FIRST FACULTY OF MEDICINE
CHARLES UNIVERSITY IN PRAGUE

Epidemiological and clinical aspects of quantitative FIT test for CRC screening

Kocna P., Májek O., Blaha M., Ngo O., Dušek L.

4.European Colorectal Cancer Days - Brno, 30. May 2015

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)

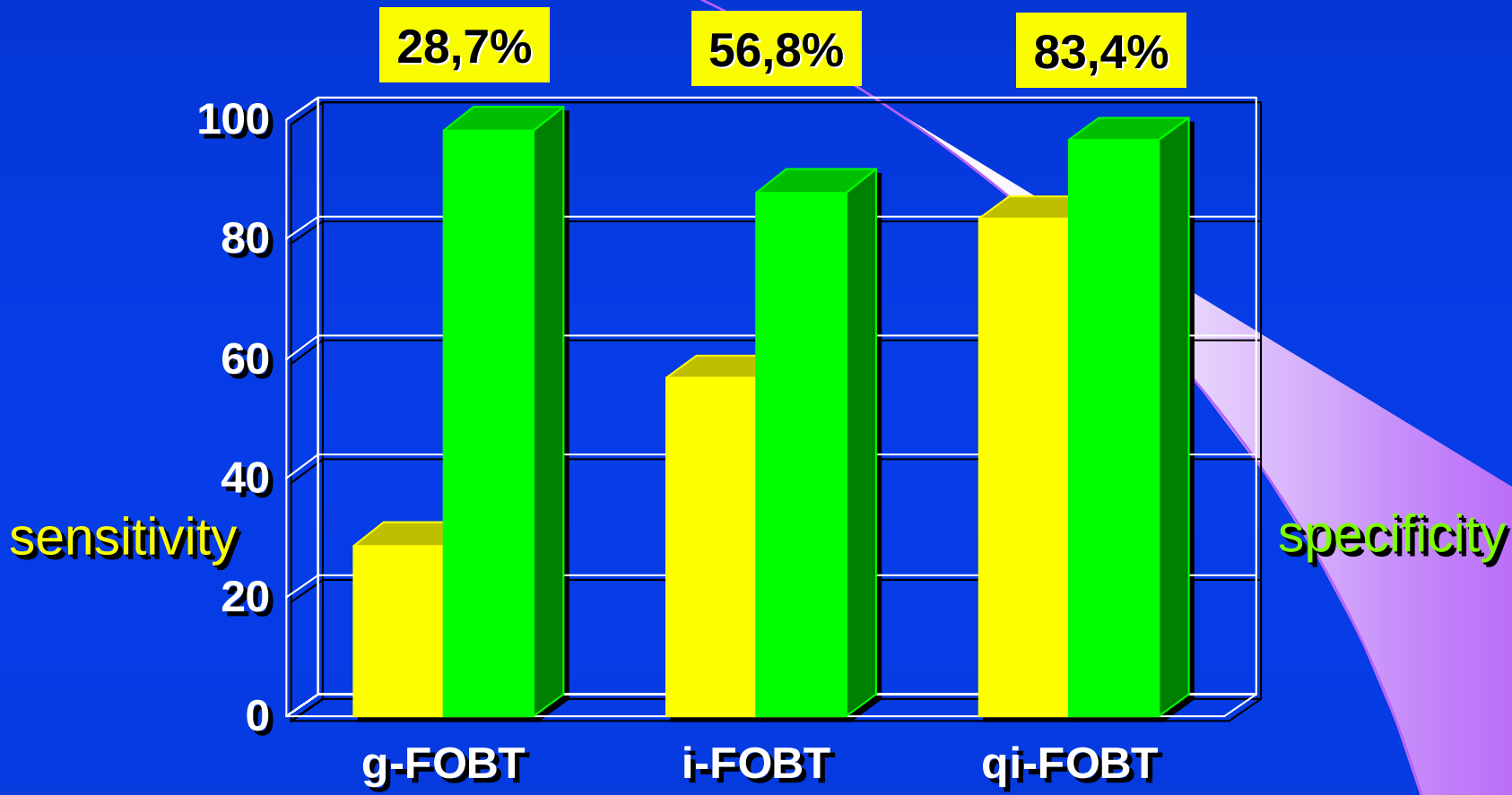
Laboratory of Gastroenterology of the
Institute of Medical Biochemistry and Laboratory Diagnostics
shows long-standing – 40 years experiences with FOBT analytics

40 years ago

1st GENERATION - GUAIAC TEST, g-FOBT

Haemoccult exclusively has been recommended for CRC screening with highest reproducibility

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



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 FIT FOR CRC SCREENING

The evidence to date suggests that faecal occult blood testing using FIT will remain the best test for CRC population-based screening for the next decade. Quantitative FIT provides the important opportunity of incorporating results into a CRC risk 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

