H. pylori Infektion- Leitlinien
Was ist neu?

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Universitätsklinikum Magdeburg

Klinik für Gastroenterologie, Hepatologie und Infektiologie

ANCIENT MICROBIOME

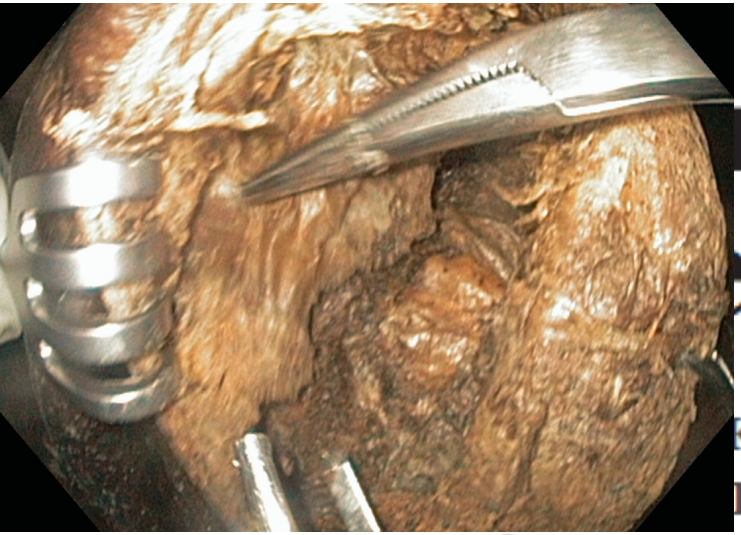
The 5300-year-old *Helicobacter pylori* genome of the Iceman

Frank Maixner,[1*†] Ben Krause-Kyora,[2†] Dmitrij Turaev,[3†] Alexander Herbig,[4,5†] Michael R. Hoopmann,[6] Janice L. Hallows,[6] Ulrike Kusebauch,[6] Eduard Egarter Vigl,[7] Peter Malfertheiner,[8] Francis Megraud,[9] Niall O'Sullivan,[1] Giovanna Cipollini,[1] Valentina Coia,[1] Marco Samadelli,[1] Lars Engstrand,[10] Bodo Linz,[11] Robert L. Moritz,[6] Rudolf Grimm,[12] Johannes Krause,[4,5‡] Almut Nebel,[2‡] Yoshan Moodley,[13,14‡] Thomas Rattei,[3‡] Albert Zink[1*‡]

The Iceman had a highly virulent strain and detectable infalammatory reaction in the stomach

