



XXII CONGRESSO NAZIONALE CARD

**I DISTRETTI DI COMUNITÀ PROTAGONISTI
DEL DM 77 E DELLA PRIMARY HEALTH CARE**

GENOVA | 17-19 OTTOBRE | 2024

STARHOTELS PRESIDENT
Corte dei Lambruschini, 4

TITOLO RELAZIONE:

**L'importanza dello screening (H.pylori)
per la prevenzione del tumore gastrico nel
territorio**

RELATORE: Peter Malfertheiner

Conflicts of interest

- **Consultancies/speakers bureau:**

Aboca, Alfasigma, Allergosan ,
Bayer, Biocodex, Malesci, Menarini,
Phathom

Objectives

- **Epidemiological aspects of gastric cancer and H.pylori infection**
 - **The role of H.pylori in gastric cancer development**
 - **The mission of gastric cancer prevention**
- **Diagnostics for screening**

Strategies for gastric cancer prevention

- **Test & Treat**
- **Screen & Treat**
- **Cost -effectiveness**

A livello mondiale

Il Cancro Gastrico 5° causa piu` frequente di malattia neoplastica

3° causa piu` frequente di mortalita` fra le malattie neoplastiche

Causa principale del Cancro Gastrico l`infezione da Helicobacter pylori

Epidemiologia del carcinoma gastrico



Incidenza

Nel 2023, sono state stimate circa
15 000 nuove diagnosi
(uomini = 9000; donne = 6000)

Mortalità

Nel 2022, sono stimati 9.900 decessi
(uomini = 5700; donne = 4200).
Le stime per il 2023 non sono disponibili

Sopravvivenza netta a 5 anni dalla diagnosi

30% negli uomini e 35% nelle donne

Probabilità di vivere ulteriori 4 anni condizionata ad aver superato il primo anno dopo la diagnosi

53% negli uomini e 59% nelle donne

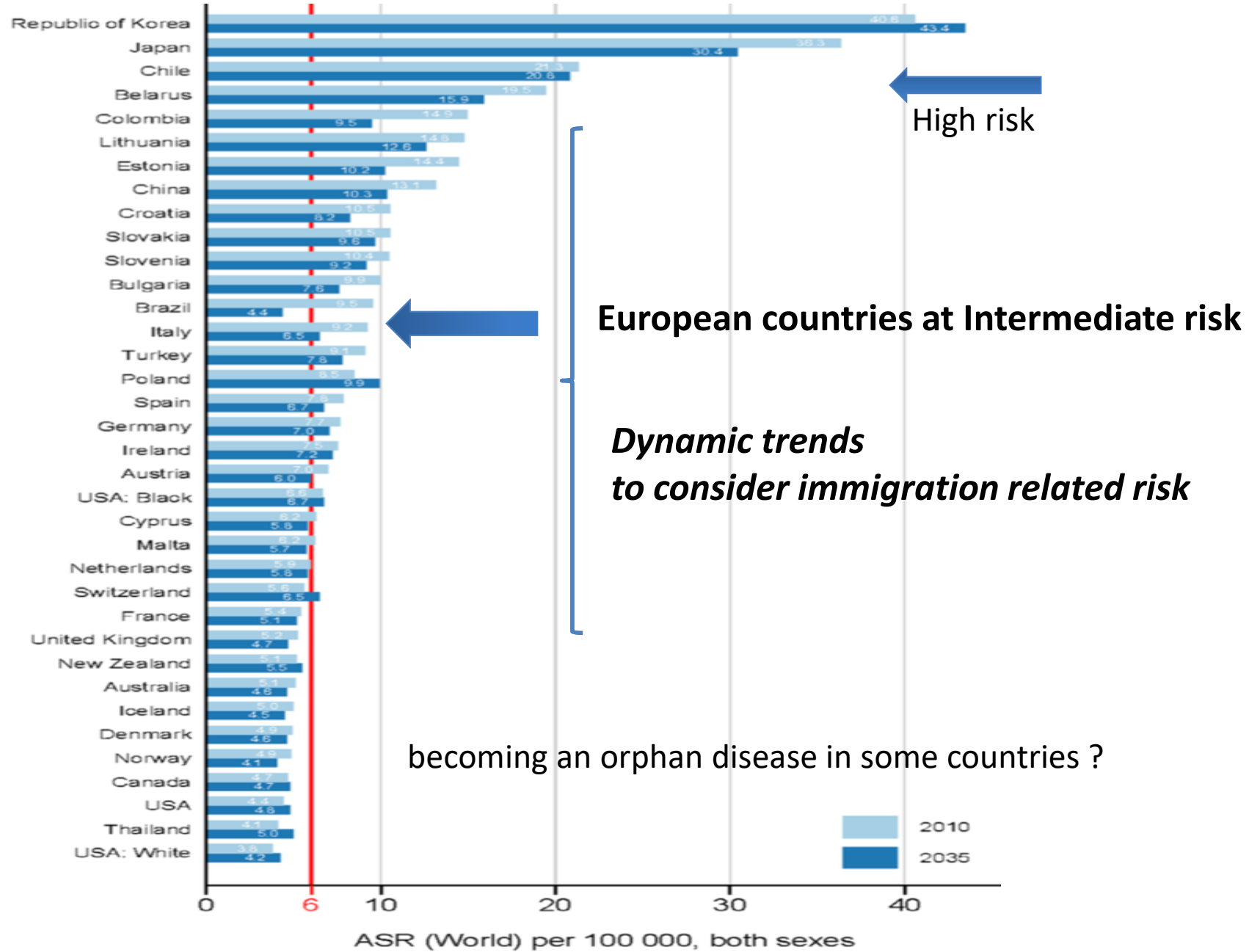
Prevalenza

82400 le persone viventi in Italia dopo una
diagnosi di tumore dello stomaco (uomini =
50300; donne = 32100)

Il 90% dell` adenocarcinoma gastrico è causato da *H.pylori*

A global assessment of predicted incidence trends to 2035.

Arnold M, Park JY, Camargo MC, Lunet N, Forman D, Soerjomataram I. Gut. 2020 May;69(5):823-829.



Helicobacter pylori (H. pylori)

L'*Helicobacter pylori* (H. pylori) è un batterio gram-negativo, **patogeno** ed **oncogeno** colonizza esclusivamente la mucosa gastrica



L'infezione da H. pylori è la piu` comune infezione batterica cronica nel mondo

GASTRODUODENAL

Global Prevalence of *Helicobacter pylori* Infection and Incidence of Gastric Cancer Between 1980 and 2022



Yi-Chu Chen,^{1,*} Peter Malfertheiner,^{2,3,*} Hao-Ting Yu,¹ Chih-Lin Kuo,¹ Yung-Yueh Chang,¹ Fan-Tsui Meng,¹ Yu-Xuan Wu,⁴ Juo-Lun Hsiao,⁵ Mei-Jyh Chen,^{6,7} Kun-Pei Lin,^{6,7,8} Chun-Ying Wu,^{9,10} Jaw-Town Lin,^{7,11} Colm O'Morain,¹² Francis Megraud,¹³ Wen-Chung Lee,^{1,§} Emad M. El-Omar,^{14,§} Ming-Shiang Wu,^{6,§} and Jyh-Ming Liou^{6,7,15,*§}