qi-FOBT / FIT POCT & LABORATORY ANALYSERS

OC-Sensor Eiken

QuikRead Orion

OC-DIANA Eiken

i-Chroma Boditech

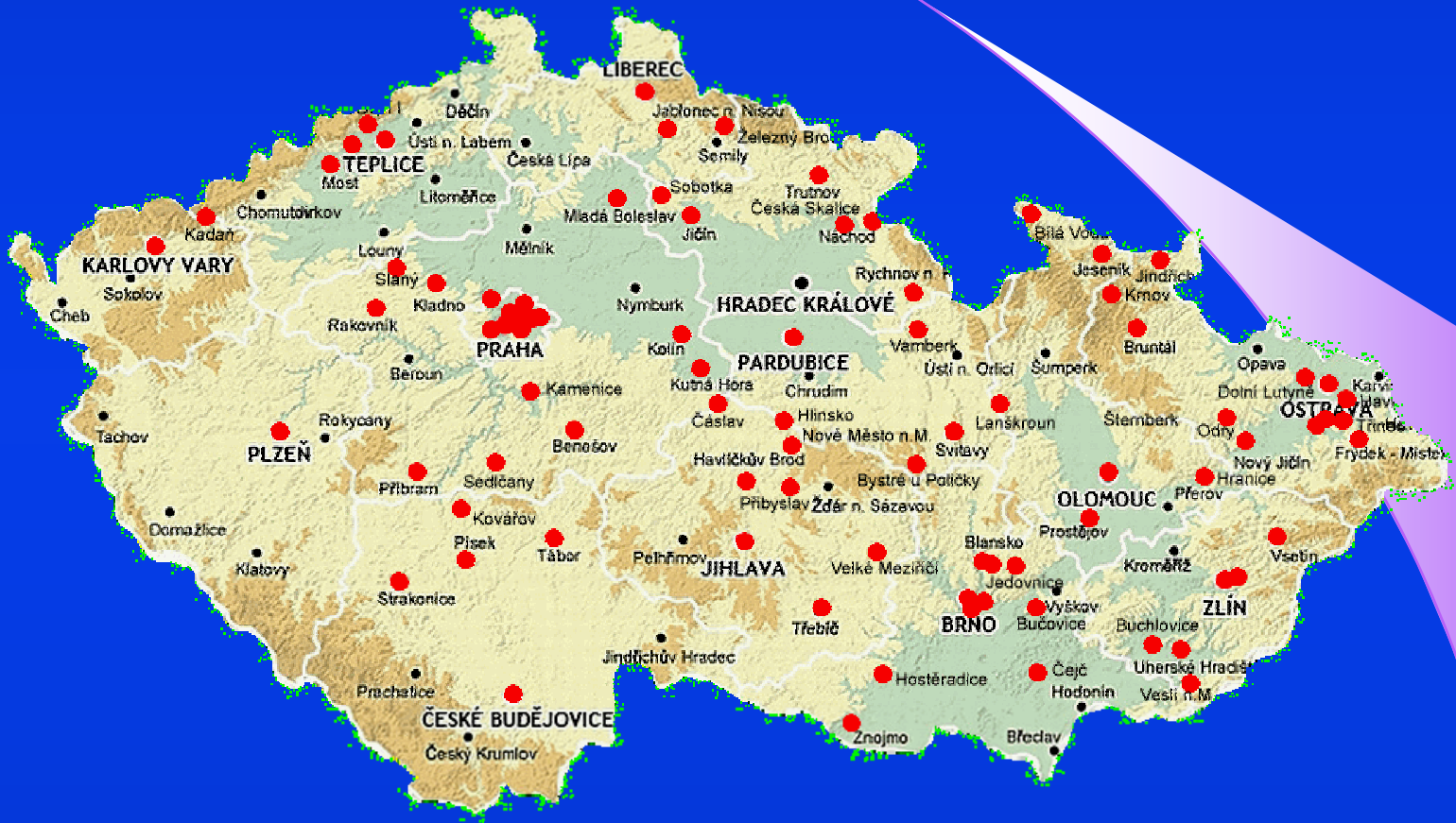
QuikReadGo Orion

SmartPlus Eurolyser

SENTi-FIT 270 Sentinel

SENTi-FIT mini Sentinel

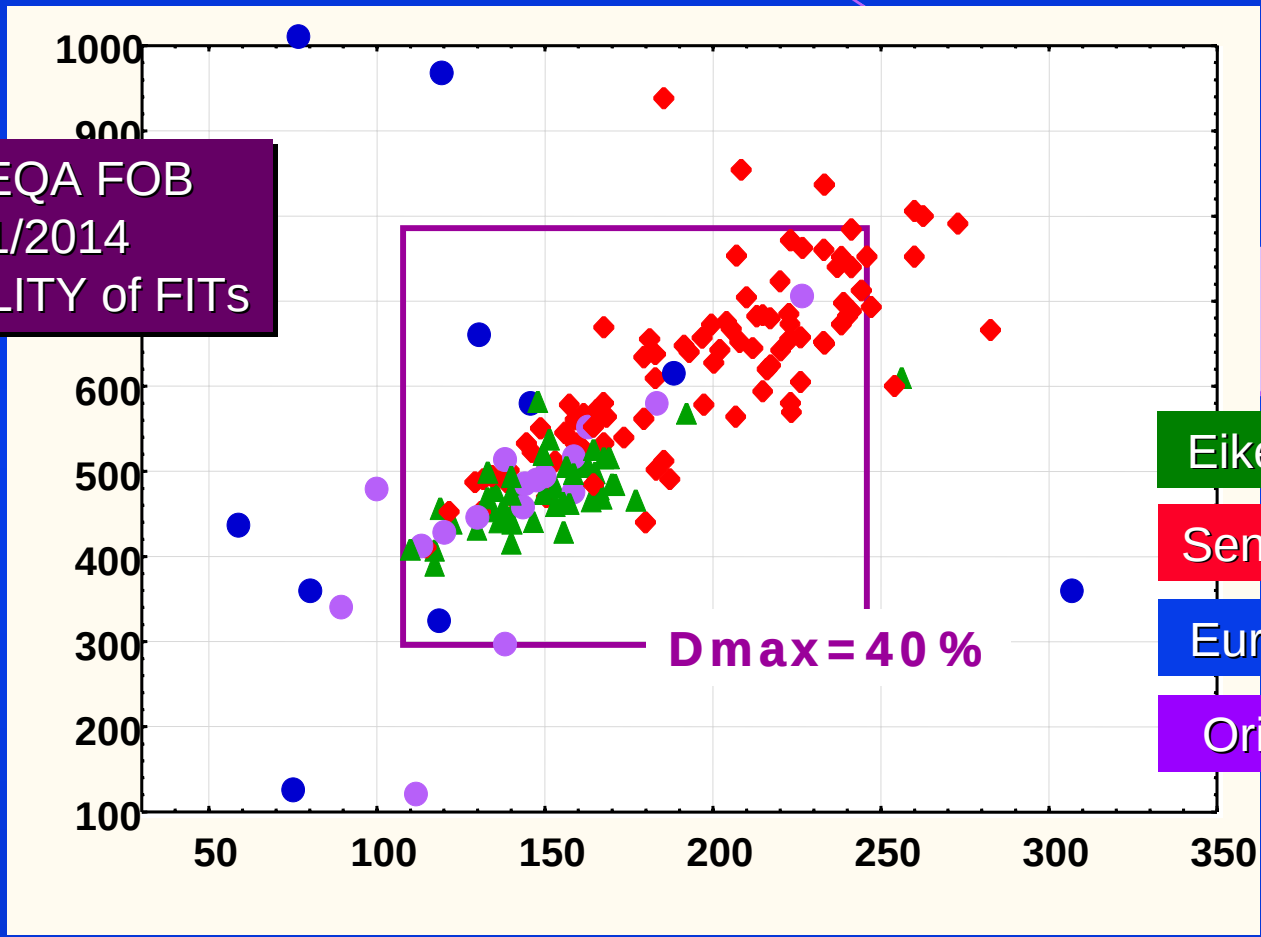
QUANTITATIVE FIT ANALYSERS IN CZECH REPUPLIC