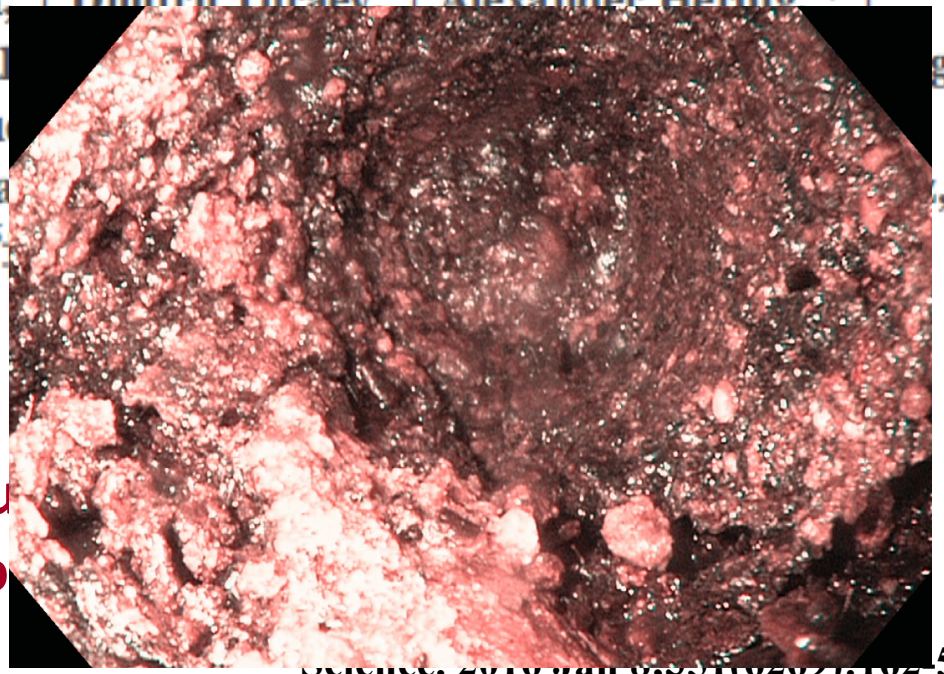
Science. 2016 Jan 8;351(6269):162-5

ANCIENT MICROBIOME



r-old *Helicobacter pylori* e Iceman

Kyora,[2†] Dmitrij Turaev,[3†] Alexander Herbig,[4,5†]
L. Hal gl,[7]
Peter Malfertheiner,[8] Francis Megrau
Valentina Coia,[1] Marco Samadelli,[1] La [6]
Rudolf Grimm,[12] Johannes Krause,[4,5]
Thomas Rattei,[3‡] Albert Zink[1*‡]



The Iceman had a highly viru
and detectable infalammato

Science. 2010 Jan 8;329(5988):162-5

Epidemiologie

Statement 1.2

Die Prävalenz der H. pylori-Infektion in Deutschland liegt zwischen 3 % (Kinder) und 48 % (Erwachsene).

Sie ist deutlich höher bei Immigranten (36 – 86 %).

Konsensusstärke: starker Konsens

Fischbach et al. Z Gastroenterol 2016:54;327-363

Empfehlung/Statement 1.4

Der enge Kontakt von Kindern mit H. pylori-infizierten Familienangehörigen stellt den wichtigsten Übertragungsweg dar.

Konsensusstärke: starker Konsens

Fischbach et al. Z Gastroenterol 2016:54327-363

S2k-Leitlinie Helicobacter pylori und gastroduodenale Ulkuskrankheit[1]

S2k-guideline Helicobacter pylori and gastroduodenal ulcer disease

Autoren W. Fischbach[1*], P. Malfertheiner[2*], P. Lynen Jansen[3], W. Bolten[4], J. Bornschein[5], S. Buderus[6], E. Glocker[7], J. C. Hoffmann[8], S. Koletzko[9], J. Labenz[10], J. Mayerle[11], S. Miehlke[12], J. Mössner[13], U. Peitz[14], C. Prinz[15], M. Selgrad[16], S. Suerbaum[17], M. Venerito[2], M. Vieth[18]

Verantwortlich für die DGVS: W. Fischbach[1], P. Malfertheiner[2]

Institute Die Institutsangaben sind am Ende des Beitrags gelistet.

Z Gastroenterol 2016:54;327-363

DGVS Statement 3.11

Vor einer geplanten Dauermedikation mit niedrig dosiertem ASS
sollen Patienten mit einer Ulkusanamnese auf eine H. pylori-Infektion untersucht und bei Keimnachweis einer Eradikationstherapie zugeführt werden.

Konsensusstärke:
starker Konsens – starke Empfehlung

Fischbach et al. Z Gastroenterol 2016:54327-363

Indikationen zur H.-pylori-Eradikation
DGVS Leitlinien 2016

	Starke Empfehlung **soll**	Empfehlung **sollte**	Empfehlung offen **kann**	Keine Empfehlung **Nein**
Peptisches Ulkus	X			
MALT-Lymphom des Magens	X			
Diffuses großzelliges B-Zell-Lymphom des Magens			X	
Funktionelle Dyspepsie (Reizmagen)			X	
Test-and-treat				X
Idiopathische thrombozytopenische Purpura (ITP)	X			
Morbus Menetrier		X		
Lymphozytäre Gastritis		X		
Ungeklärte (nach adäquater Abklärung) Eisenmangel-anämie			X	
Vor ASS-Dauermedikation (bei Ulkusanamnese)	X			
Obere gastrointestinale Blutung unter ASS	X			
Vor NSAR-Dauermedikation (bei Ulkusanamnese)	X			
Obere gastrointestinale Blutung unter NSAR	X (plus PPI bei NSAR)			
Magenkarzinomprophylaxe (bei Risikopersonen)			X	
Asymptomatische Gastritis		X		

Empfehlung/Statement 3.5

Eine nicht invasive Testung auf H. pylori mit nachfolgender Eradikationsbehandlung für Deutschland nicht allgemein empfohlen.

