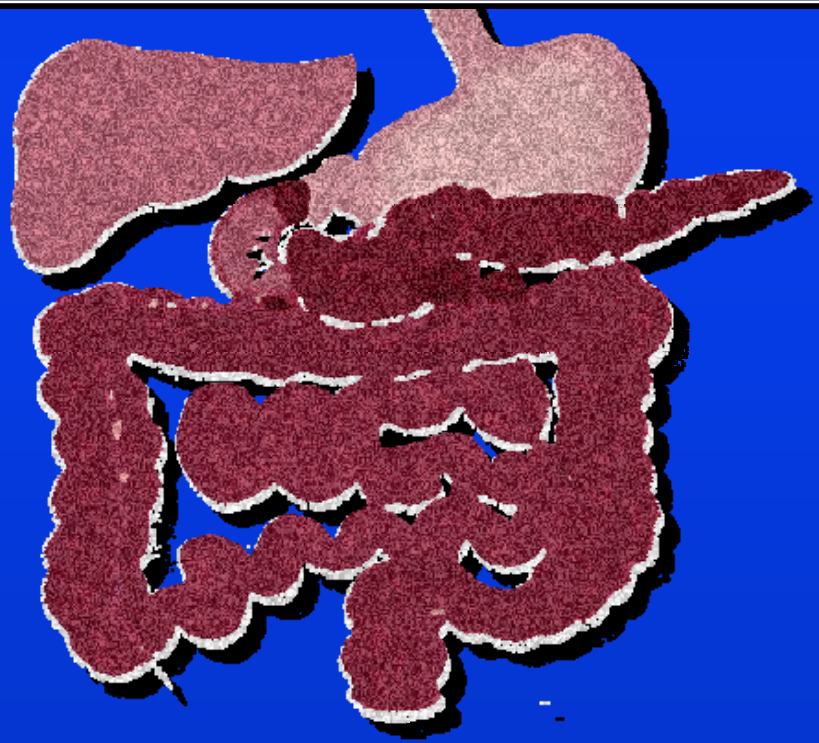
Gastropanel
serological markers of gastric mucosa status
complex solution - ELISA tests & software

