Screening for Gastric and Colorectal Cancers

Mārcis Leja

Faculty of Medicine, University of Latvia

Riga, February 12, 2016

Screening

Screening is identification of groups of individuals from general population in whom the likelyhood of asymptomatic or oligosymptomatic disease is increased by using simple diagnostic tests

The objective of screening is to decrease the mortality caused by the target disease

WHO criteria for screening

1. The condition sought should be an important health problem for the individual and community.
2. There should be an accepted treatment or useful intervention for patients with the disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable screening test or examination.
6. The test should be acceptable for the population.
7. The natural history of the disease should be adequately understood.
8. There should be an agreed policy for referring for further examination and whom to treat as patients.
9. The cost should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case finding should be a continuing process and not a once only project.

Wilson and Jungner 1968

Screening recommended by European Commission

- Breast cancer (mammography)
- Cervical cancer (*PAP-smear*)
- Colorectal cancer (occult blood in the stool)

European Commission, 2003.

Current Europen activities

- **Second Report on Cancer Screening in the European Union**

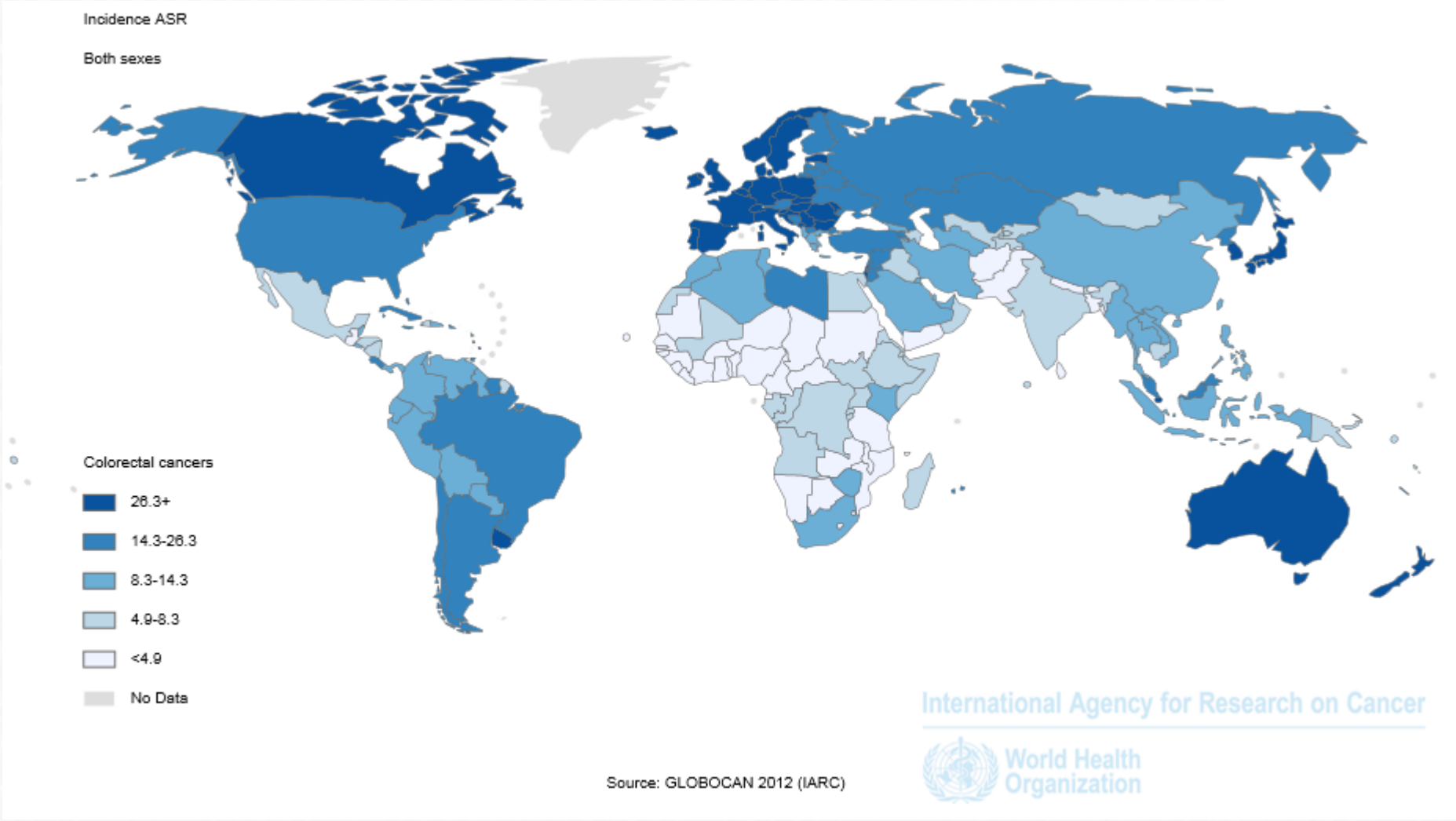
International Agency for Research on Cancer

World Health Organization

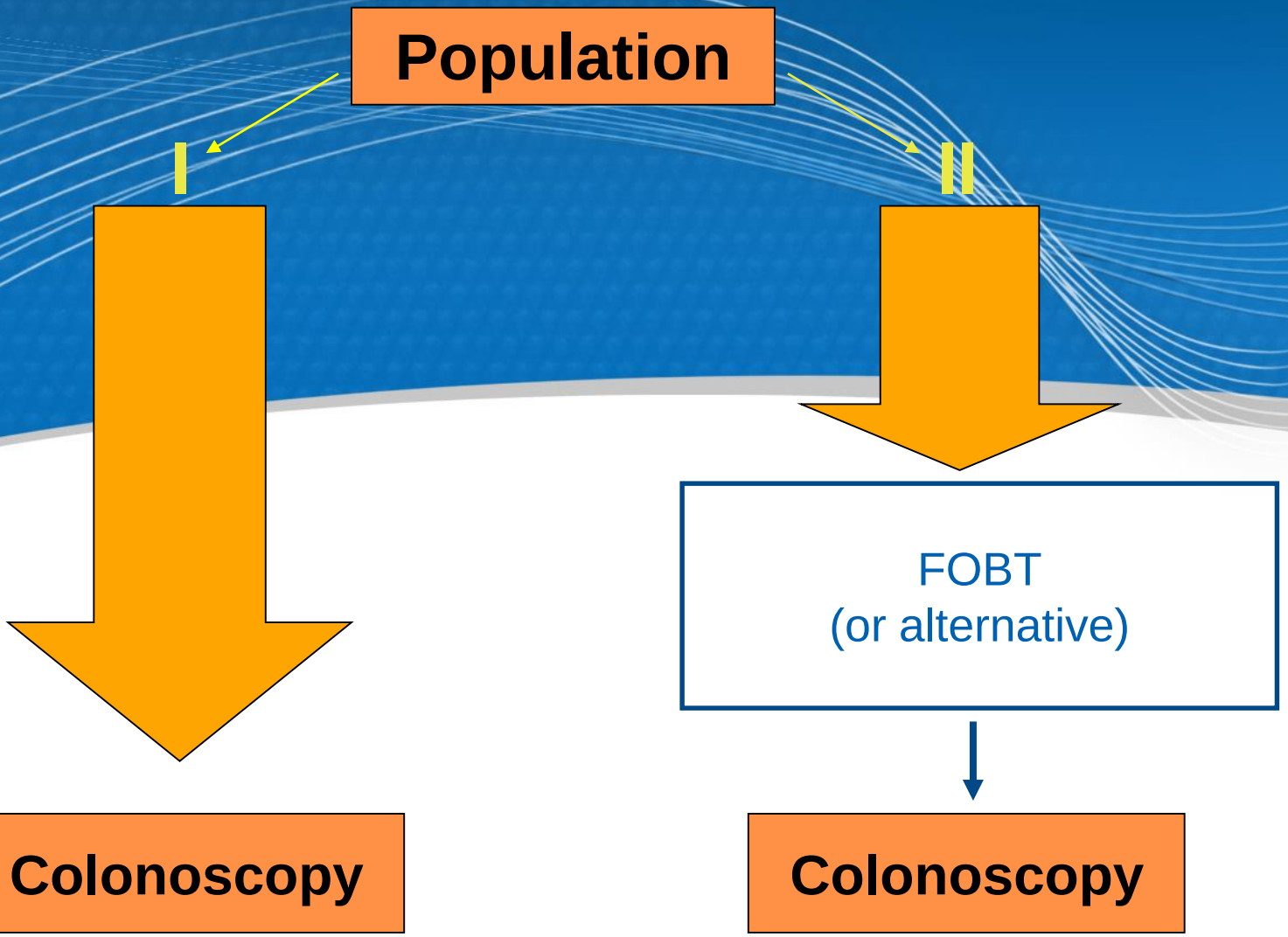
- **EU Joint Action**

CanCon
Cancer Control Joint Action

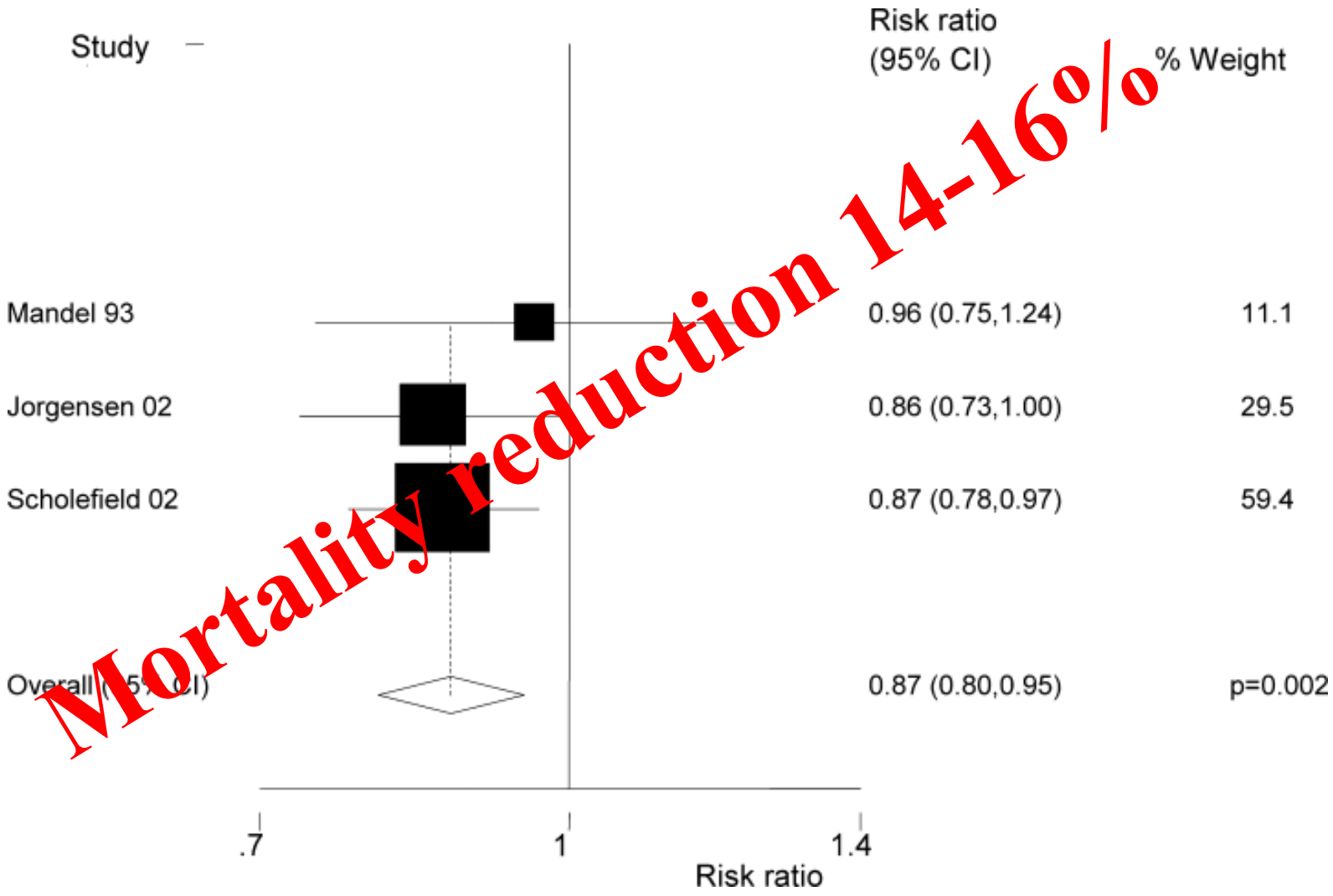
Colorectal Cancer global incidence, ASR, both genders