Map of the Czech Republic with 95 marked locations where the quantitative analysis of Hb in stool, controlled with the SEKK external control quality, is available

EXTERNAL CONTROL QUALITY SYSTEM in CR

SEKK EQA FOB
2011/2014
VARIABILITY of FITs



CV - 8.71 %

CV - 17.06 %

CV - 68.15 %

CV - 32.60 %

Eiken OC-Sensor

Sentinel FOBGold

Eurolyser - FOB

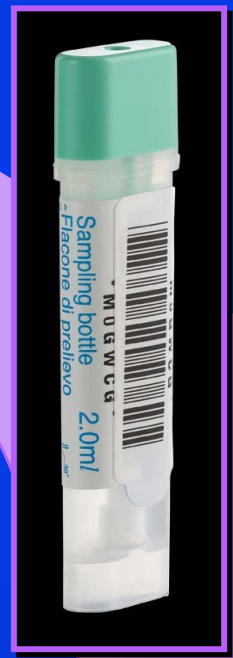
Orion QuikRead

Kocna P., Zima T., Budina M., Ichiyanagi T.: External Quality Assessment (EQA) for Quantitative Fecal Blood in Stool (FIT). Biochimica Clinica, 2013, 37, 423

QUANTITATIVE Hb STOOL ANALYSIS IN PRAGUE

EXPERIENCES IN GENERAL FACULTY HOSPITAL - PRAGUE, 2008 - 2014

Quantitative determination of Hb in stool
Eiken OC-Sensor micro analyser
General Faculty Hospital Prague
32 000 tests in distributed in 6 years
Test recovery - 60.1%
13271 individuals were tested
107 CRC diagnosed by FIT
EQAS - 100 % success rate
The relative error of Hb analysis - 4.04 %



Kocna P., Májek O., Blaha M.: Clinical and epidemiological importance of analyzing laboratory data with the data source I-COP. Sborník Medsoft 2014 - March 25; 110-122 on-line: http://creativeconnections.cz/medsoft/2014.html

POSITIVITY OF FIT (OC-SENSOR TEST)

AGE 30 – 50 YEAR (n = 2091)

µg/g	n	positivity
10	219	10.47 %
15	178	8.51 %
20	152	7.27 %
> 200	43	2.06 %

AGE 50 – 90 YEAR (n = 13282)

µg/g	n	positivity
10	2374	17.87%
15	1954	14.71 %
20	1669	12.57 %
> 200	448	3.37 %

Laboratory information system - OpenLIMS Stapro
18 029 samples of FIT - OC-Sensor method
13271 individuals were tested between 2008 - 2014

POSITIVITY OF FIT (OC-SENSOR TEST)

AGE 50 – 90 YEAR (n = 5273)

μg/g	n	positivity
10	510	9.67 %
15	390	7.40 %
20	310	5.88 %
> 200	64	1.21 %

Patients of the Center for Preventive Care & GPs

AGE 50 – 90 YEAR (n = 7938)

μg/g	n	positivity
10	1855	23.37 %
15	1556	19.60 %
20	1351	17.02 %
> 200	382	4.81 %

Patients specialized hospital clinics outpatient and inpatients

DATA-MINING TOOL I-COP

One health care
different focus
different data sources
?

Czech National Cancer Registry (CNCR)

Hospital HIS/LIS
Laboratory
Administrative data

Tumor diagnosis
TNM classification
Clinical stage
Patient referral

Laboratory values
Patient treatment
Hospital processes
Approximated cost

I-COP
analytical and datamining tool

ACCURACY OF QUANTITATIVE FIT
A HISTORICAL COHORT STUDY

cut-off 10 μg/g

	CRC +	CRC -	Total
Positive test	41	916	957
Negative test	10	5,130	5,140
Total	51	6,046	6,097

	%	95% CI
FIT Positivity	15.7	14.8-16.6
Sensitivity	80.4	66.9-90.2
Specificity	84.8	83.9-85.7
PPV	4.3	3.1-5.8

- 6097 adult patients with their first FIT performed during 2009-2011
- patients without prior CRC, minimal 1 year follow-up through CNCR records
- accuracy characteristics according to cut-off – 2 year follow up
- 2 year follow-up may be incomplete in patients tested in 2011

ACCURACY OF QUANTITATIVE FIT
A HISTORICAL COHORT STUDY

cut-off 15 μg/g

	CRC +	CRC -	Total
Positive test	39	755	794
Negative test	12	5,291	5,303
Total	51	6,046	6,097

	%	95% CI
FIT Positivity	13.0	12.2-13.9
Sensitivity	76.5	62.5-87.2
Specificity	87.5	86.7-88.3
PPV	4.9	3.5-6.7

- 6097 adult patients with their first FIT performed during 2009-2011
- patients without prior CRC, minimal 1 year follow-up through CNCR records
- accuracy characteristics according to cut-off – 2 year follow up
- 2 year follow-up may be incomplete in patients tested in 2011

ACCURACY OF QUANTITATIVE FIT
A HISTORICAL COHORT STUDY

cut-off 20 μg/g

	CRC +	CRC -	Total
Positive test	38	646	684
Negative test	13	5,400	5,413
Total	51	6,046	6,097

	%	95% CI
FIT Positivity	11.2	10.4-12.0
Sensitivity	74.5	60.4-85.7
Specificity	89.3	88.5-90.1
PPV	5.6	4.0-7.5

- 6097 adult patients with their first FIT performed during 2009-2011
- patients without prior CRC, minimal 1 year follow-up through CNCR records
- accuracy characteristics according to cut-off – 2 year follow up
- 2 year follow-up may be incomplete in patients tested in 2011

ACCURACY OF QUANTITATIVE FIT
A HISTORICAL COHORT STUDY

cut-off 30 μg/g

	CRC +	CRC -	Total
Positive test	36	515	551
Negative test	15	5,531	5,546
Total	51	6,046	6,097

	%	95% CI
FIT Positivity	9.0	8.3-9.8
Sensitivity	70.6	56.2-82.5
Specificity	91.5	90.7-92.2
PPV	6.5	4.6-8.9

