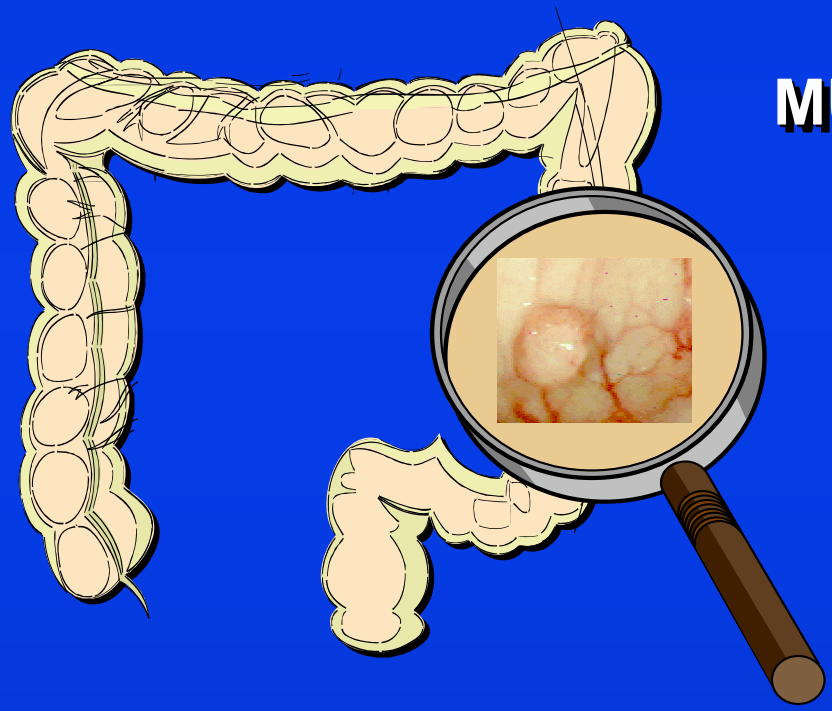
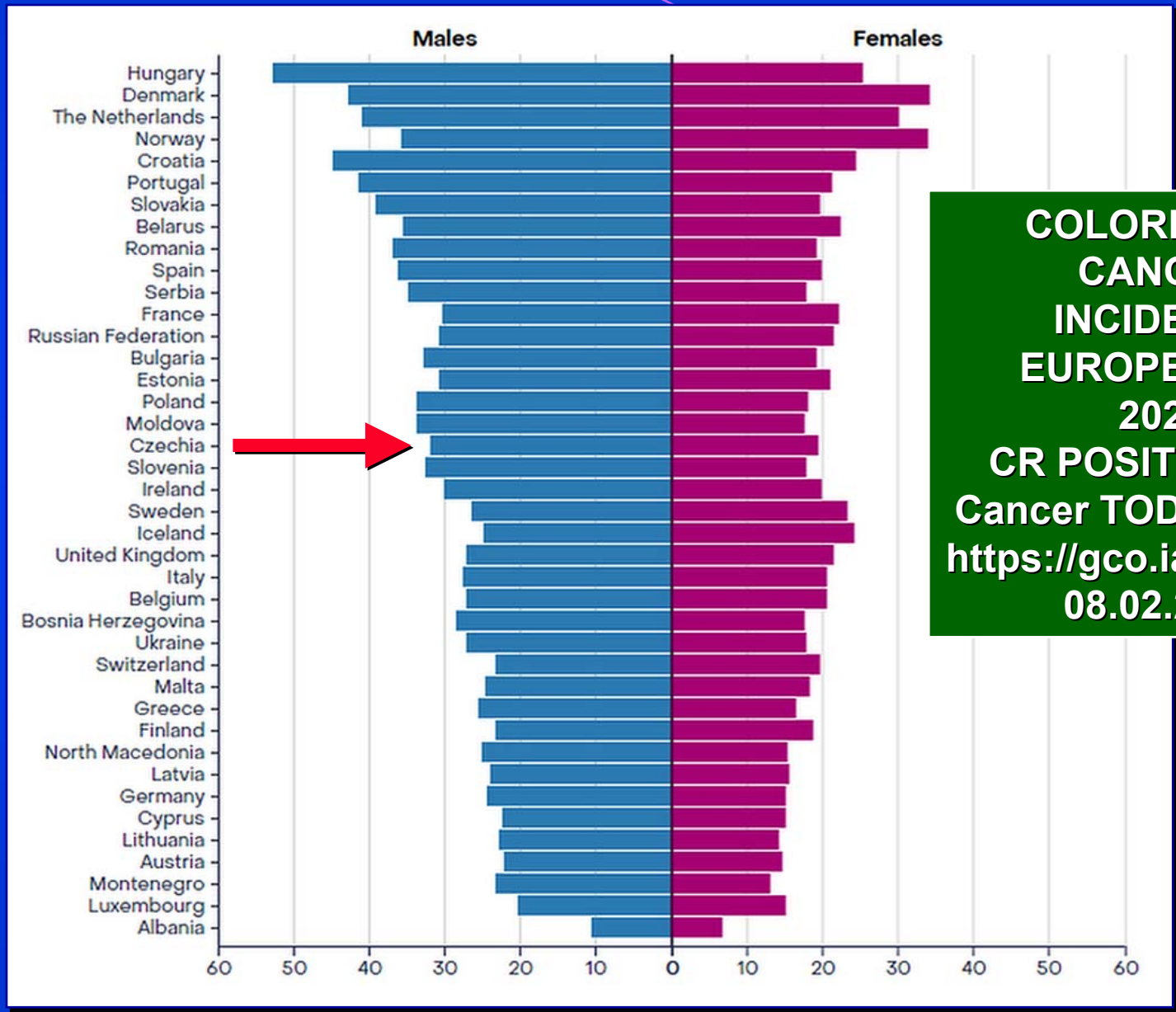
COLORECTAL CANCER SCREENING
OCCULT BLOOD IN STOOL



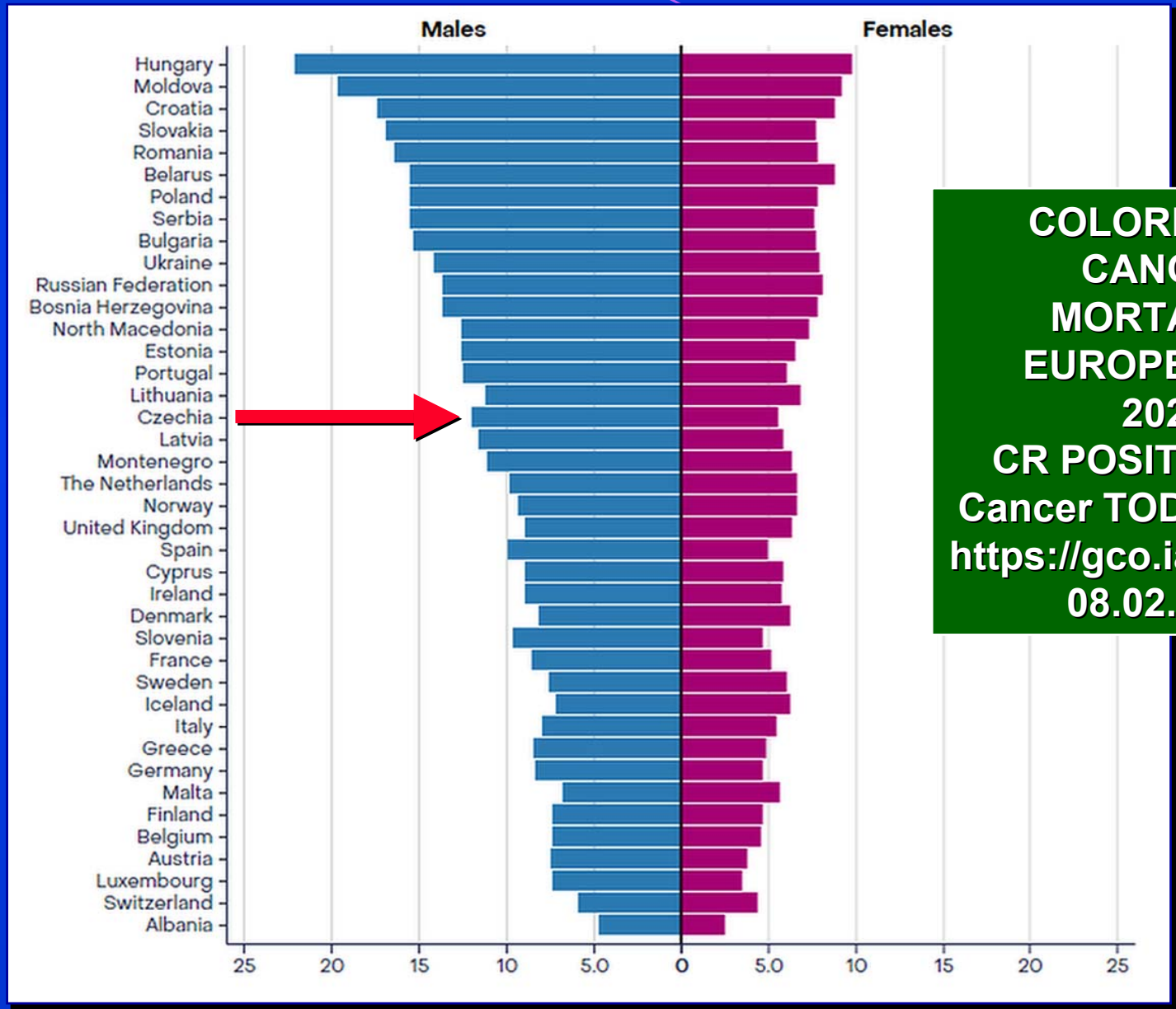
MUDr.Petr Kocna CSc.
http://gweb.zde.cz

ÚLBLD VFN a 1.LF UK

1.LF UK tutorial, July 2024

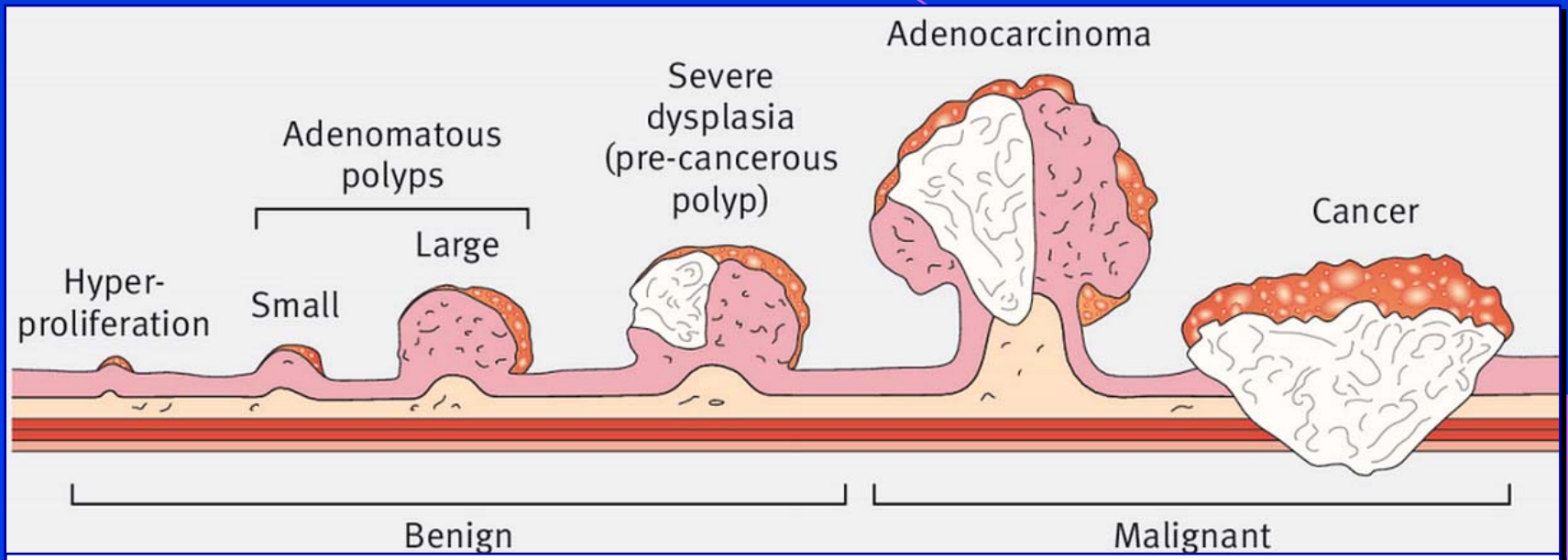


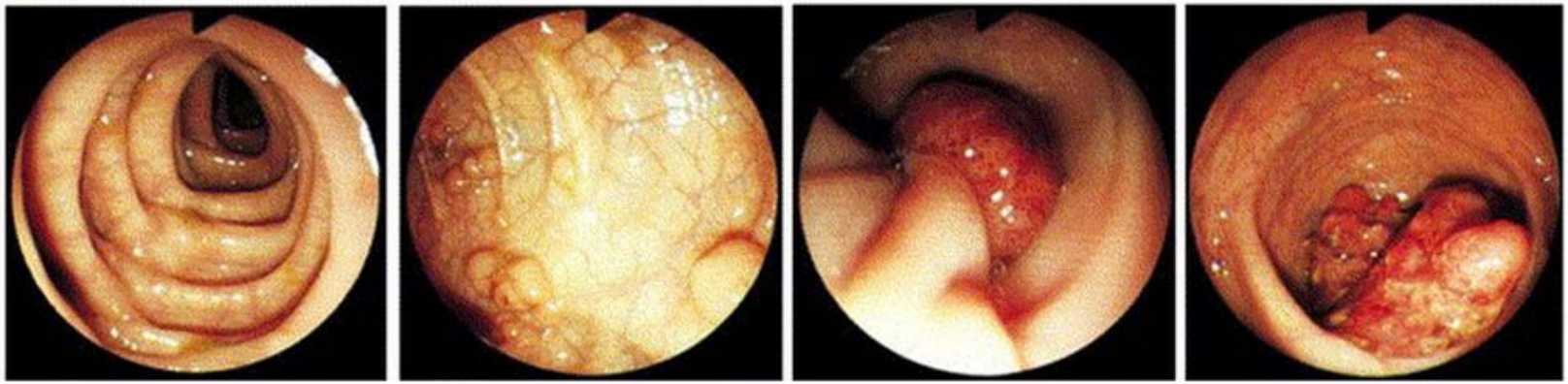
COLORECTAL CANCER INCIDENCE EUROPE - ASR 2022
CR POSITION - 18.
Cancer TODAY - IARC
https://gco.iarc.who.int
08.02.2024



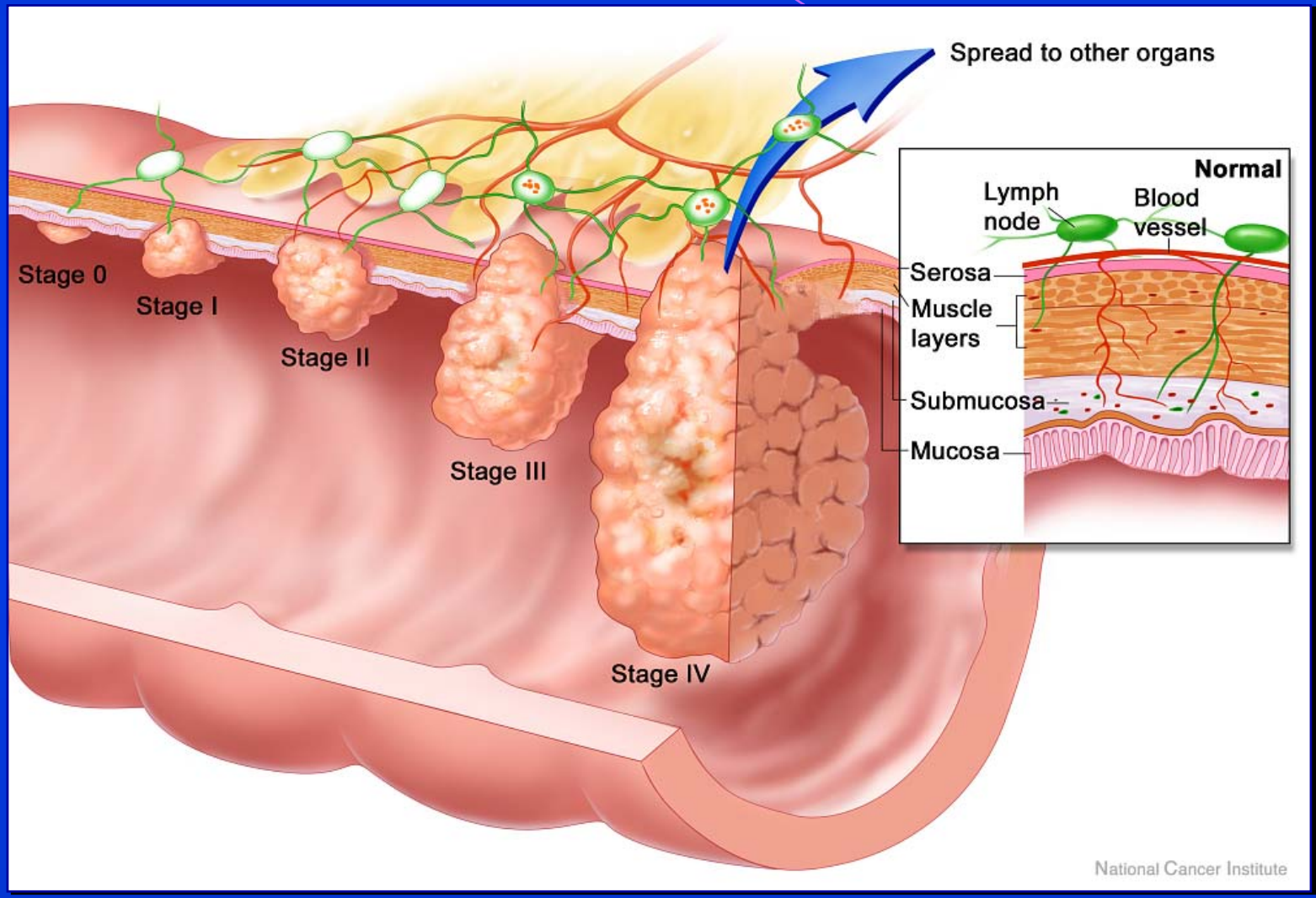
COLORECTAL CANCER MORTALITY EUROPE - ASR 2022
CR POSITION - 17.
Cancer TODAY - IARC
https://gco.iarc.who.int
08.02.2024

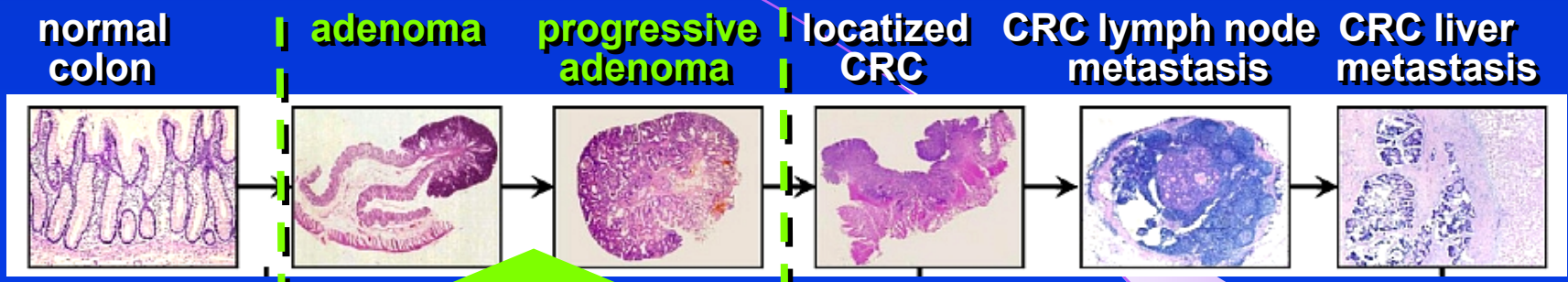
TIME SEQUENCE OF ADENOM - CARCINOMA

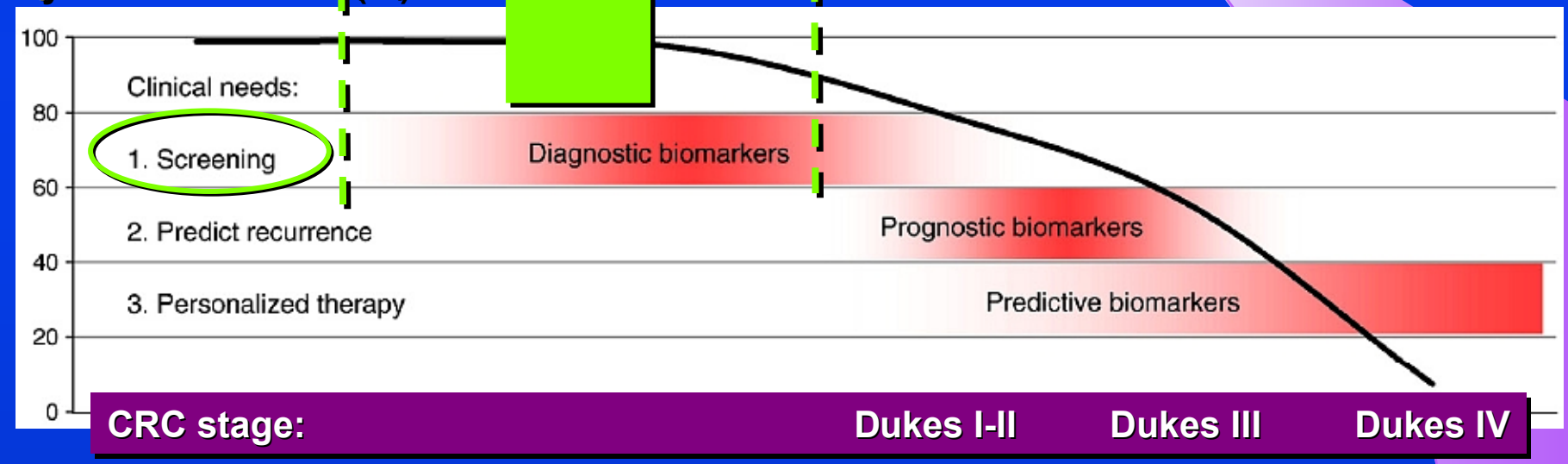




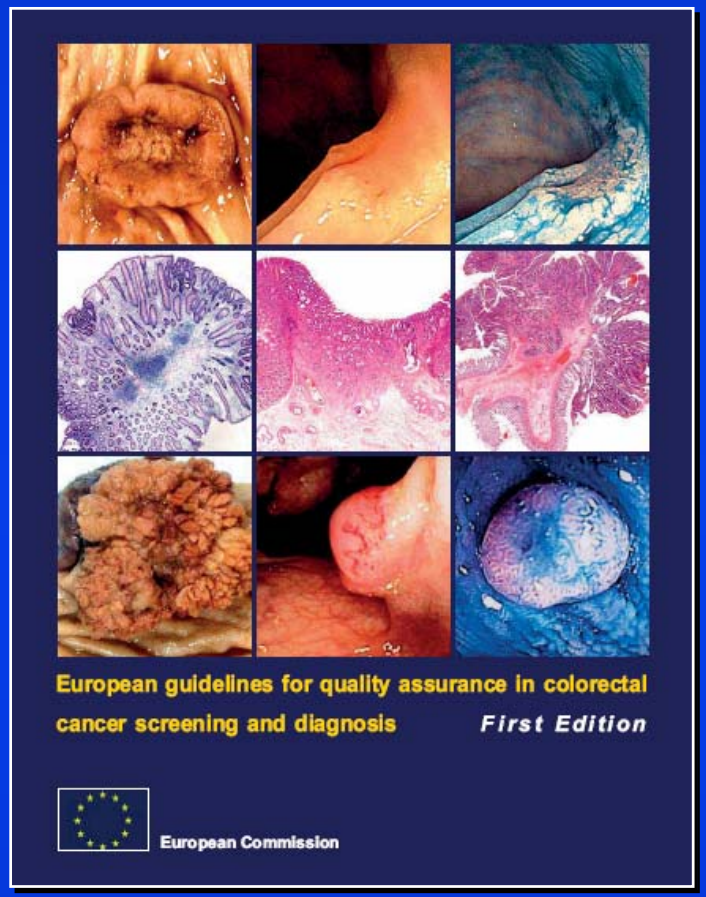
COLORECTAL CARCINOMA - STAGES, DUKES I - IV