Colorectal cancer screening strategies



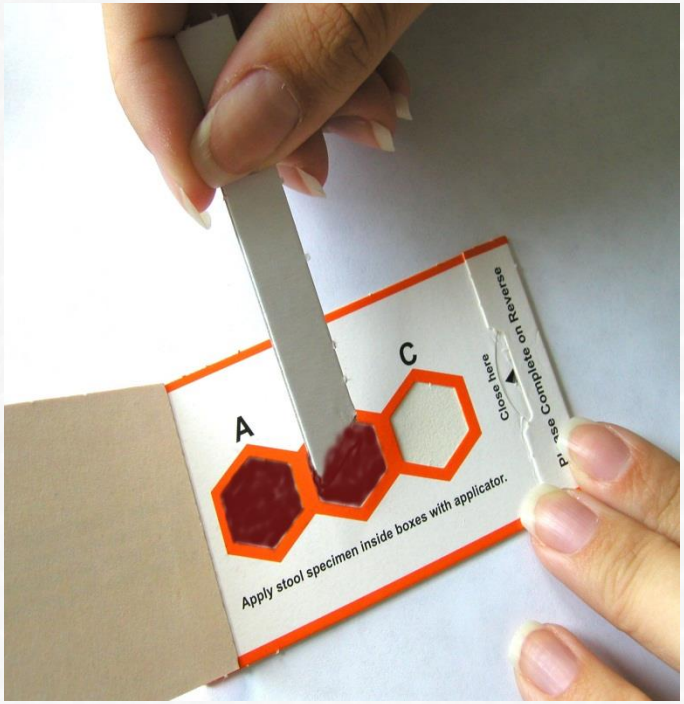
FOBT comparison to no screening in respect to the CRC caused mortality



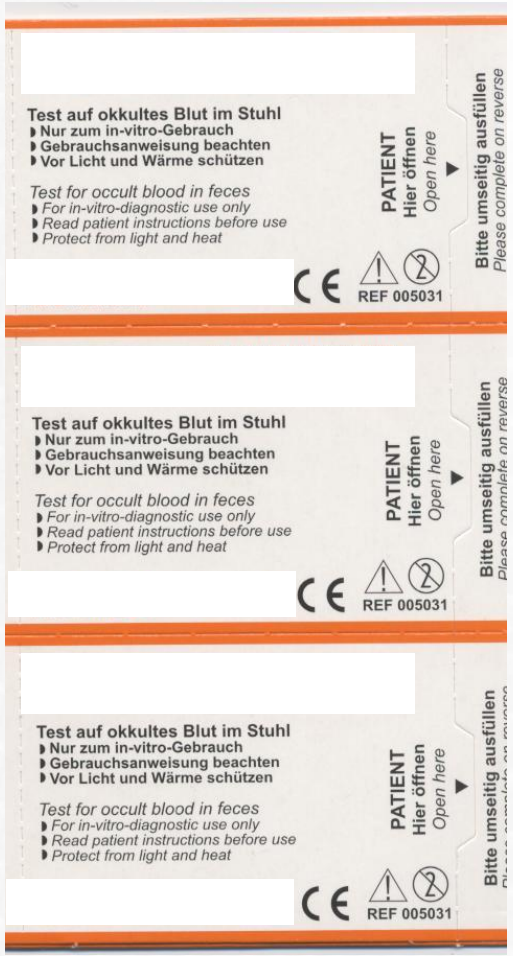
Mortality reduction 14-16%

Moayyedi P et al. Am J Gastroenterol. 2006

Patient’s part

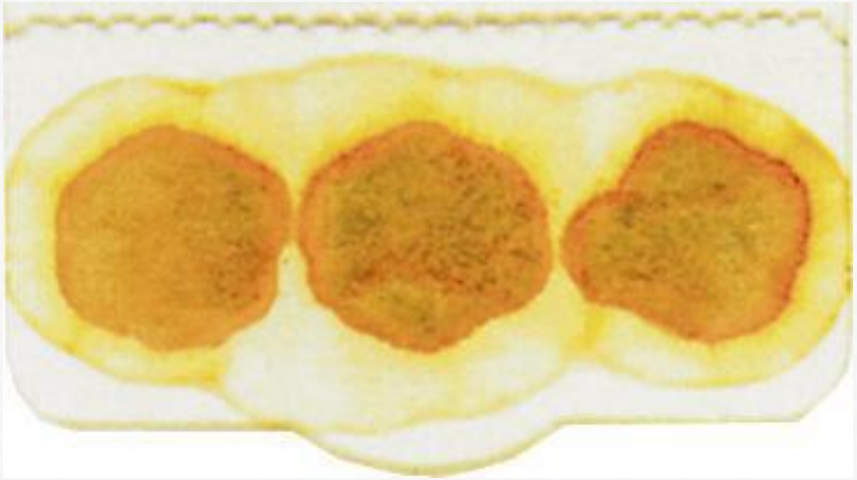


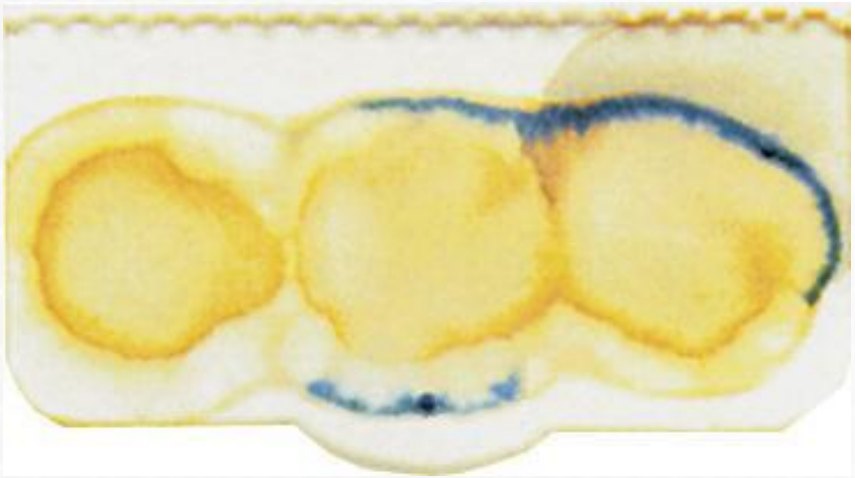
x 3

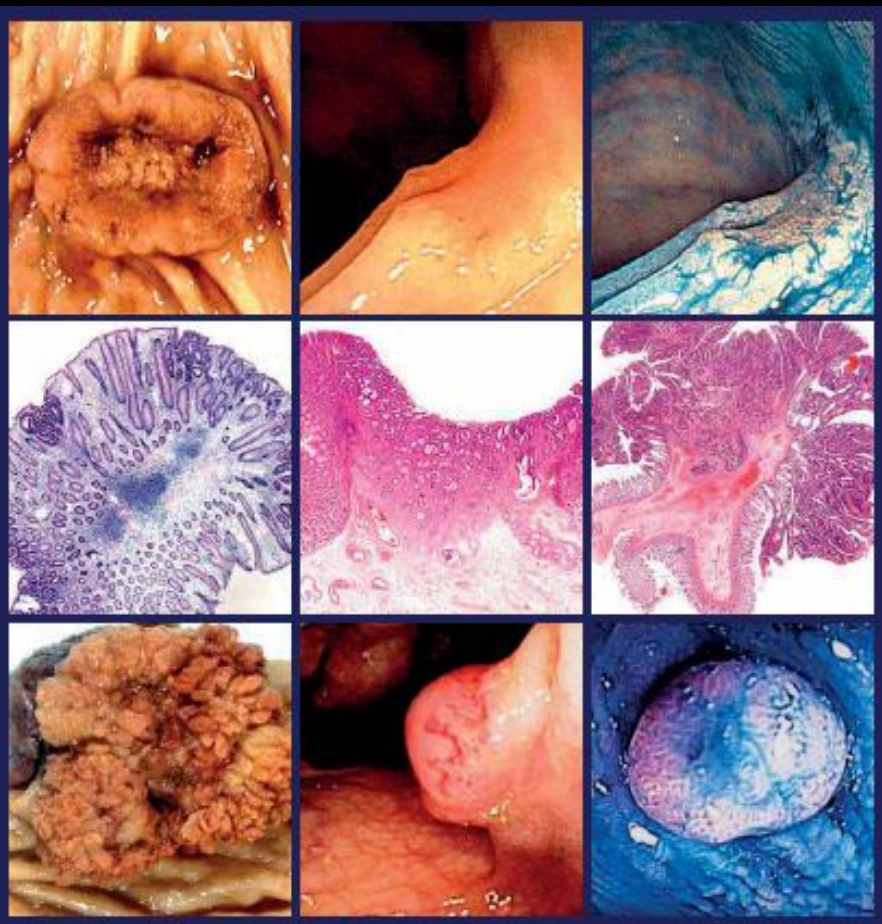


“Laboratory” part

Result







European guidelines for quality assurance in colorectal cancer screening and diagnosis

First Edition

European Commission

DAZ.online

Das Internetportal der Deutschen Apotheker Zeitung

Politik

Patienten sollen künftig zur Krebsvorsorge eingeladen werden. (Foto: Bilderbox)

KREBSBEKÄMPFUNG

Kabinett beschließt Gesetz zum Kampf gegen Krebs

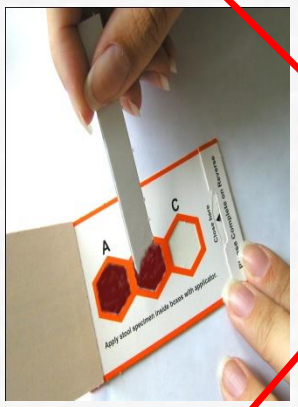
***Berlin* - Das Bundeskabinett hat in seiner heutigen Sitzung das „Gesetz zur Weiterentwicklung der Krebsfrüherkennung und zur Qualitätssicherung durch klinische Krebsregister" (Krebsfrüherkennungs- und -registergesetz) beschlossen. Es sei eine „richtungweisende strukturelle Maßnahme zur Verbesserung der Krebsfrüherkennung", erklärte Bundesgesundheitsminister Daniel Bahr (FDP). Der demographische Wandel führe zu neuen Herausforderungen im Kampf gegen die Krankheit.**

Ausgangspunkt für den Gesetzentwurf ist der „Nationale Krebsplan", der 2008 vom Bundesministerium für Gesundheit, der Deutschen Krebsgesellschaft, der Deutschen Krebshilfe und der Arbeitsgemeinschaft Deutscher Tumorzentren initiiert wurde. Ziel des Plans ist es, die Krebsfrüherkennung, die onkologischen Versorgungsstrukturen und die Qualitätssicherung und Patientenorientierung weiter voranzutreiben. Der heute vom Kabinett beschlossene Gesetzentwurf greift dabei zwei zentrale Punkte aus dem Nationalen Krebsplan auf: Die Optimierung der Krebsfrüherkennung und die Einführung flächendeckender klinischer Krebsregister.