- 6097 adult patients with their first FIT performed during 2009-2011
- patients without prior CRC, minimal 1 year follow-up through CNCR records
- accuracy characteristics according to cut-off – 2 year follow up
- 2 year follow-up may be incomplete in patients tested in 2011

DETECTED COLORECTAL CANCERS

AGE 50 – 90 YEAR (n = 4145)

µg/g	n	FIT +
15	510	9.67 %
> 200	64	1.21 %

Patients of the Center for Preventive Care & GPs

Detected CRC – 13/83

Detection rate - **2.47/1000** FIT

AGE 50 – 90 YEAR (n = 6561)

µg/g	n	FIT +
15	1855	23.37 %
> 200	382	4.81 %

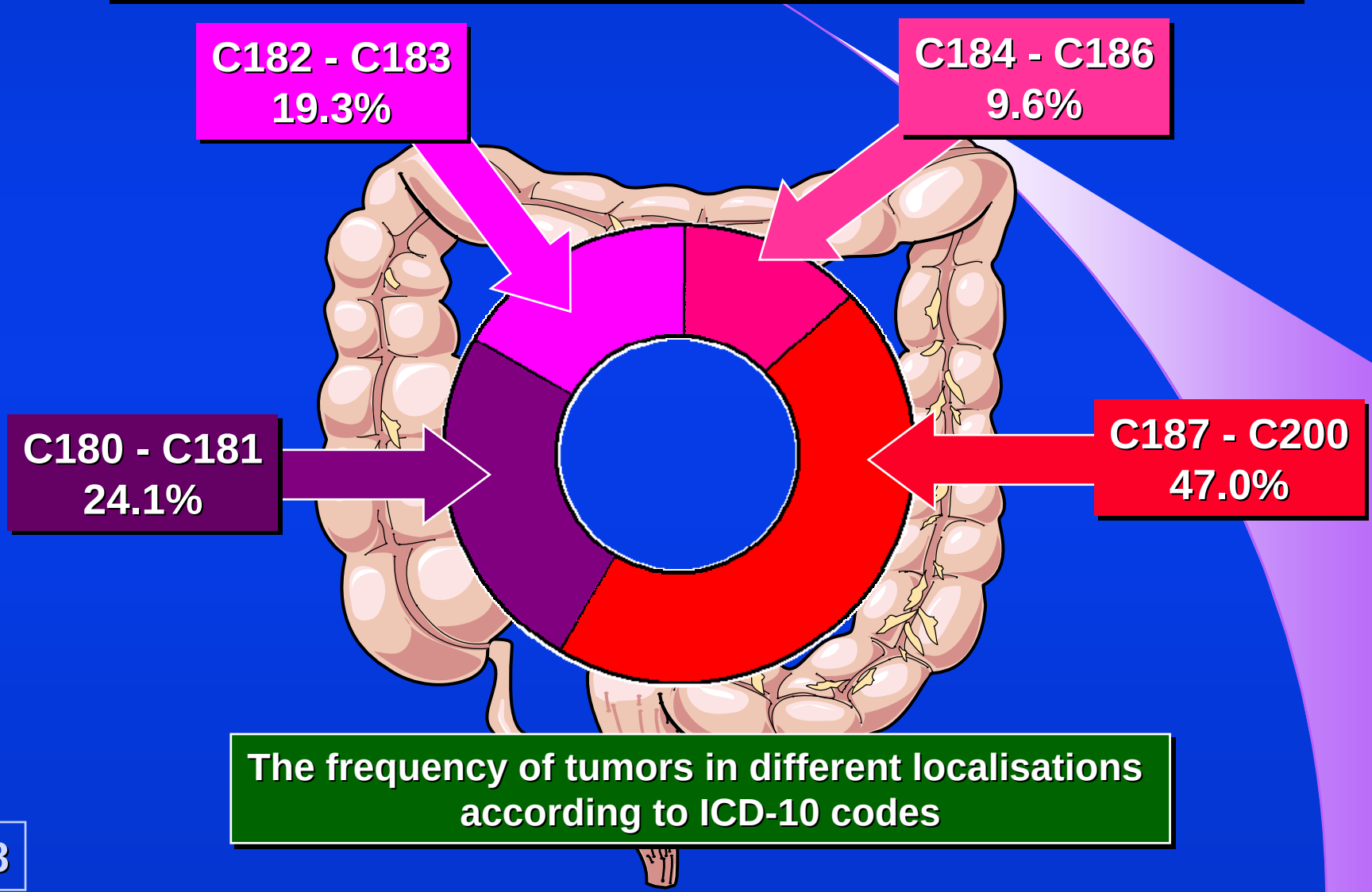
Patients specialized hospital clinics outpatient and inpatients