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



European guidelines for quality assurance in colorectal cancer screening and diagnosis

http://ec.europa.eu/health/index_en.htm

03 February 2011

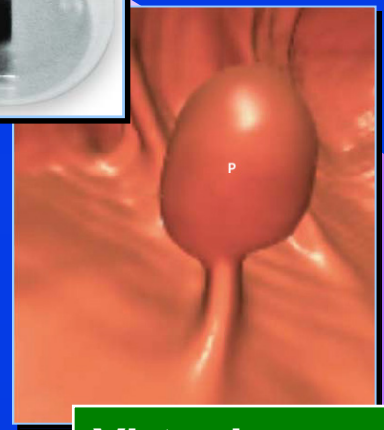
4.3.3.4 Analytical quality assurance
Internal Quality Control (IQC)
External Quality Assessment Schemes (EQAS)

CRC SCREENING METHODS AND TECHNOLOGY

FOBT, TOKS
Haemoccult

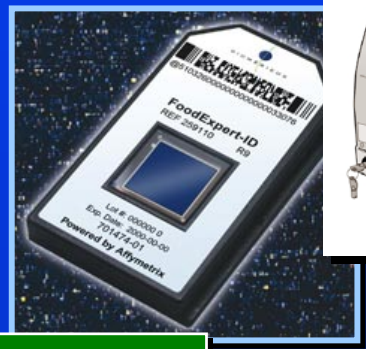
Capsule endoscopy

Screening colonoscopy



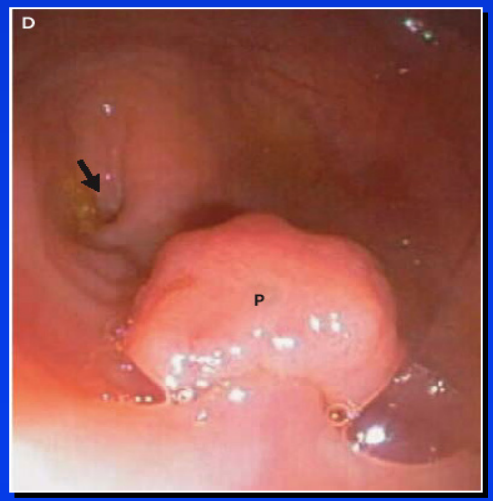
Virtual computer colonoscopy

Automatic analysis
Hb in stool

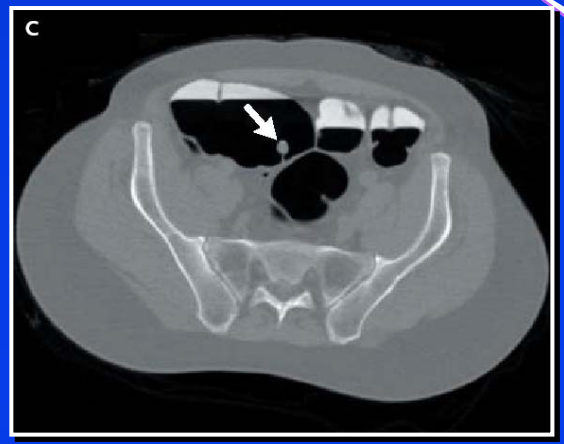


DNA chip CRC markers

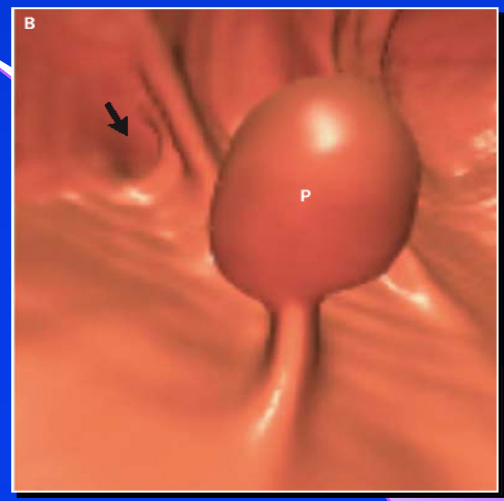
CRC SCREENING METHODS AND TECHNOLOGY



Classical - optical colonoscopy



CT scan axial 2D image



Virtual - computer colonoscopy

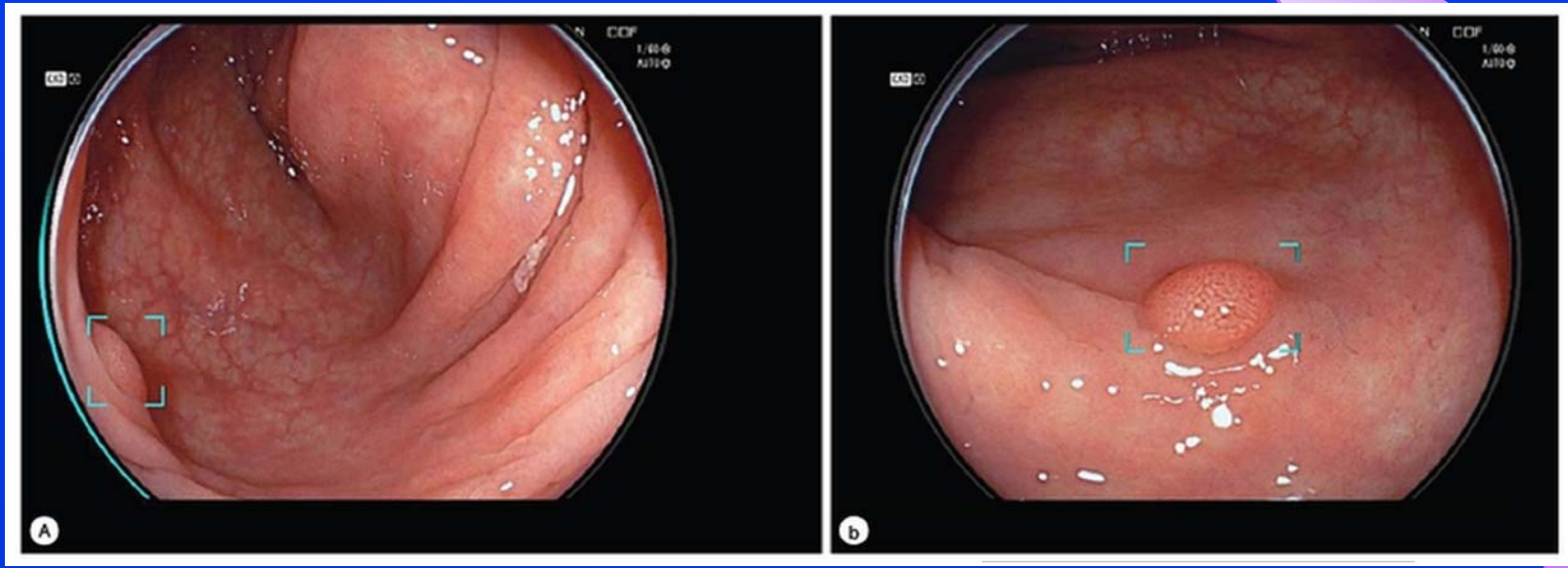
55year old man adenoma stalked 16mm in caecum

	SN / SP virtual	SN optical
polyp > 10 mm	93.8 / 96.0	87.5
polyp > 8 mm	93.9 / 92.2	91.5
polyp > 6 mm	88.7 / 79.6	92.3

Pickhardt PJ, Choi JR, Hwang I. et al.Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. N Engl J Med. 2003; 349(23): 2191-200

AI - CRC SCREENING - DETECTION OF PRECANCEROSES

Among the most important applications of AI in colonoscopy are computerized aided detection (CADe) and computer-aided diagnosis (CADx).
CADe is designed to help detect polyps during colonoscopy,
CADx is intended to predict the histology without the need for tissue biopsy.



Samarasena J, Yang D, Berzin T.M. AGA Clinical Practice Update on the Role of Artificial Intelligence in Colon Polyp Diagnosis and Management: Commentary. Gastroenterology 2023;165:1568–1573

AI - CRC SCREENING - DETECTION OF PRECANCEROSES

CAD system	Company	AI type
EndoBRAIN Cybernet Systems Corp.	Tokyo, Japan	CADx 2018
GI Genius Medtronic	Dublin, Ireland	CADe 2019
EndoBRAIN-EYE Cybernet Systems Corp:	Tokyo, Japan	CADe 2020
DISCOVERY Pentax Medical Company	Tokyo, Japan	CADe 2020
ENDO-AID Olympus Corp.	Tokyo, Japan	CADe 2020
CAD EYE Fujifilm	Tokyo, Japan	CADe,CADx 2020
Wise Vision NEC Corp.	Tokyo, Japan	CADe 2020
EndoScreener Wision A.I.	Shanghai, China	CADe 2021

Young, E.; Edwards, L.; Singh, R. The Role of Artificial Intelligence in Colorectal Cancer Screening: Lesion Detection and Lesion Characterization. Cancers 2023, 15, 5126.

AI - CRC SCREENING - DETECTION OF PRECANCEROSES

Authors, year	CADe system	Subjects number	ADR – AI	ADR - doctor
Nakashima, 2023	CAD EYE	415	59.4%	47.6%
Xu, 2023	Eagle-Eye	3059	39.9%	32.4%
Wang, 2023	EndoScreener	1261	25.8%	24.0%
Ahmad, 2022	GI Genius	658	71.4%	65.4%
Gimeno-Garcia, 2022	ENDO-AID	370	55.1%	43.8%
Repici, 2022	GI Genius	660	53.3%	44.5%
Rondonotti, 2022	CAD EYE	800	53.6%	45.3%
Shaukat, 2022	SKOUT	1359	47.8%	43.9%

Young, E.; Edwards, L.; Singh, R. The Role of Artificial Intelligence in Colorectal Cancer Screening: Lesion Detection and Lesion Characterization. Cancers 2023, 15, 5126.

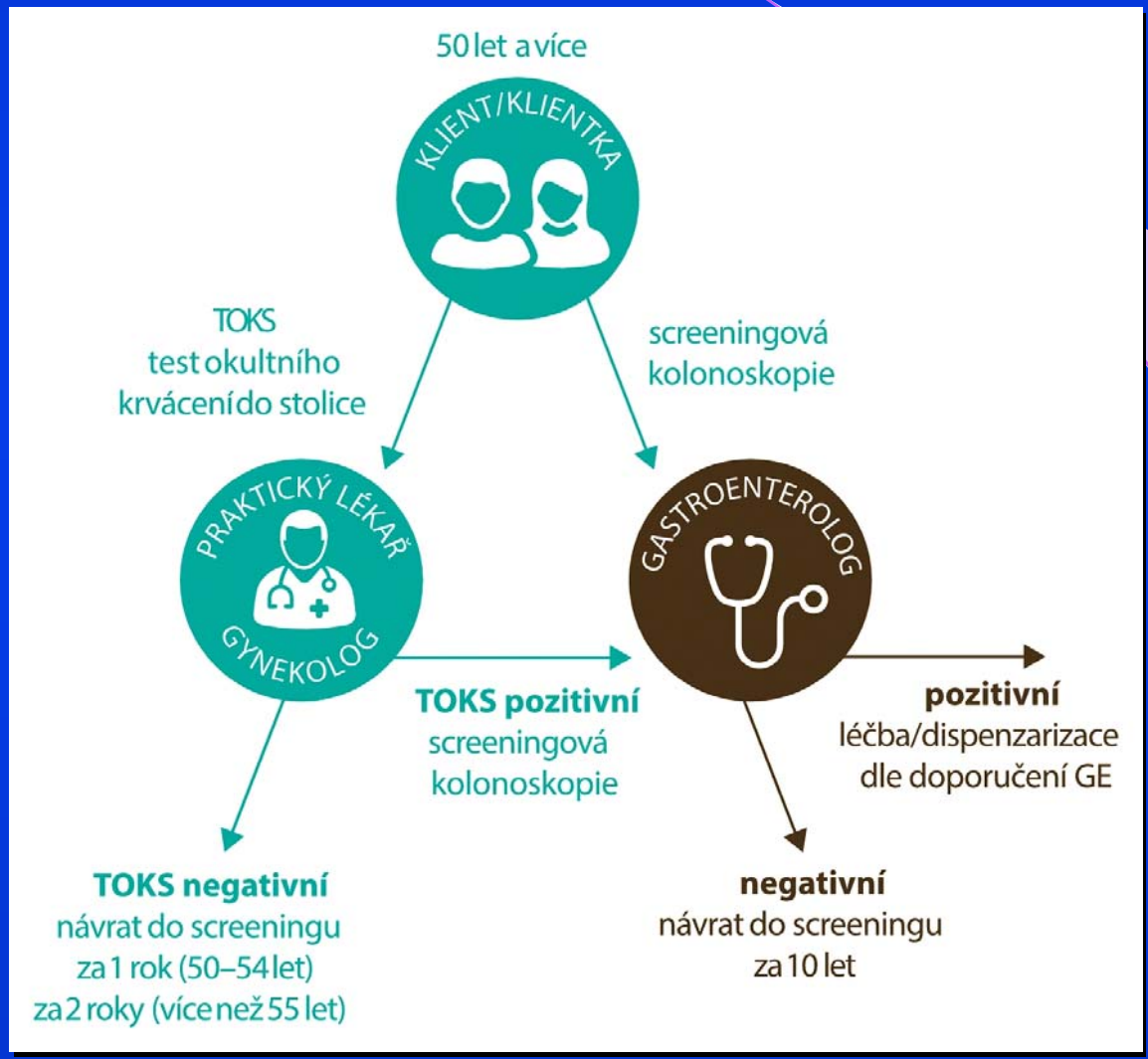
AI - CRC SCREENING - DETECTION OF PRECANCEROSES

Regarding overall histological prediction, numerous imaging-based studies and three meta-analyses demonstrated the superiority of CADx in comparison with non-expert endoscopists.
However, in none of these meta-analyses, CADx he was unable to outperform expert endoscopists

However, it has been proven that with the support of CADe can be achieved by ordinary endoscopists equivalent performance in adenoma detection as expert endoscopists with high ADR in reference centers, while standardizing the quality of service provision

Young, E.; Edwards, L.; Singh, R. The Role of Artificial Intelligence in Colorectal Cancer Screening: Lesion Detection and Lesion Characterization. Cancers 2023, 15, 5126.

COLORECTAL CANCER SCREENING PROGRAM IN CR



CRITERIA FOR SCREENING DEFINED BY THE WHO

WHO CRITERIA
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 - specifity, and few false negatives - sensitivity
6. the test or examination should be acceptable to the population
7. the cost, including diagnosis and subsequent treatment, should be economically balanced in relation to expenditure on medical care

Wilson JMG, Jungner G. & WHO: Principles and practice of screening for disease. World Health Organization, 1968. https://iris.who.int/handle/10665/37650

Validated tumor markers for screening

- Fecal Occult Blood Test (colorectal cancer)
- Prostate Specific Antigen (prostate cancer)
- Alpha Fetoprotein (hepatocellular cancer)

- Presence of a suitable and reliable tumor marker test
- Presence of a latent early symptomatic stage
- Screening provides more benefit that harm
- High prevalence
- Affordable cost

Classification of tumor markers. Characteristics of ideal tumor markers. Zima T. IFCC EuroMedLab Munich, 2022, Symposim April 12.

Evidence to date suggests that occult bleeding tested by FIT will remain the best test for population screening for CRC in the next decade. Quantitative FIT offers a significant opportunity incorporating FIT test values into the risk of KRCa screening algorithm.

Benton SC, Seaman HE, Halloran SP. Curr Gastroenterol Rep (2015) 17:7
Faecal Occult Blood Testing for Colorectal Cancer Screening: the Past or the Future

- Colorectal carcinoma is the most common tumor of the GE tract
- In the Czech Republic (2017) was diagnosed 7439 subjects with CRC, on CRC died 3685 patients, more than 50% of the mortality is due to the high proportion of patients diagnosed in advanced stages III and IV
- Screening over 50 years - the target population in the Czech Republic 2017 - includes 4,056 641 subjects
- FOBT/TOKS screening test was carried out in 2015/16 in 1 202 628 persons, ie. 29.6%
- FOBT/TOKS + indicated colonoscopy in 2017 found only 846 CRC of 8136 diagnosed CRC, which is only 11.3%

Suchanek S., Majek O., Vojtechova G., Minarikova P., Rotnaglova B., Seifert B., Minarik M., Kozeny P., Dusek L., Zavoral M.: Colorectal cancer prevention in the Czech Republic: time trends in performance indicators and current situation after 10 years of screening
European Journal of Cancer Prevention 2014, 23:18–26