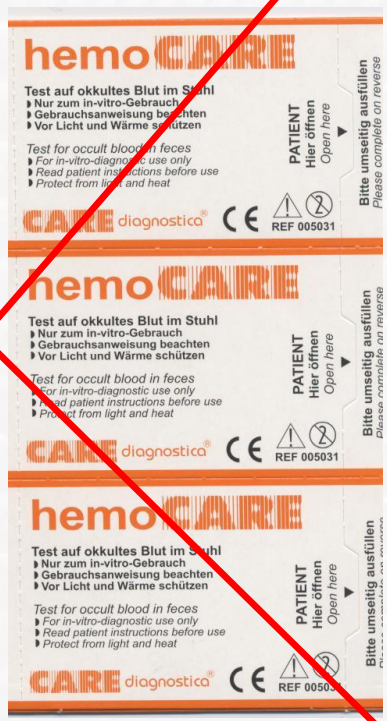
So sollen Patienten künftig stärker erreicht werden, indem sie besser über ihre Ansprüche auf Vorsorgeuntersuchungen informiert werden und persönlich zur Krebsfrüherkennung eingeladen werden. Außerdem werden die Länder im neuen Gesetz dazu verpflichtet, klinische Krebsregister mit einem festgelegten Aufgabenprofil einzurichten. Zu deren Aufgaben gehören insbesondere die Erfassung und Auswertung der Daten über das Auftreten, die Behandlung und den Verlauf von Krebserkrankungen in der ambulanten und stationären Versorgung.

Die Krebsregister sollen dabei überwiegend aus Mitteln der gesetzlichen Krankenversicherung finanziert werden. Die konkrete Gestaltung und vor allem die Finanzierung derselben ist bei den Kassen allerdings noch umstritten. Doris Pfeiffer, Vorstandsvorsitzende des GKV-Spitzenverbandes, erklärte, „Verantwortung, Finanzierung und Nutzen" stehen bei den geplanten klinischen Registern „in keinem angemessenen Verhältnis". Während der Nationale Krebsplan noch von einer geteilten Verantwortung von Bund, Ländern und Selbstverwaltung spreche, finde sich davon in dem jetzt diskutierten Entwurf nur noch wenig.