Detected CRC – 70/83

Detection rate - **8.81/1000** FIT
3.6x more compare to GPs

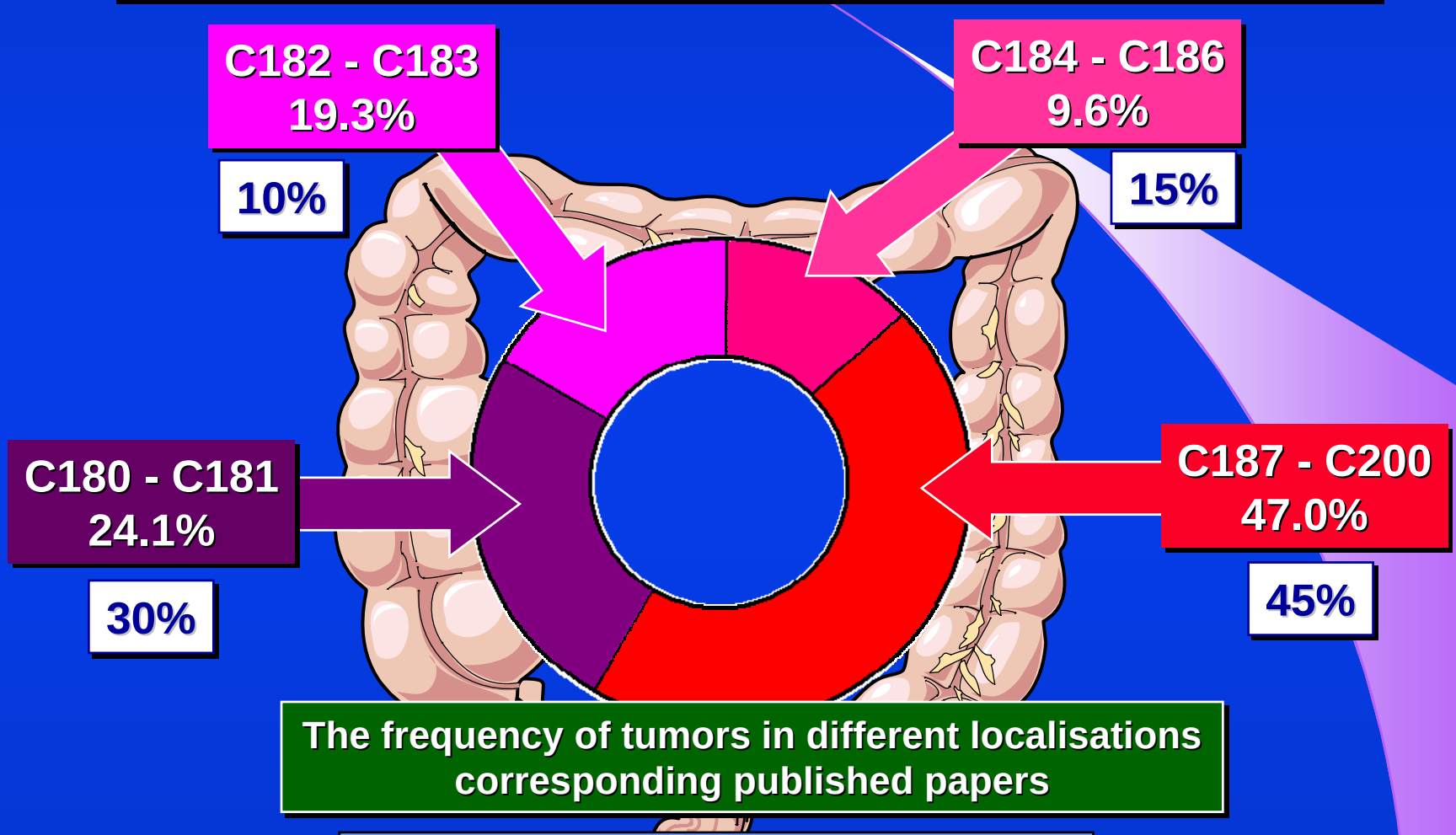
Kocna P., Májek O., Blaha M., Zima T., Dušek L.: Characteristics of colorectal cancer detected by quantitative faecal haemoglobin test in hospital opportunistic screening. WorldLab 2014, June, Istanbul

CRC TUMOR - BOWEL LOCALISATION



The frequency of tumors in different localisations according to ICD-10 codes

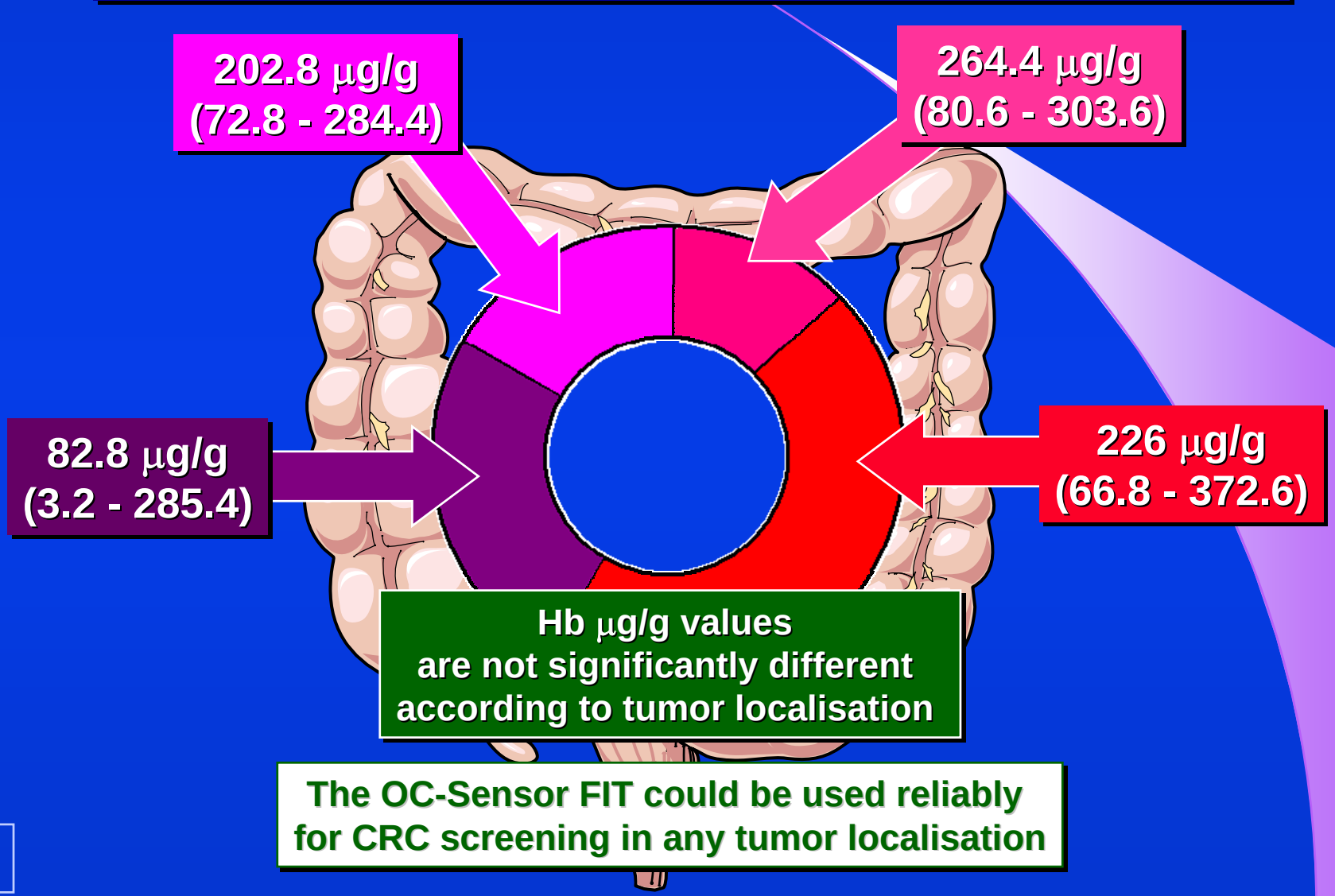
CRC TUMOR - BOWEL LOCALISATION



The frequency of tumors in different localisations corresponding published papers