Konsensusstärke:
mehrheitliche Zustimmung – Empfehlung offen

Fischbach et al. Z Gastroenterol 2016:54327-363

Therapieentscheidung zur H. pylori Eradikation

DGVS

→ 2 positive Testergebnisse
(außer bei: Ulcus duodeni, positiver Kultur, Histologie)

Maastricht V/Florenz

→ 1 positives Testergebnis

Wo und wie viele Biopsien sollten entnommen werden?

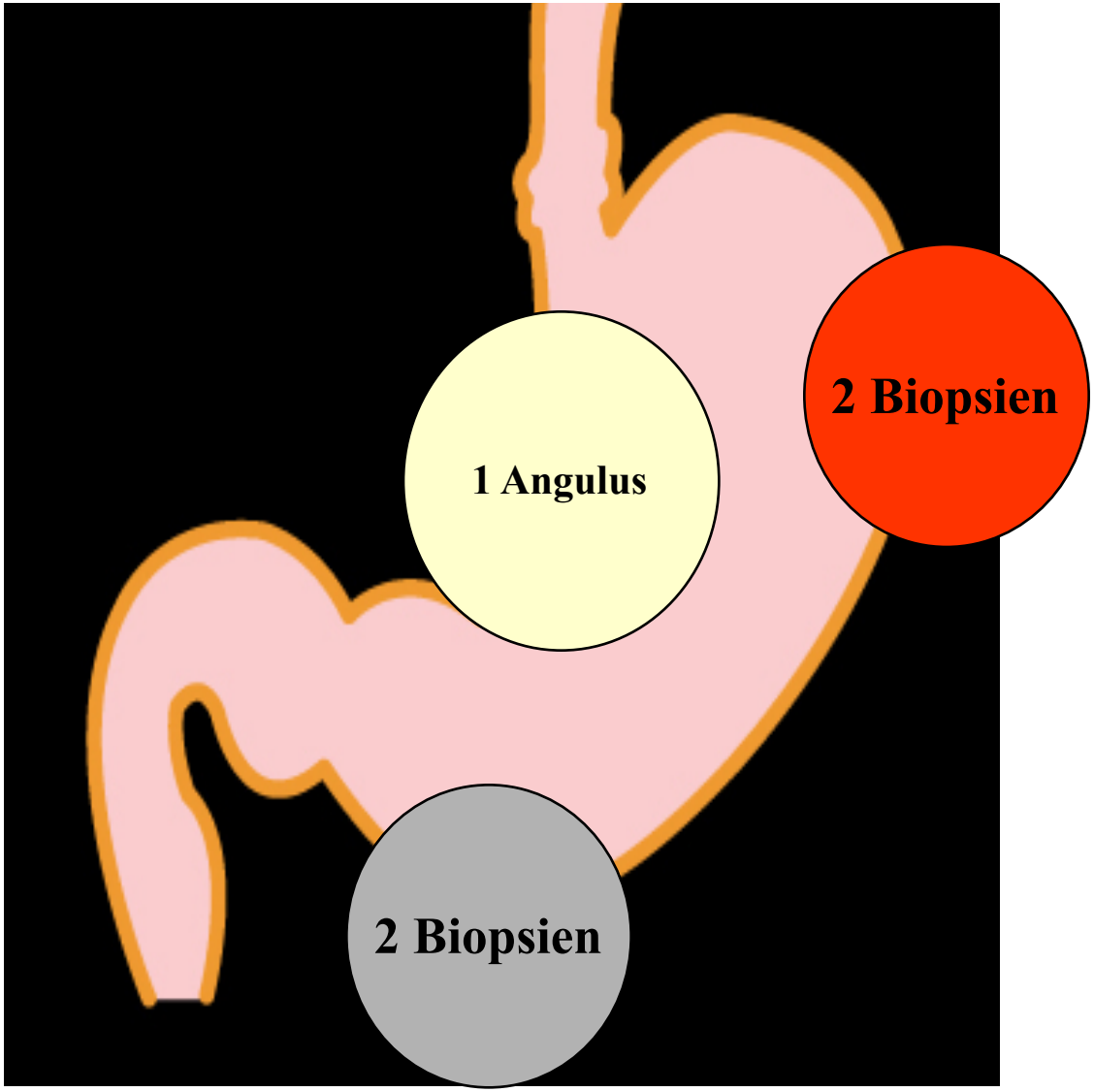
4 Biopsien — **DGVS Leitlinie 2016**

5 Biopsien — **Maastricht V / Florenz 2016**

Beurteilungsparameter:

- **H. pylori Nachweis**
- **Gastritis** - **Aktivität**
  - **Chronizität**
  - **Atrophie / Intestinale Metaplasie**

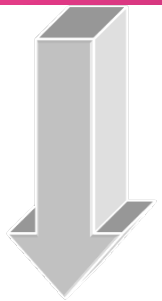
Die Diagnose Gastritis basiert auf dem histologischen Befund



Gastritis Staging

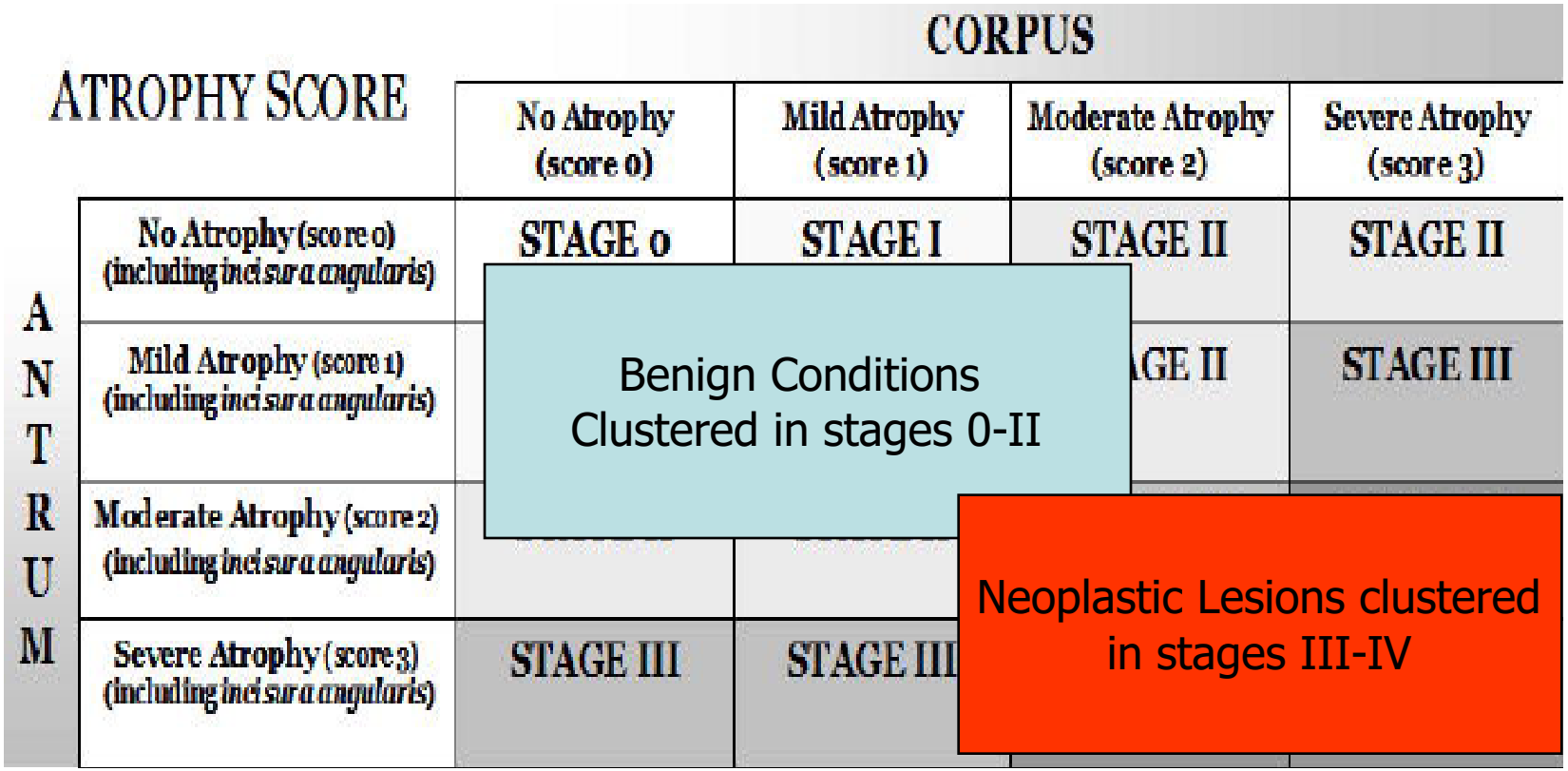
OLGA

OLGIM



Wir müssen die Gastritis charakterisieren und das Risiko für mögliche Komplikationen abschätzen