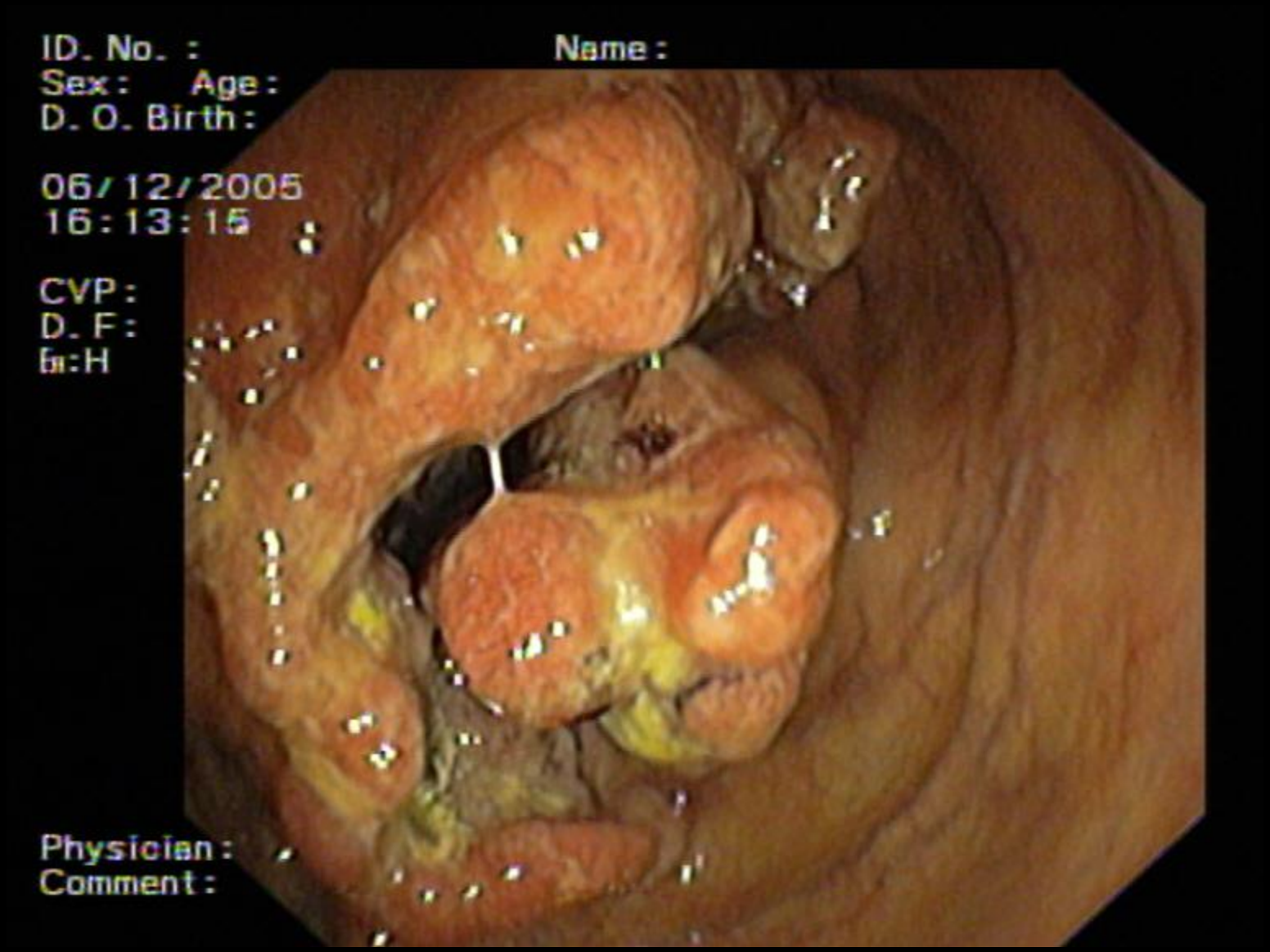
Change in the test-type



x 3

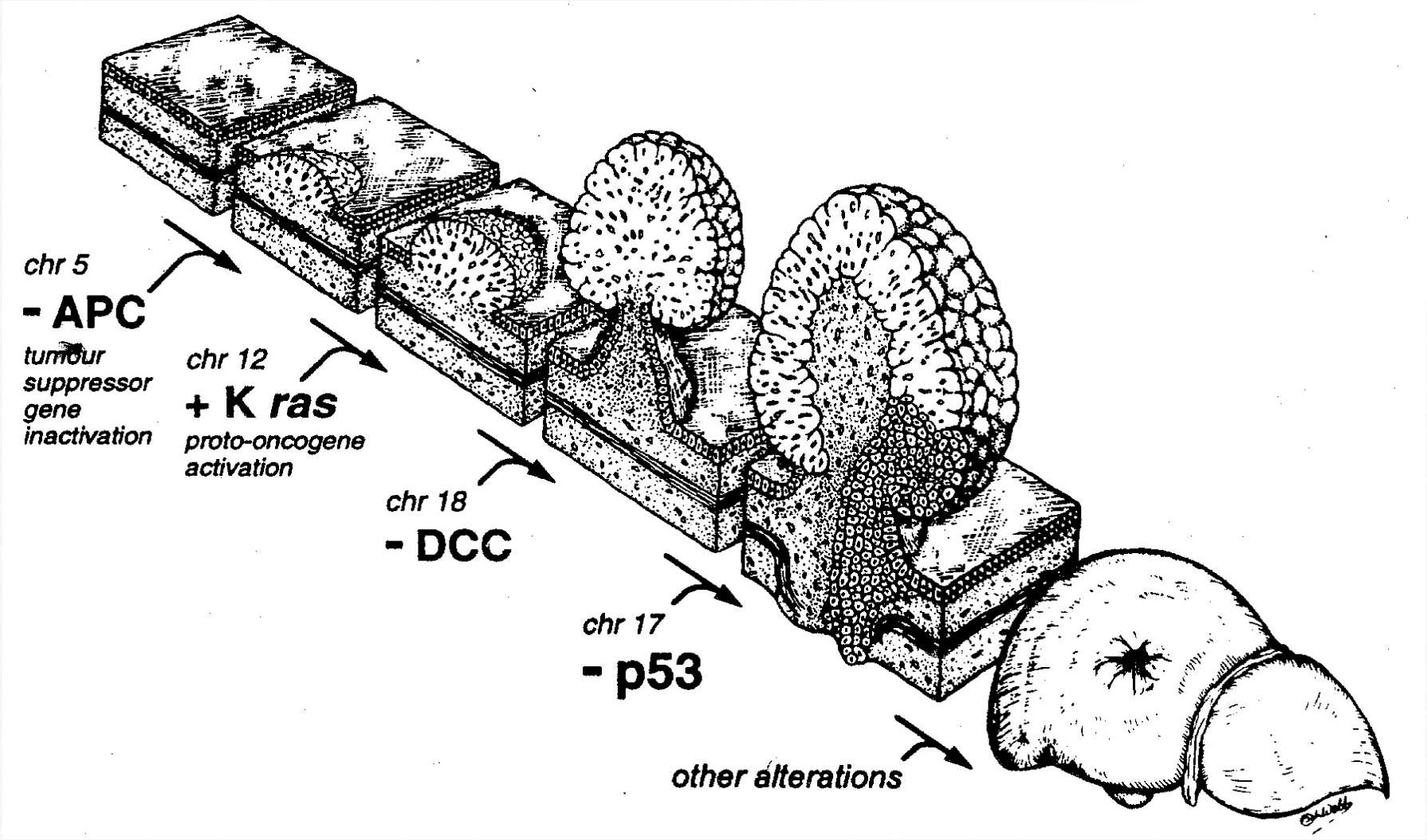


x 1



With courtesy from GASTRO archive

The development of colorectal cancer

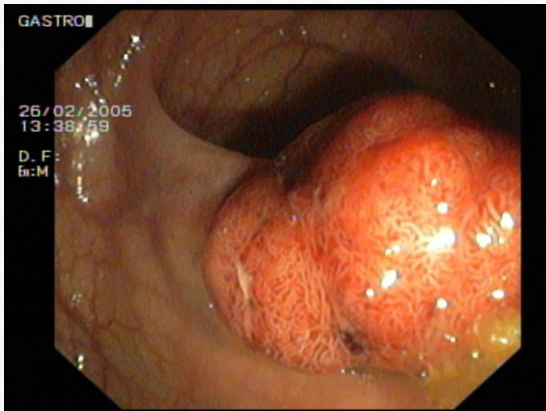


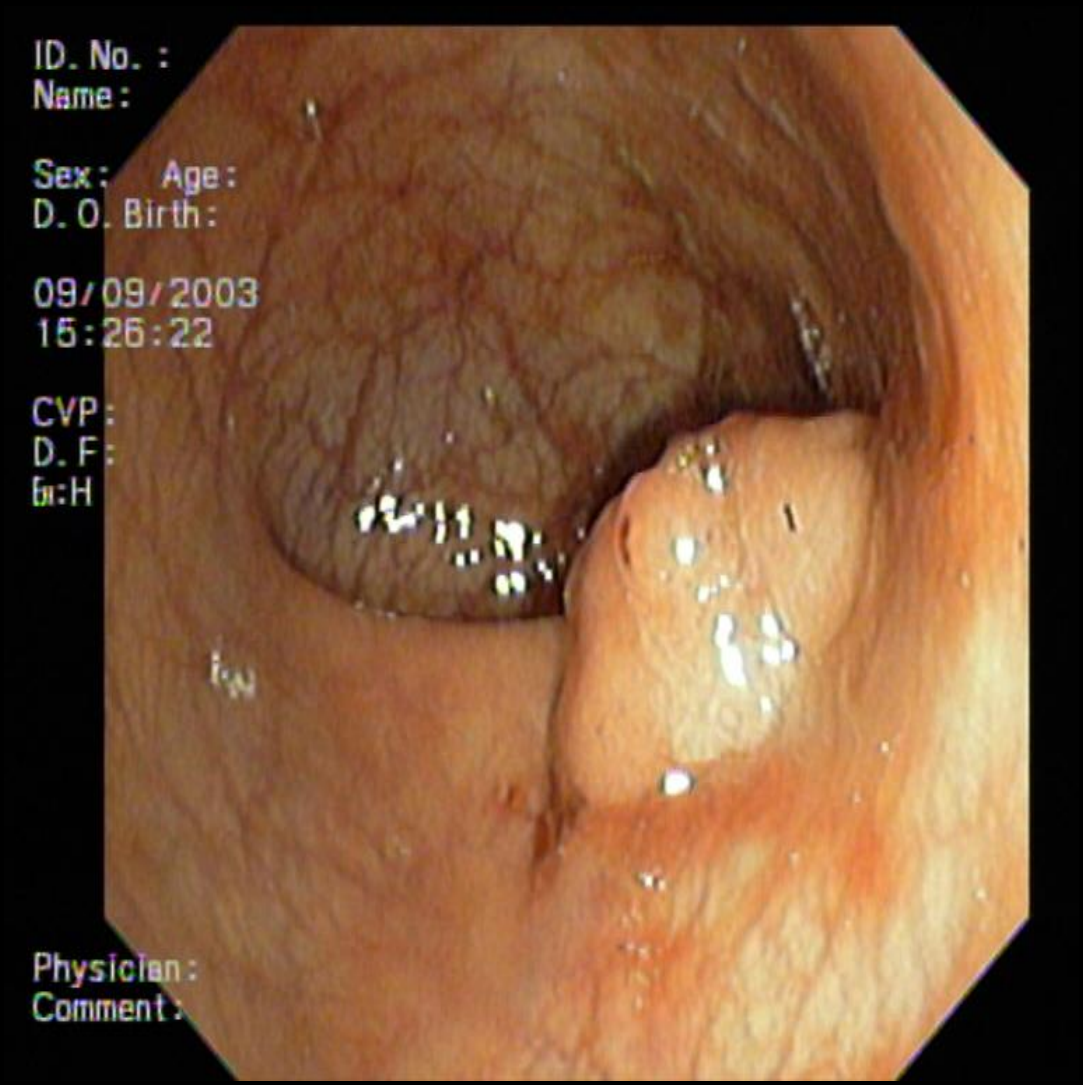
Effect of colonoscopic polypectomy on incidence of colorectal cancer

	↓ Incidence
*U.S. National Polyp Study	76-90%
+Italian Multicenter Study Group	66%

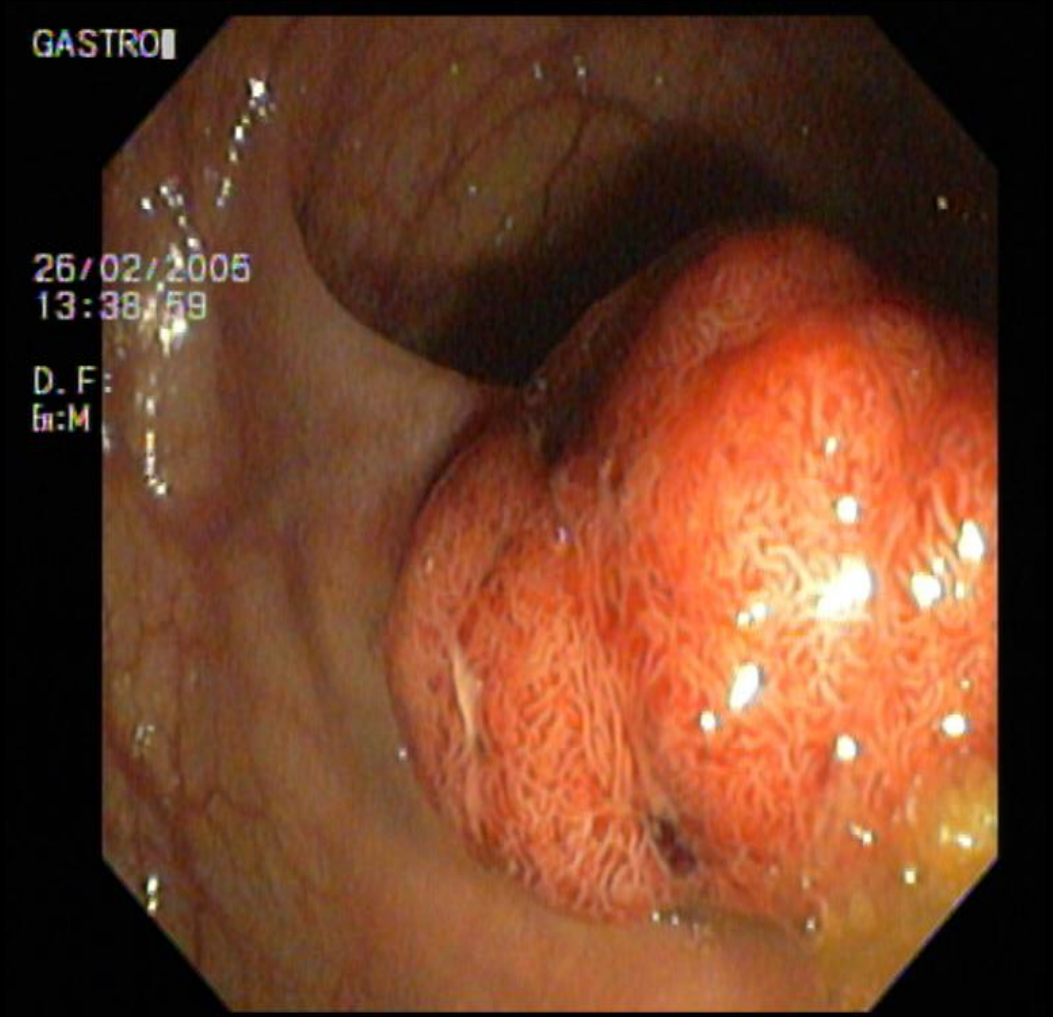
*Winawer, Zauber et al NEJM 1993

+Citarda et al GUT 2001





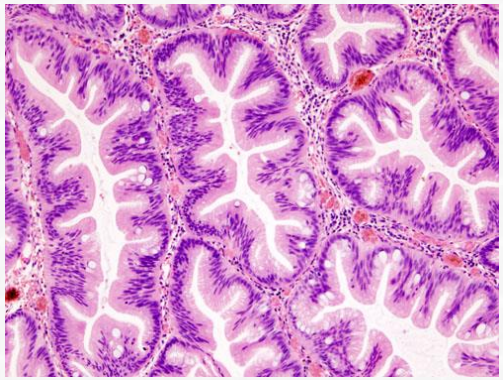
With courtesy from GASTRO archive



With courtesy from GASTRO archive

High-risk adenomas of the colon

- Adenomatous polyps > 1 cm
- Adenomatous polyps with villous component
- Adenomatous polyps with high-grade dysplasia
- Adenomatous polyps with invasive cancer

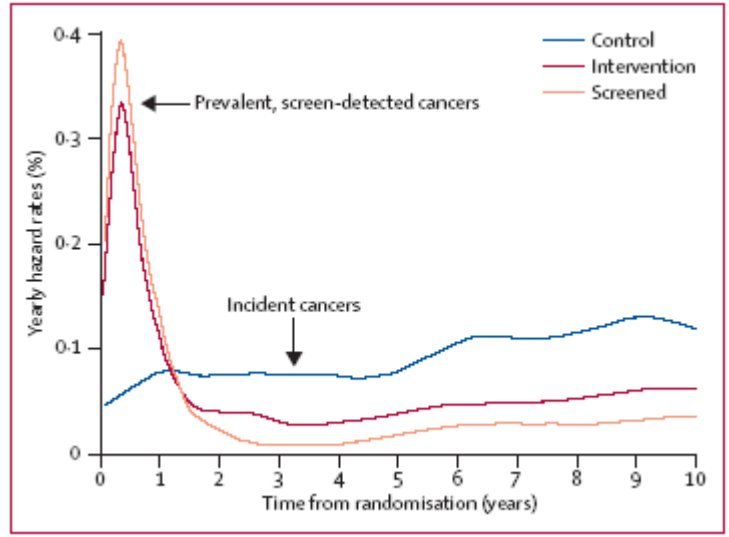


CRC in the first degree relatives

- Increase in risk
  - > double
  - Lifetime risk 10-12%
- Diagnostic method of choice
  - colonoscopy
- Age for initial diagnostics
  - 40 years or 10 years before the earliest case
  - 5-year control interval recommended

Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial

Wendy S Atkin, Rob Edwards, Ines Kralj-Hans, Kate Wooldrage, Andrew R Hart, John M A Northover, D Max Parkin, Jane Wardle, Stephen W Duffy, Jack Cuzick, UK Flexible Sigmoidoscopy Trial Investigators



Sigmoidoscopy with polypectomy significantly decrease the mortality from colorectal cancer

Atkin WS, et al. Lancet, 2010

Effective colonoscopy

- Good bowel-prep
- Intubation of *caecum* gets registered
- Registered number of detected adenomas
- Polypectomy being performed during the initial colonoscopy
- Effective polypectomy technique
- Surveillance of pts with high-risk polyps and other risk groups
- Recommendations for the follow-up investigation

Modified from Rex, AGA, 2010


全國首創-
顧胃保健康
2012年彰化縣
「胃幽門桿菌暨胃癌高危險群篩檢服務」
記者會
採便管
顧胃我健康
肝癌篩檢
大腸癌
幽門桿菌採便管

Gastric cancer – an infection-related cancer

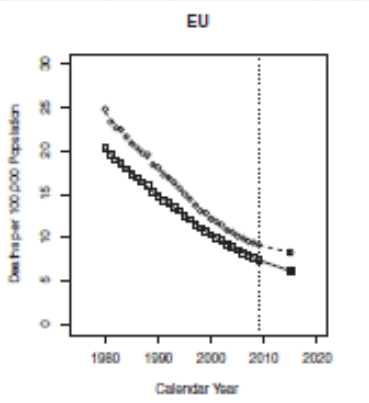
- IARC/WHO – *H.pylori* - Class I carcinogen
  - 1994 - IARC Working Group on the Evaluation of Carcinogenic Risks to Humans
  - Reinforced by WHO, 2011
- The proportion of infection-related cancers
  - *H.pylori* is the cause of at least 90% of non-cardia gastric cancer
- Subtyping of *H.pylori* strain virulence
  - Not recommended by the current guidelines

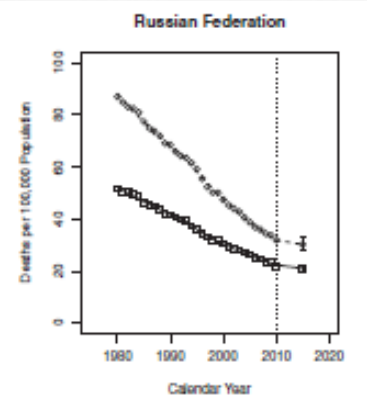
IARC Monogr Eval Carcinog Risks Hum . 1994
IARC. A Review of Carcinogen—Part B: Biological Agents . 2011
Dr Martel et al. The Lancet Oncology. 2012.