□ global crude prevalence of *H pylori* infection decreased

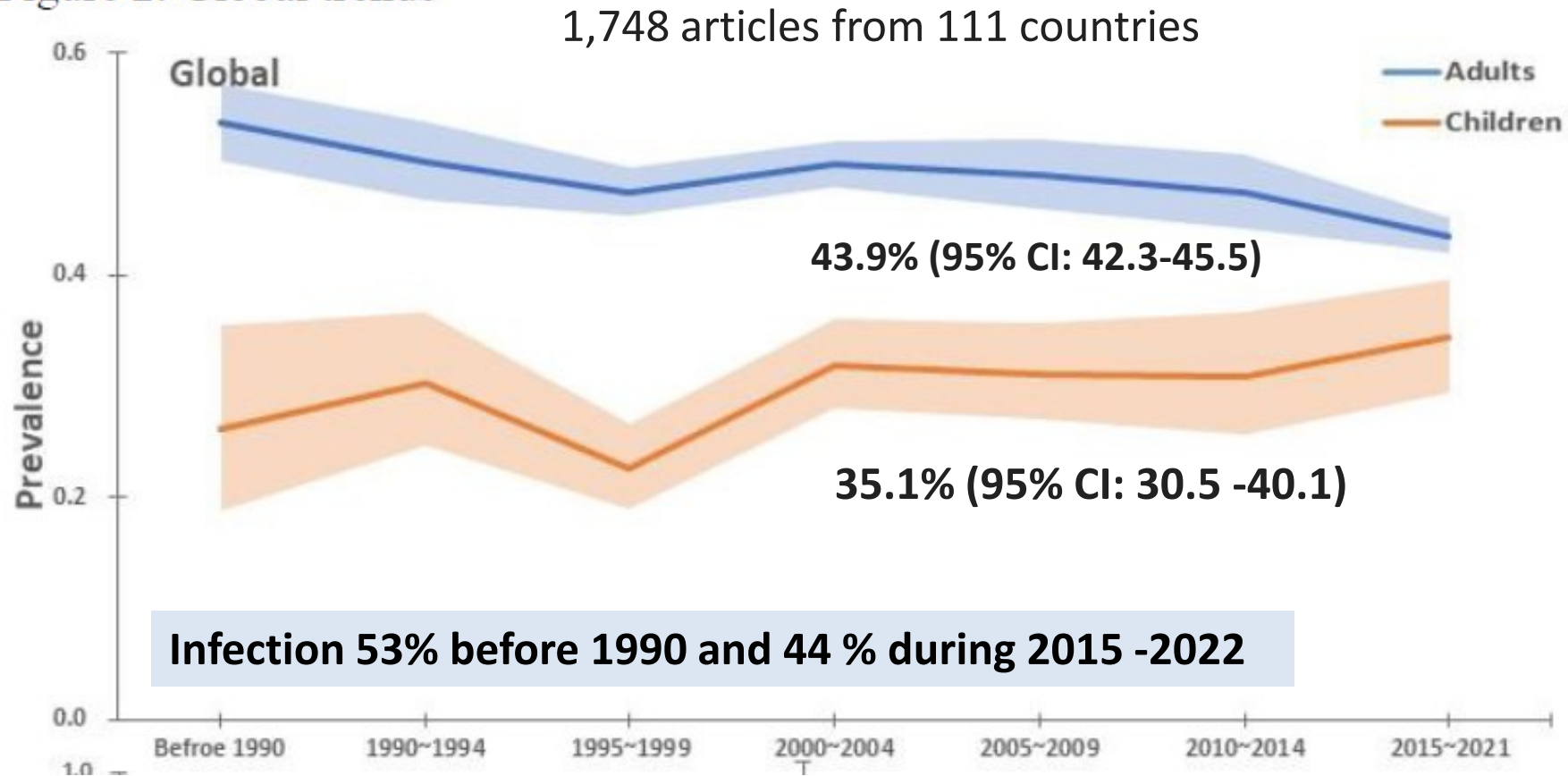
➤ 52.6% before 1990

➤ 43.9% during 2015 to 2022 in adults

❖ *but still as high as 35.1% in children/adolescents during 2015 to 2022*

H.pylori prevalence in adults and children

Figure 2. Global trends



Global prevalence of Helicobacter pylori infection and incidence of gastric cancer between 1980 and 2022.

Aspetti epidemiologici

- *H. pylori* infetta più della metà della popolazione mondiale.²



Prevalenza stimata del 50%
nei paesi in via di sviluppo¹

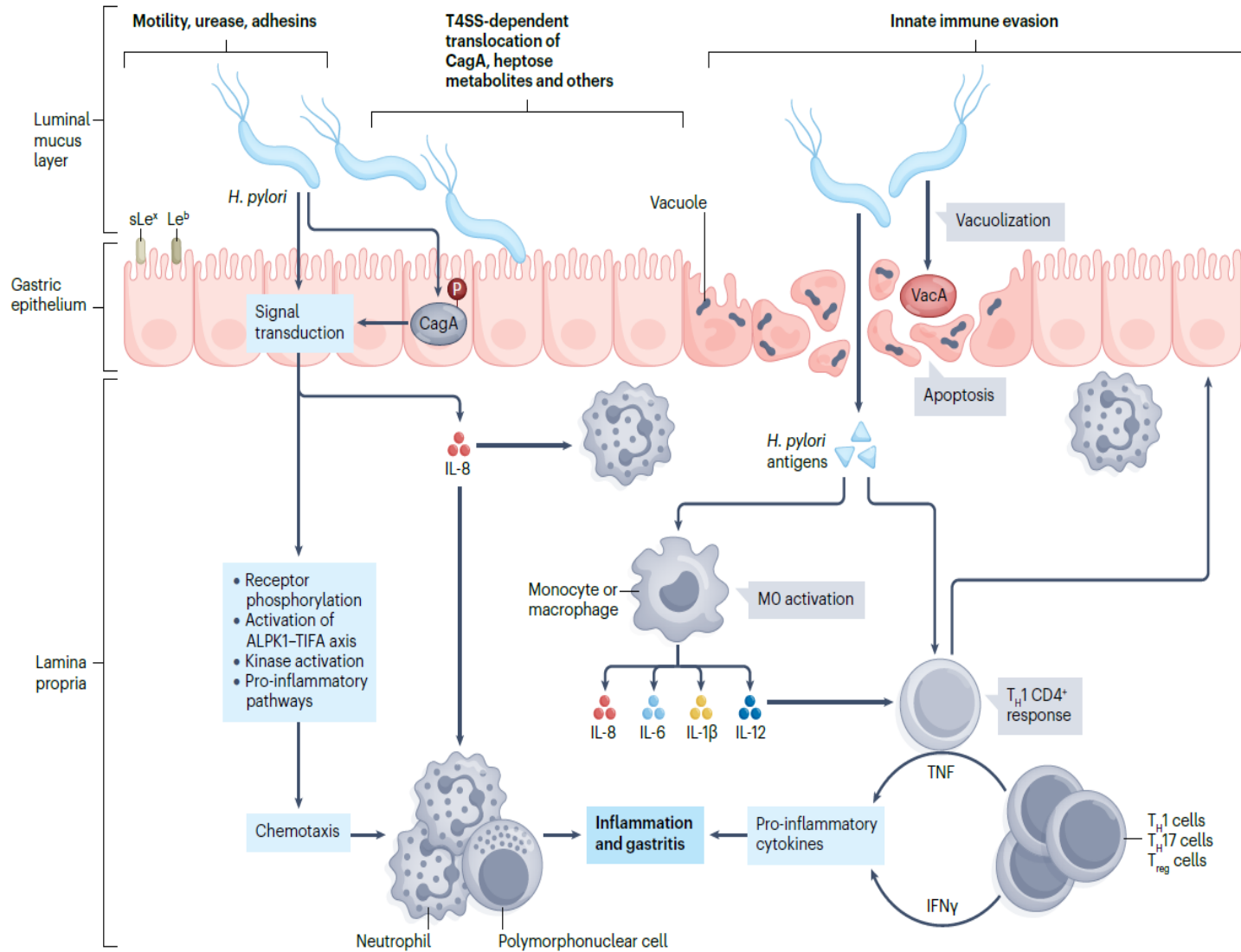
- In Italia ne sono affetti approssimativamente un terzo degli adulti.³

ITALIA
27%



Cosa succede nello stomaco di un individuo infettato da H.pylori ?

H.pylori colonizza ed infetta esclusivamente l'epitelio gastrico ,ne consegue gastrite cronica



Principali Fattori di Virulenza

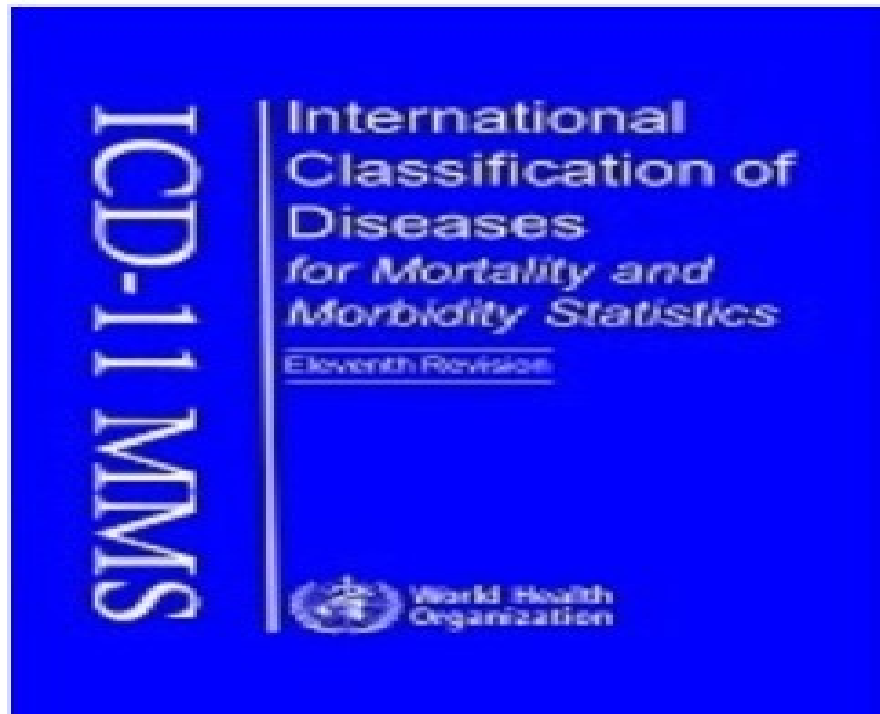
- Flagella
- Ureasi
- Adesine, Bab A, Sab A
- Cag PAI
- Vac A
- Diversi altri enzimi