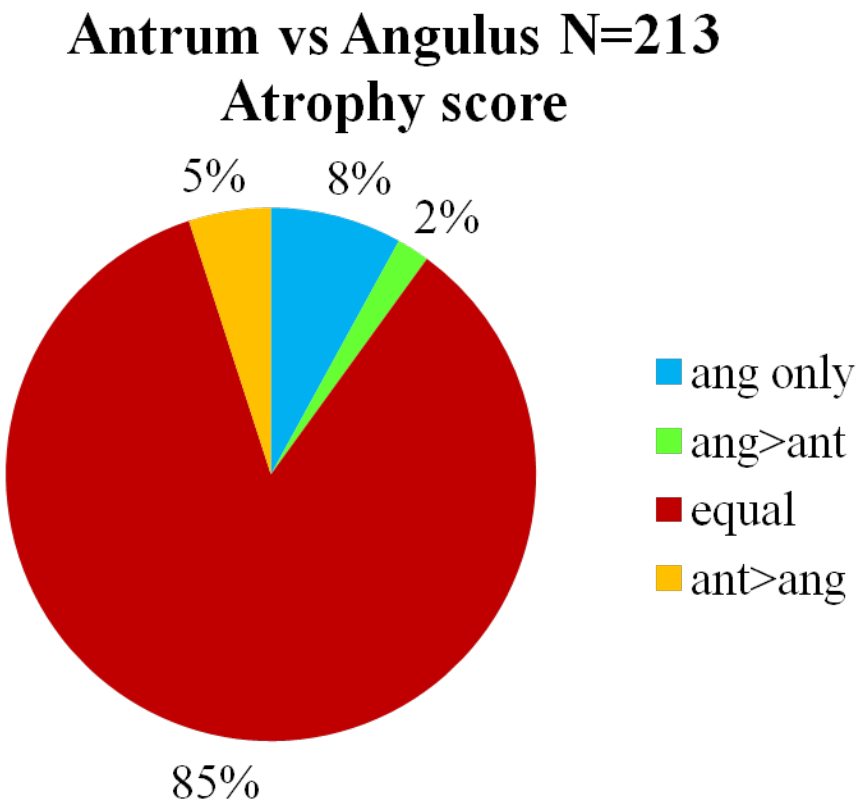
Gastritis Grading: OLGA Staging

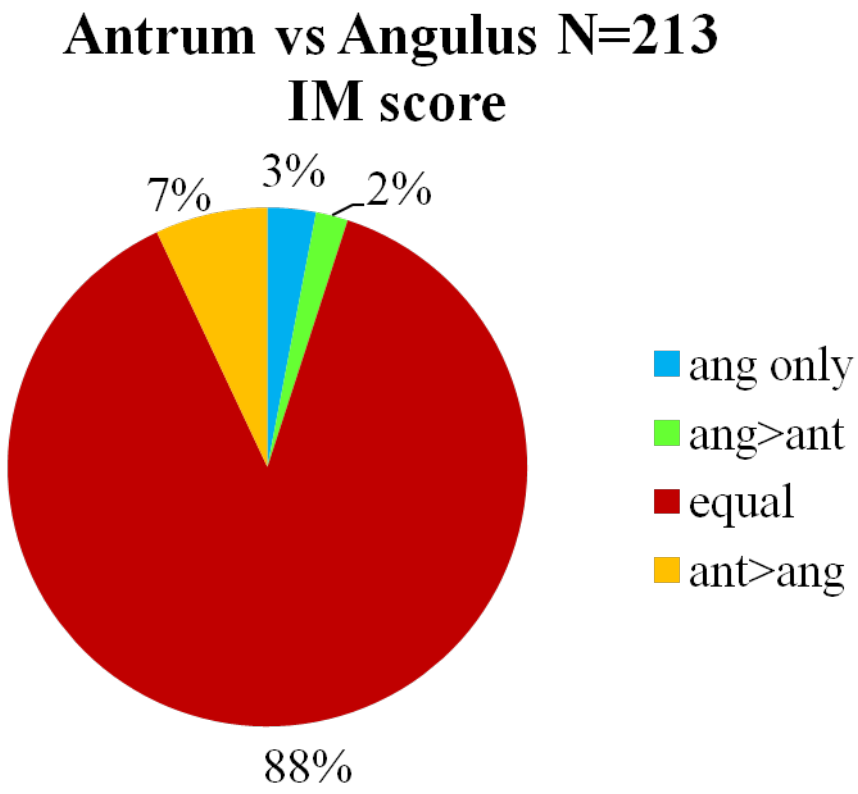


M. Rugge, Gastritis staging in clinical practice: the Olga staging system Gut. 2007

Updated Sydney system scores for atrophy and intestinal metaplasia in the angulus compared with antrum in the overall study population.