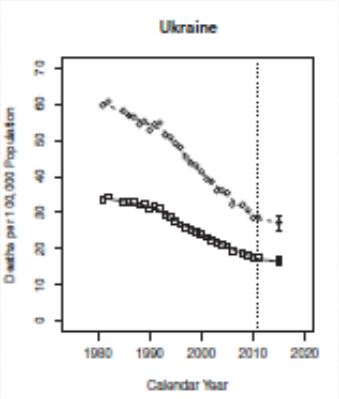
Worldwide trends in gastric cancer mortality (1980–2011), with predictions to 2015, and incidence by subtype

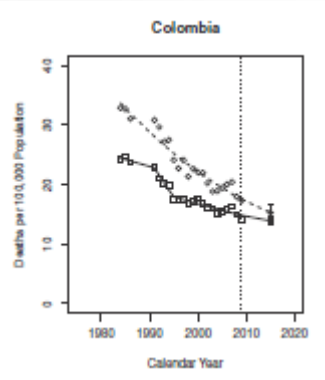
Ana Ferro [a], Bárbara Peleteiro [a,b], Matteo Malvezzi [c], Cristina Bosetti [c], Paola Bertuccio [c], Fabio Levi [d], Eva Negri [c], Carlo La Vecchia [c,e], Nuno Lunet [a,b,*]

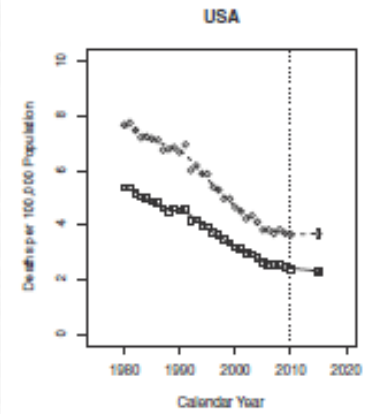
Eur J Cancer, 2014

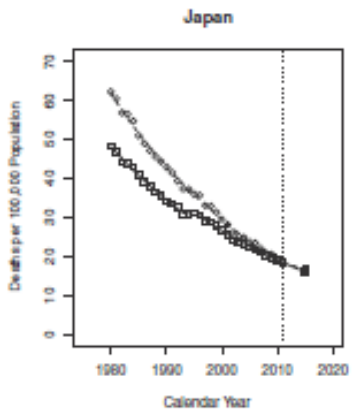


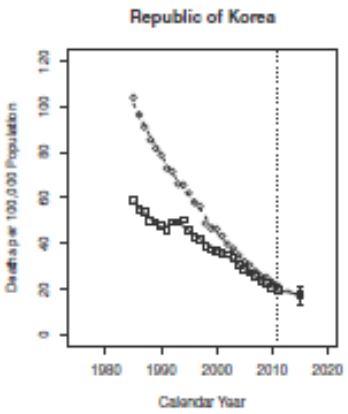












Mortality in males

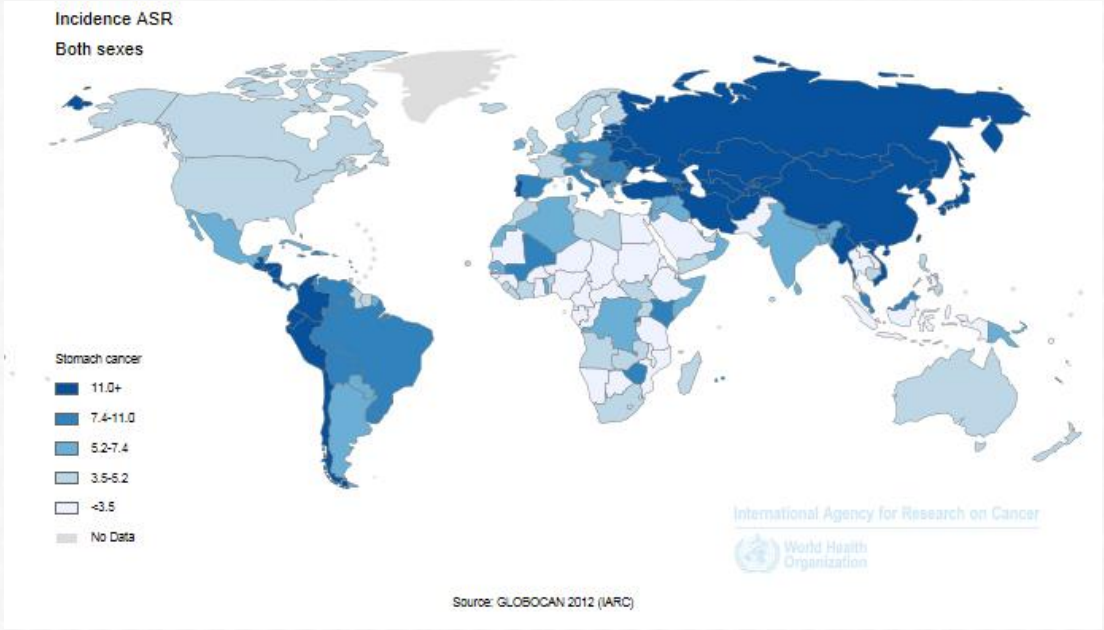
Crude data

□ - *all ages*

○ - *age 35-64*

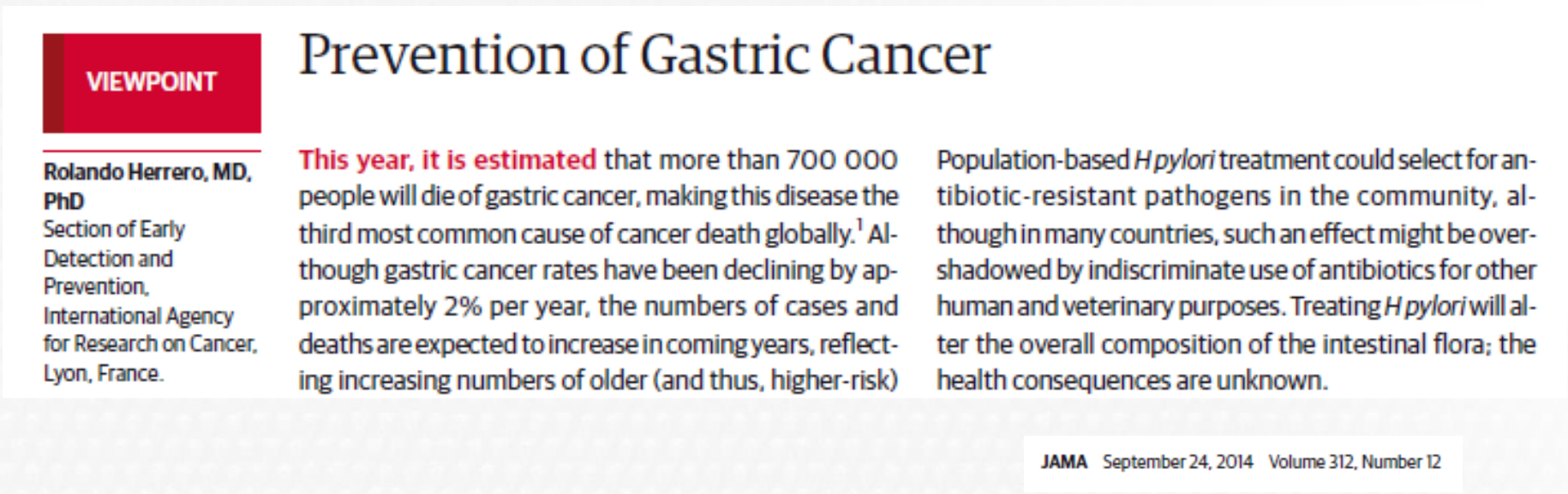
Neglected disease

- ~ 1 M new cases annually
- ~ 1 M new cases in forseeable future (30 years)



Forman & Sierra. IARC Working Group Reports, No. 8 2014

Changing emphasis



VIEWPOINT

Prevention of Gastric Cancer

Rolando Herrero, MD, PhD
Section of Early Detection and Prevention, International Agency for Research on Cancer, Lyon, France.

This year, it is estimated that more than 700 000 people will die of gastric cancer, making this disease the third most common cause of cancer death globally.[1] Although gastric cancer rates have been declining by approximately 2% per year, the numbers of cases and deaths are expected to increase in coming years, reflecting increasing numbers of older (and thus, higher-risk) Population-based *H pylori* treatment could select for antibiotic-resistant pathogens in the community, although in many countries, such an effect might be overshadowed by indiscriminate use of antibiotics for other human and veterinary purposes. Treating *H pylori* will alter the overall composition of the intestinal flora; the health consequences are unknown.

JAMA September 24, 2014 Volume 312, Number 12

Changing attitude of IARC

Expert workshop, Dec., 2013

IARC Position in gastric cancer prevention Lyon, December 4-6, 2013

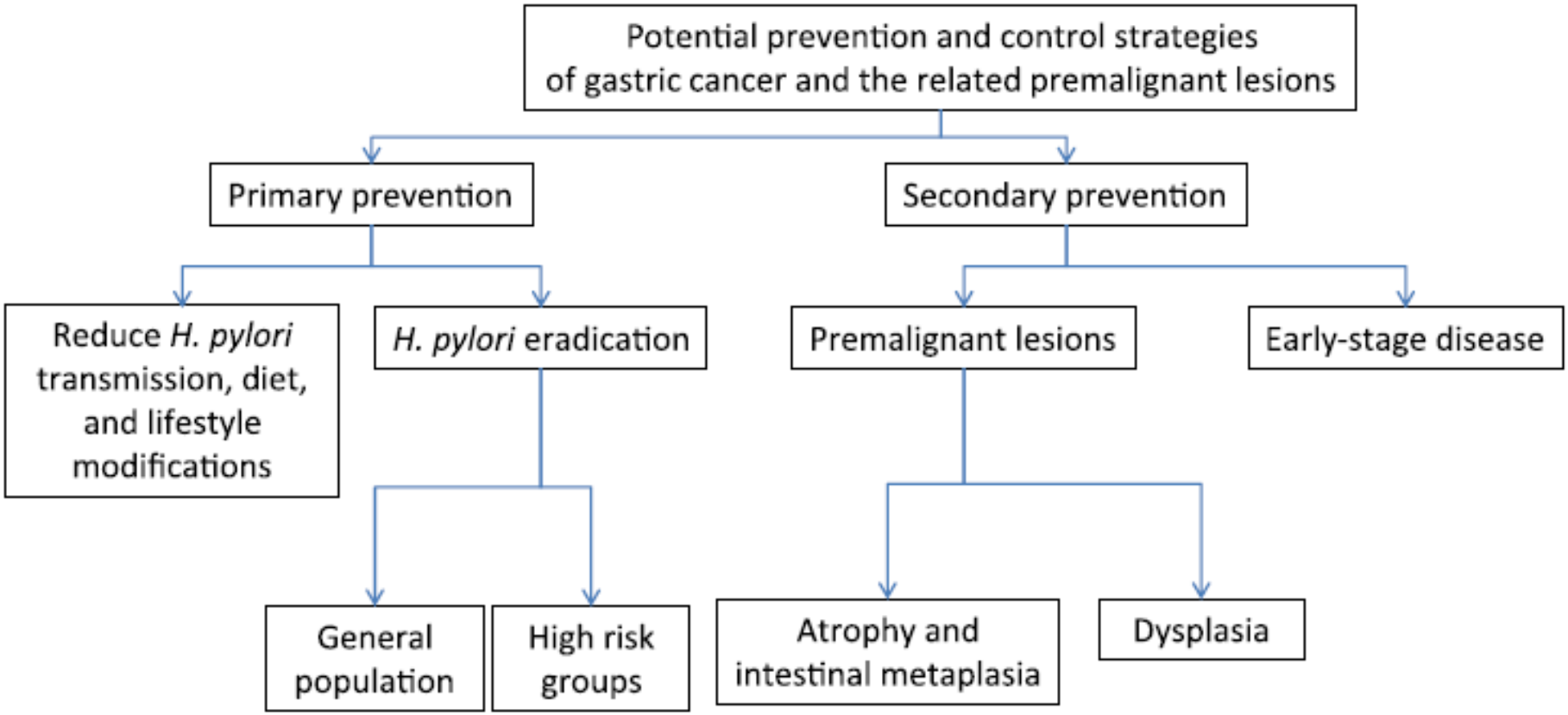
International Agency for Research on Cancer