COLORECTAL CANCER SCREENING PROGRAM IN CR

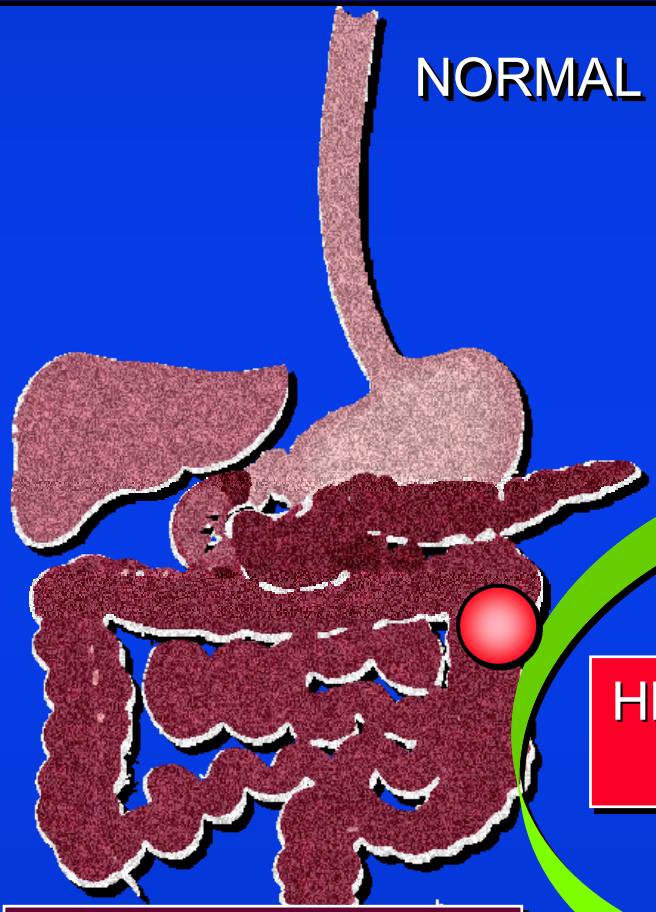
GENERAL PRACTITIONERS

LABORATORY

GASTROENTEROLOGY

BLOOD LOOS IN HEALTHY SUBJECTS

NORMAL LEVEL, CUT-OFF



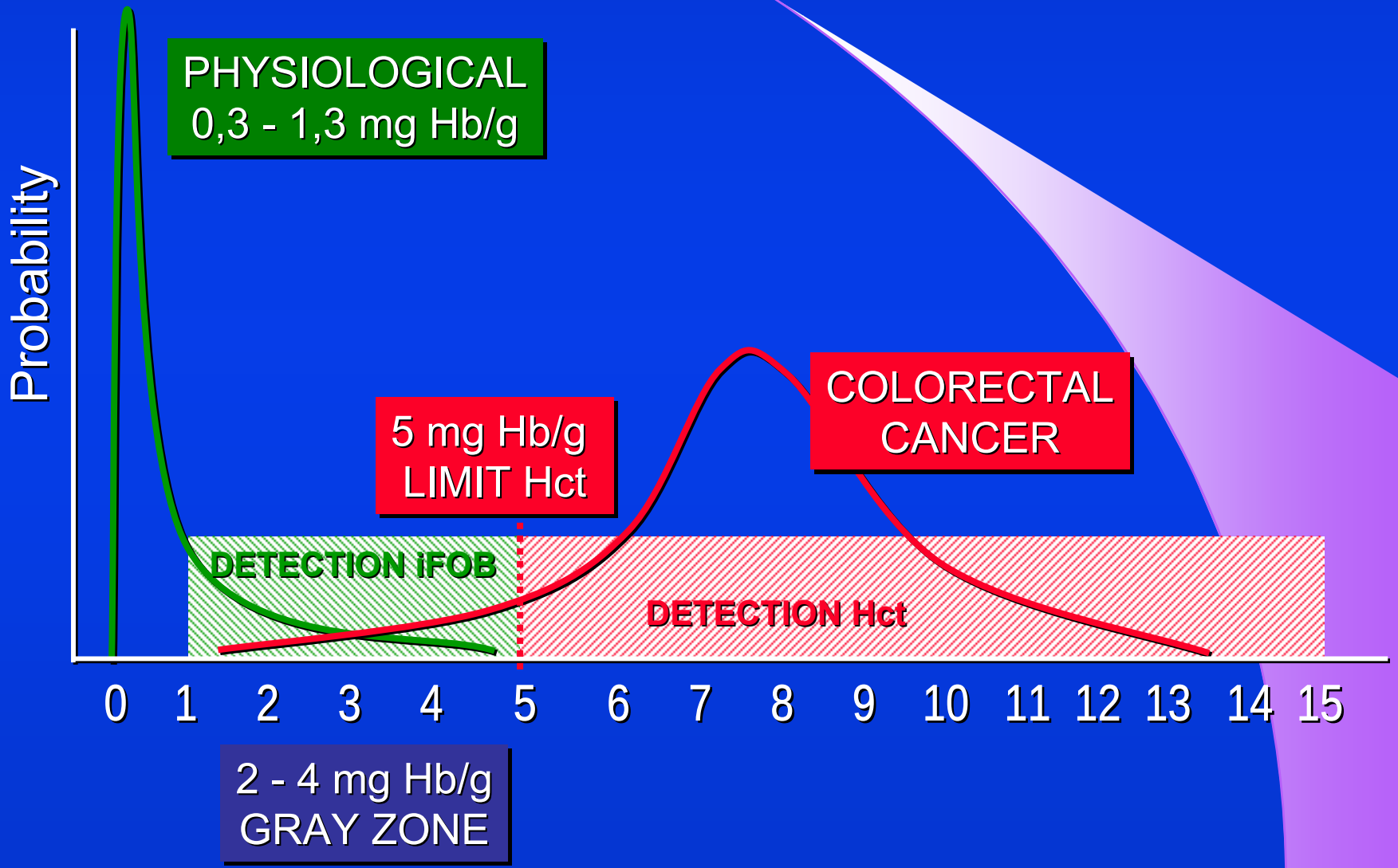
BLOOD LOOS IN HEALTHY
0,5 - 2,5 ml BLOOD 24 hr.

Hb CONCENTRATION
120 - 150 mg/ml

STOOL AMOUNT
300 - 450 g in 24 hr.

Hb CONCENTRATION
0,3 - 1,3 mg Hb/g STOOL

CONCENTRATION of Hb/g STOOL in CRC



2000

National Colorectal Cancer Screening Program
Guaiac detection of occult bleeding - TOKS (Haemoccult)

TESTS FOR OCCULT BLEEDING IN STOOL - FOBT/TOKS

1974 - 50 years ago

Laboratory of the Internal Department

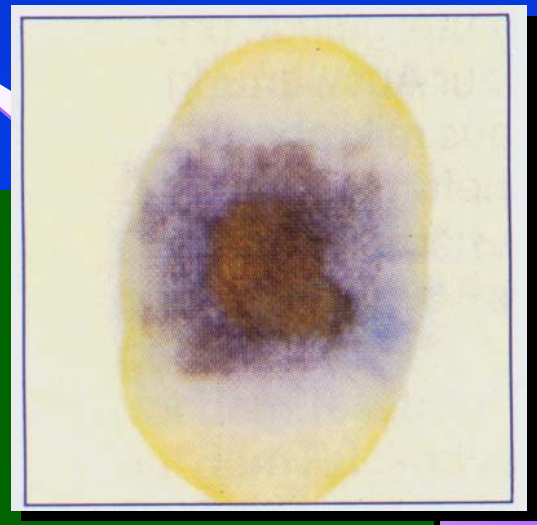
prof. MUDr. Přemysl Frič, DrSc.

Haemoccult has been exclusively recommended for CRC screening for reproducibility and accuracy of stool blood analysis

died March 2024

Frič, P.: The use of haemoccult test in the early diagnosis of colerectal cancer – experience from six pilot studies in Czechoslovakia, in: Haemoccult screening for the early detection of colorectal cancer Schattauer, Stuttgart 1986, p. 73-74

TESTS FOR OCCULT BLEEDING IN STOOL - FOBT/TOKS

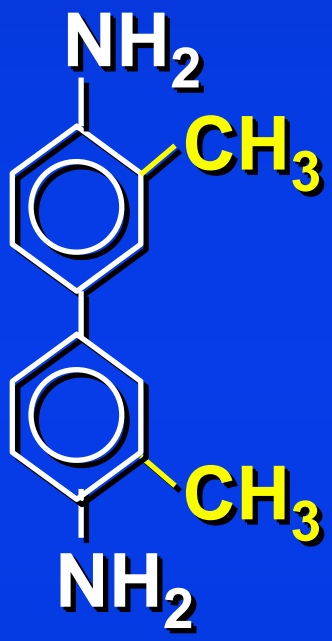


- Guaiac test – TOKS – gFOBT
- Chemical reaction Hb
- The test required dietary preparation
- The patient collected 3 stool samples
- The test showed almost 100% specificity
- The sensitivity of gFOBT for KRCA was about 30%
- Haemoccult was the only approved test in the Czech Republic

Ferkl, M.; Kocna, P.; Frič, P., Srovnání stanovení okultního krvácení ve stolici imunochemickou a biochemickou metodou, Časopis lékařů českých, 1992, 131, 5, 149-151

TESTS FOR OCCULT BLEEDING IN STOOL - FOBT/TOKS

CHEMICAL METHODS



BENZIDIN *p-diamino-diphenyl*

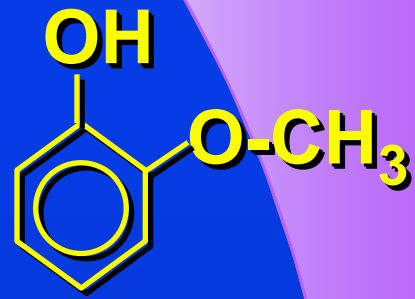
o-TOLIDIN *dimethylbenzidin*

TMB *tetramethylbenzidin*

GUAJAC RESIN

G.officinale, G.sanctum

GUAJACOL *o-methoxyphenol*



PSEUDOPEROXIDASE REACTION

TESTS FOR OCCULT BLEEDING IN STOOL - FOBT/TOKS

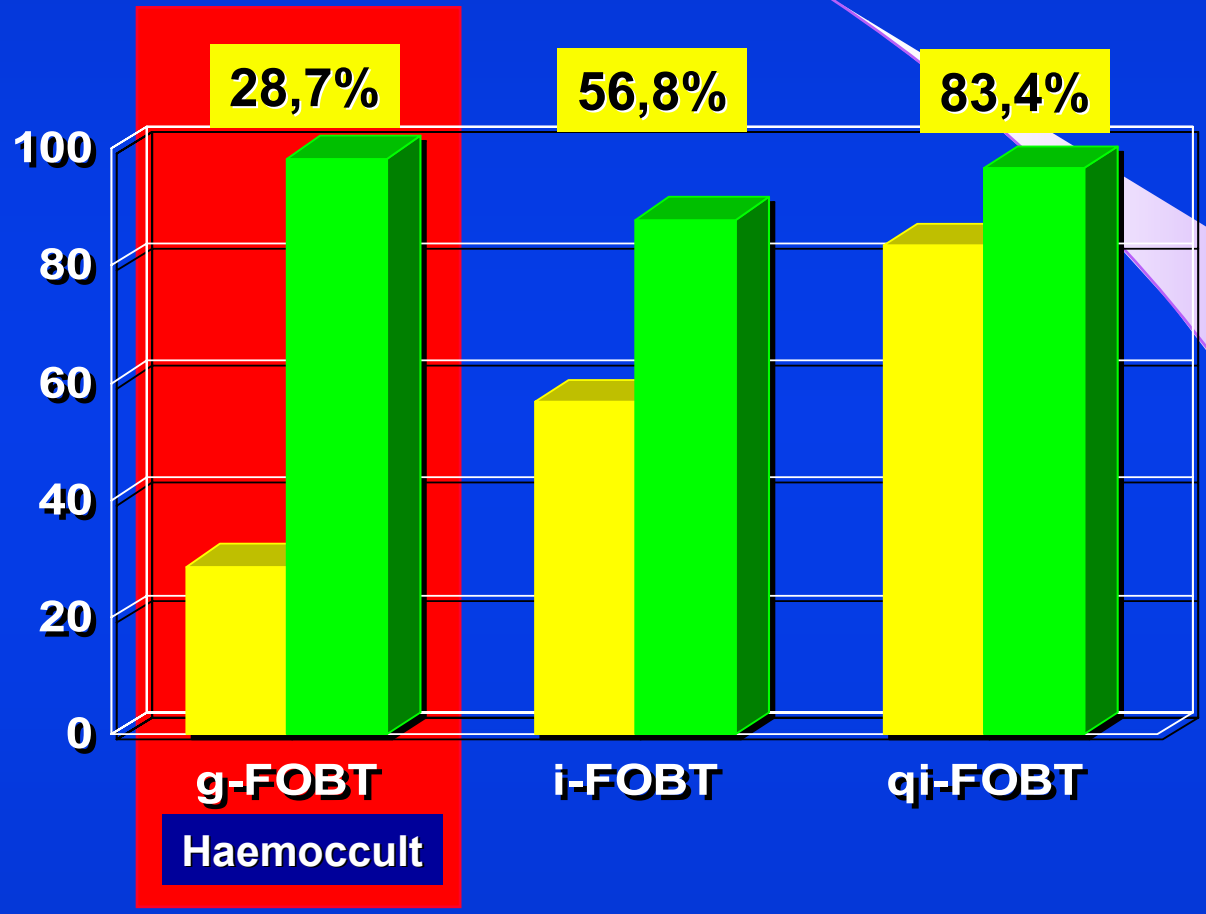
- HAEMOCCULT
- HEMO CARE
- HEMDETECT
- HEMA-CHECK
- COLOSCREEN
- HEMASCREEN

GUAJAC RESIN

- KRYPTO-HAEM

o-TOLIDIN

g-FOBT – GUAJAC TEST, HAEMOCCULT



g-FOBT WITH SENSITIVITY < 30% USED TILL 31.12. 2012

Commitee of CRC screening at Ministry of health CR, July 2012

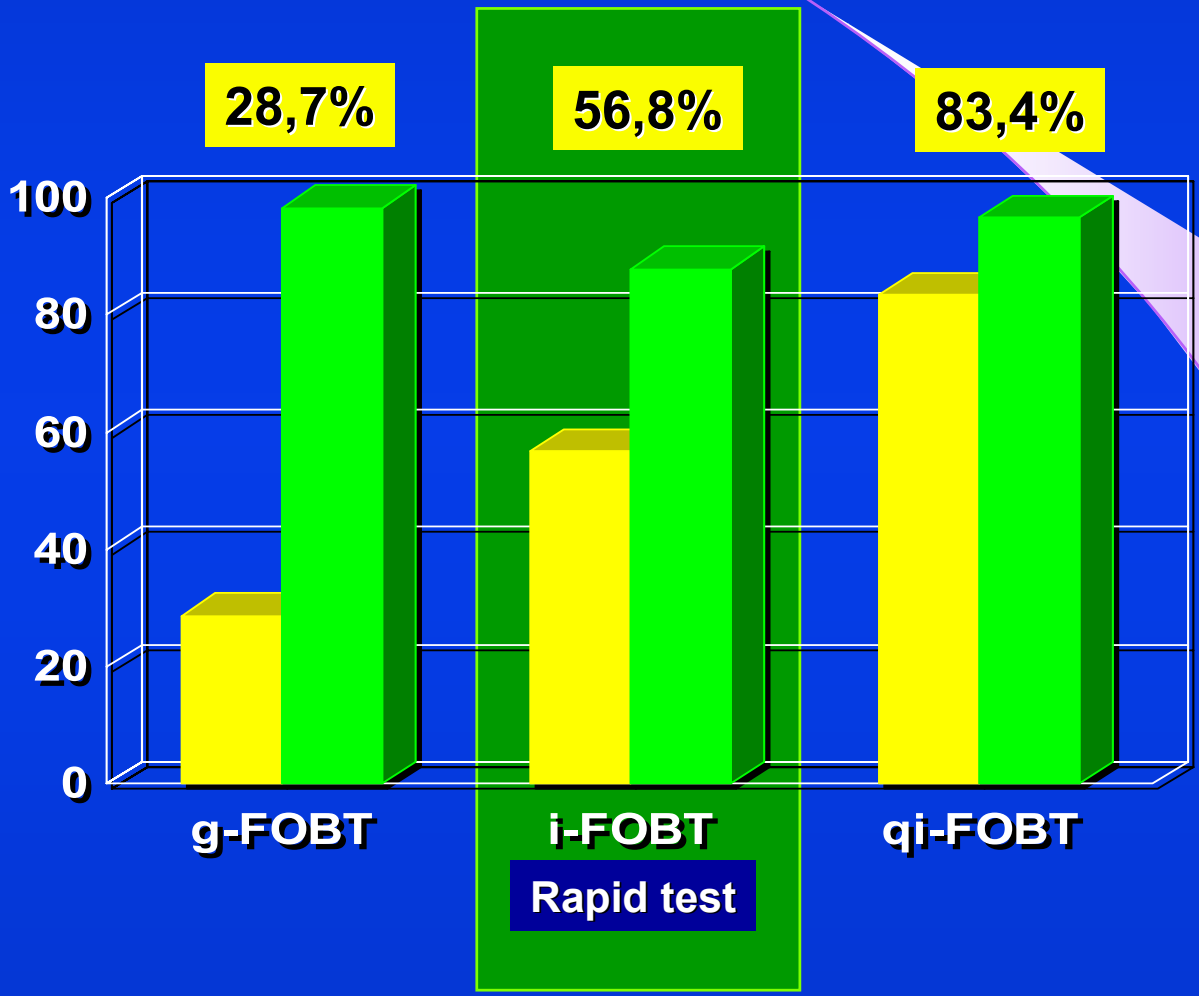
2000

National Colorectal Cancer Screening Program
Guaiac detection of occult bleeding - TOKS (Haemoccult)

2010

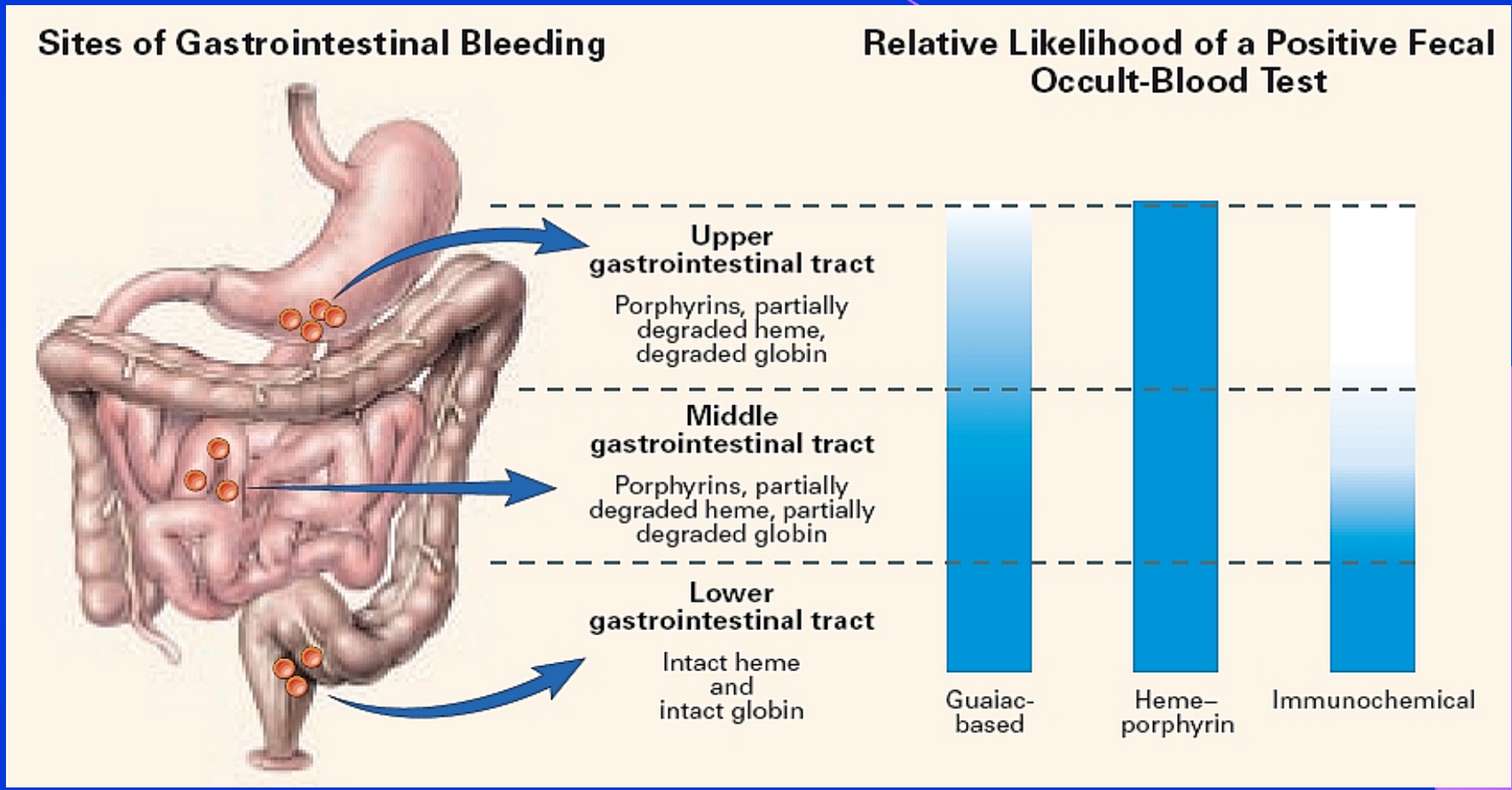
TOKS by the guaiac or immunochemical method
g-FOBT/ i-FOBT, Publication of the Ministry of Health

i-FOBT QUALITATIVE, RAPID TEST



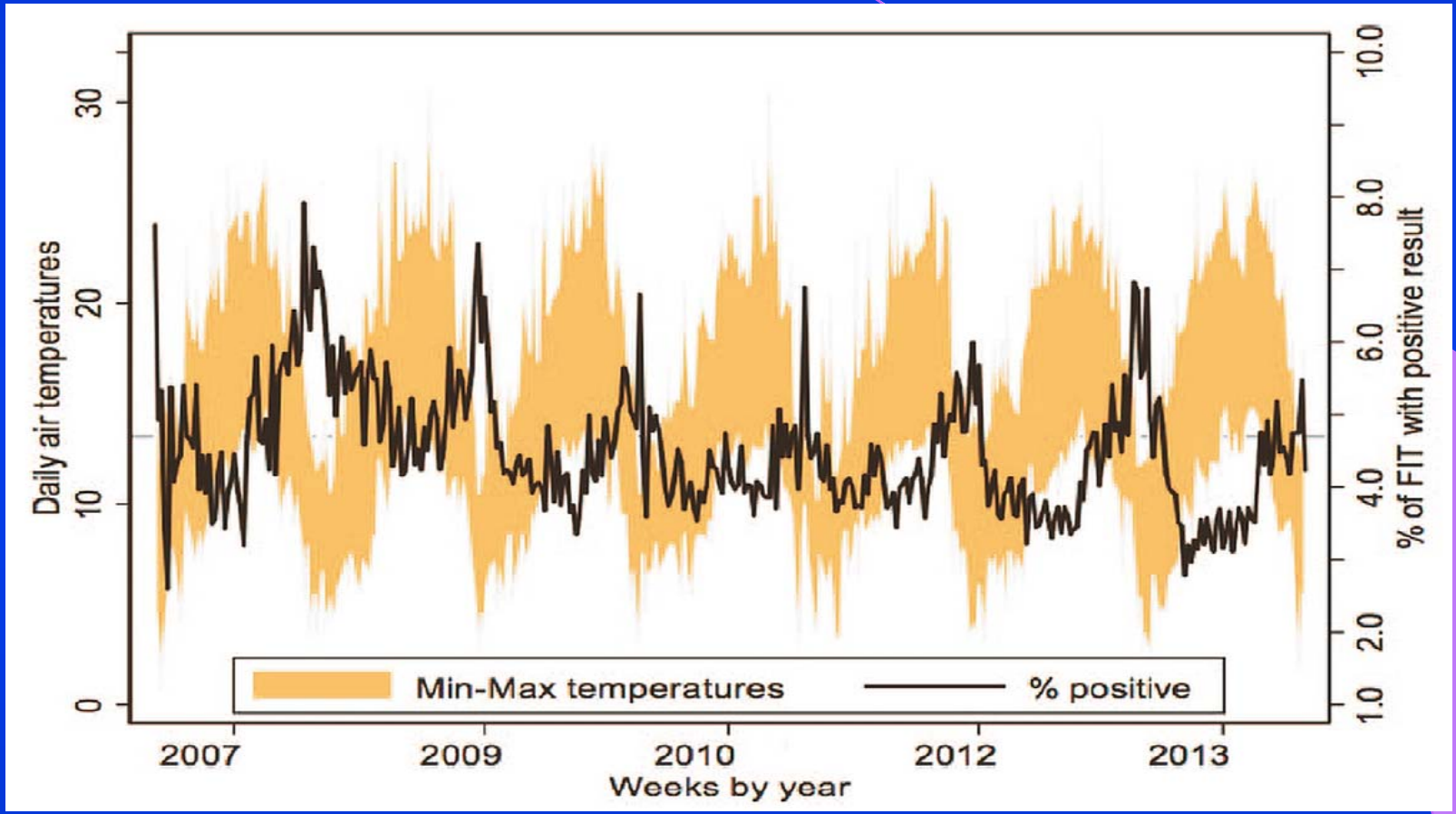
2 TIMES HIGNER SENSITIVITY OF i-FOBTs TO GUAJAC g-FOBTs

METHOD OF DETECTION OF OCCULT BLEEDING



Rockey DC, Auslander A, Greenberg PD. Am J Gastroenterol. 1999; 94: 344-50
Detection of upper gastrointestinal blood with fecal occult blood tests.