H. pylori gastritis an infectious disease -change in paradigme- *NEW in ICD 11*

Kyoto, Sugano et al Gut 2015

Maastricht V/ Florence ,Malfertheiner et al Gut 2017

H.pylori gastritis with structural and functional abnormalities even in the absence of symptoms



DA42 Gastritis

DA42.0 Autoimmune gastritis

DA42.1 Helicobacter pylori induced gastritis

▶ DA42.2 Eosinophilic gastritis

DA42.3 Lymphocytic gastritis

▶ DA42.4 Allergic gastritis

DA42.5 Gastritis due to duodenogastric reflux

DA42.6 Menetrier disease

▶ DA42.7 Gastritis of unknown etiology with specific endoscopic or pathological features

▶ DA42.8 Gastritis due to external causes

DA42.9 Gastric phlegmon

DA42.Y Other specified gastritis

DA42.Z Gastritis, unspecified

The Rationale

H.pylori test & and treat for gastric cancer prevention

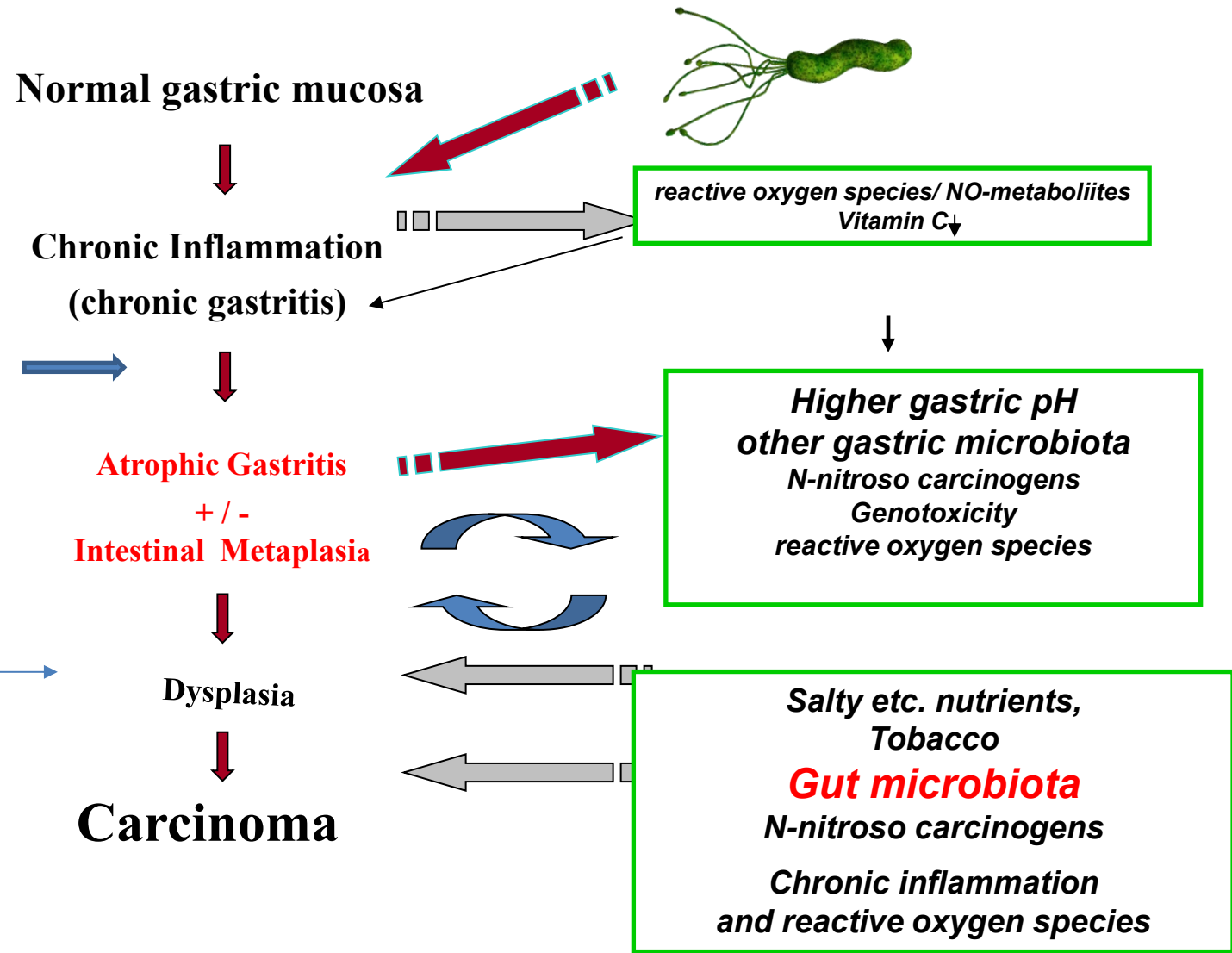
The stepwise progression

in gastric carcinogenesis

offers opportunities for intervention

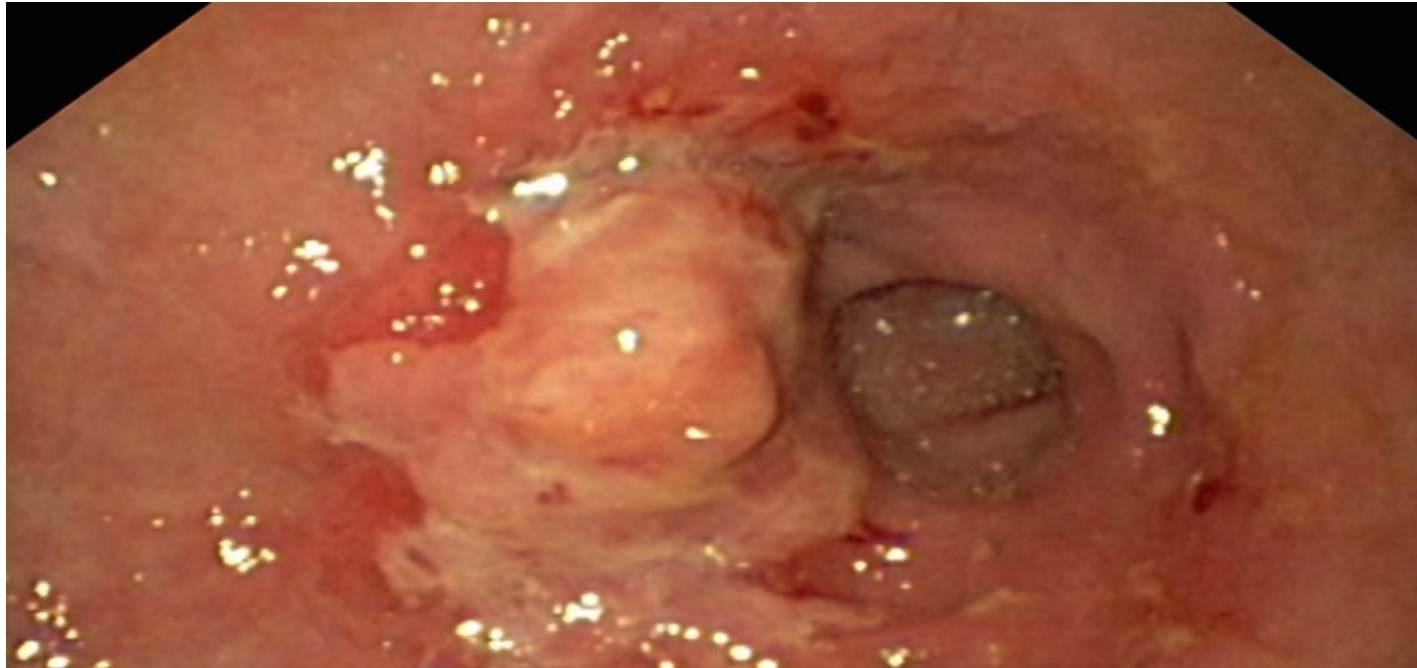
H.pylori Gastritis and the „Correa“ cascade towards gastric cancer

- H.pylori virulence factors
- Host genetics
- Environment
- Lifestyle



Gastric cancer prevention!