World Health Organization

- GC – likely to remain condition of high global health importance for the foreseeable future unless effective control measures are implemented
- The importance has been ignored in many parts of the world
- *H.pylori* eradication middle-aged population is to decrease the risk reduction of 35-40%, and is cost-effective
- Implementation of wide eradication by meand of rigorous clinical trials should be considered

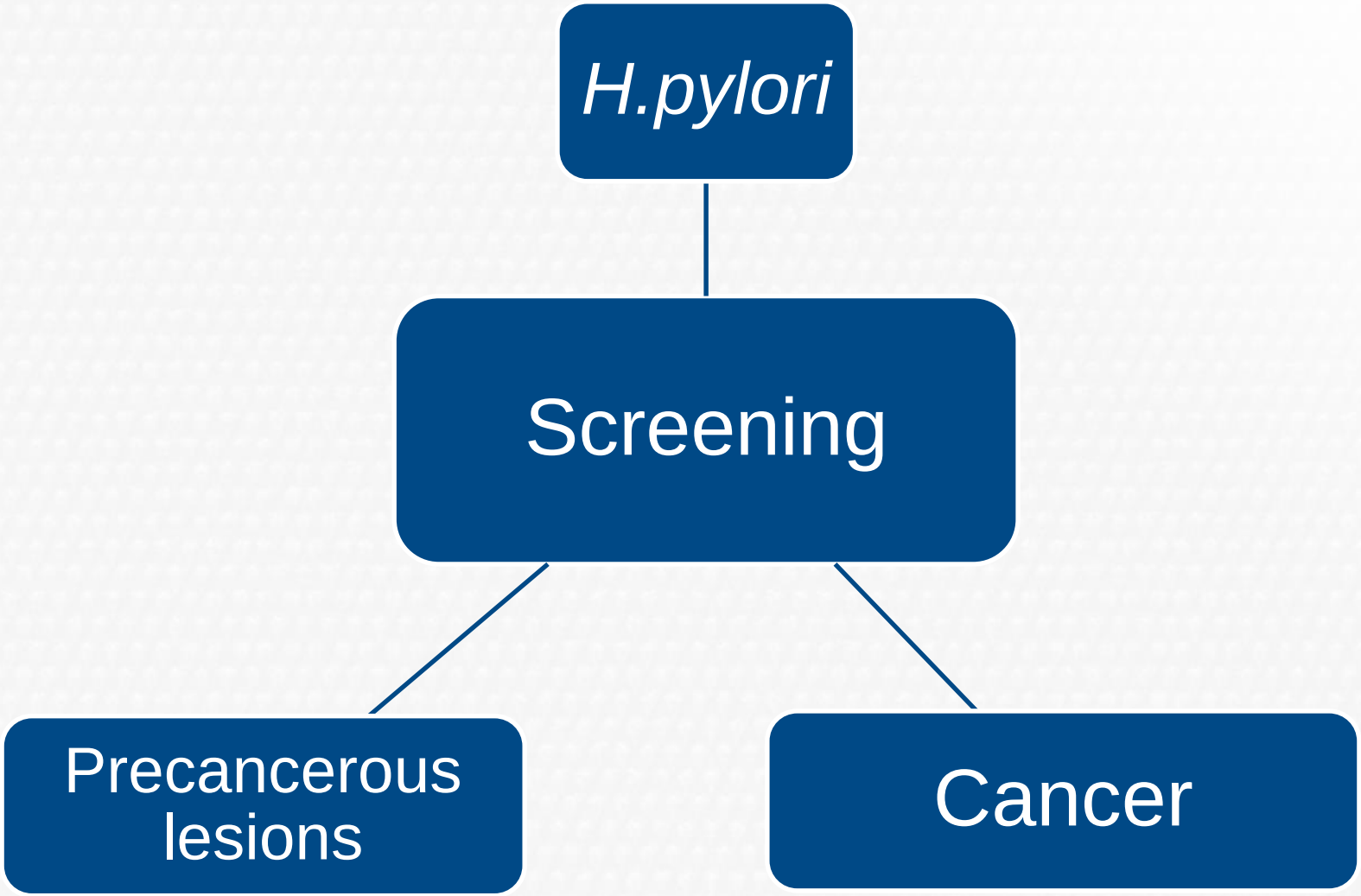
IARC. 2014

Prevention strategies



Leja et at. Best Pract Res Clin Gastroenterol. 2014

Screening options to decrease gastric cancer-cause mortality



Organized, nationwide cancer screening programs

Country	Japan	S.Korea
Initiation	1983	1999
Target population	≥40 y, both genders	≥40 y, both genders
Method	X-ray	1) Endoscopy 2) X-ray
Frequency	Annual	Biennial
Coverage	~ 4 M /year	~6.1 M in 2011
Participation	9-20%	44.5% in 2011

Leja et al Best Pract & Res Clinical Gastroenterol 2014

Opportunistic, regional cancer screening programs

Country	China	Costa Rica	Kazakhstan
Initiation	2008	1996	2013
Target population	40-69 y, both genders	50-74 y, both genders	50-60 y, both genders
Method	Endoscopy	X-ray	Endoscopy
Frequency	Annual	Single-time	Biennial
Coverage (total)	400,000	43,255	306,480 (until June, 2014)
Participation	60-80%	~20%	ND

Leja et al Best Pract & Res Clinical Gastroenterol 2014

Screen-and-treat for H.pylori

- Three recent meta-analysis suggesting the cost-efficacy of this approach
  - *Areia M et al., Helicobacter, 2013*
  - *Lansdorp-Vogelaar I, et al. Best Pract Res Clin Gastroenterol. 2013*
  - *Moayyeddi P. IARC Working Group Reports, No. 8 2014*
- Concerns
  - Adverse events
  - Resistance
- No country has implemented the strategy

H.pylori population-based eradication pilots

Region / Country	Lunqu /China	Matsu / Taiwan	Changhua / Taiwan
Initiation	2011	2004	2012
Target population	24-58 y, both genders	≥ 30 y, both genders	50-69 y, both genders
Method	UBT	UBT	Faecal HpAg
Frequency	Single-time	Single-time	Single-time
Coverage (total)	~200,000	~5,000	~12,000
Participation	55%	~80%	~30%

Leja et al Best Pract & Res Clinical Gastroenterol 2014

Mass eradication of *H.pylori* in Matzu

The benefit of mass eradication of *Helicobacter pylori* infection: a community-based study of gastric cancer prevention

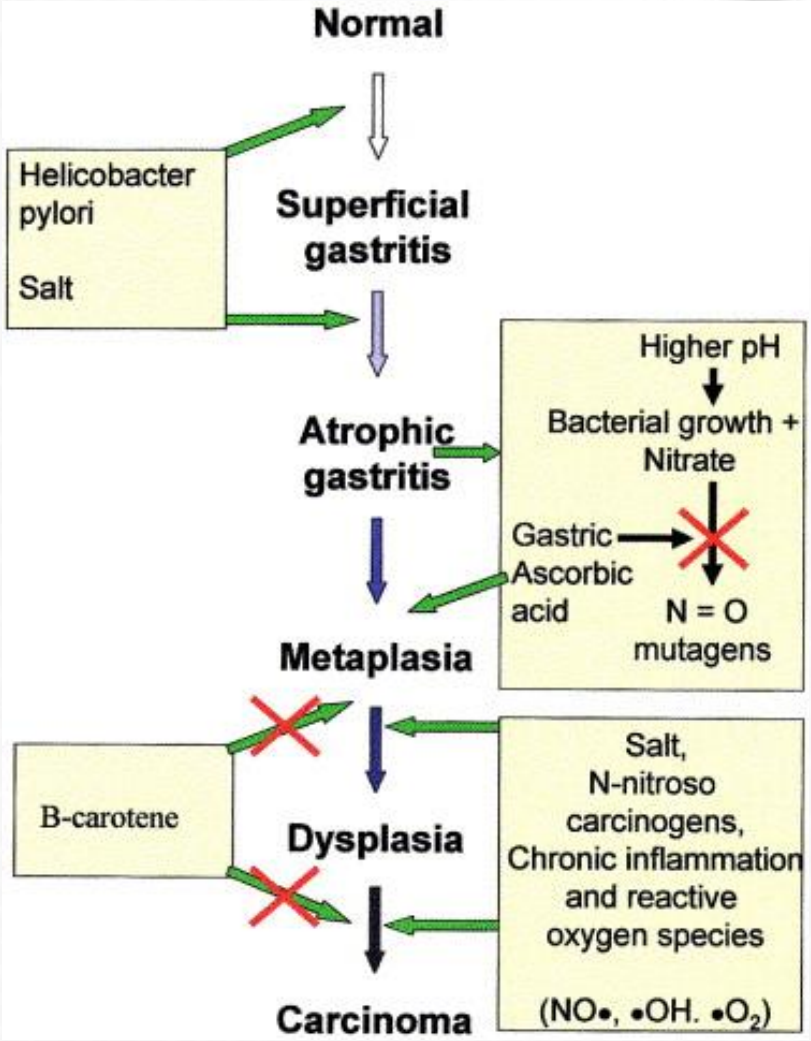
Yi-Chia Lee,[1,2] Tony Hsiu-Hsi Chen,[1] Han-Mo Chiu,[2] Chia-Tung Shun,[3] Hung Chiang,[4] Tzeng-Ying Liu,[5] Ming-Shiang Wu,[2,6] Jaw-Town Lin[2]

Gut, 2013

- 25% reduction of gastric cancer incidence
- 78.7% reduction of *H.pylori* infection
- 77.2% reduction of atrophy
- No change in IM
- BUT: observational interventional study

Multistep Model for the Progression of Gastric Cancer

Dec. 4, 2013

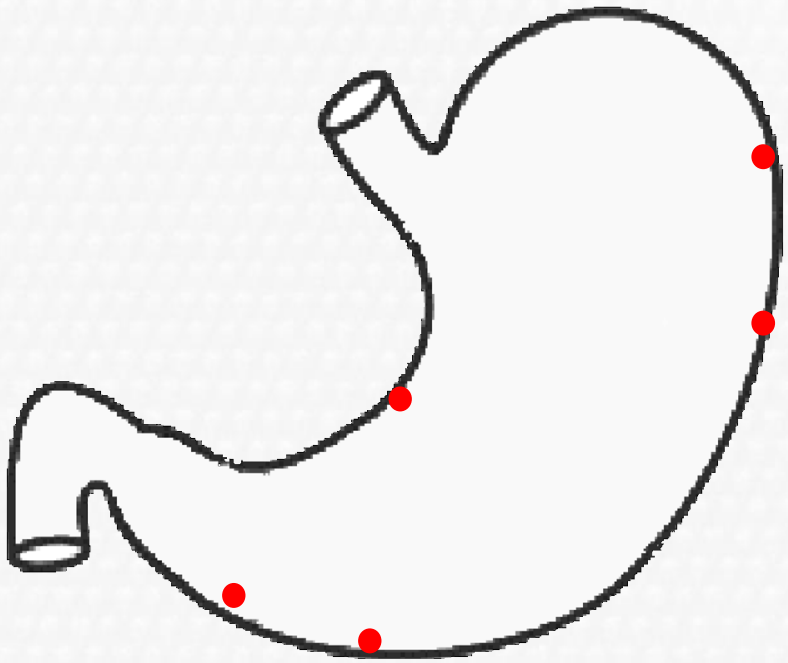


Correa P et al. Lancet, 1975

Fox JG, Wang TC. N Engl J Med 2001.