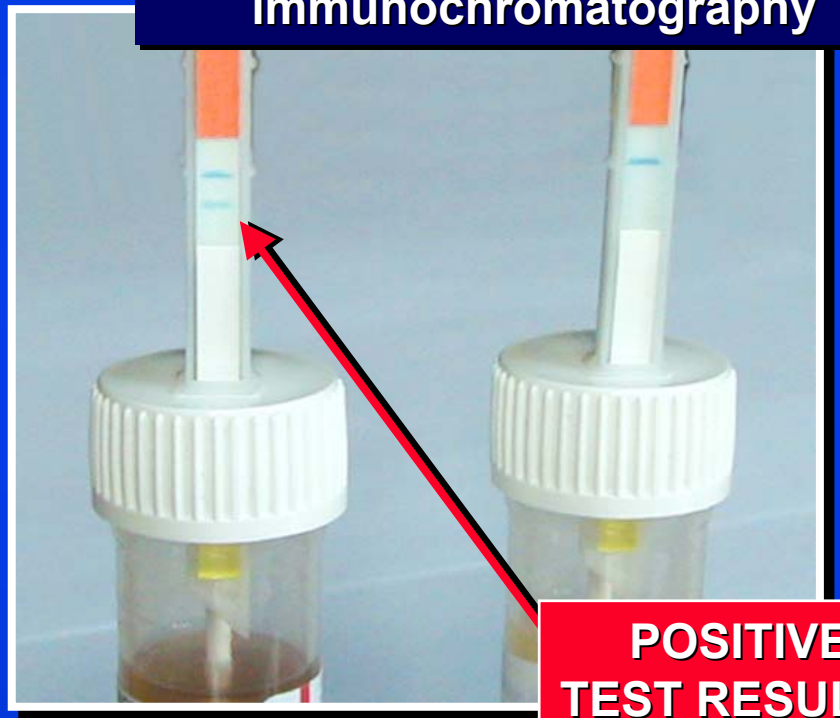
FIT TEST POSITIVITY – THE EFFECT OF TEMPERATURE



Doubeni CA, Jensen CD, Fedewa SA. et al. J Am Board Fam Med. 2016; 29(6):672-681.
Fecal Immunochemical Test (FIT) for Colon Cancer Screening:
Variable Performance with Ambient Temperature.

IMMUNOCHEMICAL METHODS OF FOBT

Actim Fecal Blood (Medix Bioch.) immunochromatography



POSITIVE TEST RESULTS

NO CONTACT WITH STOOL SAMPLES

Hexagon OBTI (Labmark) immunochromatography

PRINCIPLE : IMMUNOAFINITY CHROMATOGRAPHY

IMMO-CARE
CARE Diagnostica

2000	National Colorectal Cancer Screening Program Guaiac detection of occult bleeding - TOKS (Haemoccult)
2010	TOKS by the guaiac or immunochemical method g-FOBT/ i-FOBT, Publication of the Ministry of Health
2014	**TOKS only by immunochemical method i-FOBT quantitative and qualitative tests**

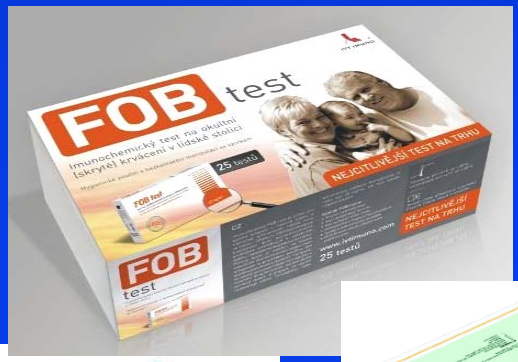
QUALITATIVE FIT METHODS, RAPID TESTS - POCT

German study - Dtsch Med Wochenschr - 05/2016

- There are different FITs on the market,
  namely qualitative FITs (point-of-care tests) and quantitative FITs.
- European Guidelines for quality assurance in colorectal cancer screening
  only recommend quantitative FITs
- The use of qualitative FITs is not a tenable option for a
  quality-assured screening program.

Haug U., Becker N. Dtsch med Wochenschr 2016; 141(10): 729-731
Immunochemical fecal occult blood tests for colorectal cancer screening: Point-of-care tests are not tenable for a quality-assured program

WIDE OFFER OF iFOBT RAPID TESTS IN THE CZECH REPUBLIC



i-FOBT QUALITATIVE, RAPID TESTS

- ✓ iFOBT Rapid tests available in the CR from 20 producers
- ✓ iFOBT tests varied highly in the sensitivity and accuracy
- ✓ iFOBT tests sensitivity varied from 100 ng Hb/ml to 2000 ng Hb/ml
- ✓ Rapid iFOBT tests use very different sampling devices
- ✓ Rapid iFOBT tests varied in the Hb/extract buffer stability

Haug U, Hundt S, Brenner H. - Am J Gastroenterol. 2010 Mar;105(3):682-690
Quantitative immunochemical fecal occult blood testing for colorectal adenoma detection: evaluation in the target population of screening and comparison with qualitative tests.

- ✓ Mayo Clinic study of 750 subjects, colonoscpy verified
- ✓ FIT qualitative - false positivity - 7.4%
- ✓ FIT quantitative - false positivity - 3.8%

Colorectal Cancer Screening Committee, DDW 2012 Workshop
Expert Working Group – Fit for Screening - prof. Stephen Halloran
Director: NHS Bowel Cancer Screening

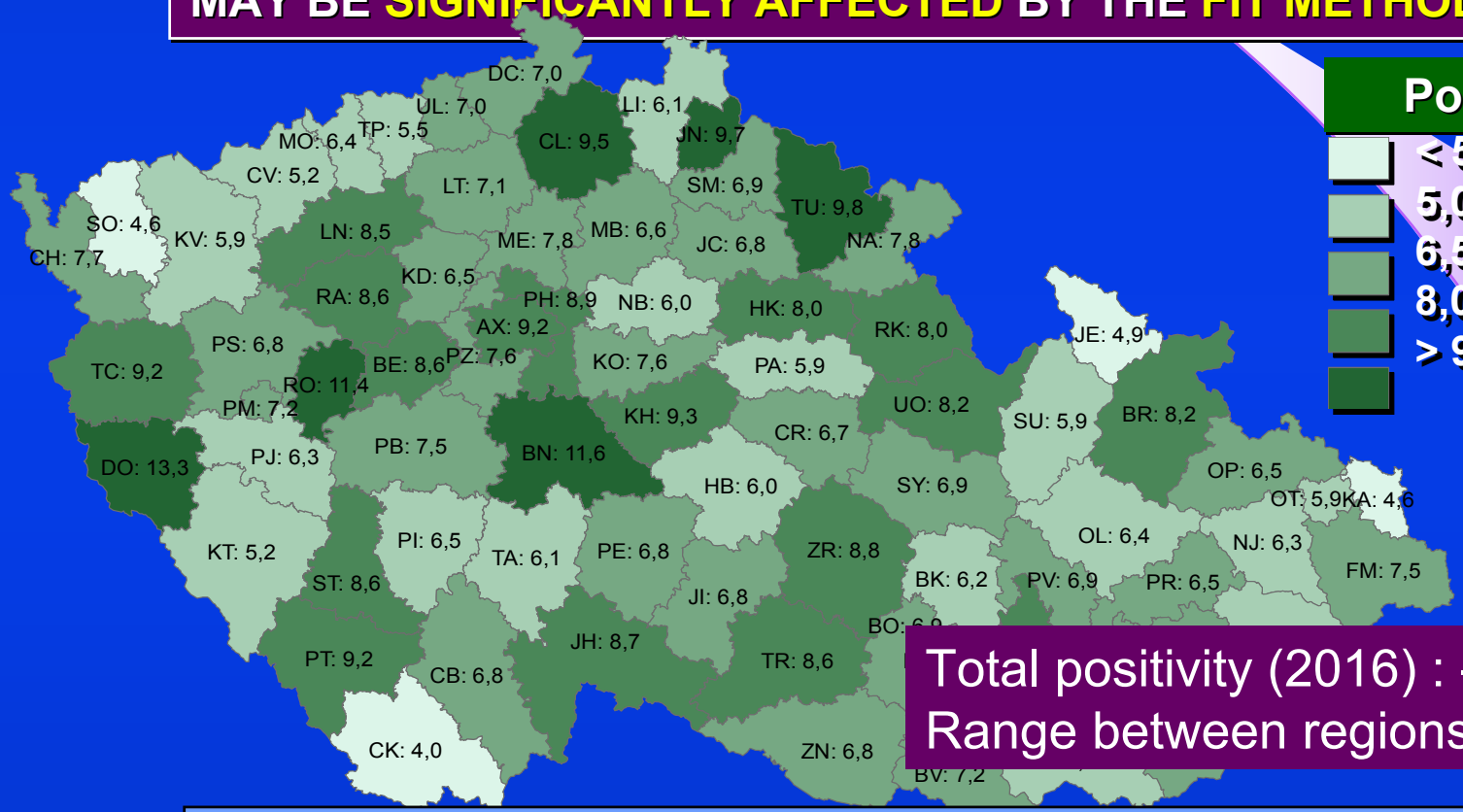
UNITS & CUT-OFF VALUE (ng Hb/ml / mg Hb/g stool)

FIT test	Sampling	Conc.	Ratio	cut-off	cut-off
		mg/ml		ng/ml	mg/g
ColonView	1mg/2ml	0.50	1	40	80
immo-Care-C	11.5 mg/2.5ml	4.60	9,2	50	11
FOB Test	10mg/2ml	5.00	10	40	8
OC-Light	10mg/2ml	5.00	10	50	10
EpiTuub® iFOB	5-10mg/1.1ml	4,5-9	9-18	50	5.5-11
Hema-screen™	x /1.7-1.8ml	1.00	2	50	50
FOB test	3-10mg/3ml	1.0-3,3	2-6,6	10	3.3-10
Hb FECALE	100-200mg/2ml	50-100	100-200	40	0.4-0.8
Actim Fecal Blood	10-20mg/10ml	1.0-2.0	2-4	50	25-50
Easy-Card				200	
SureScreen FOB				50	

Tests with **identical** cut-off in Hb ng/ml
may have up to **200x times higher, or lower**, cut-off in mg Hb/g stool

POSITIVITY OF FIT IN THE CZECH REPUBLIC

POSITIVITY OF FIT IN INDIVIDUAL REGIONS MAY BE SIGNIFICANTLY AFFECTED BY THE FIT METHOD USED



Total positivity (2016) : - 7.2 %
Range between regions: 4.0 - 13.3 %

Májek O., Suchánek Š. Quality-assured immunochemical testing – proposal for a pilot project in the Czech Republic European Digestive Cancer Days, Prague - 26. September 2017

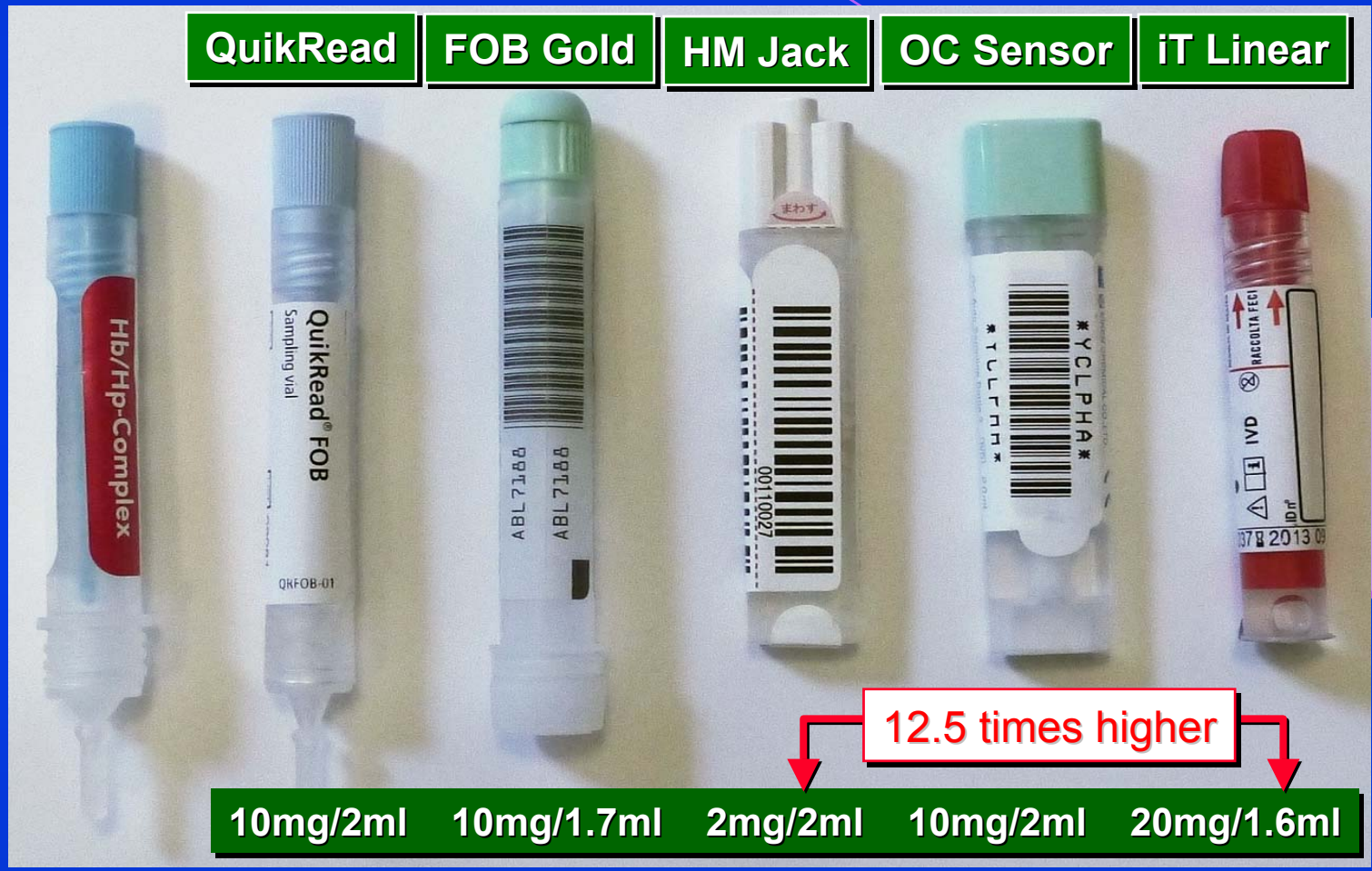
- Most available immunoassays use different sample collection methods, differ in the volume and characteristics of the sampling buffer with respect to Hb stability, and report Hb concentrations in different ways.
- The current lack of consistency in units of Hb concentration is particularly problematic because apparently similar Hb concentrations obtained by different devices can lead to very different clinical interpretations.
- Consistent adoption of an internationally accepted method for reporting results would facilitate comparison of the results of these tests. We propose a simple strategy for reporting stool Hb concentration.

J Natl Cancer Inst - 04/2012

WEO

Fraser CG, Allison JE, Halloran SP, Young GP, Expert Working Group on Fecal Immunochemical Tests for Hemoglobin, Colorectal Cancer Screening Committee WEO. J Natl Cancer Inst 2012;104:810–14. A proposal to standardize reporting units for fecal immunochemical tests for hemoglobin.

UNITS & CUT-OFF VALUE (ng Hb/ml / mg Hb/g stool)



VARIABLE SAMPLING DEVICES FOR FIT, WITH DIFFERENT CONCENTRATION OF STOOL IN THE SAMPLING SOLUTION

cut-off 100 ng Hb/ml = 20 μg Hb/g stool (10 mg stool - 2 ml buffer)

20 mg stool

5 mg stool

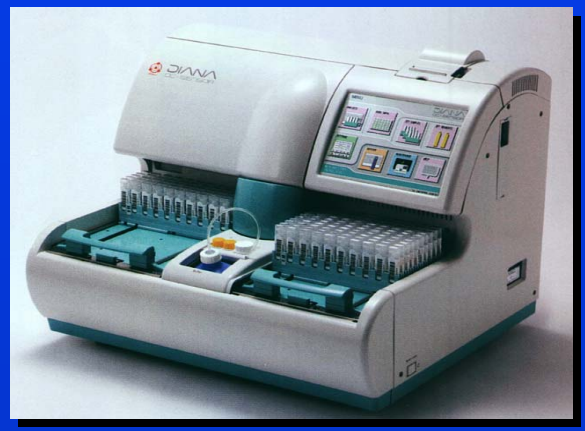
4x lower stool concentration
reacts positively up to
4x higher concentration of Hb in stool

4 ml buffer

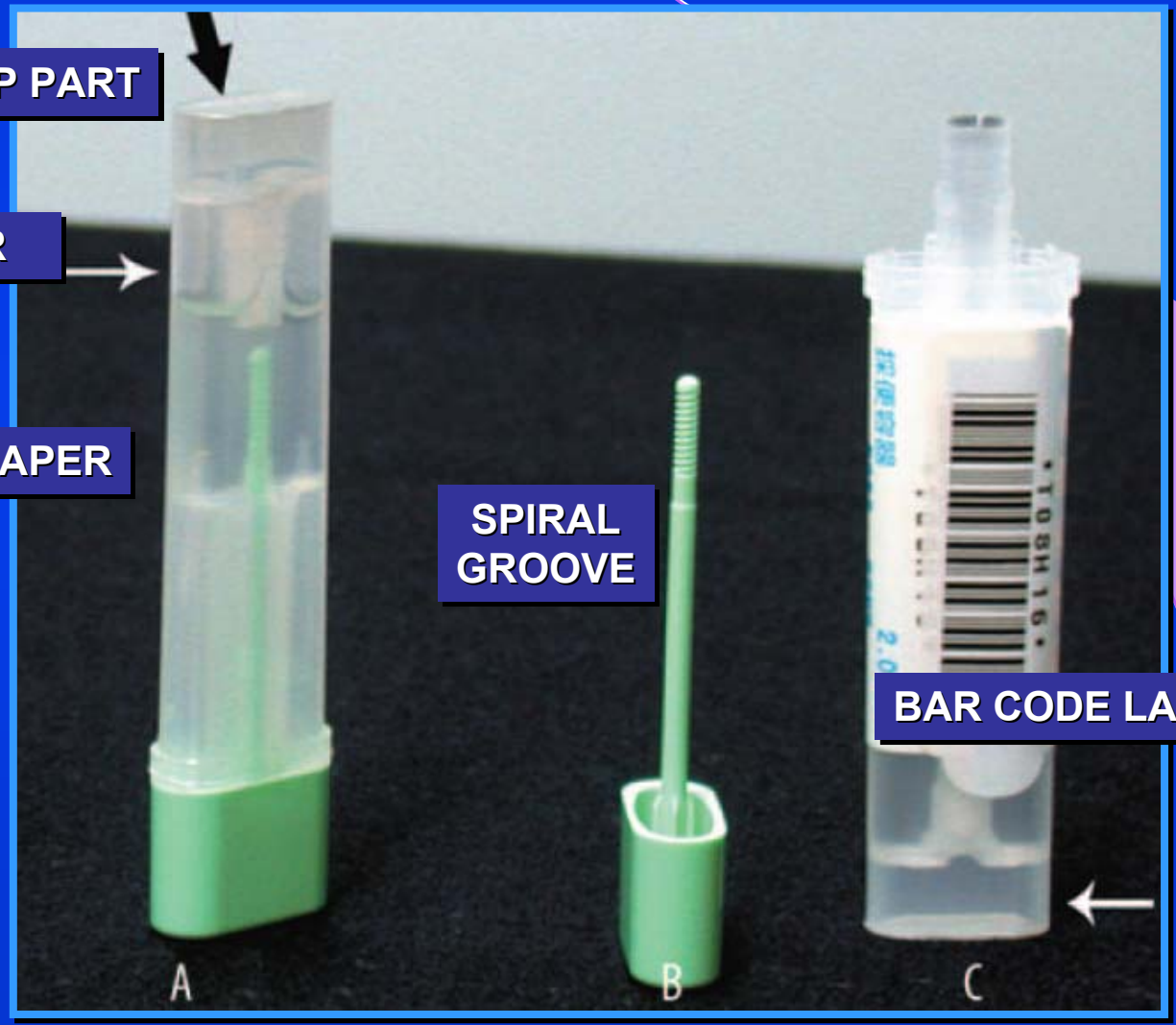
1 ml buffer

4x higher stool concentration
responds positively to
4x lower concentration of Hb in stool