The mission



Gastric cancer burden will continue to increase for the next decades because of the demographic development

***H. Pylori* infection is carcinogenic to humans and responsible for 90 % of gastric cancer cases worldwide**

Screen and Treat

Option endoscopy

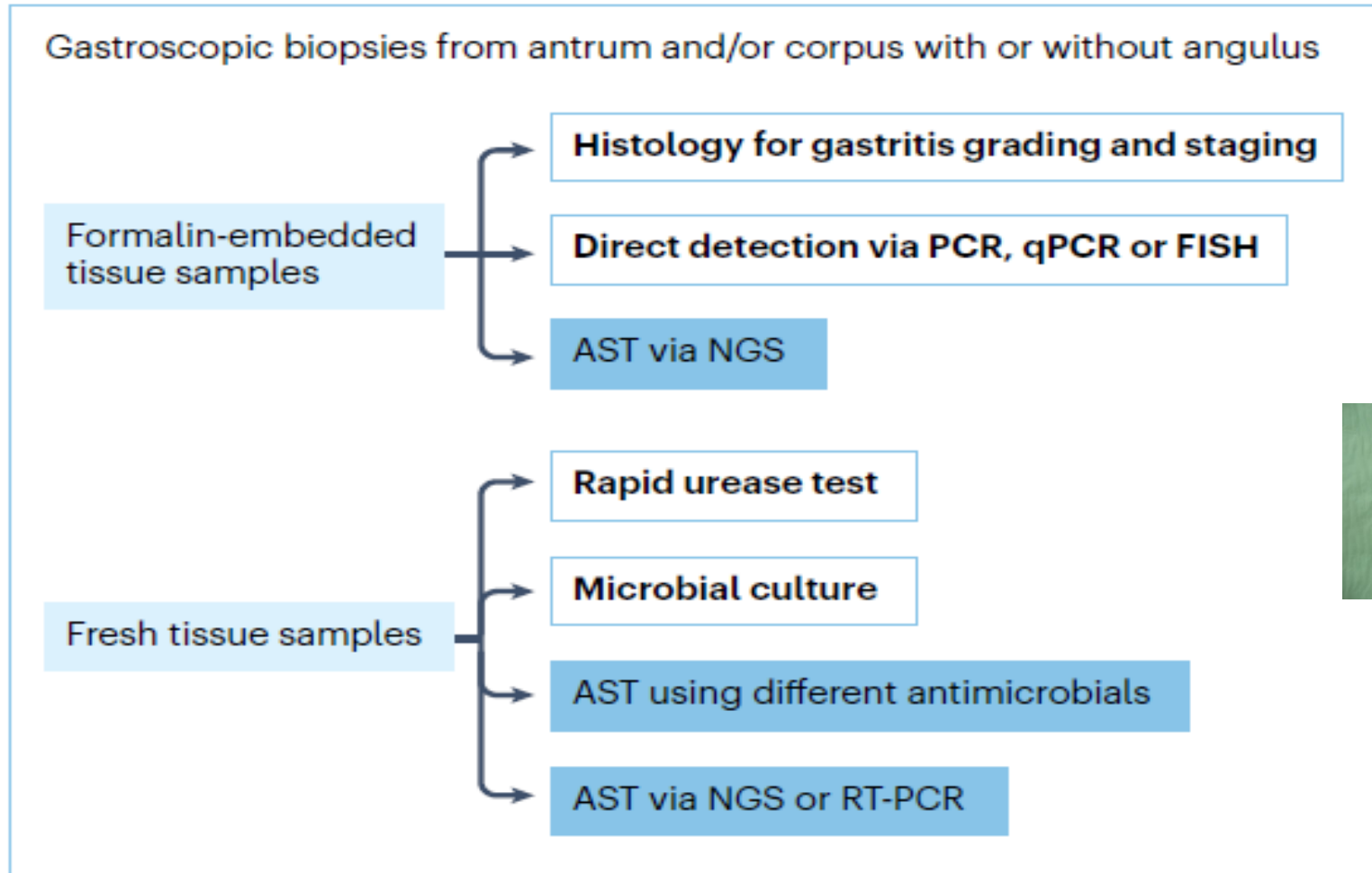
Option „non-invasive“

Come arrivare alla diagnosi dell'Infezione da H.pylori ?

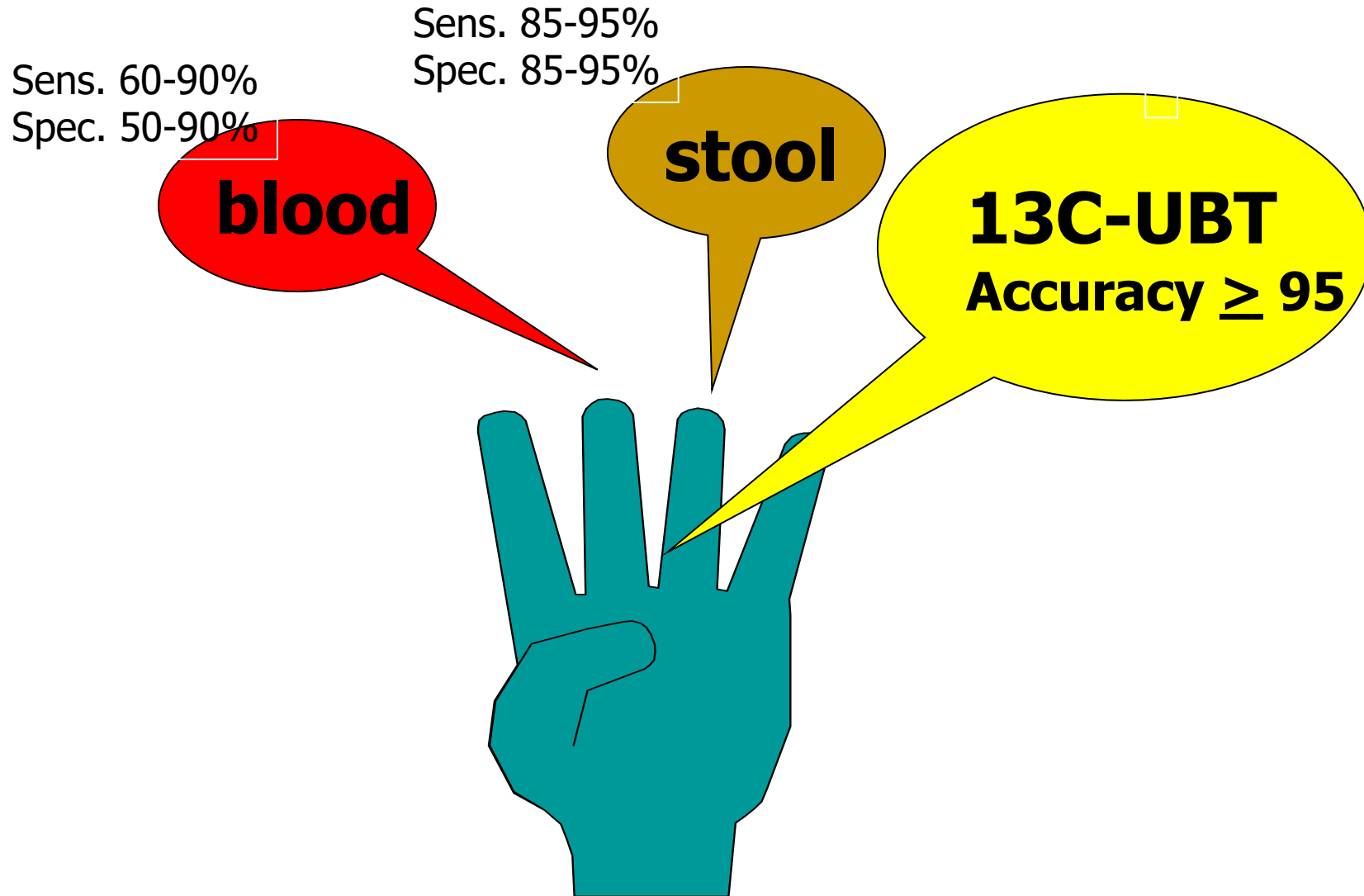
Il metodo diagnostico deve essere scelto in base a criteri rilevati dall'anamnesi in paziente/individuo