Houghton J, Wang TC. Gastroenterology 2005

Biopsy sampling (updated Sydney classification)



1/s .Materiāls : biopsija -

1) 2 gab. no antrum mazās kurvatūras, 2) 1 gab. no leņķa rajona, 3) 2 gab. no korpusa mazās kurvatūras.

Makroskopija

1. 2 biopsijas gabaliņi, vidēji 2 mm ⌀, (A1-2)
2. 1 biopsijas gabaliņš, vidēji 2 mm ⌀, (B1)
3. 2 biopsijas gabaliņi, vidēji 2 mm ⌀, (C1-2)

Mikroskopija

Lokalizācija	*H.pylori kolonizācija*	*Neitrofīlie leikocīti*	*Mononukleārās šūnas*	*Atrofija*	*Intestinālā metaplāzija*
Korpuss	+	++	+++	++	-
Leņķis	+	++	++	+	-
Antrums	+	++	++	+	-

Nav – 0 pakāpe (-); Nedaudz – 1 pakāpe (+); Vidēji – 2 pakāpe (++); Izteikti – 3 pakāpe (+++)

Slēdziens

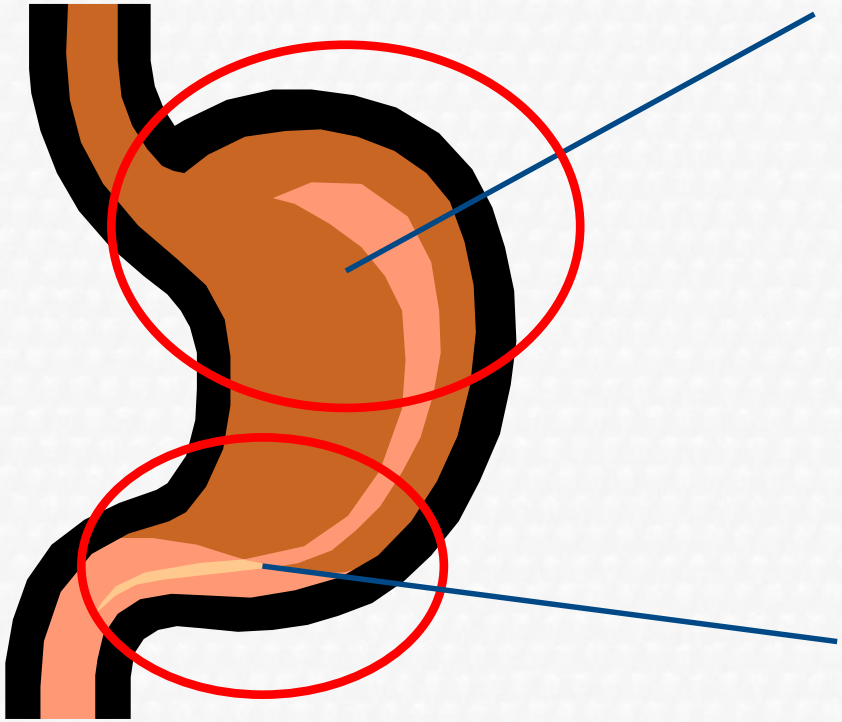
Izteikts aktīvs hronisks atrofisks korpus un antrum gastrīts. H.pylori (+).

s/s .Manipulācijas kods: 54009 -

Arhīvs: Makro [-] Bloki [5] Stikli [10] Krāsojums [Giemsa,H&E,]

Testēšanas pārskata beigas.

Biomarkers for atrophy (pepsinogens, *GastroPanel*)



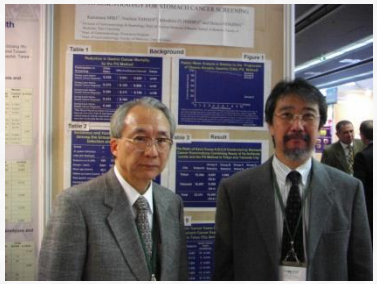
Pg I ⇩
Pg I / Pg II ⇩

G-17 ⇩
stimulated G-17 ⇩

***GastroPanel*:**
Pg I, Pg II, G17
IgG antibodies to *H.pylori*

Agreus et al. Scand J Gastroenterol. 2012

Pepsinogens for screening



REVIEW

Meta-analysis on the validity of pepsinogen test for gastric carcinoma, dysplasia or chronic atrophic gastritis screening

M Dinis-Ribeiro,[1,2,3] G Yamaki,[1] K Miki,[4] A Costa-Pereira,[3] M Matsukawa[1] and M Kurihara[1]

J Med Screen 2004;**11**:141–147

Scandinavian Journal of Gastroenterology, 2007; 42: 2–10

informa healthcare

CURRENT OPINION

Importance of atrophic gastritis in diagnostics and prevention of gastric cancer: Application of plasma biomarkers

PENTTI SIPPONEN[1,2] & DAVID Y. GRAHAM[3]

[1]*Division of Pathology, HUSLAB, Helsinki University Central Hospital (HUCH), Finland,* [2]*Department of Pathology, Jorvi Hospital, Espoo, Finland, and* [3]*Department of Medicine, Veterans Affairs Medical Center, and Baylor College of Medicine, Houston, Texas, USA*

Available online at www.sciencedirect.com

ScienceDirect

Digestive and Liver Disease

Digestive and Liver Disease 40 (2008) 523–530

www.elsevier.com/locate/dld

Mini-Symposium

Non-invasive tests in gastric diseases

F. di Mario *, L.G. Cavallaro

Section of Gastroenterology, Department of Clinical Sciences, University of Parma, Italy

Received 31 January 2008; accepted 18 February 2008
Available online 24 April 2008

Pepsinogen testing in current guidelines

- Asia-Pacific – useful marker to identify populations at high risk for GC

SPECIAL ARTICLE

Asia–Pacific consensus guidelines on gastric cancer prevention

Kwong Ming Fock,* Nick Talley,† Paul Moayyedi,‡ Richard Hunt,‡ Takeshi Azuma,§ Kentaro Sugano,¶ Shu Dong Xiao,** Shiu Kum Lam,†† Khean Lee Goh,‡‡ Tsutomu Chiba,§§ Naomi Uemura,¶¶ Jae G Kim,*** Nayoung Kim,††† Tiing Leong Ang,* Varocha Mahachai,‡‡‡ Hazel Mitchell,§§§ Abdul Aziz Rani,¶¶¶ Jyh Ming Liou,**** Ratha-korn Vilaichone†††† and Jose Sollano‡‡‡‡

Fock et al. J Gastroenterol Hepatol 2008.

- Maastricht IV – pepsinogens as tool for risk stratification

Malfertheiner et al. Gut. 2012.

- MAPS – pepsinogens can predict extensive atrophic gastritis

Guidelines for the Management of Precancerous Conditions and Lesions in the Stomach (MAPS)

An European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology (ESP) and Sociedade Portuguesa de Endoscopia Digestiva (SPED) Guideline

Dinis-Ribeiro M[1,5], Areia M[2,5], de Vries A[3], Marcos-Pinto R[4,6], Monteiro-Soares M[5], O'Connor A[7], Pereira C[8], Pimentel-Nunes P[1], Correia R[5], Ensari A[9], Dumonceau JM[10], Machado JC[11], Macedo G[12], Malfertheiner P[13], Matysiak-Budnik T[14], Megraud F[15], Miki K[16], O'Morain C[7], Peek RM[17], Ponchon T[18], Ristimaki A[19,20], Rembacken B[21], Carneiro F[12,22], Kuipers EJ[3]

Dinis-Riberiro et al. Endoscopy & Virchows Archiv .2012.

Increased risk of gastric cancer in individuals with decreased pepsinogens

- *Hisayama study* (2446 individuals >40y; follow-up 14 years)
  - HR 4.56 (95% CI: 2.42-8.60) in men
  - HR 5.84 (95% CI: 2.0-17.11) in women

Oishi et al. Am J Epidemiol 2006

- *Wakayama City Study* (5209 men; follow-up 10 years)
  - HR 3.60 (95% CI: 2.17-5.96) overall
  - HR 4.47 (95% CI: 2.37-8.42) for intestinal
  - HR 2.41 (95% CI: 1.02-5.71) for diffuse type

Yanaoka et al. Cancer epidemiology, biomarkers & prevention 2008

- *Watabe et al.* (9293 individuals; follow-up 4.7 years)
  - HR 6.0 (95% CI: 2.4-14.5) in Group C
  - HR 8.2 (95% CI: 3.2-21.5) in Group D

Watabe et al. Gut 2005

- *Kyoto Prefecture Study* (2,859)
  - HR 11.23 (95% CI: 2.71-46.51) in Group C
  - HR 14.81(95% CI: 2.47-88.80) in Group D

Mizuno et al. Dig Dis Sci 2010

Population-based study in Russia (Siberia)

- Case-control study based on study population of 9360 individuals
- Recruited during HAPIEE program in 2003-2005; followed 2012
- Age 45-69 years
- 60 GC cases revealed, 54 included to the analysis

Group	Indicators of AG and HP infection (%)				
	PGI <30 µg/l	PGII <3 µg/l	PGI/PGII <3	G-17 <1 pmol/l	*H. pylori* IgG (>30 EIU)
Gastric cancer	34.6	15.7	39.2	19.6	80.0
Control	15.4	2.0	16.2	11.5	90.1
p-Value	0.006	0.001	0.002	0.179	0.134
OR (95% CI)	2.9 (1.3-6.4)	9.0 (1.8-44.3)	3.3 (1.5-7.3)	1.8 (0.7-4.8)	0.4 (0.1-1.3)

Kurilovich et al. Anticancer Res. 2016

PLOS ONE 2015

RESEARCH ARTICLE

Significance of Serum Pepsinogens as a Biomarker for Gastric Cancer and Atrophic Gastritis Screening: A Systematic Review and Meta-Analysis