INCREASED RISK & SCREENING OF ATROPHIC GASTRITIS

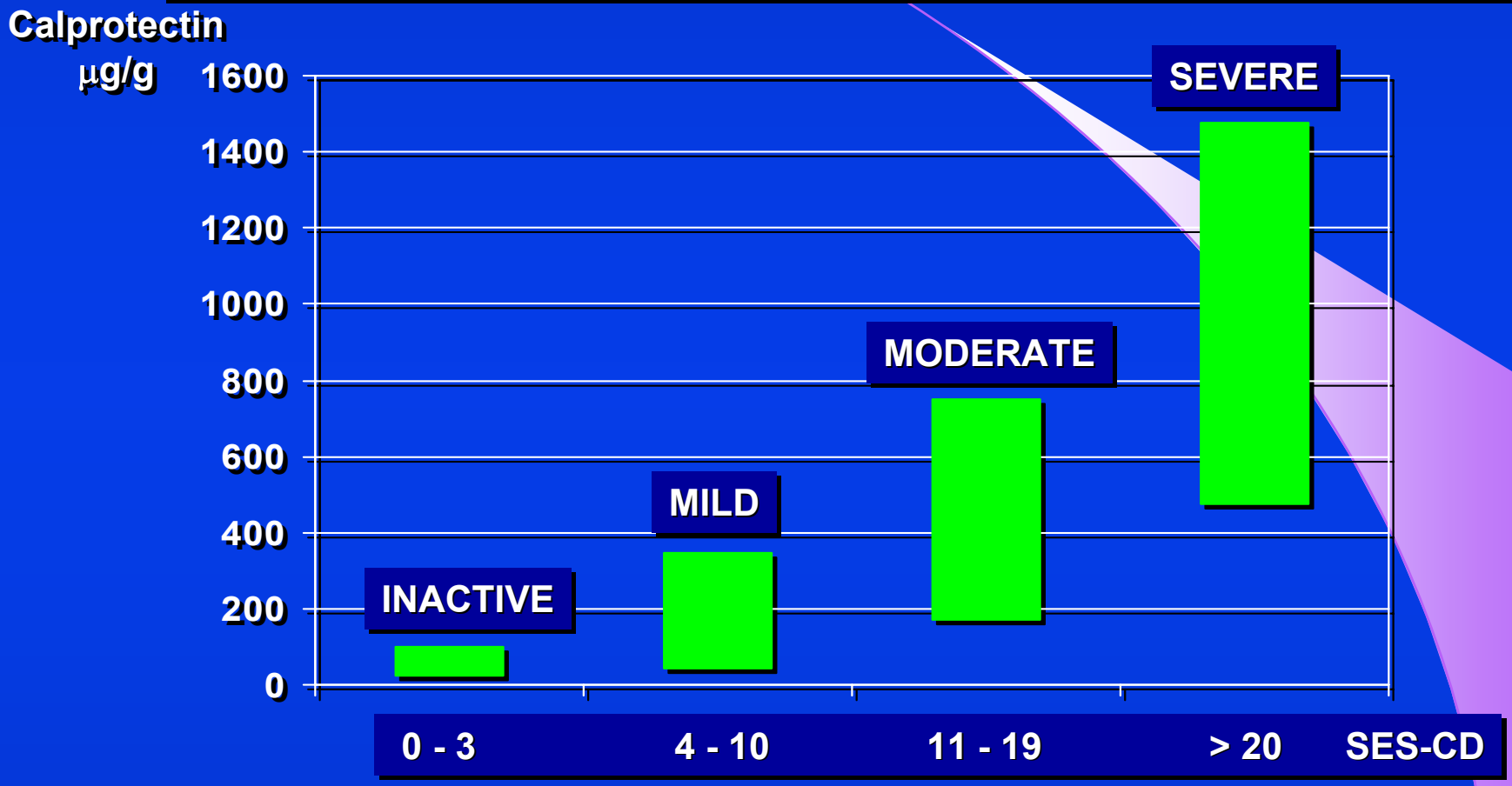
Age	Number	ACG	H.pylori
< 39	644	2 - 0.3%	0 - 0%
40 - 49	660	11 - 1.7%	5 - 45%
50 - 59	1091	27 - 2.5%	13 - 48%
60 - 69	1117	48 - 4.3%	19 - 40%
> 70	744	62 - 8.3%	19 - 31%
total	4256	150 - 3.5%	56 - 37%

Prevalence of undiagnosed advanced atrophic corpus gastritis in Finland: an observational study among 4,256 volunteers without specific complaints. Telaranta-Keerie A, Kara R, Paloheimo L, Härkönen M, Sipponen P. Scand J Gastroenterol. 2010 Sep;45(9):1036-41.