Diagnosi H.pylori

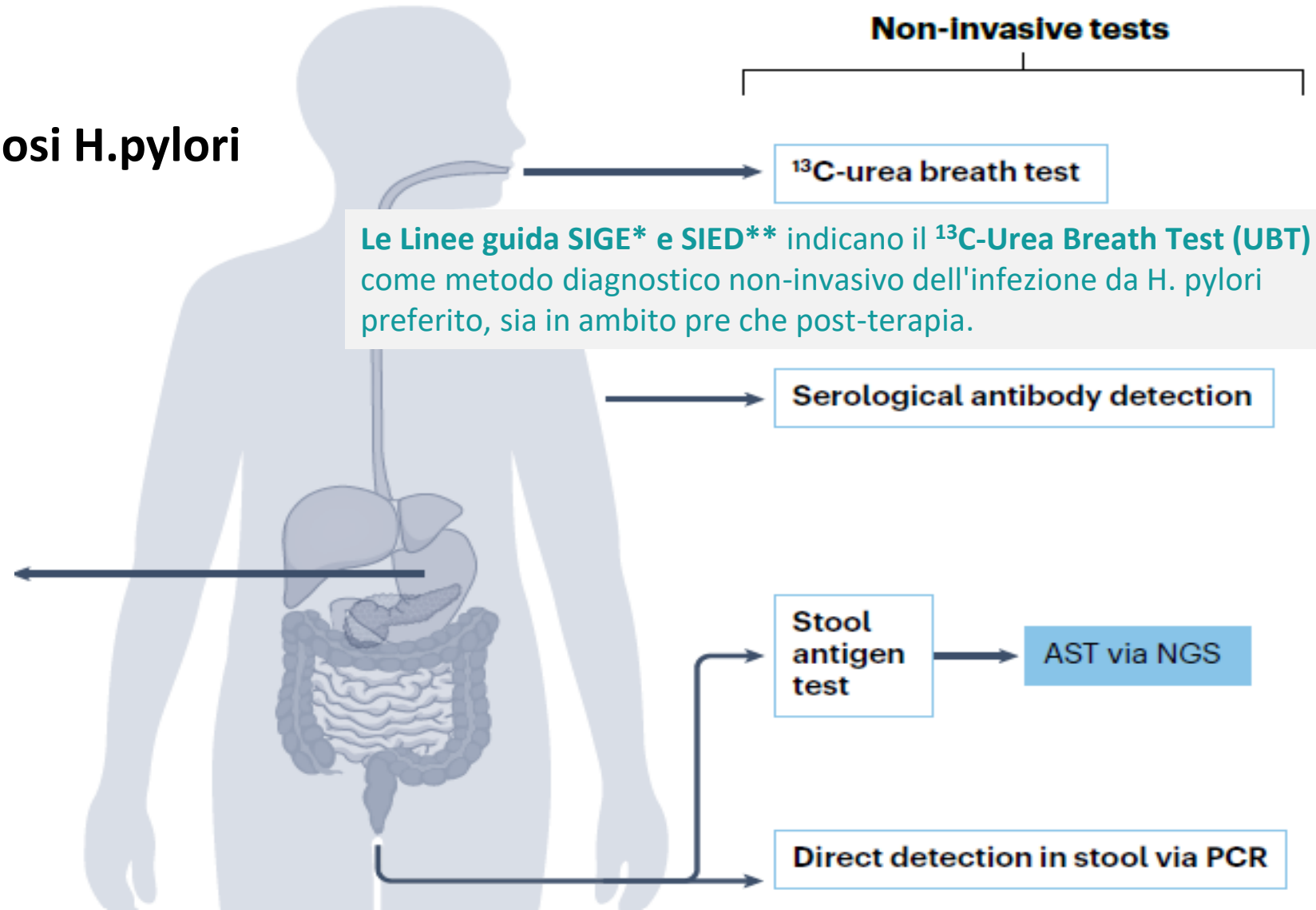
Invasive tests



Non invasive tests for H.pylori detection (surrogate markers of gastritis)



Diagnosi H.pylori



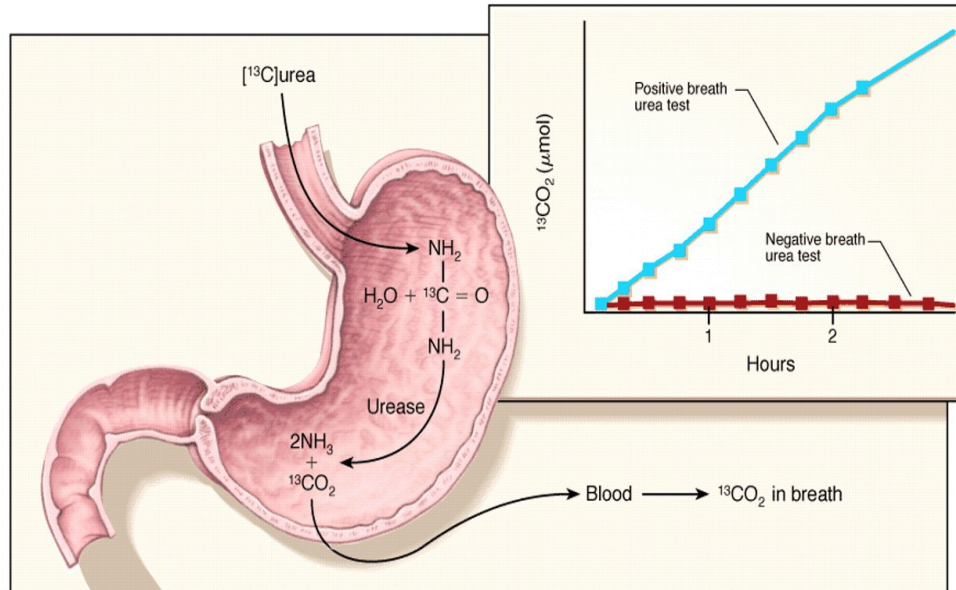
Malfertheiner P, et al *Helicobacter pylori* infection.
Nat Rev Dis Primers. 2023 Apr 20;9(1):19. doi: 10.1038/s41572-023-00431-8

- Romano M, Gravina AG, Eusebi LH, et al. Management of *Helicobacter pylori* infection: Guidelines of the Italian Society of Gastroenterology (SIGE) and the Italian Society of Digestive Endoscopy (SIED). Dig Liver Dis. 2022;54(9):1153-1161.

^{13}C -Urea Breath Test (^{13}C -UBT)

Il ^{13}C -Urea Breath Test sfrutta la capacità dell'*H. pylori* di metabolizzare la ^{13}C -urea

- *H. pylori* utilizza l'ureasi per scindere l'urea in ammoniaca e anidride carbonica (CO_2)
- Un aumento di $^{13}\text{CO}_2$ cioè della CO_2 marcata rispetto al valore di base indica l'attività dell'ureasi



Sensitivity 96%

Specificity 93%

- 75 mg of ^{13}C -Urea and 200 ml with citric acid 1%
- Breath samples before and 30 minutes after ingestion
- Delta over Baseline (DOB)
- Positive if $\text{DOB} > 4$

• Keller J, Hammer HF, Afolabi PR, et al. European guideline on indications, performance and clinical impact of 13 C-breath tests in adult and pediatric patients: An EAGEN, ESNM, and ESPGHAN consensus, supported by EPC. *United European Gastroenterol J.* 2021;9(5):598-625.

• Romano M, Gravina AG, Eusebi LH, et al. Management of Helicobacter pylori infection: Guidelines of the Italian Society of Gastroenterology (SIGE) and the Italian Society of Digestive Endoscopy (SIED). *Dig Liver Dis.* 2022;54(9):1153-1161.

Gestione del paziente asintomatico a rischio

- Rischio familiare
- Residenza in regione a media/alta incidenza del cancro gastrico
- Eta` > 50 anni

Tests non-invasivi

13 C-UBT

Test Antigene fecale

Serologia (sieropositività richiede conferma con 13 C-UBT)

- **13 C-UBT positivo richiede terapia eradicante**
- **controllo del successo terapeutico con 13C-UBT**

Test/Screen and Treat

At what age ?

Maastricht VI/ Florence

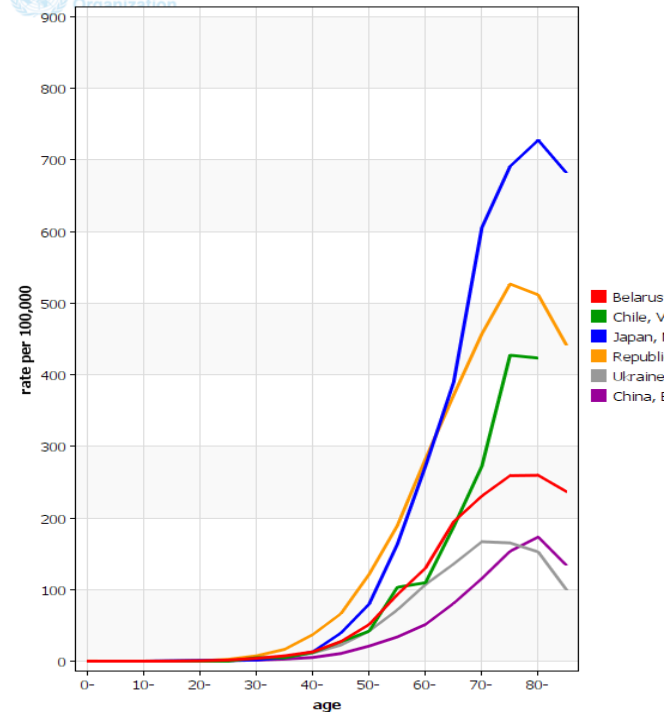
Statement 14: Asymptomatic individuals at age above 50 years are considered vulnerable and at increased risk of gastric cancer compared with younger individuals.