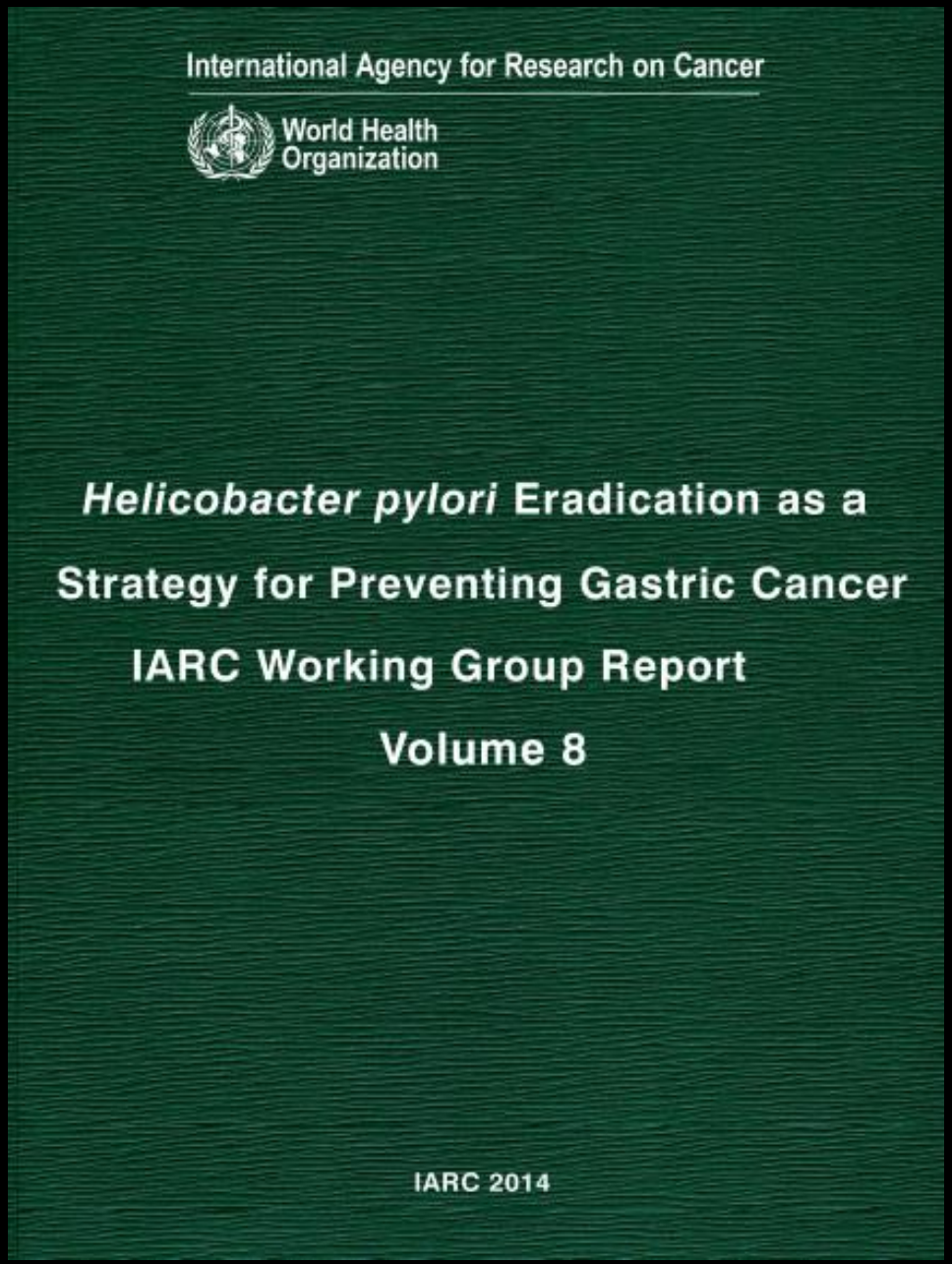
Ya-kai Huang, Jian-chun Yu*, Wei-ming Kang, Zhi-qiang Ma, Xin Ye, Shu-bo Tian, Chao Yan

- PGs for GC: Sensitivity: 69%; Specificity: 73%
- PGs for AG: Sensitivity: 69%; Specificity: 88%

Kyoto conference

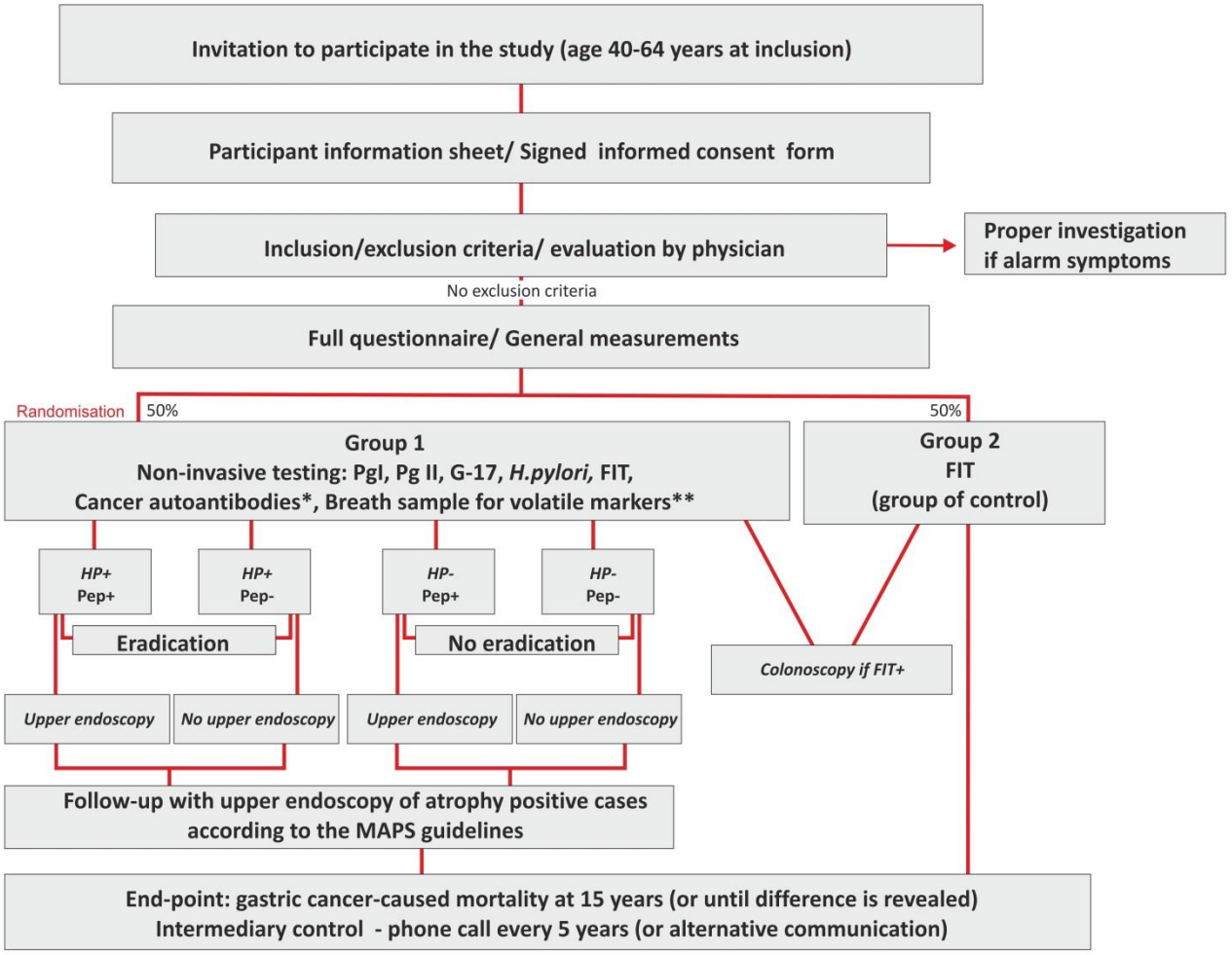
- *H. pylori* gastritis should be defined as an **infectious disease**
- *H. pylori* infected individuals **should be offered eradication therapy**, unless there are competing considerations
- The **maximum benefit** of *H. pylori* eradication is obtained if it is done while the mucosal damage is still non-atrophic
- Eradication regimens should be based on the best locally effective regimen, ideally using individual susceptibility testing or community antibiotic susceptibility, or **antibiotic consumption data and clinical outcome data**. The choice of agents available differs in different regions and in part dictates what regimens are possible

Sugano et al. GUT. 2015



http://www.iarc.fr/en/publications/pdfs-online/wrk/wrk8/index.php

GISTAR study design



* All patients with positive gastric cancer-related autoantibodies will be referred for upper endoscopy

** Based on volatile marker test results referral for upper endoscopy will be done only if specific panel characteristic for gastric cancer will be revealed

What’s new at the horizon?

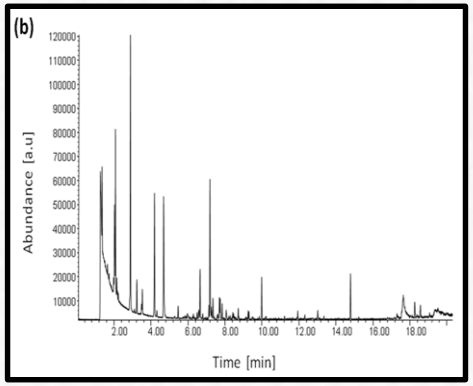
Potential other approaches (research agenda)

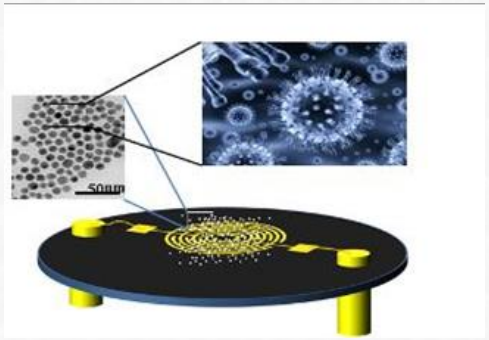
- Other tests for atrophy
  - Ghrelin
  - TFF3
- Marker profiling, panels of miRNA
- Cancer autoantibodies
- Volatile markers
- Computing approaches for risk stratification
  - Patient-related risk-factors
  - Genetic predisposition
  - *H.pylori* virulence factors
  - Presence of precancerous lesions

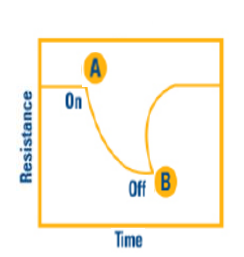
Approaches to volatile marker testing

GC-MS

Sensor technologies e.g. NA-NOSE



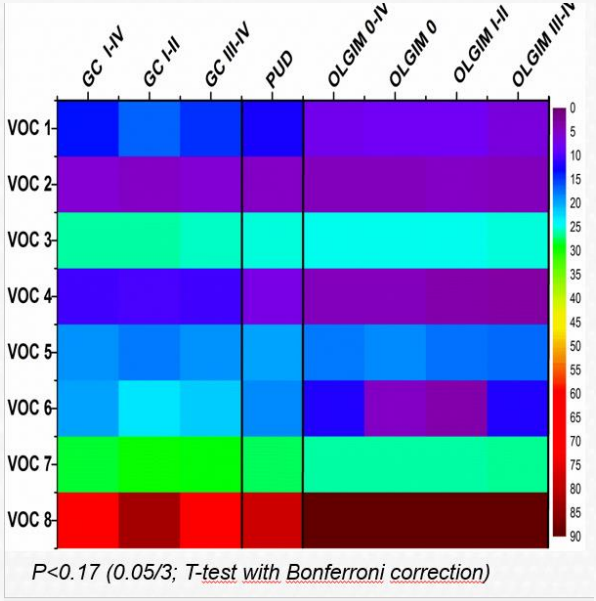




ORIGINAL ARTICLE

Detection of precancerous gastric lesions and gastric cancer through exhaled breath

Haitham Amal,[1] Marcis Leja,[2,3,4] Konrads Funka,[2,3,4] Roberts Skapars,[2,3] Armands Sivins,[2,3] Guntis Ancans,[2,3] Inta Liepniece-Karele,[2,3,5] Ilze Kikuste,[2,4] Ieva Lasina,[2] Hossam Haick[1]



2-propenitrile
Furfural
2-butoxy ethanol
Hexadecan
4-methyl octane
1,2,3 Trimethylbenzene
α-methylstyrene
2-Butanone

Sensor performance:

Normal + low-risk lesions (OLGIM 0-II) vs. GC

Se.: 97%

Sp.: 84%

Amal H et al. Gut. 2015

Conclusions

1. The possibilities to reduce digestive cancer mortality are far underutilized
2. Mortality from preventable digestive cancers can be further decreased by identification and surveillance of pre-malignant lesions (adequate biopsy work-up, non-invasive tests)
3. CRC screening has to be implemented in organized screening program settings
4. Studies like GISTAR is the way to go in implementing GC prevention strategies
5. There is still space to improve the existing screening tests


Thank you!