Ang, angulus; ant, antrum; IM, intestinal metaplasia.



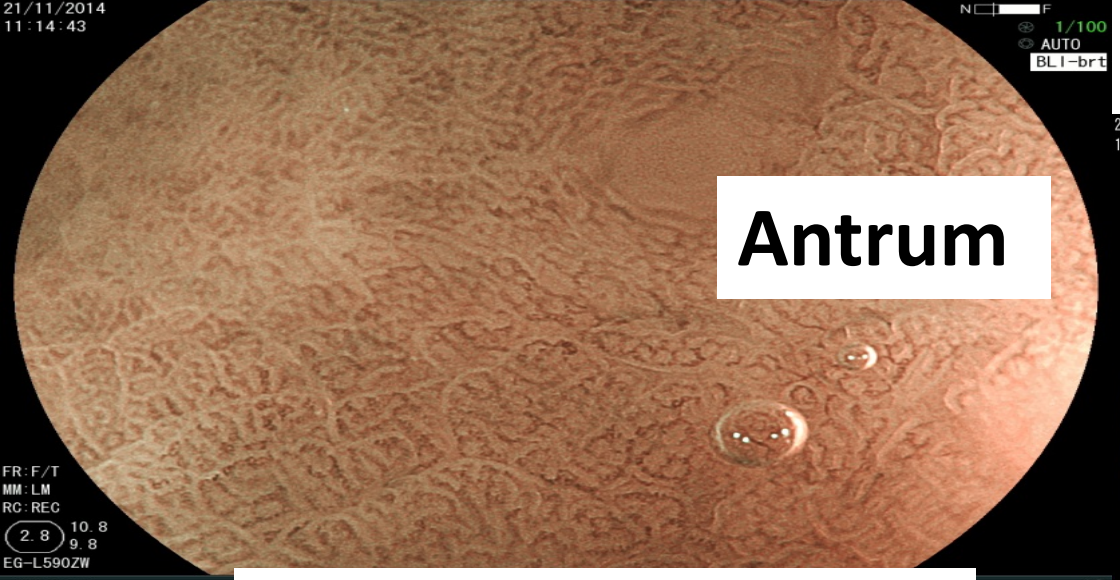


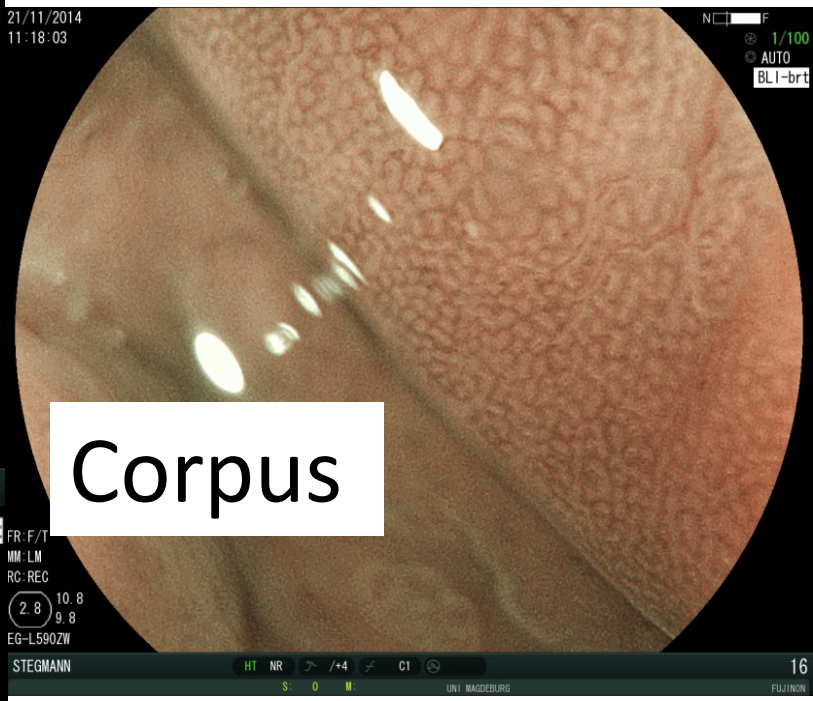
Varbanova et al. J Clin Pathol. 2016 Jan;69(1):19-25.