Agreement 97%

Grade 1A

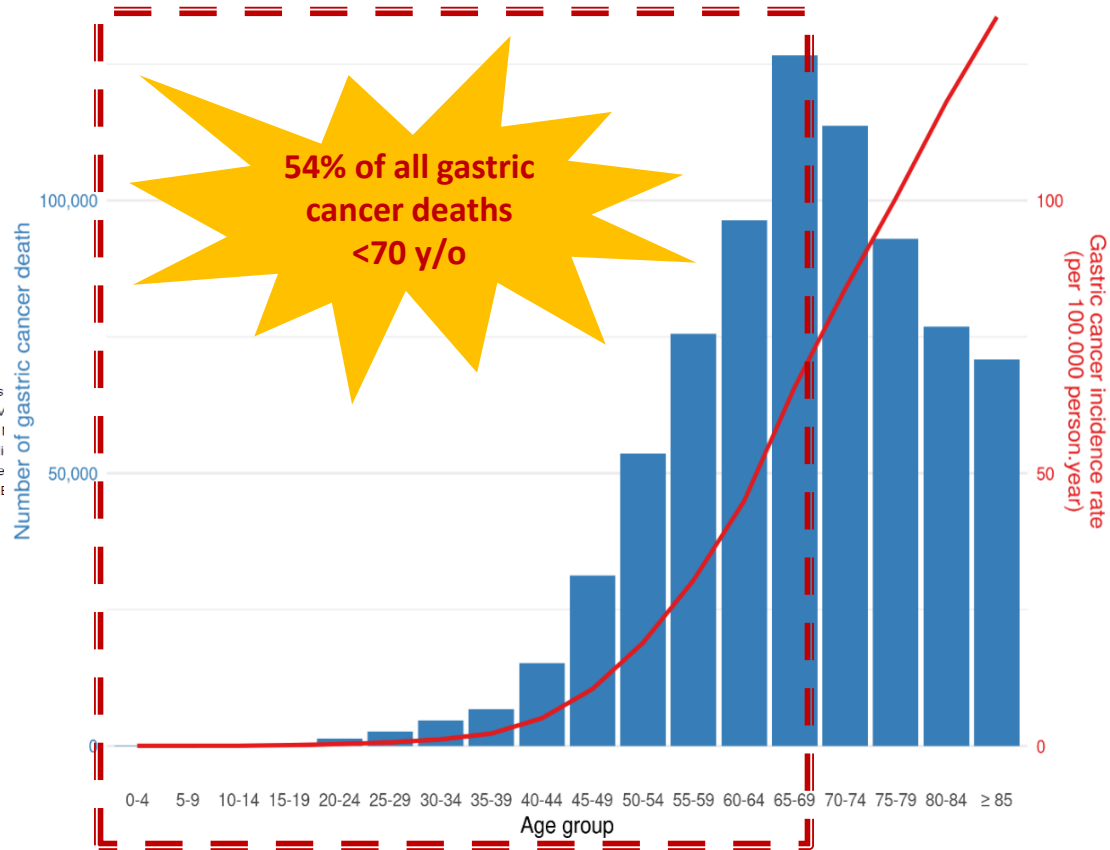
Gastric cancer sharply rises above the age 50 years

International Agency for Research on Cancer
World Health Organization



CIS-XI. International Agency for Research on Cancer (IARC) - 18.11.2020

Source: CIS, GLOBOCAN 2020, IARC





March 22, 2018

Helicobacter pylori Treatment for Gastric Cancer Prevention

Peter Malfertheiner, M.D.

Gastric cancer has become a potentially preventable disease through eradication of *Helicobacter pylori*. However, issues that are associated with “screen and treat” strategies — their effectiveness, proper selection of populations, and cost–benefit considerations — interfere with the application of such strategies in regular practice.

A major uncertainty relates to the optimal timing for the implementation of a screen-and-treat program. One factor influencing this uncertainty is whether *H. pylori* eradication is effective at stopping the carcinogenic process in patients with severe chronic atrophic gastritis, an advanced precursor lesion to gastric cancer.¹

In this issue of the *Journal*, Choi et al.² report the results of their randomized, placebo-controlled trial, in which at a median follow-up of 5.9 years, *H. pylori* eradication was effective in the prevention of gastric cancer. The overall benefit of such health systems is high, and the disease is difficult to treat because diagnosis is usually made in an advanced stage. The clinical course is characterized by a high symptom burden and an

should be encouraged in combination with screening for colorectal cancer in patients older than 50 years of age in Western societies (low or intermediate risk of gastric cancer.)

that are aimed at the detection of gastric cancer at an early and more curable stage have led to a significant reduction in mortality from the disease.⁴

The most relevant new target in gastric cancer prevention is *H. pylori* infection. Unequivocal evidence from epidemiologic, basic, and clinical research has identified *H. pylori* as a primary fac-

Maastricht VI/ Florence

Statement 18: Screening modalities for gastric cancer prevention (noninvasive or endoscopic) combined with colorectal cancer screening is an opportunity

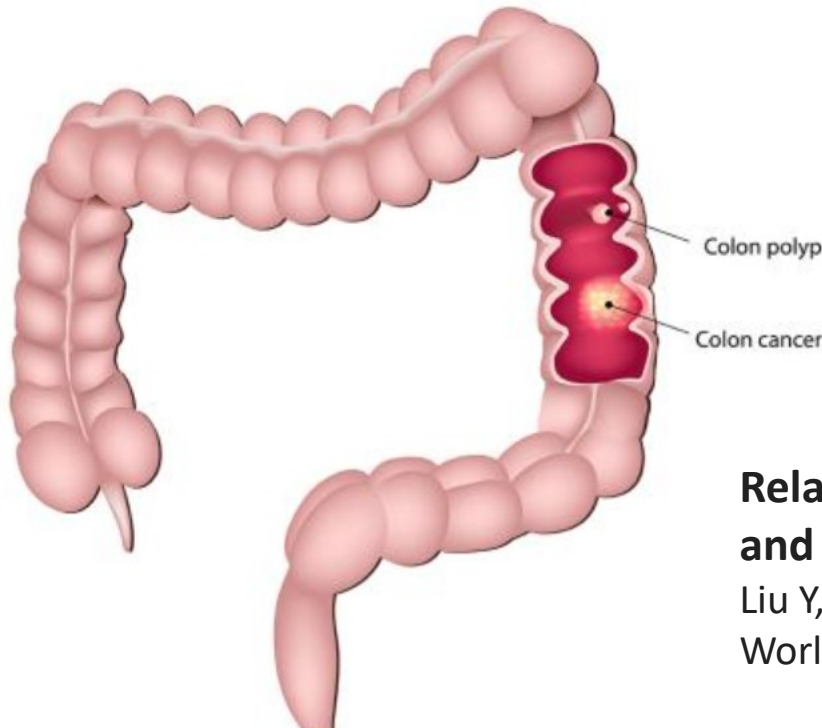
Agreement 81%

Grade C2

H.pylori with an extension of its carcinogenic potential



**COLON CANCER
AND POLYP**



Helicobacter pylori but not gastrin is associated with the development of colonic neoplasms.

Selgrad M, Bornschein J, Kandulski A, Hille C, Weigt J, Roessner A, Wex T, Malfertheiner P.

Int J Cancer. 2014 Sep 1;135(5):1127-31.

Relationship between *Helicobacter pylori* infection and colorectal polyp/colorectal cancer.

Liu Y, Yang DQ, Jiang JN, Jiao Y.

World J Gastrointest Surg. 2024 Apr 27;16(4):1008-1016.