2000	National Colorectal Cancer Screening Program Guaiac detection of occult bleeding - TOKS (Haemoccult)
2010	TOKS by the guaiac or immunochemical method g-FOBT/ i-FOBT, Publication of the Ministry of Health
2014	TOKS only by immunochemical method i-FOBT quantitative and qualitative tests
2020	FIT-TOKS only by a quantitative immunochemical method on a laboratory or POCT analyzer



SAMPLING SYSTEM - OC SENSOR μ

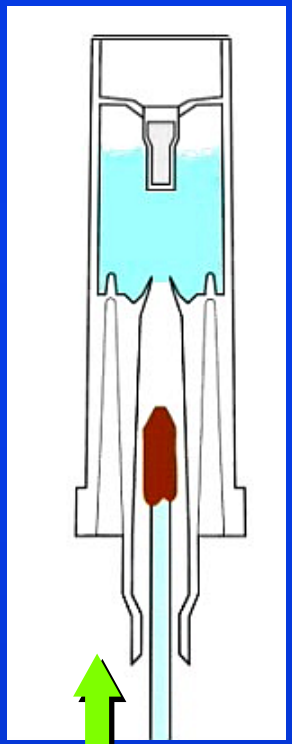


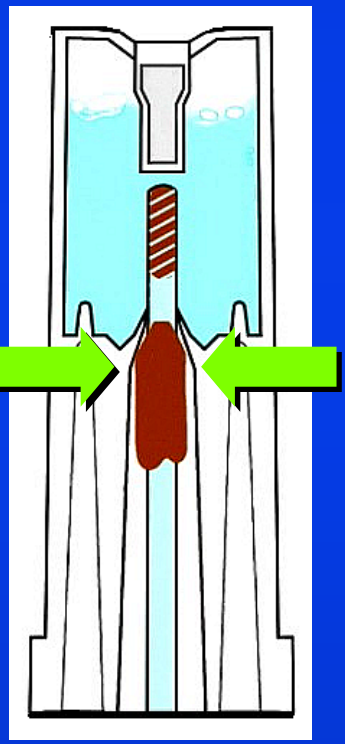
SAMPLING SYSTEM - OC SENSOR μ

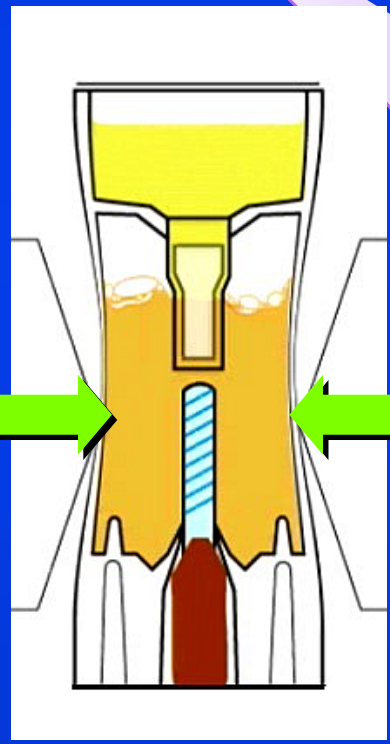
STOOL SAMPLE INSERT

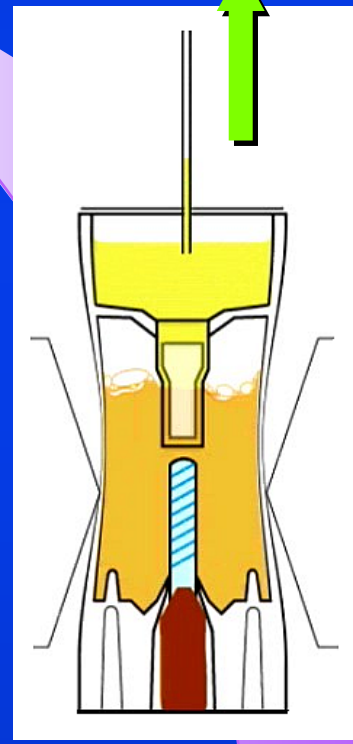
ALUMINIUM FOIL PERFORATION

25 μl INJECT TO CUVETTE





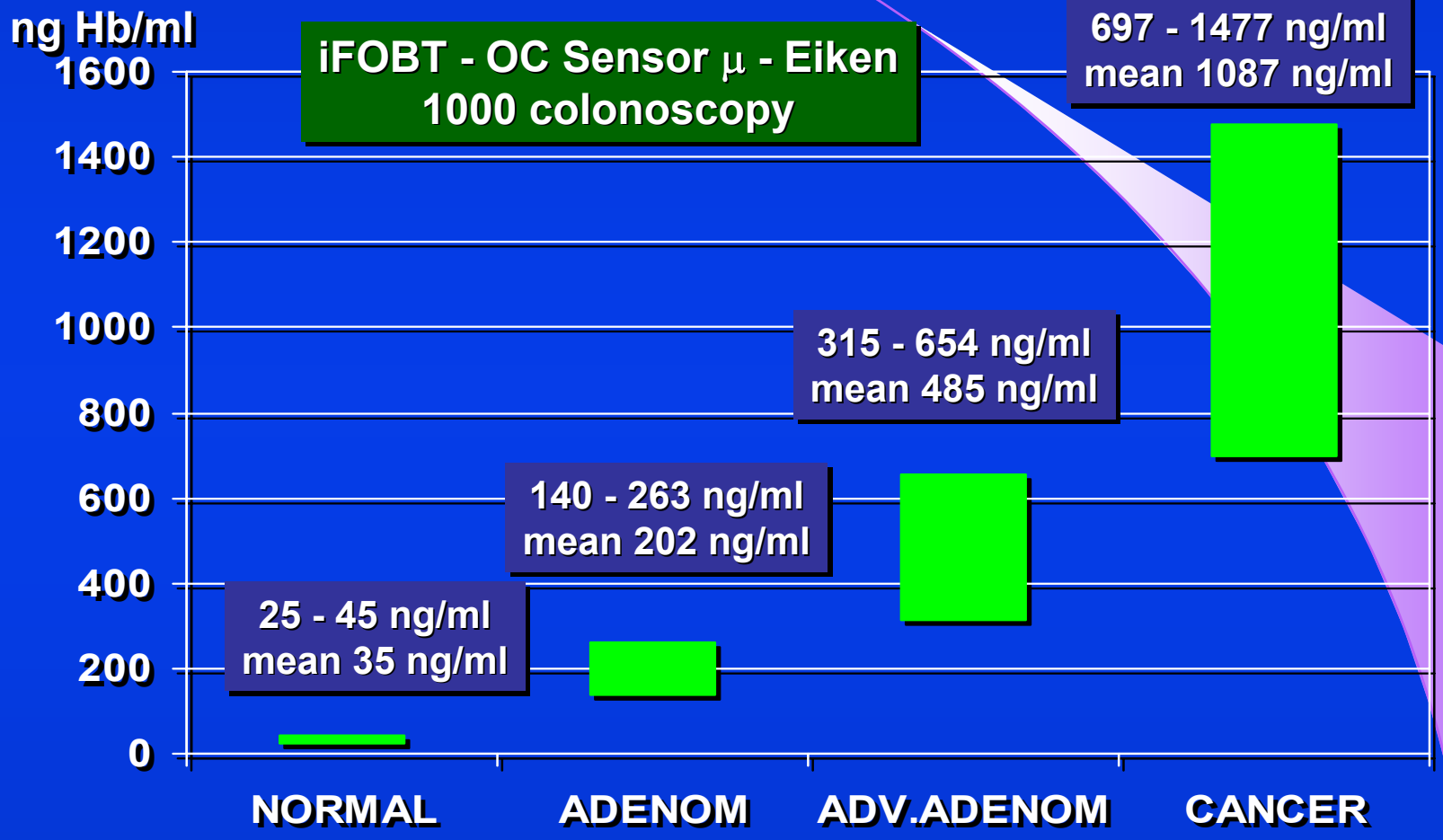




TRANSFER of 10 mg STOOL SAMPLE

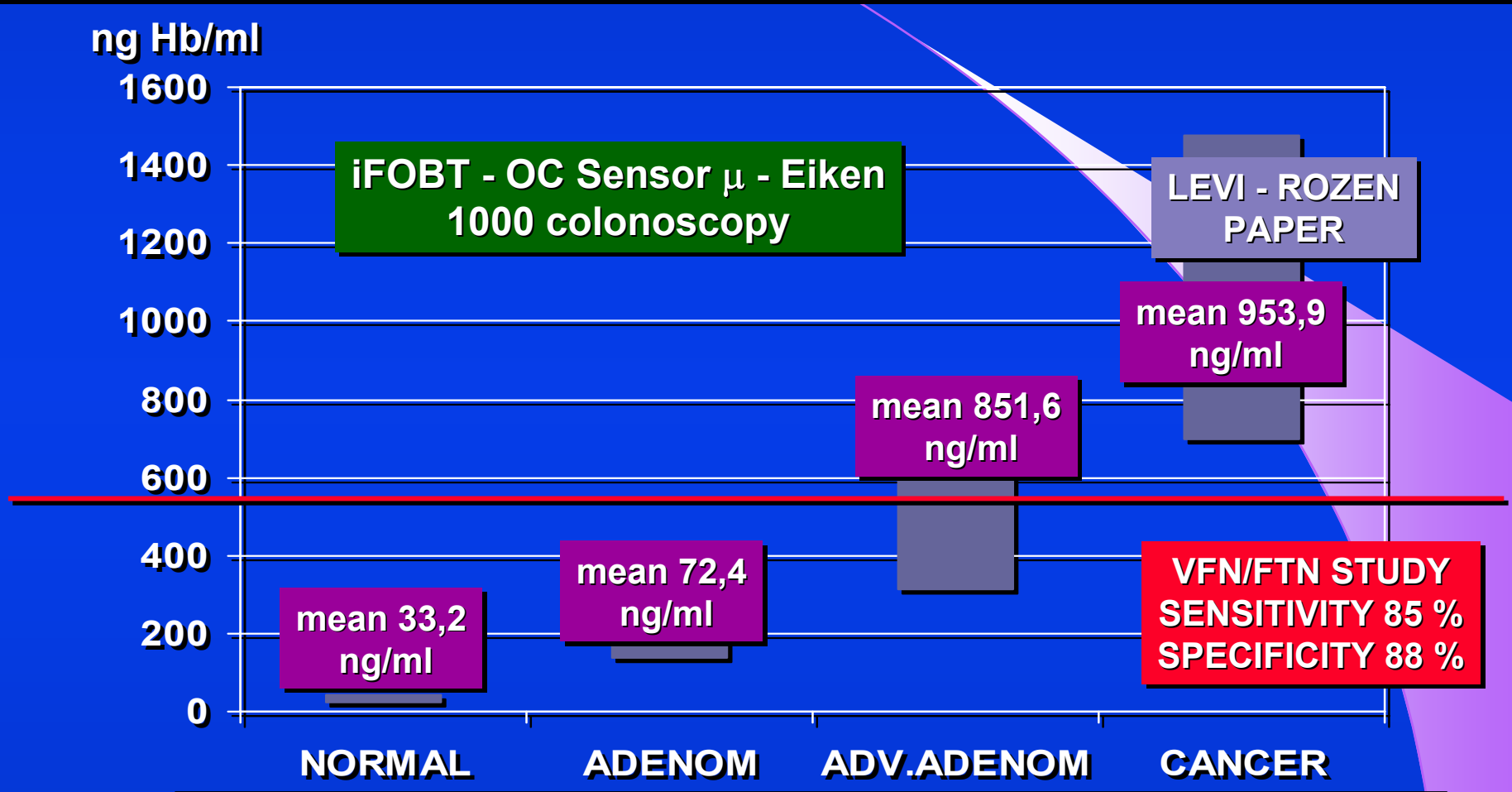
FILTRATION OF SAMPLE EXTRACT

SYMPTOMATIC SUBJECTS FOR COLONOSCOPY



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
A Quantitative Immunochemical Fecal Occult Blood Test for Colorectal Neoplasia

SYMPTOMATIC SUBJECTS FOR COLONOSCOPY - CR STUDY



Kovářová JT, Zavoral M, Zima T, Žák A, Kocna P. et al.: Improvements in colorectal cancer screening programmes – quantitative immunochemical faecal occult blood testing . Biomed Pap 2012, 156(2):143-150

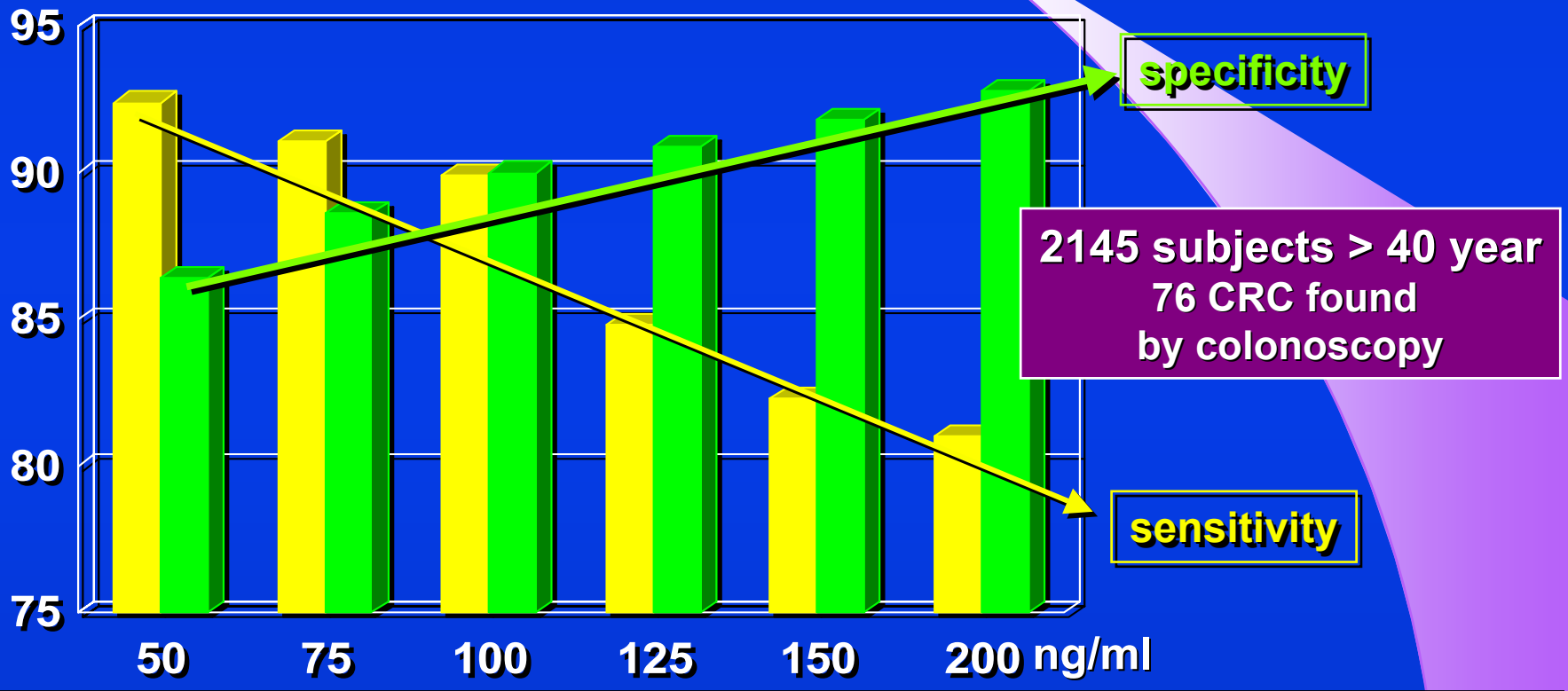
DUTCH SCREENING STUDY 2008 – gFOBT x OC SENSOR

iFOBT - OC Sensor μ - Eiken
cut-off 100 ng/ml

	20 623 SAMPLES RANDOMIZATION	
	g-FOBT	i-FOBT
INVITATION	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

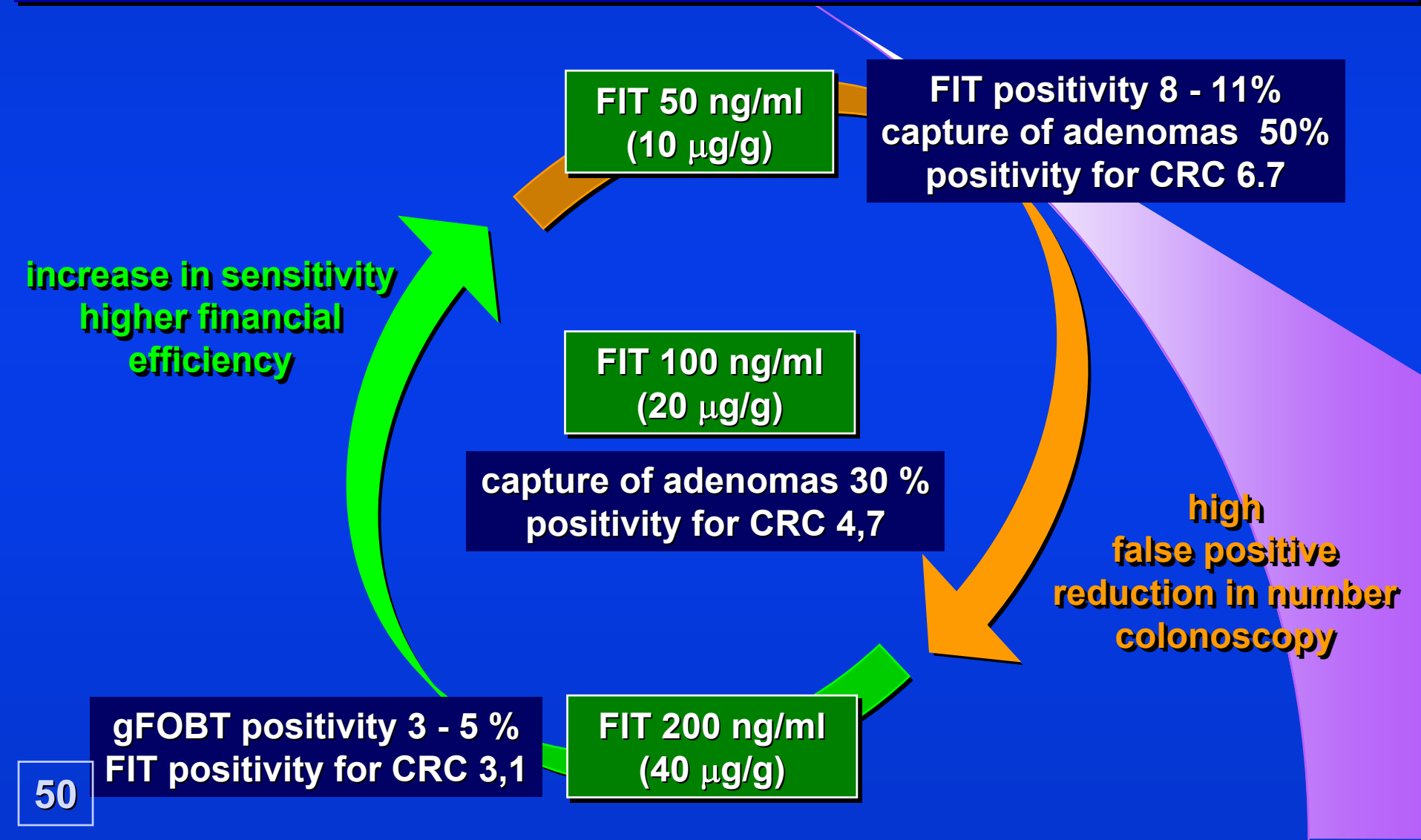
van Rossum LG, van Rijn AF, Laheij RJ. et al.: Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology. 2008;135(1):82-90

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% ?

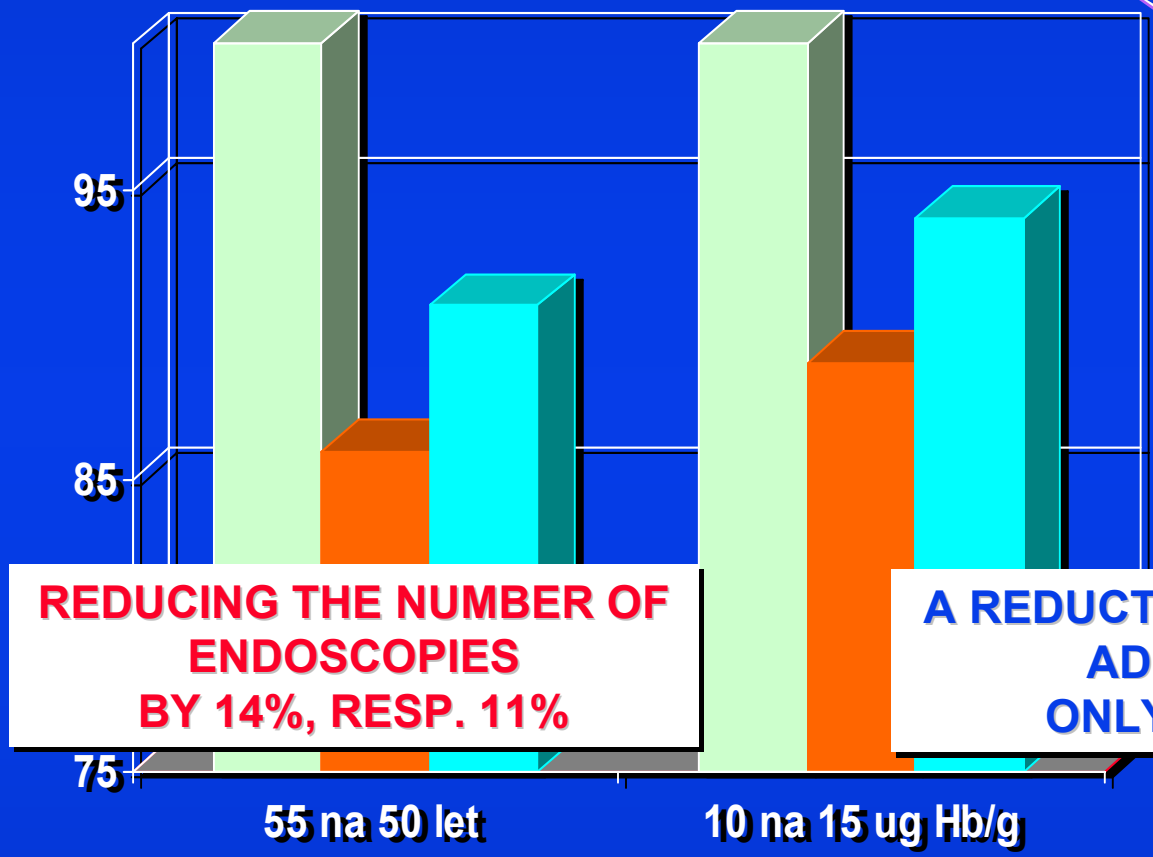


Terhaar sive Droste JS, Oort FA, van der Hulst RW. et al. Cancer Epidemiol Biomarkers Prev 2011, Higher fecal immunochemical test cutoff levels: lower positivity rates but still acceptable detection rates for early-stage colorectal cancers.