Mit NBI,FICE,BLI

bei der Gastritis Diagnostik umdenken?

BLI


21/11/2014
11:14:43
1/100
AUTO
BLI-brt
Antrum
FR:F/T
MM:LM
RC:REC
2.8
10.8
9.8
EG-L590ZW
STEGMANN


21/11/2014
11:18:03
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AUTO
BLI-brt
Corpus
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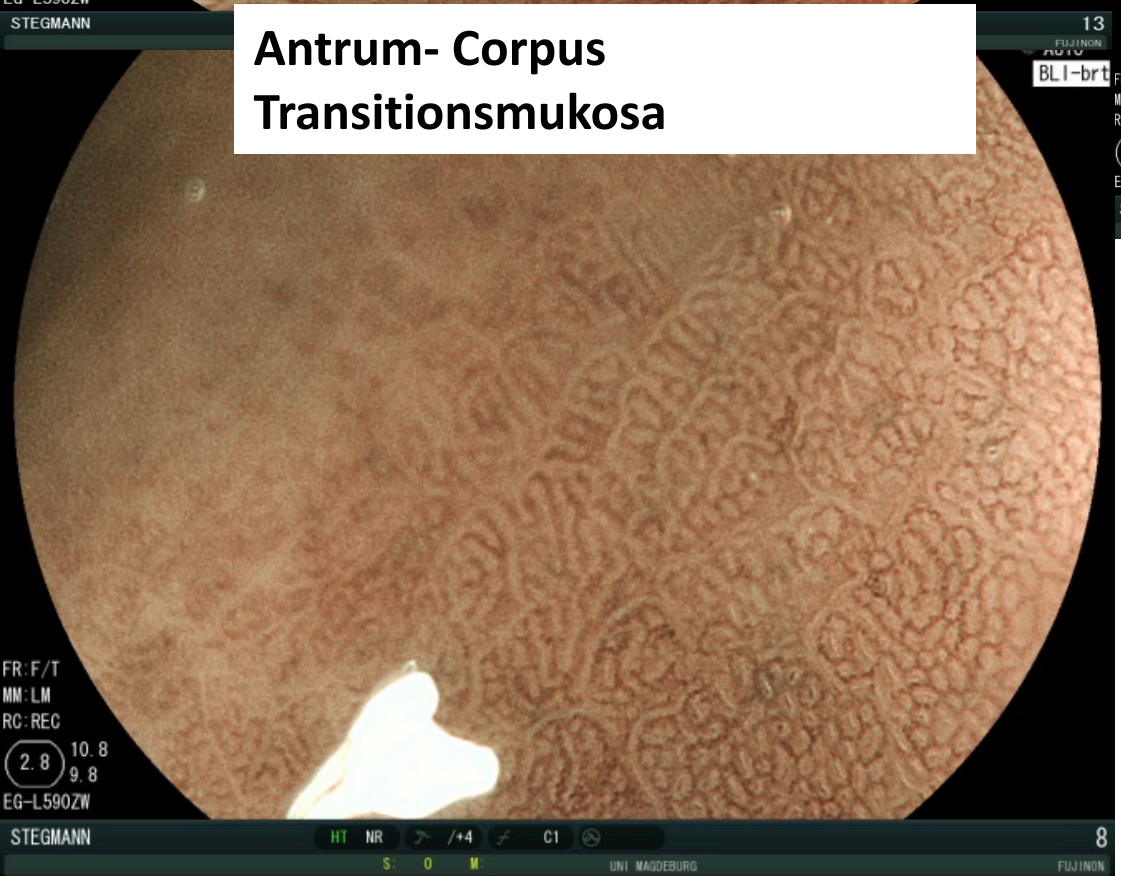
RC:REC
2.8
10.8
9.8
EG-L590ZW
STEGMANN
16