Impact of Helicobacter pylori Infection and Treatment on Colorectal Cancer in a Large, Nationwide Cohort

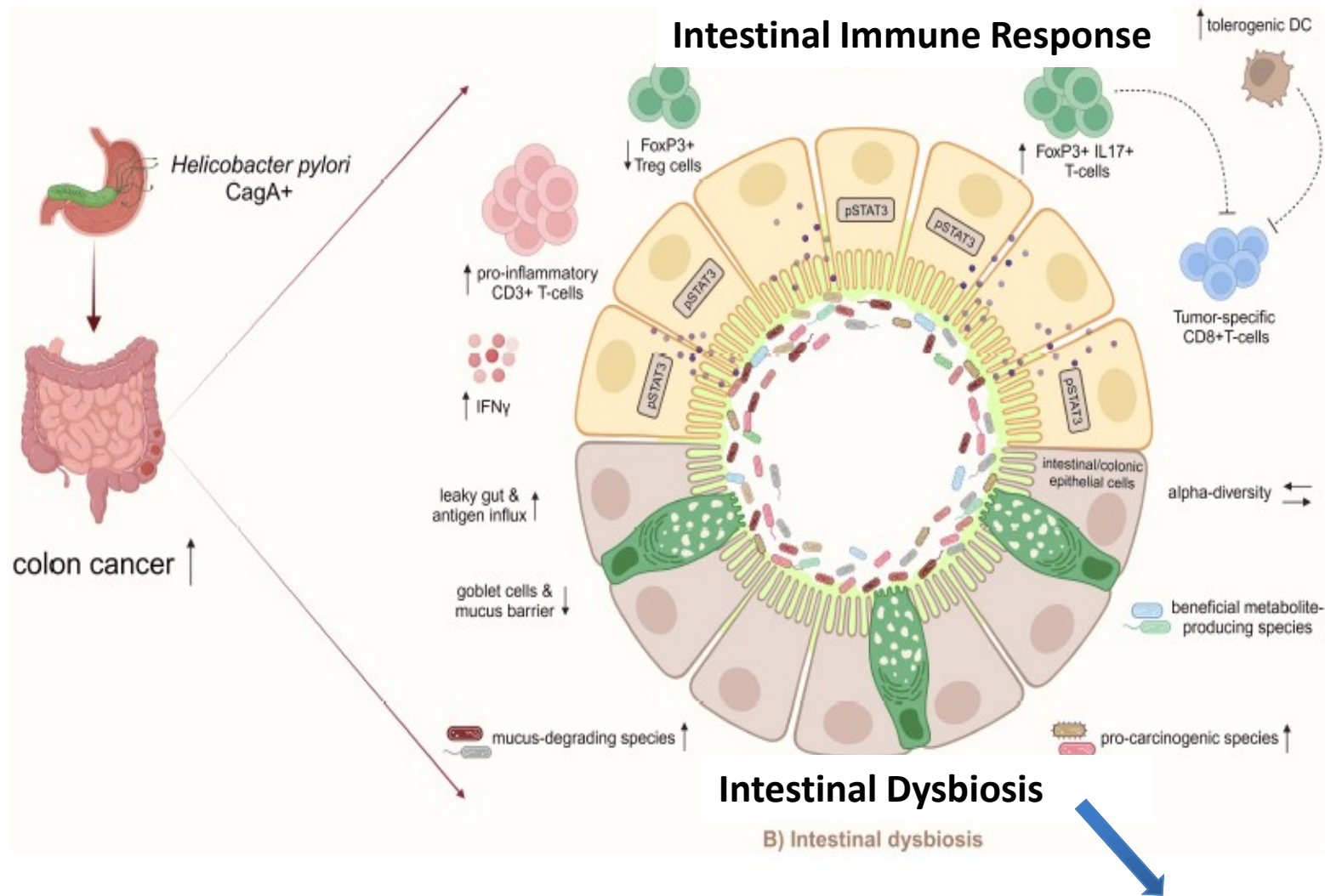
Shah SC, Camargo MC, Lamm M, Bustamante R, Roumie CL, Wilson O, Halvorson AE, Greevy R, Liu L, Gupta S, Demb J. J Clin Oncol. 2024 Jun 1;42(16):1881-1889.

- ❑ Among 812,736 individuals tested for H. pylori, 205,178 (25.2%) tested positive.

- H. pylori treatment versus no treatment was associated with lower CRC incidence and mortality (absolute risk reduction 0.23%-0.35%)

- - 15-year follow-up.

H.pylori induces a procarcinogenic Milieu in the Colon



**reversible with H.pylori eradication
in the animal experiment**

H.pylori test-and-treat strategies on population level should be structured and adapted to local regional needs and possibilities

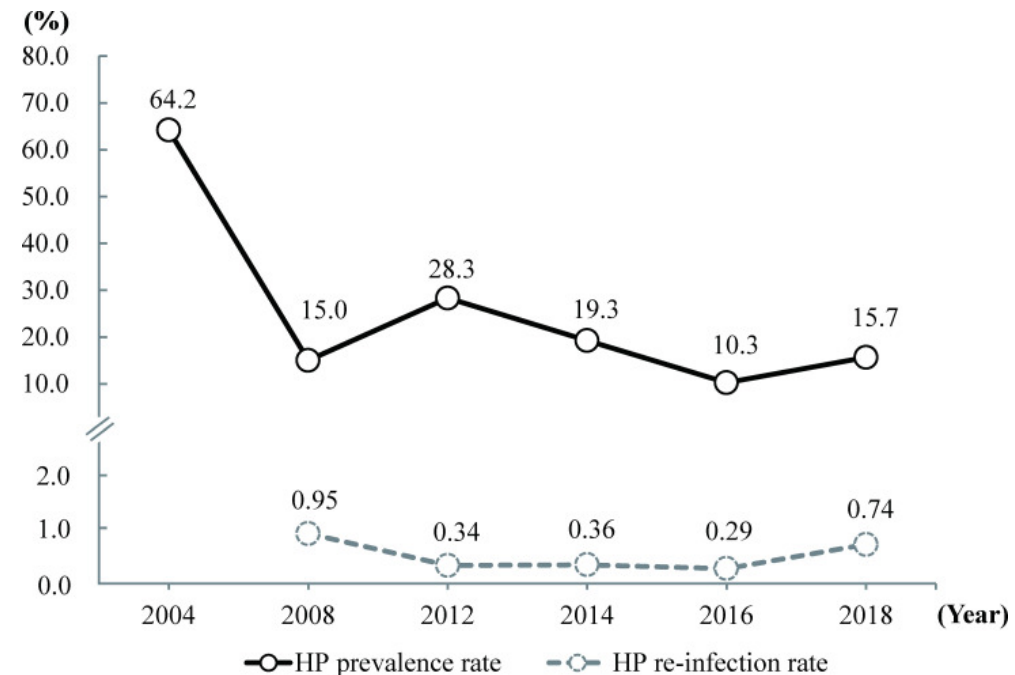
(in a differentiated context embedded in national/ international programme)

- Selection of testing modalities,
- Selection of eradication therapy
- Surveillance

Towards gastric cancer elimination

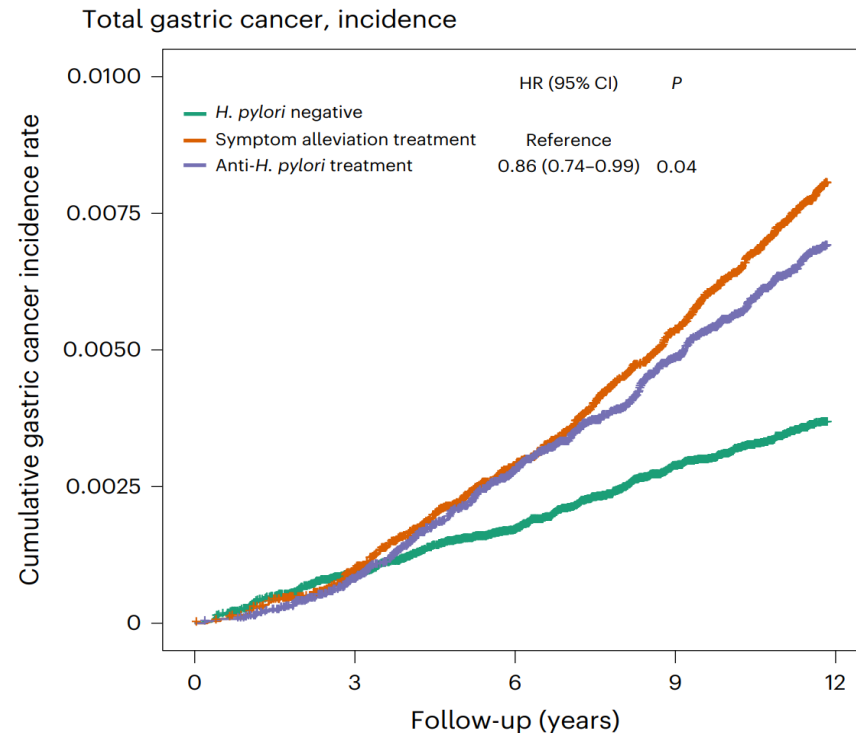
Mass eradication of *Helicobacter pylori* to reduce gastric cancer incidence and mortality: a long-term cohort study on Matsu Islands

- 6 rounds of population-based screen and treat programs (2004-2018)
- HP prevalence 64% down to 15%
- Reinfection rate <1% per person-year
- atrophic gastritis and intestinal metaplasia decreased over time
- **53% reduction in gastric cancer incidence compared with the historical control period of 1995-2003**
- No significant changes in antibiotic resistance rate



Gastric cancer prevention by community eradication of *Helicobacter pylori*: a cluster-randomized controlled trial

Pan KF, et al Nat Med. 2024 Jul 30. doi: 10.1038/s41591-024-03153-w. Epub ahead of print. PMID: 39079993.