DISEASE SCREENING
COLORECTAL CANCER
COELIAC DISEASE
ATROPHIC GASTRITIS
INFLAMATORY BOWEL DISEASE

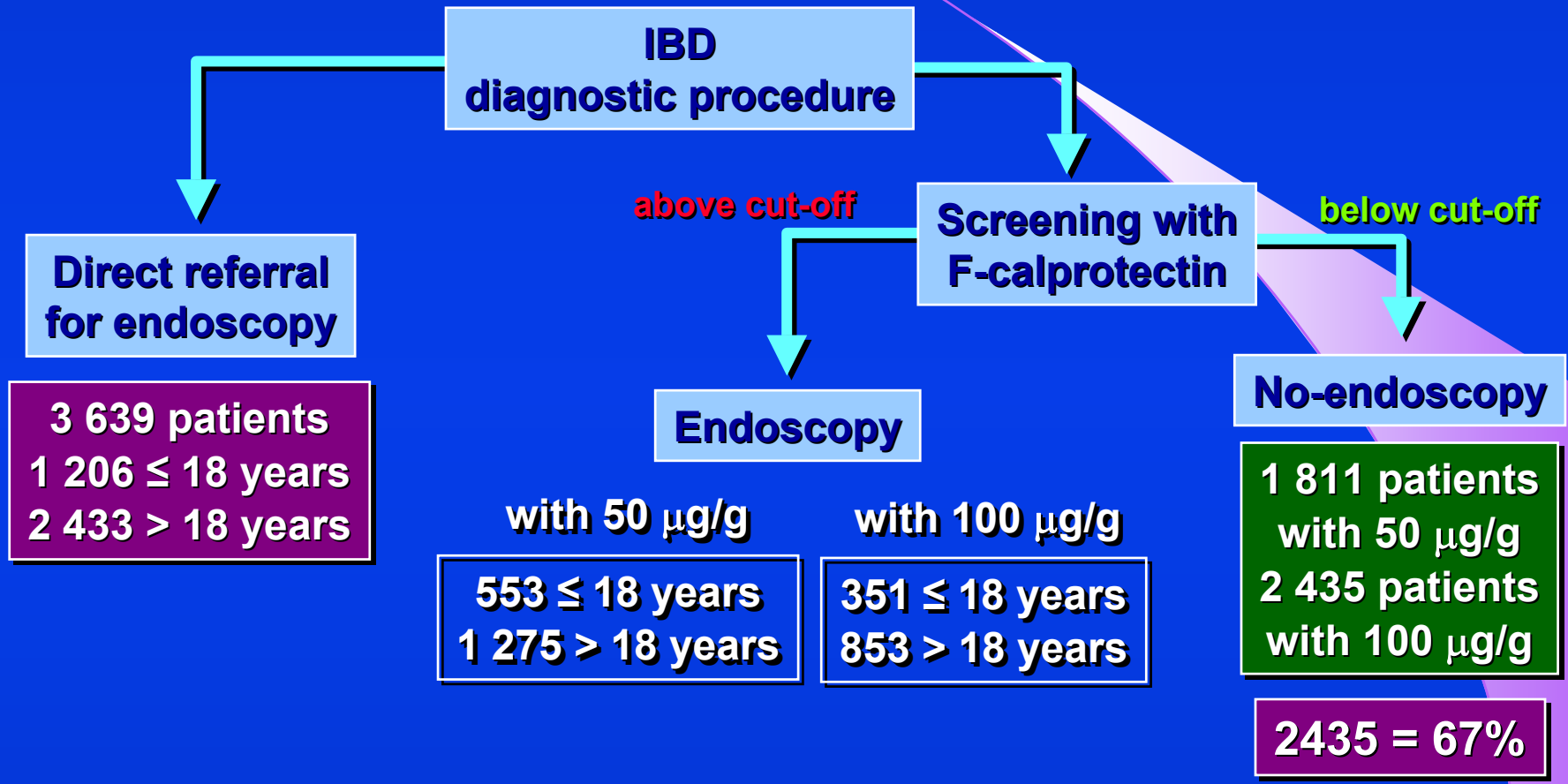


CORRELATION OF FECAL CALPROTECIN WITH SES-CD SCORE



Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. Schoepfer AM. Et al. - Am J Gastroenterol. 2010 Jan;105(1):162-169

PRE-ENDOSCOPIC SCREENING WITH F-CALPROTECTIN



Ruling out IBD: estimation of the possible economic effects of pre-endoscopic screening with F-calprotectin.
Mindemark M, Larsson A. Clin Biochem. 2012; 45(7-8): 552-555

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ✓ Diagnosing inflammatory bowel disease requires invasive and time consuming endoscopy
- ✓ In a relatively large proportion of patients with suspected inflammatory bowel disease the results of endoscopy are negative
- ✓ Faecal calprotectin is a sensitive marker of intestinal inflammation
- ✓ Use of faecal calprotectin as screening test reduces the number of endoscopies with negative results in both adults and young with suspected inflammatory bowel disease

Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis.
van Rheenen PF, Van de Vijver E, Fidler V. - BMJ. 2010 Jul 15; 341: c3369

Laboratory methods for screening in gastroenterology that meets at least five WHO criteria preventing gastrointestinal tumors

Gastrointestinal tumor	Gastrointestinal disease	Laboratory screening test
Colorectal cancers	Colorectal adenomas	Quantitative FIT
Intestinal & GE cancers	Celiac disease	IgA atTG / IgG DGP
Gastric cancers	Atrophic gastritis	Pepsinogen I/II ratio


THANK YOU