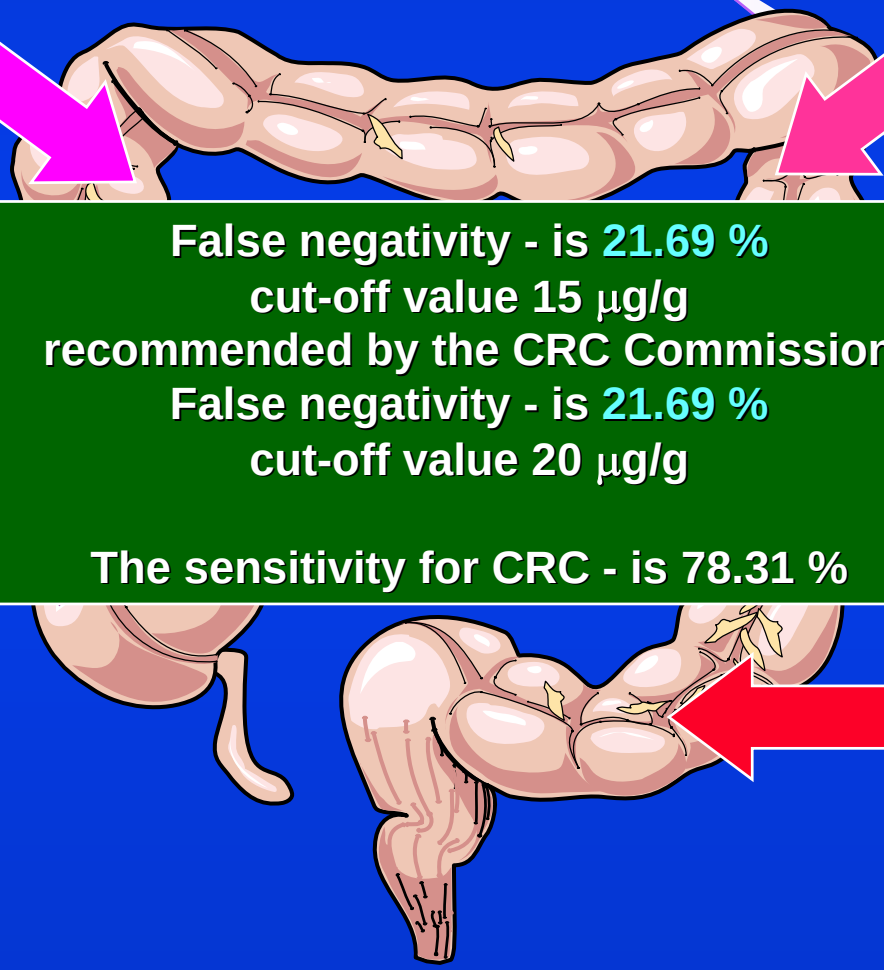
Johns Hopkins Colon Cancer Center
http://www.hopkinscoloncancercenter.org

CRC TUMOR - BOWEL LOCALISATION & FIT VALUE



The OC-Sensor FIT could be used reliably for CRC screening in any tumor localisation

OC - SENSOR FIT FALSE NEGATIVITY



3/16

18.8%

1/8

12.5%

False negativity - is 21.69 %
cut-off value 15 μg/g
recommended by the CRC Commission
False negativity - is 21.69 %
cut-off value 20 μg/g

The sensitivity for CRC - is 78.31 %

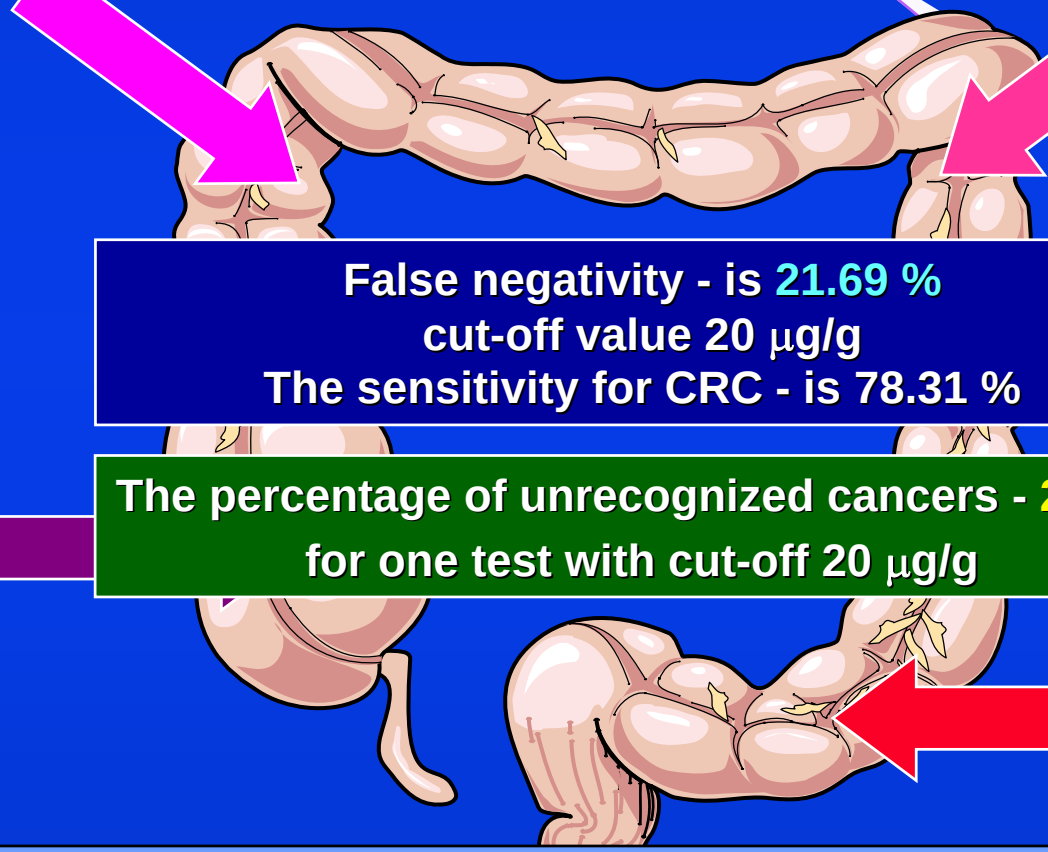
7/20

35.0%

7/39

17.9%

OC - SENSOR FIT FALSE NEGATIVITY



3/16

18.8%

1/8

12.5%

False negativity - is 21.69 %
cut-off value 20 μg/g
The sensitivity for CRC - is 78.31 %