OPTIMIZATION OF CUT-OFF VALUE FOR FIT



OPTIMIZATION OF CUT-OFF VALUE FOR FIT



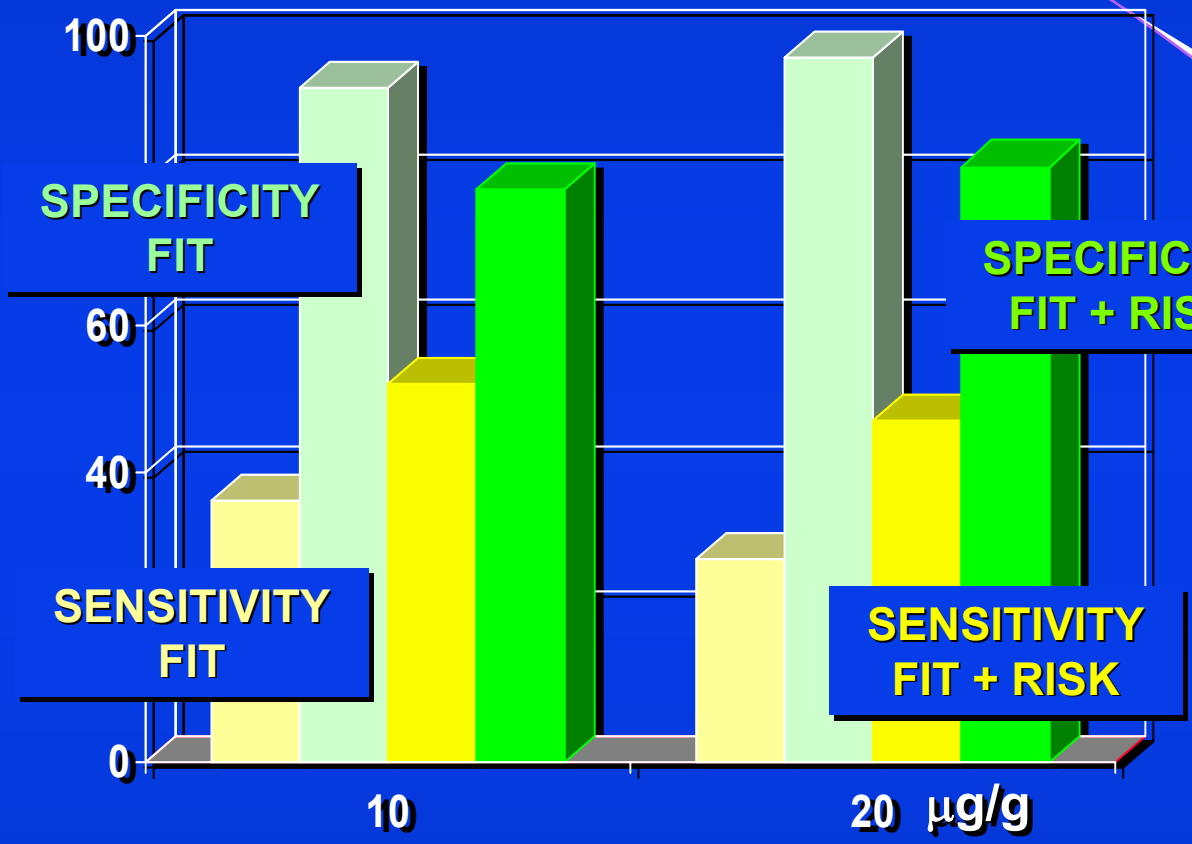
Optimizing CRC screening by increasing the age from 50 to 55 years or by lowering the cut-off from 10 µg Hb/g to 15 µg Hb/g

REDUCING THE NUMBER OF ENDOSCOPIES BY 14%, RESP. 11%

A REDUCTION IN THE NUMBER OF ADENOMAS FOUND ONLY BY 9%, RESP. 6%

Wieten E, Schreuders EH. et al. Clin Gastroenterol Hepatol. 2016, 14(12):1771-1777. Effects of increasing screening age and fecal hemoglobin cut-off concentrations in a colorectal cancer screening program.

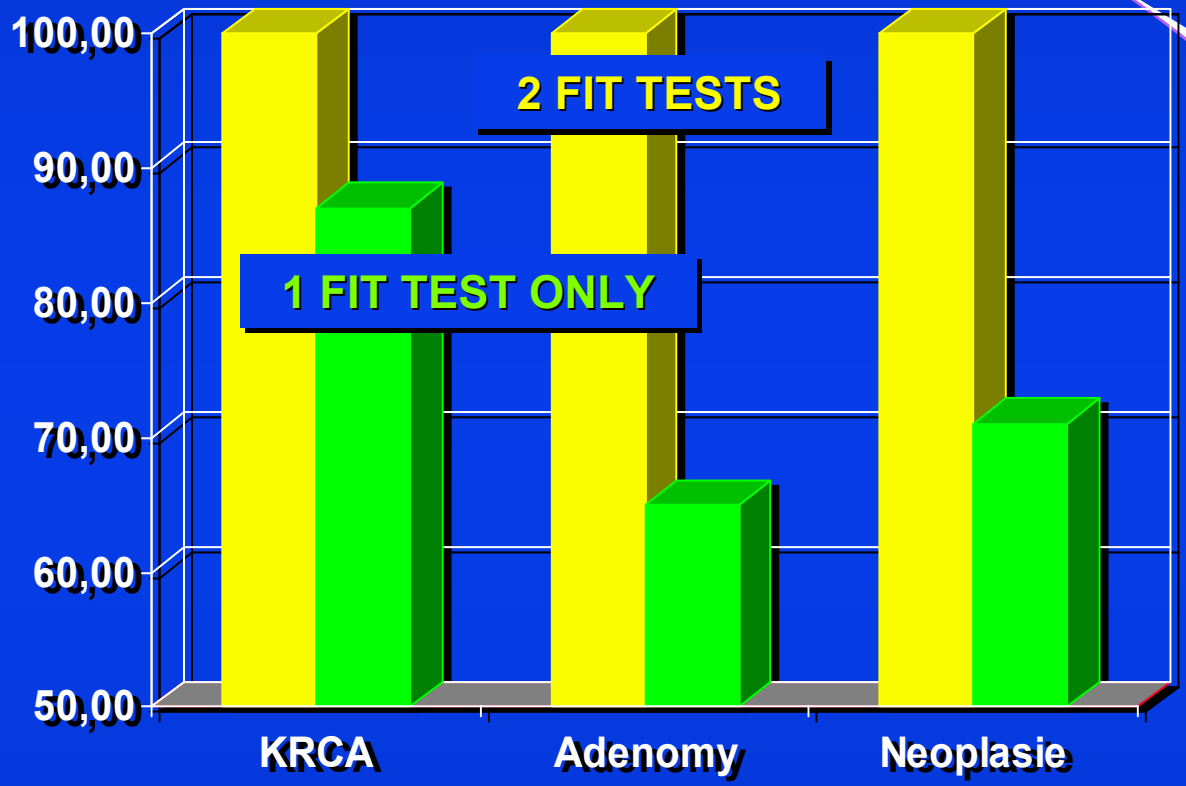
OPTIMIZATION OF CUT-OFF VALUE FOR FIT



At 10 µg Hb/g FIT detection of advanced neoplasia sensitivity increases from 36% to 52% however, the specificity decreases from 93% to 79%

Kallenberg FG, Vleugels JL, de Wijkerslooth TR. et al.
Aliment Pharmacol Ther. 2016 Jul;44(1):88-96
Adding family history to faecal immunochemical testing increases the detection of advanced neoplasia in a colorectal cancer screening programme.

OPTIMIZATION OF CUT-OFF VALUE FOR FIT



British Columbia Population Screening,

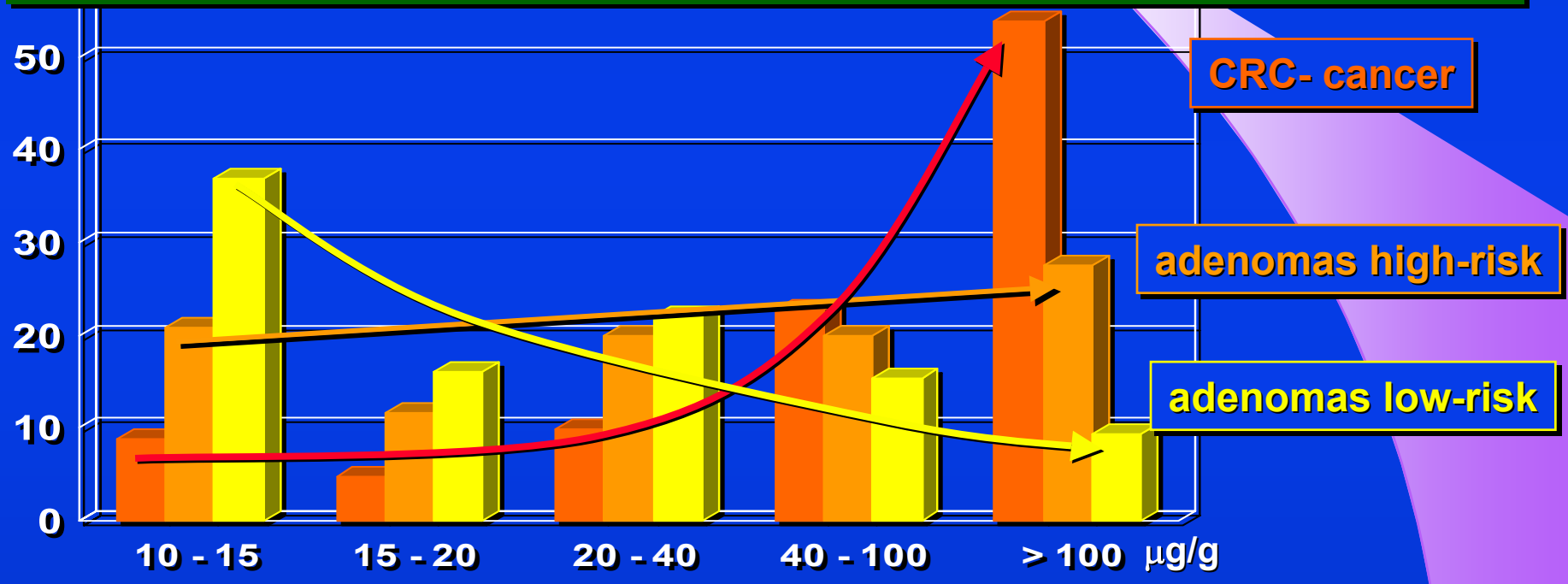
17,031 people aged 50-75, January 2009 - April 2013, by mail 2 OC-Sensor tests, analysis in a central laboratory, cut-off 20 mg/ml (100 ng/ml).

The added value of the second FIT test is 12% for CRC and 23% for high-risk polyps

Moosavi S, Enns R, Gentile L et al. Can.J.Gastro.Hepato, October, 2016. Comparison of One versus Two Fecal Immunochemical Tests in the Detection of Colorectal Neoplasia in a Population-Based Colorectal Cancer Screening Program

OPTIMIZATION OF CUT-OFF VALUE FOR FIT

Quantitative one FIT test (NS-Plus, Alfresa) with a limit of ≥ 10 µg/g
20,322 FIT-positive participants underwent colonoscopy
The criterion of ≥10 µg/g with the detection of all adenomas exceeds the national one recommendations and endoscopic resources must be considered.



Shahidi N. Gentile L. Gondaraet L. al.: Can.J.Gastro.Hepatol. 2016
Correlating Quantitative Fecal Immunochemical Test Results with Neoplastic Findings on Colonoscopy in a Population-Based Colorectal Cancer Screening Program.

OPTIMIZATION OF CUT-OFF VALUE FOR FIT

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

Value defined by manufacturer (Eiken): **100 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

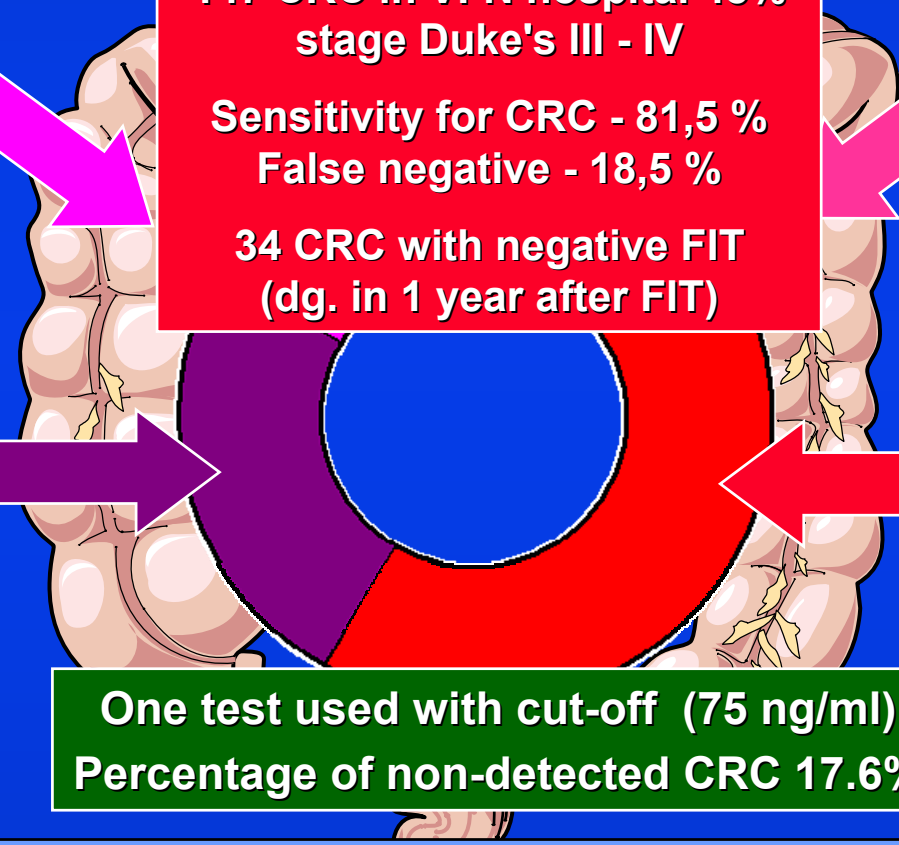
Pilot study in the Czech Republic: **75 ng/ml**

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

CRC TUMOUR POSITION - FALSE NEGATIVE



4/24
18.1%

4/14
28.5%

147 CRC in VFN hospital 48%
stage Duke's III - IV

Sensitivity for CRC - 81,5 %
False negative - 18,5 %

34 CRC with negative FIT
(dg. in 1 year after FIT)

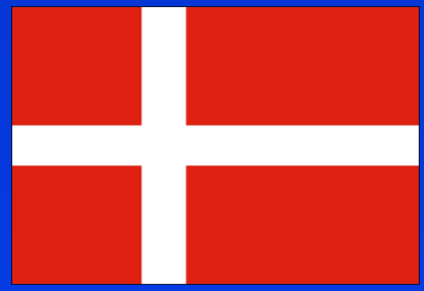
3/24
12.5%

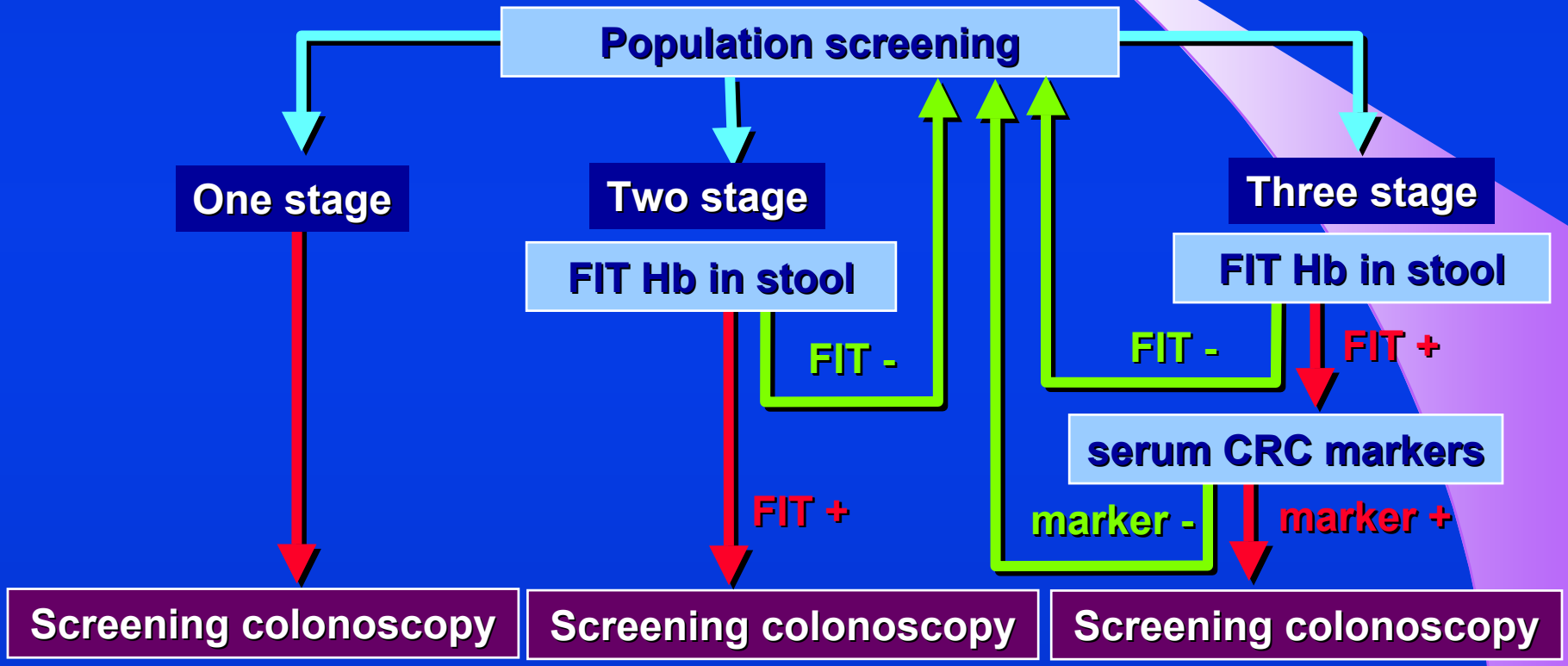
10/53
18.8%

One test used with cut-off (75 ng/ml)
Percentage of non-detected CRC 17.6%

Kelley L, Swan N, Hughes DJ. - Colorectal Dis. 2013 Sep; 15(9): e512-21
An analysis of the duplicate testing strategy of an Irish immunochemical FOBT colorectal cancer screening programme

Increasing the FIT cut-off FIT is considered to reduce colonoscopies. Three-step screening (FIT/blood test/colonoscopy) could be to reduce the number of unnecessary colonoscopies by 25%





Serological biomarkers in triage of FIT-positive subjects? Nielsen HJ, Christensen IJ, Andersen B et al.: Scand J Gastroenterol. 2017; 52(6-7):742-744

QUANTITATIVE ANALYSIS OF Hb IN STOOL – CZECH REPUBLIC

Eiken OC-Sensor mikro, OC-Sensor IO, Sentinel FOB-Gold
Aidian (Orion) QuikRead go, Quick Plus, Quick Seal, iChroma Boditech, Biosensor Standard F200, Standard FIA Labmark, Eurolyser Cube-S, Exdia Axonlab, VedaLab