The cluster-randomized, controlled MITS trial based on participants aged 25–54 years confirmed that ***H. pylori* treatment reduced gastric cancer risk, albeit modestly.**

Supports implementation of mass *H. pylori* screening and treatment from early adulthood as a public health policy and clinical practice for gastric cancer prevention in high-risk communities










Esempio Giappone

- ❑ Since 2013, the Ministry of Health, Labour and Welfare approved the expansion of National Health Insurance coverage for *H. pylori* eradication treatment in patients with chronic gastritis.
- ❑ Between 2013 and 2019, 8.5 million patients diagnosed with chronic gastritis were treated with *H. pylori* eradication
- ❑ *H. pylori* screening resulted in significant cost savings and health impacts for GC prevention



Original research

Large-scale, national, family-based epidemiological study on *Helicobacter pylori* infection in China: the time to change practice for related disease prevention





Xian-Zhu Zhou ¹, Nong-Hua Lyu ², Hui-Yun Zhu ¹, Quan-Cai Cai ¹,
Xiang-Yu Kong ¹, Pei Xie,¹ Li-Ya Zhou ³, Song-Ze Ding ⁴, Zhao-Shen Li ¹,
Yi-Qi Du ¹ On behalf of the National Clinical Research Center for Digestive Diseases (Shanghai), Gastrointestinal Early Cancer Prevention & Treatment Alliance of China (GECA), *Helicobacter pylori* Study Group of Chinese Society of Gastroenterology and Chinese Alliance for *Helicobacter pylori* Study.

- ❑ **Exposure to infected family members is likely the major source of its spread.**
- ❑ **supporting evidence for the strategic changes from *H. pylori* individual-based treatment to family-based management**
- the notion has important clinical and public health implications for infection control and related disease prevention



Original research

Eradicating *Helicobacter pylori* via ¹³C-urea breath screening to prevent gastric cancer in indigenous communities: a population-based study and development of a family index-case method

Wei-Yi Lei,¹ Jian-Yu Lee,² Shu-Ling Chuang,³ Ming-Jong Bair,⁴ Chien-Lin Chen ¹, Jeng-Yih Wu,⁵ Deng-Chyang Wu,⁵ Felice Tien O'Donnell,⁶ Hui-Wen Tien,⁷ Yi-Ru Chen,⁸ Tsung-Hsien Chiang,⁸ Yu-Hsin Hsu,⁹ Tsui-Hsia Hsu,⁹ Pei-Chun Hsieh,⁹ Li-Ju Lin,⁹ Shu-Li Chia,⁹ Chao-Chun Wu,⁹ Yi-Maun Subeq,¹⁰ Shu-Hui Wen,¹¹ Hsiu-Chun Chang,¹² Yu-Wen Lin,¹³ Kuo-Ping Sun,¹³ Chia-Hsiang Chu,¹⁴ Ming-Shiang Wu,⁸ David Y Graham ¹⁵, Hsiu-Hsi Chen ¹⁶, Yi-Chia Lee ^{3,8,16}

15 057 participants (8852 indigenous and 6205 non-indigenous)

Gut 2023;**72**:2231–2240.

doi:10.1136/gutjnl-2023-329871

- participation rate of 80.0% (15 057 of 18 821 invitees).
- *H.pylori* positive 44.1% (95% CI 43.3% to 44.9%).

- 6643 testing positive,
- 5493 (82.6%) received treatment

□ eradication rates
ITT 91.7% (89.1% to 94.3%)
92.1% (89.2% to 95.0%),

proof-of-concept study with 72 indigenous families(258 participants),
family members of a positive index case had **1.98 times (95% CI 1.03 to 3.80) higher Hp prevalence** than those of a negative index case.

adverse effects leading to treatment discontinuation was low at 1.2% (0.9% to 1.5%).

Test & Treat Cost- effectiveness (example Spain)

Endpoint: Gastric cancer

	Costs	Probability of Gastric Cancer	Cost per Gastric Cancer avoided
Test Treat	522.91	0.0022	524.07
Endoscopy	713.95	0.0026	715.79
Symptomatic treatment	693.41	0.0031	695.55
UBT Test and Treat	417.41	0.002	418.26

Costs to be spent each year to prevent 1 potential gastric cancer which might appear over 10 years time-horizon

**Test & Treat strategy
as “opportunistic” gastric cancer prevention**

Beresniak A, et al
Helicobacter. 2020;e12693. doi:10.1111/hel.12693

Europe's Beating Cancer Plan



Improving cancer screening in the European Union



- The Cancer Plan aims to tackle the entire disease pathway
- Four pillars: (1) prevention; (2) early detection; (3) diagnosis and treatment; and (4) quality of life of cancer patients and survivors
- Gastric cancer: (1) Preventing cancers caused by infections

Furthermore, the Commission will help ensure access to vaccination against Hepatitis B and to treatments to prevent liver and gastric cancers associated with the Hepatitis C virus and *Helicobacter pylori* infections

(2) Improving early detection of cancer

available scientific evidence. Extending targeted cancer screening beyond breast, colorectal and cervical cancer to include additional cancers, such as prostate, lung and gastric cancer, will be considered.



SAPEA (Science Advice for Policy by European Academies) recommendations

- Well-designed screen and treat strategies for reducing *H. pylori* infection provide a key opportunity to prevent gastric cancer in EU member countries with intermediate to high incidence of the disease and could be considered on a regional or national basis alongside

Conclusion: Gastric cancer screening

While there is insufficient evidence to recommend endoscopic screening of gastric cancer in Europe, the screen and treat strategy for reducing *H. pylori* infection provides an opportunity to prevent gastric cancer in EU member countries with intermediate to high gastric cancer incidence.

TOGAS

TOWARDS GASTRIC CANCER SCREENING
IMPLEMENTATION IN THE EUROPEAN UNION

Coordinator M. Leja

Under the guidance of Prof Marcis Leja, more than 20 partners are working on the TOGAS project to aid policymakers in incorporating gastric cancer screening into healthcare priorities while balancing its effectiveness, feasibility and acceptability with long-term potential adverse effects. Along with Prof Leja, the project team includes researchers from Latvia, Slovenia, France, The Netherlands, Belgium, Portugal, Spain, Lithuania, Romania, Austria, Poland, Croatia, Ireland and Germany. The project will be running for three years, and is funded with over 9 million euros.

- ❑ **evaluation of effectiveness of various strategies for prevention of gastric cancer mortality in EU countries with various burden of gastric cancer and prevalence of H.pylori**
- ❑ **screen and treat strategy extended to 6 000 young individuals (aged 30-35 years) in 7 centres of 6 countries (Croatia, Ireland, Latvia, Poland, Romania and Slovenia)**
- **investigate the presence of stomach precancerous lesions in individuals aged >50 years undergoing colonoscopy within colorectal cancer screening program.**



Several options and modalities

Screening and eradication of *Helicobacter pylori* for gastric cancer prevention: the Taipei global consensus.

Liou JM, Malfertheiner P, Lee YC et al

Gut. 2020 Oct 1:gutjnl-2020-322368. doi: 10.1136/gutjnl-2020-322368. Epub ahead of print. PMID: 33004546.

- Evidence supports the proposal that eradication therapy should be offered **to all individuals infected with *H. pylori***
- Vulnerable subjects should be tested, and treated if the test is positive
- Mass screening and eradication of *H. pylori* should be considered in populations at higher risk of GC

Take Home Message

- Gastrite da H.pylori è una malattia infettiva
- responsabile del 90% dei casi con cancro gastrico
- *H.pylori gastrite rappresenta il rischio principale per ulcera peptica e **cancro gastrico***
- ***Test & Treat e`raccomandato in soggetti sintomatici***
- ***Screen & Treat e` raccomandato in soggetti asintomatici con rischio maggiorato per carcinoma gastrico***
- ***“ strategies tailored to country specifics”***



Test non-invasivi (eg 13 C-UBT) sono idonei in strategie di prevenzione del cancro gastrico



WELL ALLRIGHT,
MY FRIEND-
SAY BYE-BYE!