The percentage of unrecognized cancers - 23.5%
for one test with cut-off 20 μg/g

7/20

35.0%

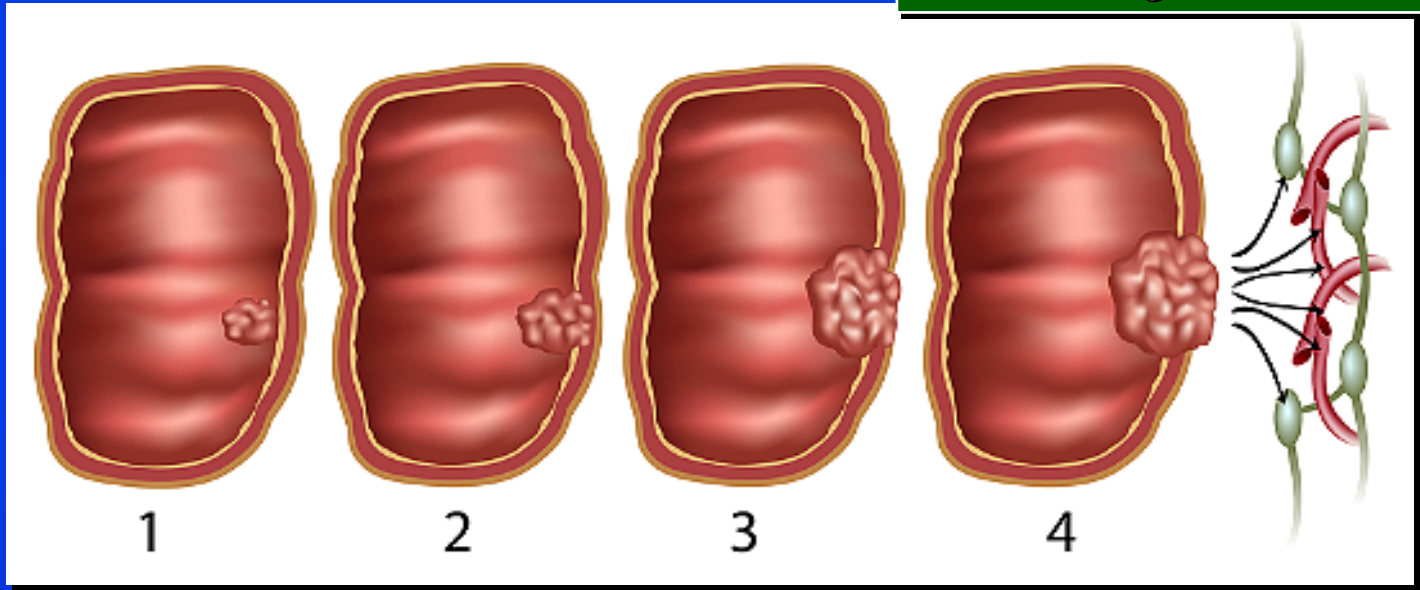
7/39

17.9%

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

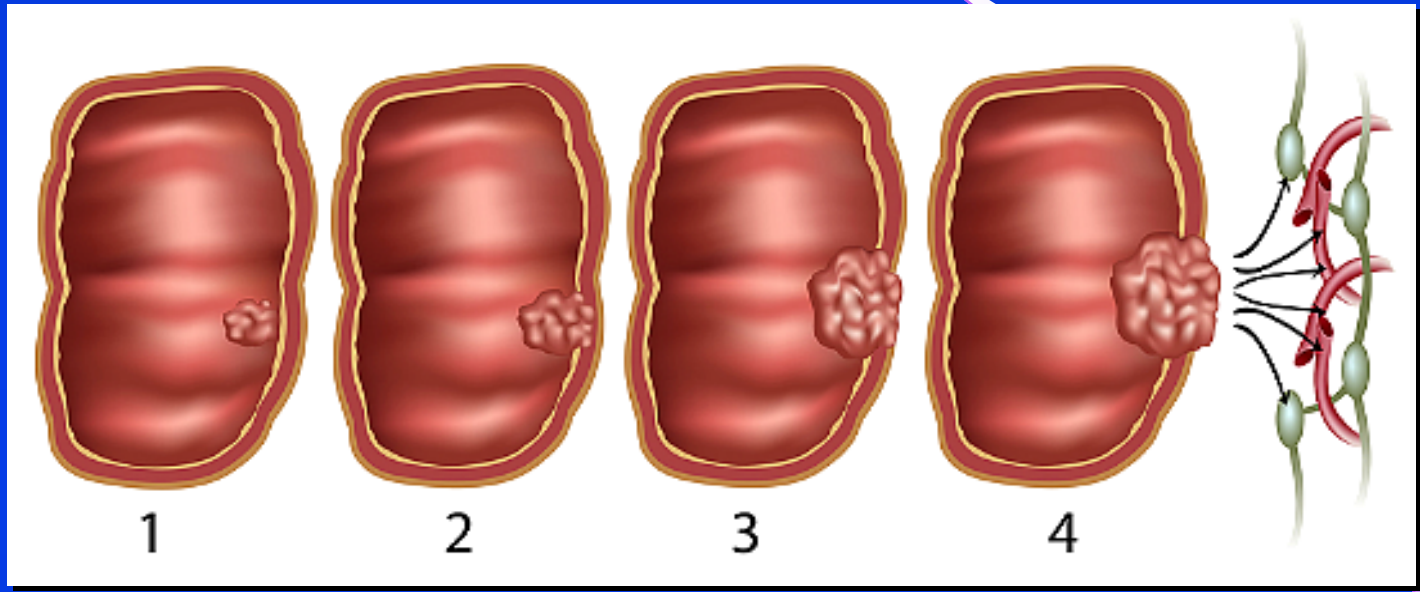
CRC TUMOR STAGE & FIT VALUE

Hb μg/g values are not significantly different according to tumor stages



CRC stage I (n=18)	CRC stage II (n=24)	CRC stage III (n=23)	CRC stage IV (n=18)
202.8 μg/g (13.2 - 339.2)	227.4 μg/g (99.6 - 327.8)	250.6 μg/g (66.8 - 476.8)	53.2 μg/g (1.8 - 237.4)