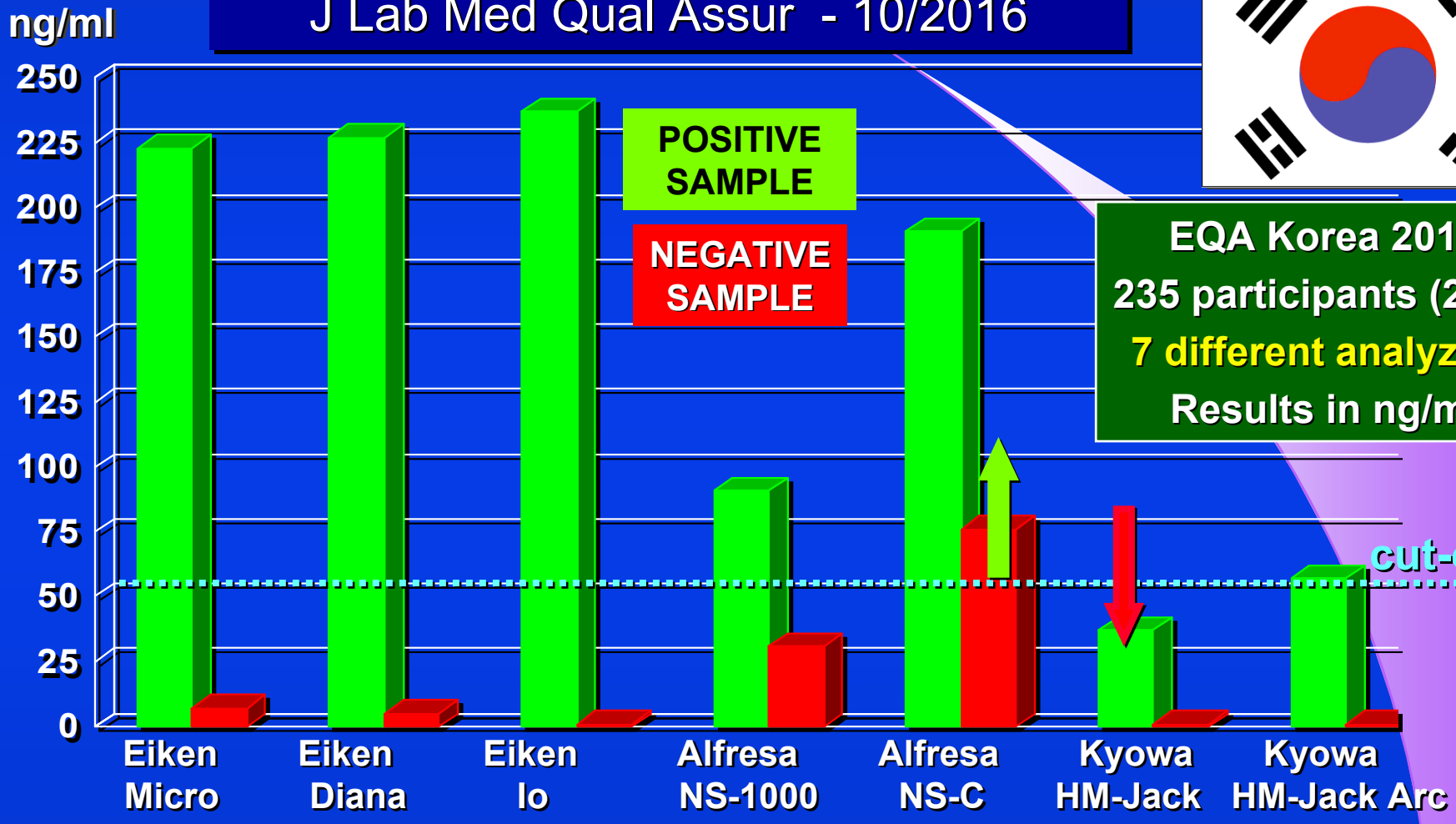
RISK OF CRC - FIT BELOW 10µg Hb/g

- After 8 years of follow-up, participants with baseline concentrations of 8-10 µg fHb/g had a higher cumulative incidence of advanced neoplasia (33%) than participants with 0 µg fHb/g (5%) p <.001.
- For persons with concentrations of 8-10 µg fHb/g (p <.001), the risk score increased from a value of 1.2 - for persons with concentrations of 0-2 µg fHb/g - to 8.2.
- Participants with two consecutive fHb concentrations of 8 µg Hb/g had a 14-fold increased risk of advanced neoplasia compared with participants with two consecutive fHb concentrations of 0 µg Hb/g (p <0.001)
- Baseline and follow-up fHb concentrations are independent predictors for the development of advanced neoplasia. This information can be used in designing personalized strategies for KRCA screening.

Association Between Concentrations of Hemoglobin Determined by Fecal Immunochemical Tests and Long-term Development of Advanced Colorectal Neoplasia. Grobbee EJ, Schreuders EH, Hansen BE et al.: Gastroenterology. 2017;153(5):1251-1259

2000	National Colorectal Cancer Screening Program Guaiac detection of occult bleeding - TOKS (Haemoccult)
2010	TOKS by the guaiac or immunochemical method g-FOBT/ i-FOBT, Publication of the Ministry of Health
2014	TOKS only by immunochemical method i-FOBT quantitative and qualitative tests
2020	FIT-TOKS only by a quantitative immunochemical method on a laboratory or POCT analyzer
2023	Obligation of external quality control once a year Publication of the Ministry of Health of the Czech Republic

J Lab Med Qual Assur - 10/2016

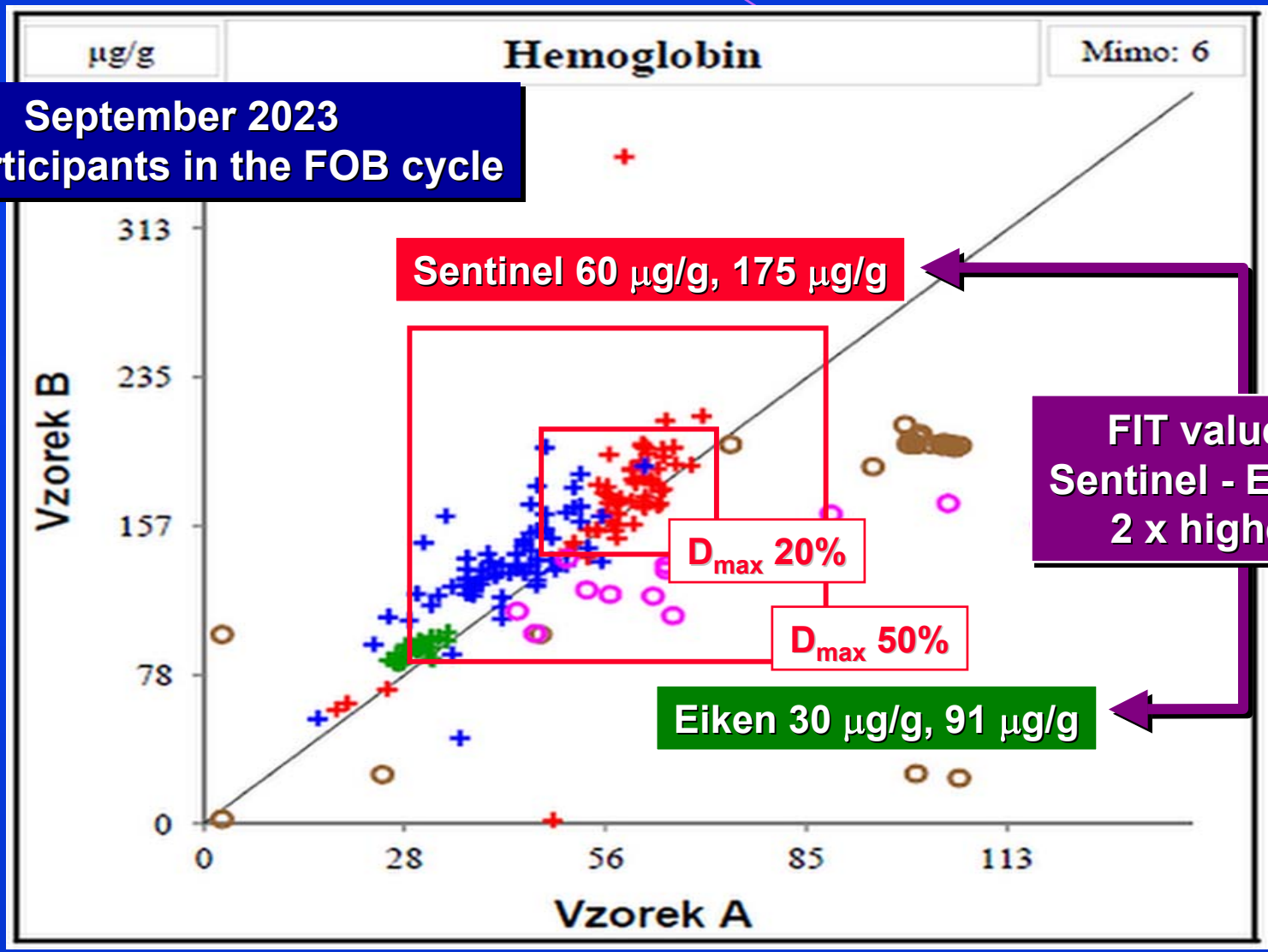


EQA Korea 2015
235 participants (29%)
7 different analyzers
Results in ng/ml

Chang-Ho Jeon and A-Jin Lee, J Lab Med Qual Assur 2016;38:120-128
Annual Report on the External Quality Assessment Scheme for Urinalysis and Faecal Occult Blood Testing in Korea (2015)

SEKK EHK FOB – EXTERNAL QUALITY CONTROL

September 2023
211 participants in the FOB cycle



FIT values Sentinel - Eiken 2 x higher

2000	National Colorectal Cancer Screening Program Guaiac detection of occult bleeding - TOKS (Haemoccult)
2010	TOKS by the guaiac or immunochemical method g-FOBT/ i-FOBT, Publication of the Ministry of Health
2014	TOKS only by immunochemical method i-FOBT quantitative and qualitative tests
2020	FIT-TOKS only by a quantitative immunochemical method on a laboratory or POCT analyzer
2023	Obligation of external quality control once a year Publication of the Ministry of Health of the Czech Republic
????	Intelligent evaluation of FIT analysis Personalized population screening

INTEGRATION OF CRC RISK FACTORS

Guideline ACS 2018 - CRC screening > 45 years

Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin 2018;68:250-281.

Age is important, but also several other factors, such as gender, first-degree relationship with CRC, high body mass index (BMI), metabolic syndrome, cigarette smoking, diet, use of certain drugs (aspirin, nonsteroidal anti-inflammatory drugs, hormone replacement therapy) and adherence.

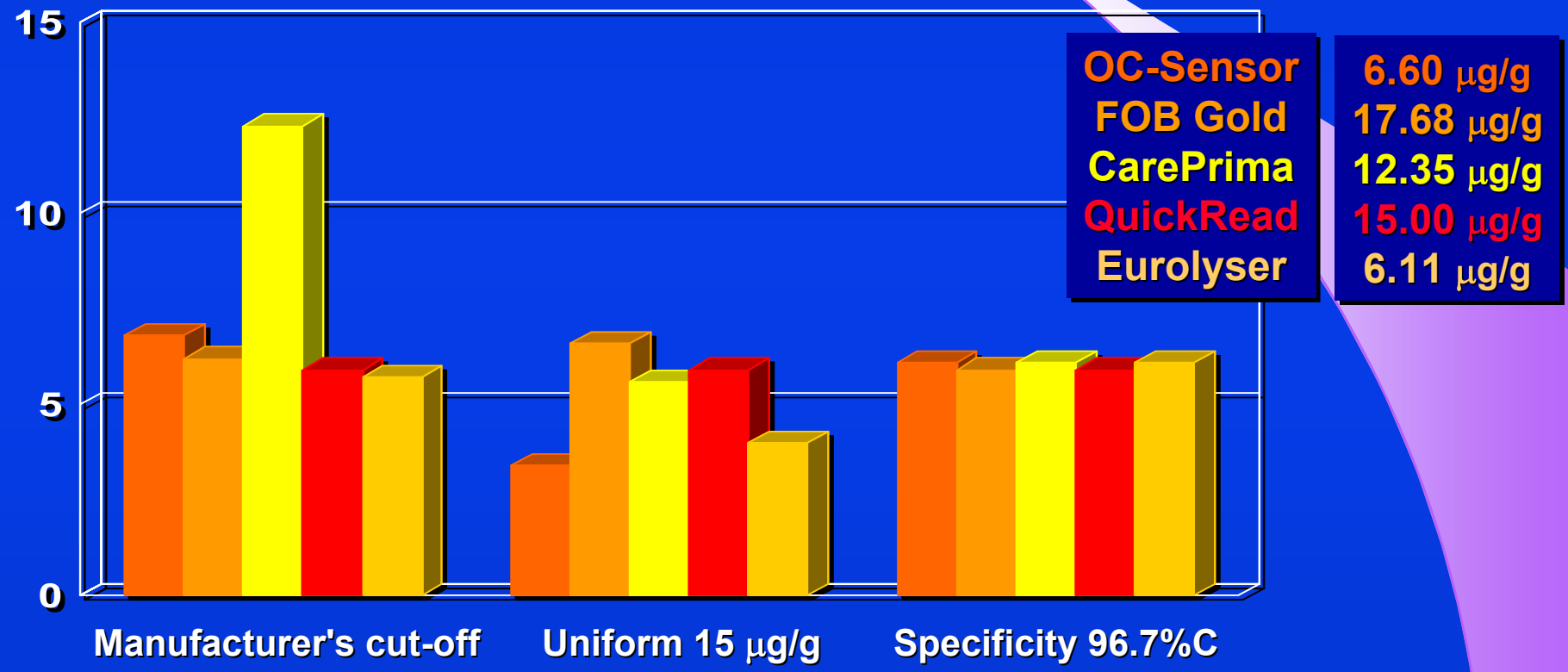
The disadvantage is the inability to integrate these factors into personalized screening.

Clin Gastroenterol Hepatol. 10/2018

Lowering the Starting Age for Colorectal Cancer Screening to 45 Years: Who Will Come…and Should They? Imperiale TF, Kahi CJ, Rex DK.: Clin Gastroenterol Hepatol. 2018 (10):1541-1544

ANALYTICAL VARIABILITY OF FIT TESTS

FIT positivity for different analyzers. Cut-off given by the manufacturer - A, uniform 15 μg/g - B, calculated for specificity 96.7% - C



Direct Comparison of Diagnostic Performance of 9 Quantitative Fecal Immunochemical Tests for Colorectal Cancer Screening. Gies A, Cuk K, Schrotz-King P, Brenner H. Gastroenterology 2018;154:93 -104

2.8 million FIT in 2018
12 different FIT manufacturers
no fixed cut-off
requirement: 25% sensitivity for advanced neoplasia and > 90% specificity

WEO

Laboratory analyzers	Number	Cut-off	Positivity
OC-Sensor - MastGroup	1 347061	10 μg/g	10.2 %
Immundiagnostik Dynex-ELISA	613 311	10 μg/g	7.5 %
FOB Gold - Sysmex	532 133	17 μg/g	7.9 %
R-Biopharm Dynex-ELISA	259 452	6-12 μg/g	17.1 %
ScheBo Biotech AG	50 678	25 μg/g	8.2 %
NS Plus - Care diagnostics	31 763	6 μg/g	5.1 %

Ulrike Haug - Update on CRC screening in Germany
WEO Colorectal Cancer Screening Committee - Barcelona, October 2019

2.8 million FIT in 2018
12 different FIT manufacturers
no fixed cut-off
requirement: 25% sensitivity for advanced neoplasia and > 90% specificity

POCT analyzers	Number	Cut-off	Positivity
Care DF - ImmoCare-C	2 316	4 μg/g	1.9 %
Orion Diagnostica	7 278	15 μg/g	13.8 %
CerTest BIOTEC	1 015	8 μg/g	21.1 %
Eurolyser Diagnostica	177	4 μg/g	13.3 %

ANALYTICAL VARIABILITY OF FIT TESTS

Hersteller	Tests, n	Positiv, n (Schwellenwert)	(%)	Nicht verwertbar, n	(%)
Mast Group	1.347.061	138.048 (10 µg/g)	(10,2 %)	8.799	(0,7 %)
Immundiagnostik AG	613.311	46.187 (10 µg/g)	(7,5 %)	55.349	(9,0 %)
Sysmex GmbH	532.133	42.153 (17 µg/g)	(7,9 %)	14.119	(2,7 %)
R-Biopharm AG	259.452	44.329 (6-12 µg/g)	(17,1 %)[1]	9.860	(3,8 %)
ScheBo Biotech AG	50.678	4.170 (25 µg/g)	(8,2 %)	1.254	(2,5 %)
CARE diagnostica					
Care prime	31.763	1610 (6 µg/g)	(5,1 %)	594	(1,8%)
immoCare-C	2.316	227 (4 µg/g)	(1,9 %)	170	(7,3%)
Orion Diagnostica	7.278	1.008 (15 µg/g)	(13,8 %)	236	(3,2 %)
CerTest BIOTEC	1.015	214 (8 µg/g)	(21,1 %)	67	(6,6 %)
Bestbion dx GmbH	881	84 (10 µg/g)	(9,5 %)	55	(6,2 %)
Roche Diagnostics	609	40 (15 µg/g)	(6,6 %)	64	(10,5 %)
Eurolyser Diagnostica GmbH	177	36 (4 µg/g)	(20,3 %)	6	(3,4 %)
Gesamt	2.846.674	278.106	(9,8 %)	90.573	(3,2 %)

Der iFOBT im Darmkrebs-Screening: Ergebnisse der medizinischen Laboratorien für das Jahr 2018 - dr.Ulrike Haug

WEO

Screening with a cut-off of 15 μg/g according to the OC-Sensor - Eiken study

Predicted positivity - 6.3%

Screening implemented with a test FOB Gold - Sentinel

Positivity FIT - 12.2 %

Cut-off modify to 47 μg/g for positivity 6.3 %

The most effective screening - FIT, annually, 45-80 years, 10μg/g

→

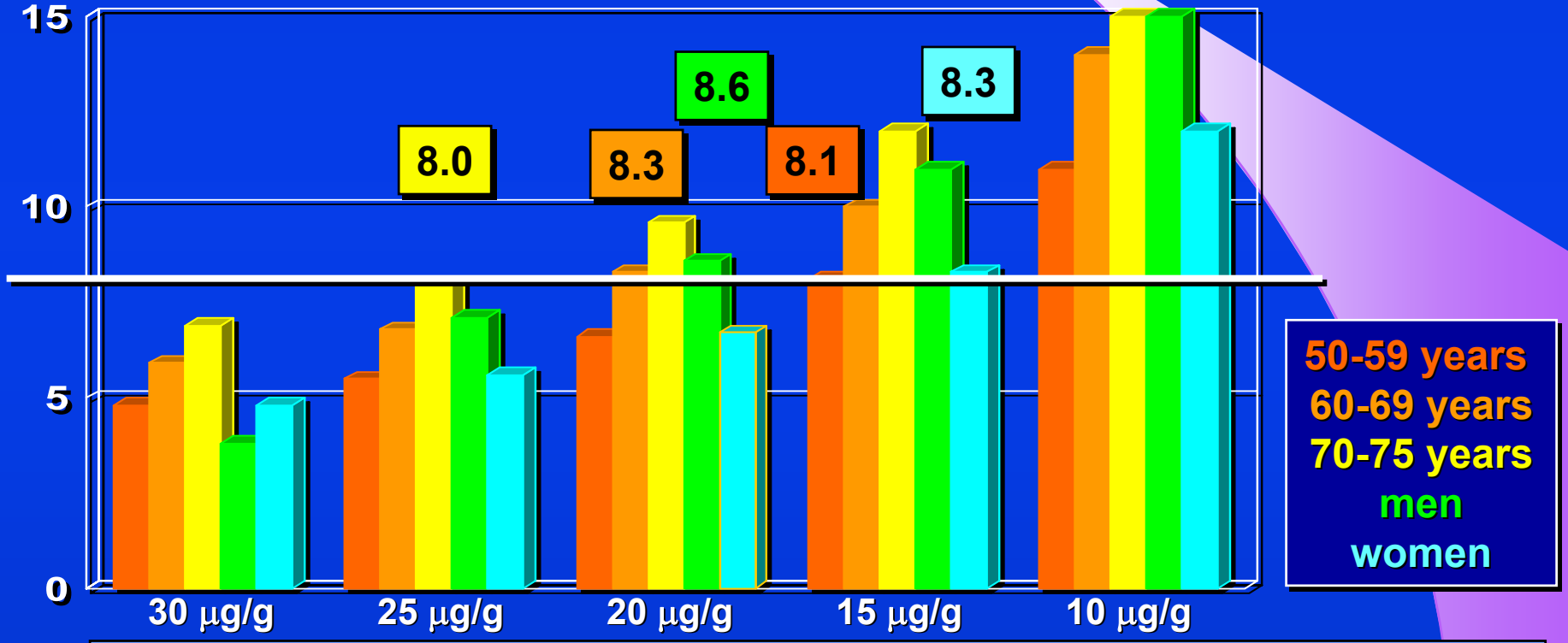
Currently implemented screening - FIT, 1x every 2 years, 55-75 years, 47μg/g

Entitlement to colonoscopies < One third of the most effective screening

Iris Lansdorp-Vogelaar - Optimal FIT Screening for Men and Women in Case of Limited Colonoscopy Capacity: A Cost-Effectiveness Analysis
WEO CRC Screening Committee - FIT for Screening, Barcelona, October 2019

VARIABILITY OF FIT ACCORDING TO AGE AND GENDER

Kaiser Permanente, 640 859 subjects, cut-off for positivity 8%
men 20 μg/g, women 15 μg/g,
50-59 years 15 μg/g, 60-69 years 20 μg/g, 70-75 years 25 μg/g



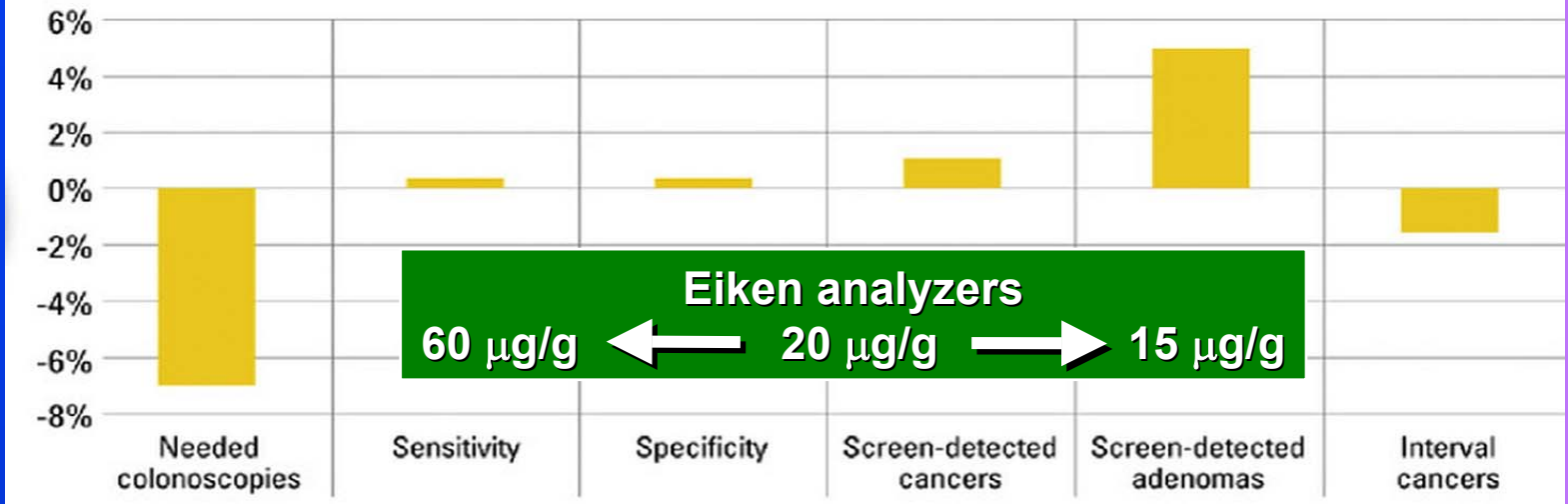
Influence of Varying Quantitative Fecal Immunochemical Test Positivity Thresholds on Colorectal Cancer Detection. Selby K, Jensen CD, Lee JK, et al. Ann Intern Med. 2018 Oct 2;169(7):439-447

FIT CUT-OFF VARIABILNÍ PODLE VĚKU A POHLAVÍ

Danish study, 531,828 people - increase in detection of cancer by 1.1%, adenomas by 5%, decrease in interval cancers by 1.5% and decrease in the number of colonoscopies by 7%

	50–54 years	55–59 years	60–64 years	65–69 years	70–74 years
Men	300 ng Hb/ml	300 ng Hb/ml	100 ng Hb/ml	100 ng Hb/ml	75 ng Hb/ml
Women	300 ng Hb/ml	100 ng Hb/ml	100 ng Hb/ml	75 ng Hb/ml	75 ng Hb/ml

Change in % if using age and gender specific cut-offs instead of 100 ng Hb/ml for everyone



Varying fecal immunochemical test screening cutoffs by age and gender: a way to increase detection rates and reduce the number of colonoscopies. Njor SH, Rasmussen M, Friis-Hansen L. et al. Gastrointest Endosc. 2022; 95(3):540-549.