OC - SENSOR FIT FALSE NEGATIVITY



CRC stage I (n=18) 5/18	CRC stage II (n=24) 2/24	CRC stage III (n=23) 5/23	CRC stage IV (n=18) 6/18
27.8%	8.3%	21.7%	33.3%

FOBT - THE PAST

20 YEARS WE USED g-FOBT
WITH LOW SENSITIVITY
BUT THE SAME RELIABILITY IN ALL
REGIONS OF THE CZECH REPUBLIC

FOBT - THE PRESENT

IN 2013 WE CHANGED TO i-FOBT, FIT
WITH 2-TIMES HIGHER SENSITIVITY
BUT DISTINCTLY INCREASING VARIABILITY
IN REGIONS OF THE CZECH REPUBLIC

FOBT - THE FUTURE

QUANTITATIVE FIT SHOULD BE USED ONLY
MODIFY THE SCREENING RULES

Automated analysers for qiFOBT are ready to start CRC screening
with qiFOBT optimised for Czech Republic screening
EQAS control system is since January 2012 available

Committee for CRC screening
Ministry of Health
of the Czech Republic

National screening programme in the Czech Republic
should be modified to use **quantitative qiFOBT** technology

2 years ago

Quantitative immunochemical qi-FOBT OC-Sensor
Meeting with EC & EP – Prague, January 11, 2012

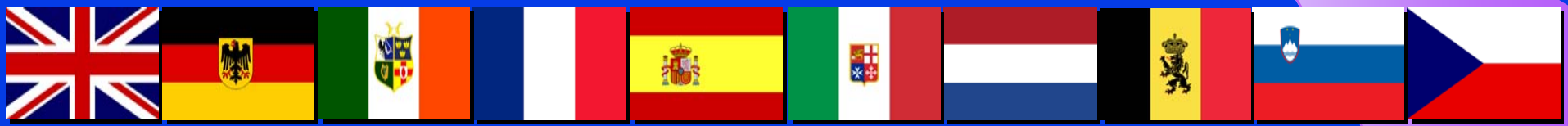
EUROPEAN EXPERIENCES WITH FIT

We analysed 180 scientific publications, available on web

Publications focusing on CRC screening by FIT

Publications published in the last 6 years (2008-2014)

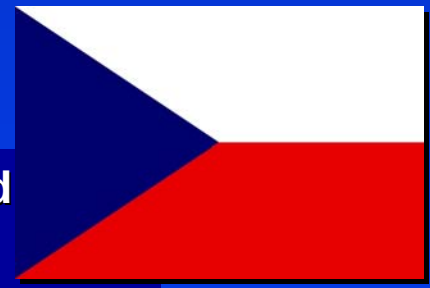
The presentation was focused only on studies of European countries



'EVIDENCE BASED' RECOMMENDATIONS AND EXPERIENCES ARE NOW AVAILABLE

Kocna P.: The European experiences with FIT tests. Proceedings 2nd National Congress on Colorectal Cancer, Prague 2013, 359-369

Biomedical Papers - 06/2012



FIT test before colonoscopy - 815 people, two centers (VFN and
Comparison of a two-FIT tests and different cut-off values
FIT test - OC-Sensor micro

Hb cut off - ng/ml	50	75	100	125	150
Sensitivity CRC - FIT 1	88.6% (73.2 -96.7)	85.7% (69.7 - 95.1)	85.7% (69.7 - 95.1)	80.0% (63.1 - 91.5)	80.0% (63.1 - 91.5)
Sensitivity CRC - FIT 2	88.6% (73.2 -96.7)	85.7% (69.7 - 95.1)	85.7% (69.7 - 95.1)	85.7% (69.7 - 95.1)	85.7% (69.7 - 95.1)
Specificity CRC - FIT 1	87.2% (83.6 -90.2)	90.1% (86.8 - 92.8	91.0% (87.9 - 93.6)	93.0% (90.1 - 95.2)	93.5% (90.6 - 95.6)
Specificity CRC - FIT 2	81.4% (77.3–85.0)	84.7% (80.9 - 88.1)	86.9% (83.3 - 90.0)	89.1% (85.7 - 91.9)	90.1% (86.8 - 92.8)

Recommendation of Czech pilot study - one FIT test with cut-off value 75 ng/ml

Kovarova JT, Zavoral M, Zima T, Zak A, Kocna P. et al. Biomed Pap 2012 Jun; 156(2): 143 - 150: Improvements in colorectal cancer screening programmes - quantitative immunochemical faecal occult blood testing - how to set the cut-off for a particular population.

EDUCATION ON IMPORTANCE OF FIT VALUES

Man 66 year (born 1946)
29.4.2009 - **FIT: 0 μg/g**
8.8.2011 - FIT: **271 μg/g**
NO reaction
11.7.2012 - FIT: **370.8 μg/g**
14.8.2012 - colonoscopy, sigmoid CRC
6.9.2012 - tumour resection, stage 3
FIT - surgery time: **12.96 months**

Two cases with FIT value 0 μg/g and CRC

Man 72 year (born 1941)
13.5.2010 - **FIT: 0 μg/g**
14.11.2012 - FIT: **148.2 μg/g**
NO reaction
5.3.2013 - FIT **327.4 μg/g**
10.4.2013 - colonoscopy, sigmoid CRC
13.5.2013 - tumour resection, stage 3
FIT - surgery time: **5.92 months**

FIT_surgery interval (median): **1.42**
Range: 0.1 - 45.2 months

Kocna P., Májek O., Blaha M.: Clinical and epidemiological importance of analyzing laboratory data with the data source I-COP. Sborník Medsoft 2014 - March 25; 110-122 on-line: http://creativeconnections.cz/medsoft/2014.html

HIGHLIGHT QUANTITATIVE FIT

- ✓ qFIT is 3 times more sensitive and reliable than gFOBT
- ✓ qFIT analysis is based on specific antibody technique
- ✓ qFIT on automatic analyser eliminates subjective evaluation
- ✓ qFIT allows the quantitative analysis
- ✓ qFIT could be possible to optimise selecting screening cut-off
- ✓ qFIT allows comparing the values on a European scale
- ✓ qFIT may be monitor by quality control system EQAS


THANK YOU FOR YOUR ATTENTION