FIT CUT-OFF VARIABILITY ACCORDING TO GENDER

Screening of 21,993 persons in Finland, FOB-Gold mailed test, return 79.3%, cut-off 70 µg Hb/g for men, 25 µg Hb/g for women

	Men %, (95%CI)	Women, % (95%CI)
Positivity	2.8 (2.5 -3.1)	2.4 (2.2 -2.7)
PPV for CRC	6.6 (4.0 -10.3)	6.4 (3.9 -9.8)
PPV for AA	25.7 (20.6 -31.4)	15.5 (11.6 -20.2)
PPV (colono) for CRC	9.0 (5.4 -13.8)	8.8 (5.4 -13.4)
PPV (colono] for AA	34.8 (28.3 -41.8)	21.3 (16.0 -27.4)
CRC detection	1.8 (1.1 -2.9)	1.6 (0.9 -2.4)
AA detection	7.2 (5.6 -9.1)	3.8 (2.8 -5.0)

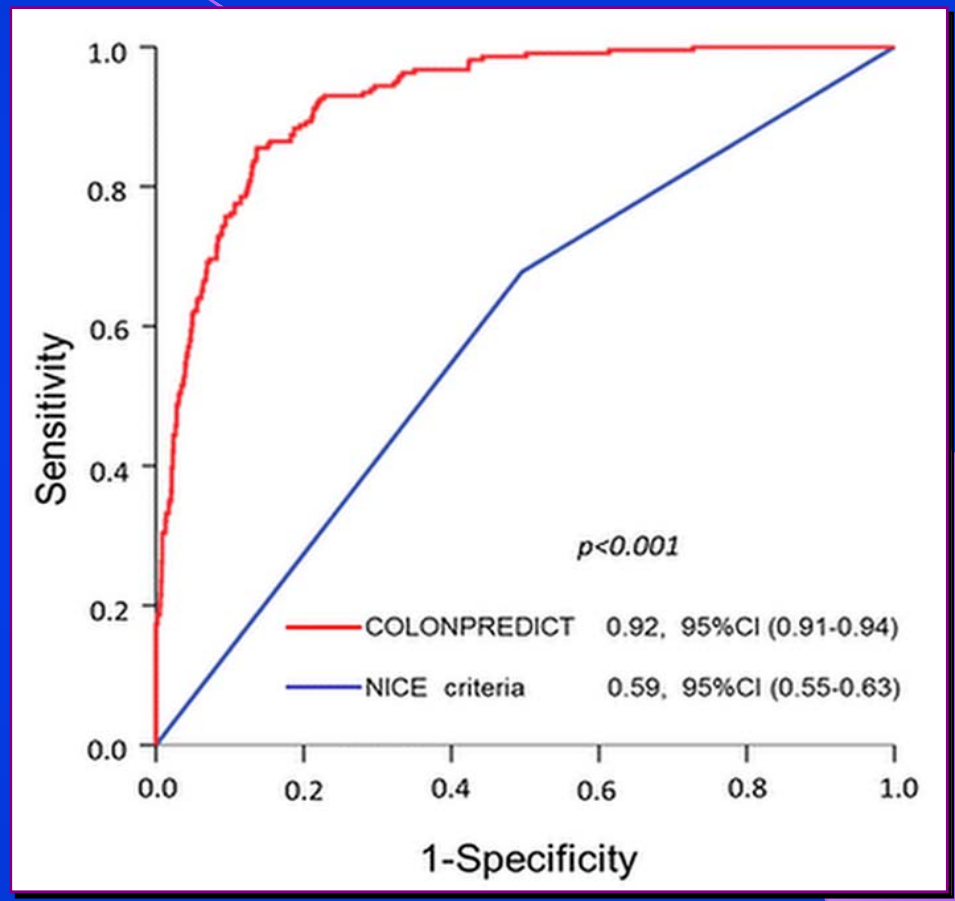
Piloting gender-oriented colorectal cancer screening with a faecal immunochemical test: population-based registry study from Finland. Sarkeala T, Färkkilä M, Anttila A. et al.: BMJ Open. 2021; 11(2):e046667

CRC PREDICTION MODEL - COLONPREDICT

Prediction model with 11 variable

Characteristics	OR
Age (years)	1.04
Sex (male)	2.2
Hb - fecal ≥ 20 µg/g	17.0
Hb - blood < 10 g/dl	4.8
CEA ≥ 3 ng/ml	4.5
Colonoscopy in 10 years	0.1
Rectal bleeding	2.2
Change in bowel habit	1.7

Low risk	value	< 3.5
Intermediate risk	value	3.5 - 5.6
High risk	value	≥ 5.6

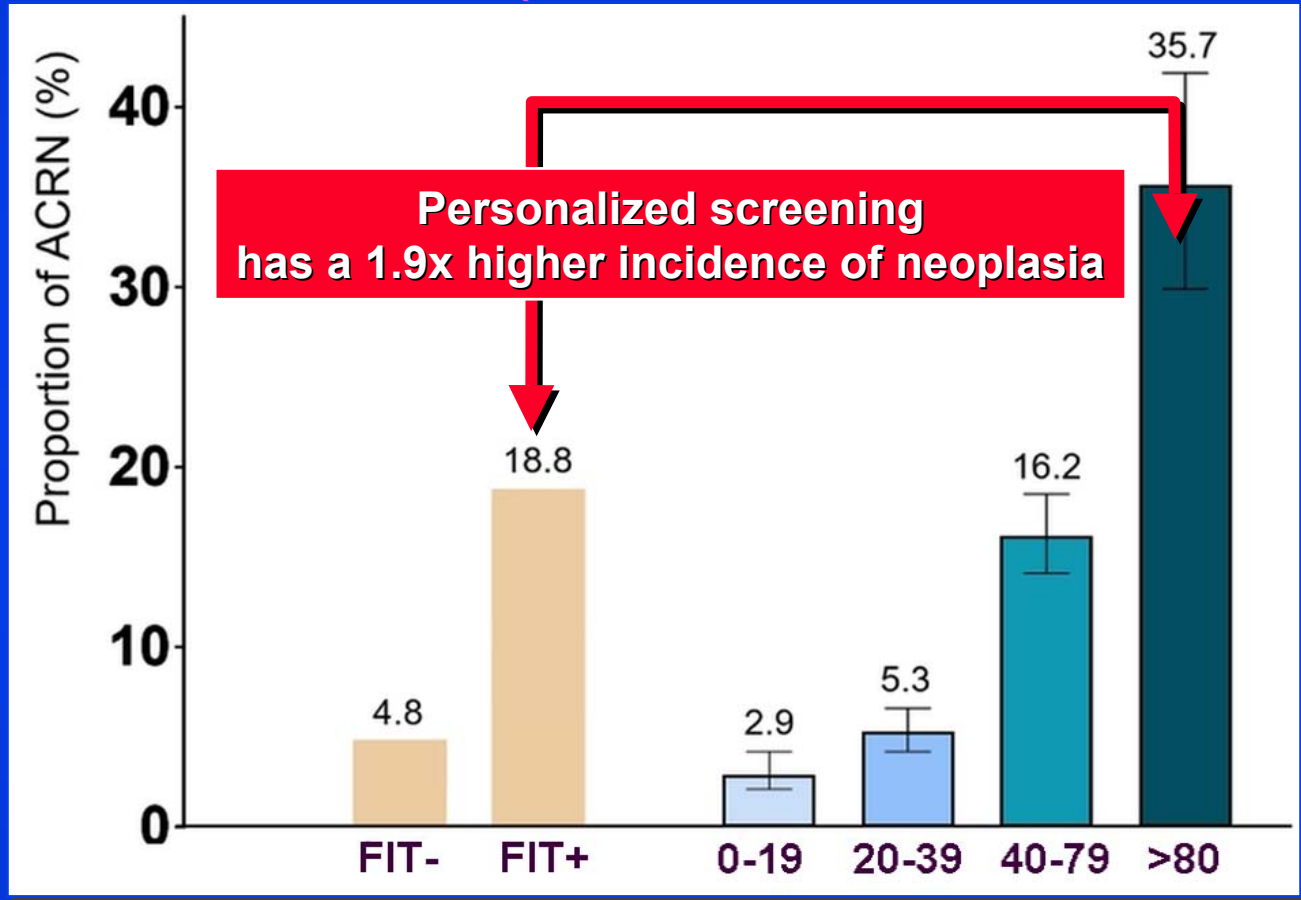


Development and external validation of a faecal immunochemical test-based prediction model for colorectal cancer detection in symptomatic patients
Cubiella J, Vega P, Salve M. et al. BMC Medicine 2016, 14:128

PERSONALIZED SCREENING - DETECTION OF ADENOMAS AND CRC

Percentage of advanced found colorectal neoplasia

1. by the FIT method cut-off 20 mg/g stool
2. risk criterion including FIT, age, gender, obesity, smoking, diabetes

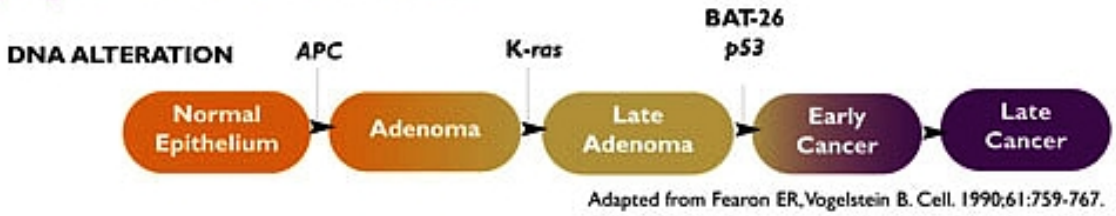


Usefulness of risk stratification models for colorectal cancer based on fecal hemoglobin concentration and clinical risk factors. Park CH, Jung YS, Kim NH, et al. Gastrointest Endosc. 2019 Jun; 89(6): 1204 - 1211

DNA CHIPs FOR COLORECTAL CANCER SCREENING

PreGen-Plus - 23 CRC MOLECULAR MARKERS
21 MUTATIONS - APC, K-ras, p53
MIKROSATELLITE INSTABILITY - BAT-26

Colorectal cancer develops in well-defined stages and arises from molecular alterations in multiple genes within an individual cell.



Adapted from Fearon ER, Vogelstein B. Cell. 1990;61:759-767.

PreGen-Plus is a single test comprised of 23 molecular markers of colorectal cancer. These include:

- 21 point mutations in *APC*, K-*ras*, and *p53*
- One microsatellite instability marker, BAT-26
- One Long DNA marker, DNA Integrity Assay (DIA®)

Cologuard® - DNA stool test (Exact Sciences)
approved by FDA, September 04, 2014
test price - 600 U$, www.medscape.com

mt-sRNA FOR COLORECTAL CANCER SCREENING

8920 participants in the CRC-PREVENT study / US for mt-sRNA test
7607 participants in the BLITZ study / Germany for FOB Gold-FIT test.

Colonoscopy	CRC PREVENT mt-sRNA		CRC PREVENT FIT		BLITZ FIT
	number	sensitivity	number	sensitivity	sensitivity
CRC – canacre	34	94,4 %	28	77,8 %	94,9 %
Adenomas	278	45,9 %	175	28,9 %	44,7 %

Cut-off FIT in CRC-PREVENT - 20 μg/g, according to the manufacturer
Cut-off FIT in BLITZ set to equal positivity 17% - 8,83 μg/g

Niedermaier T, Seum T, Hoffmeister M, Brenner H. Lowering Fecal Immunochemical Test Positivity Threshold vs Multitarget Stool RNA Testing for Colorectal Cancer Screening. JAMA. 2024 Jun 1 - ePpub

COMBINATION OF MARKERS IN FACES – FIT + TRANSFERIN

Screening included 12,255 persons, 8,223 men and 4,032 women
Automatic analyzer NS-Plus detection of hemoglobin and transferrin

	Hb positivity	Tf positivity with negative Hb	Total positivity
Men	7,1 %	2,7 %	9,8 %
Women	5,7 %	4,9 %	10,5 %
Significance	p = 0,003	p < 0.001	p = 0,281

The percentage rate of constipation in Hb positives is 11.7%, in Tf positives 17.1%

Clinical benefit of measuring both haemoglobin and transferrin concentrations in faeces: demonstration during a large-scale colorectal cancer screening trial in Japan. Takashima Y, Shimada T, Yokozawa T., Diagnosis (Berl). 2015 Feb 1;2(1):53-59

COLORECTAL CARCINOMA SCREENING - MARKER COMBINATION

A study is now underway in the Netherlands validating the mt-FIT combination of hemoglobin, calprotectin, and protein 2 serpin F family, which increases the sensitivity for advanced neoplasia to 42.9% versus 37.3% for FIT alone (p=0.025) with an identical specificity of 96.6 %.

Clinical Validation of a Multitarget Fecal Immunochemical Test for Colorectal Cancer Screening : A Diagnostic Test Accuracy Study. de Klaver W, Wisse PHA, van Wifferen F. et al. Ann Intern Med. 2021; 174(9): 1224-1231

The combination of FIT with calprotectin has a higher diagnostic accuracy compared to individual tests and its use as a pre-endoscopic tool allows to reduce the number of colonoscopies by 39.4% and reduce the total costs by 20.5%, the negative predictive value for this combination is 94.1%.

The combination of quantitative faecal occult blood test and faecal calprotectin is a cost-effective strategy to avoid colonoscopies in symptomatic patients without relevant pathology.
Lué A, Hijos G, Sostres C. et al. Therap Adv Gastroenterol. 2020;13:ePub

GASTRIC AND COLORECTAL CANCER SCREENING

Gastric cancer screening - HpSAg antigen Helicobacter pylori positivity

Colorectal cancer screening - positive gFOBT / FIT test.

4200 people invited, 3172 analyzed

HpSA +
(n = 789)

↓ **Gastroscopy**

Neoplasia 42 x

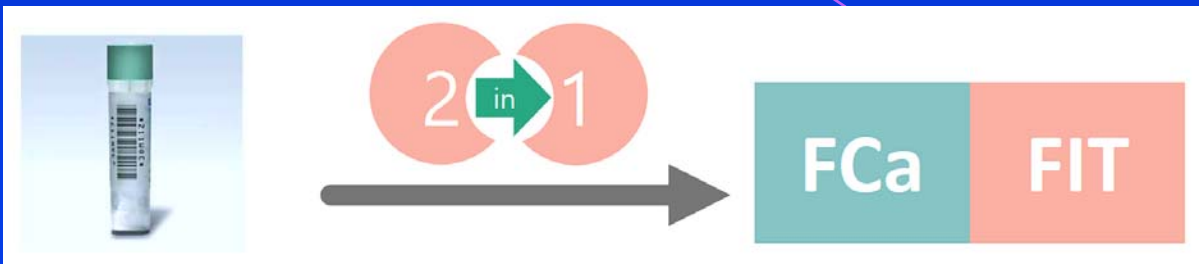
gFOBT / FIT +
(n = 466)

↓ **Colonoscopy**

Neoplasia 76 x

Accuracy of faecal occult blood test and Helicobacter pylori stool antigen test for detection of upper gastrointestinal lesions.
Lee YC, Chiu HM, Chiang TH, et al. BMJ Open 2013;3:e003989.

EIKEN - OC SENSOR PLEDIA, CERES - 2 in ONE



One sampling cartridge for both analytes three-channel system filter in the sampling cartridge

Eiken - OC Sensor turbidimetric analysis
Pledia -160 tests/hour
Ceres -90 tests/hour
FOB - Calprotectin

ALFRESA - NS PRIMA ANALYZER

One sampling cartridge for all three analytes

Alfresa Pharma NS-Prime
immunochemical analyzer
agglutination - colloidal gold
300 tests/hour
FIT - Calprotectin - Transferrin

http://www1.lf1.cuni.cz/~kocna/glab/glency1.htm

http://gelab.zde.cz

Skupina metodik funkce tenkého střeva, malabsorpce, screening céliakie, střevní propustnost, bakteriální přerůstání

- Anti-endomysium IgA
- Anti-gliadin IgA, IgG
- Anti-tTG IgA, IgG
- Anti-gliadin, tTG ve stolici
- A-vitamin zátěžový test
- ß-karoten
- ß-karoten zátěžový test
- Céliakie - screening
- Dechový test s laktózou
- Dechový test s xylózou
- Laktózový toleranční test
- Laktulózo/mannitolový test
- Xylózový toleranční test

Intro

Abecední přehled metodik

Miniencyklopedie laboratorních metod v gastroenterologii

GastroLab

Protilátky ke tkáňové transglutamináze (atTG) - IgA a IgG

Tkáňová transglutamináza má přímý vztah k patogenezi onemocnění a byla popsána jako vlastní, chemický substrát endomysia. Tkáňová transglutamináza - (isoenzym transglutaminasa II, TG2 - EC 2.3.2.13, je transferázou, systémový název je protein-glutamin:amin-g-glutamyltransferasa. Je to Ca2+ dependentní enzym, katalyzující deaminaci glutaminu na glutamát, rovněž vede ke vzniku intramolekulární vazby glutaminu na další primární amin, např. lysin a vede k agregaci glutaminových peptidů. Stanovení protilátek ke tkáňové transglutamináze (atTG) má proto rovněž velmi vysokou diagnostickou efektivitu, podobně jako EmA protilátky (senzitivita 87-97% a specificita 88-98%). Stanovení atTG je prováděno klasickou metodou ELISA, což je pro rutinní diagnostiku technika dostupnější než immunofluorescenční průkaz EmA.

Protilátky atTG lze na rozdíl od EmA stanovovat ve třídě IgA i IgG, což má význam pro nemocné se selektivním deficitem IgA. Metoda byla popsána s použitím morčecího antigenu, který je použit ve většině starších souprav, novější soupravy již používají jako antigen tkáňovou transglutaminázu izolovanou z lidských buněk, z lidských erytrocytů, nebo rekombinantní tTG izolovanou na E.coli. Referenční hodnoty se liší u jednotlivých souprav, většinou je pro IgA protilátky uváděna horní hranice normy 10 - 15 IU/l, některé soupravy definují i tzv. gray-zone v rozsahu 10 - 20 IU/l. Stanovení protilátek atTG s lidským, rekombinantním antigenem vykazuje nižší falešnou pozitivitu než metody s morčecím antigenem. Nejnovější studie porovnávají protilátky třídy IgA a IgG, a POCT metodiky stanovení atTG protilátek. Stanovení protilátek atTG ve třídě IgA je doporučeno jako základní screeningový test pro diagnostiku celiakie. Pro screening byla v roce 2011 použita i technologie detekce atTG ve slinách, a nejnovější studie popisují zcela nové technologie detekce protilátek elektrochemickými imunosenzory.

Reference

Volta U. - Gastroenterol Hepatol Bed Bench. 2023, Medline - link PubMed

Infantino M. - J Immunol Met... 2021, Medline - link PubMed

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