Antrum- Corpus
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2.8
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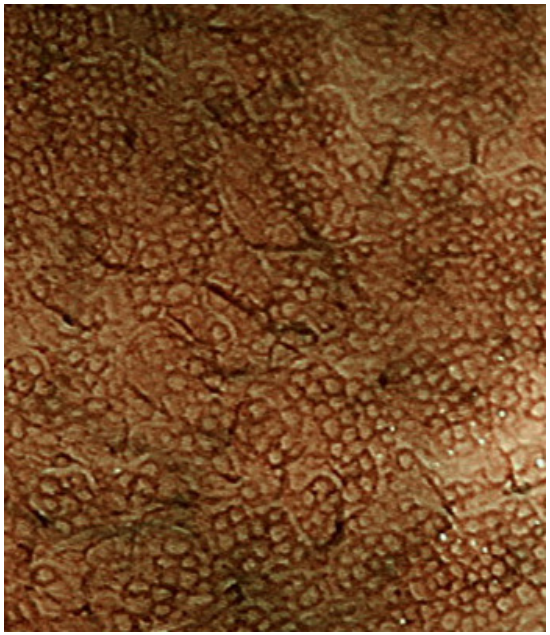
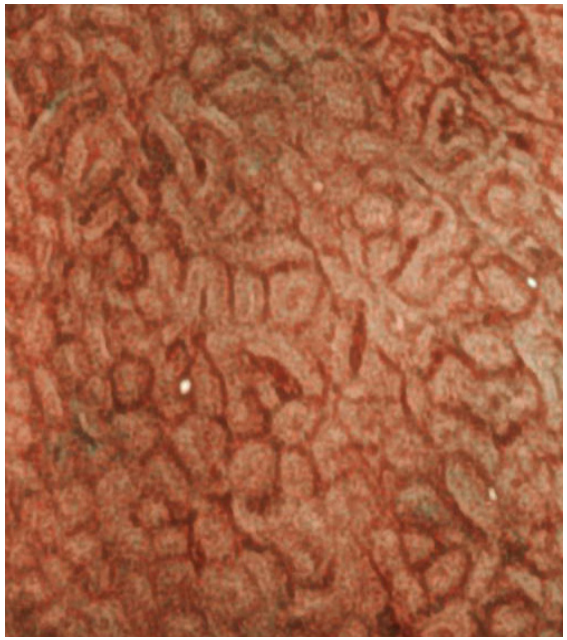
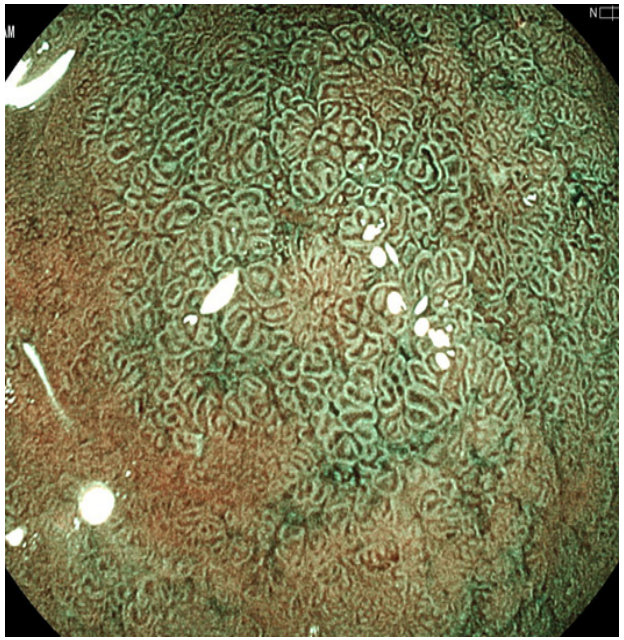
UNI MAGDEBURG
FUJINON

Blue Laser Imaging (BLI) of the gastric mucosa







Indikationen zur H.-pylori-Eradikation
DGVS Leitlinien 2016

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Magenkarzinomprophylaxe (bei Risikopersonen)			X	
Asymptomatische Gastritis		X		

Kyoto global consensus report on *Helicobacter pylori* gastritis

Kentaro Sugano,[1] Jan Tack,[2] Ernst J Kuipers,[3] David Y Graham,[4] Emad M El-Omar,[5] Soichiro Miura,[6] Ken Haruma,[7] Masahiro Asaka,[8] Naomi Uemura,[9] Peter Malfertheiner,[10] on behalf of faculty members of Kyoto Global Consensus Conference

Gut 2015;64:1353

Key messages

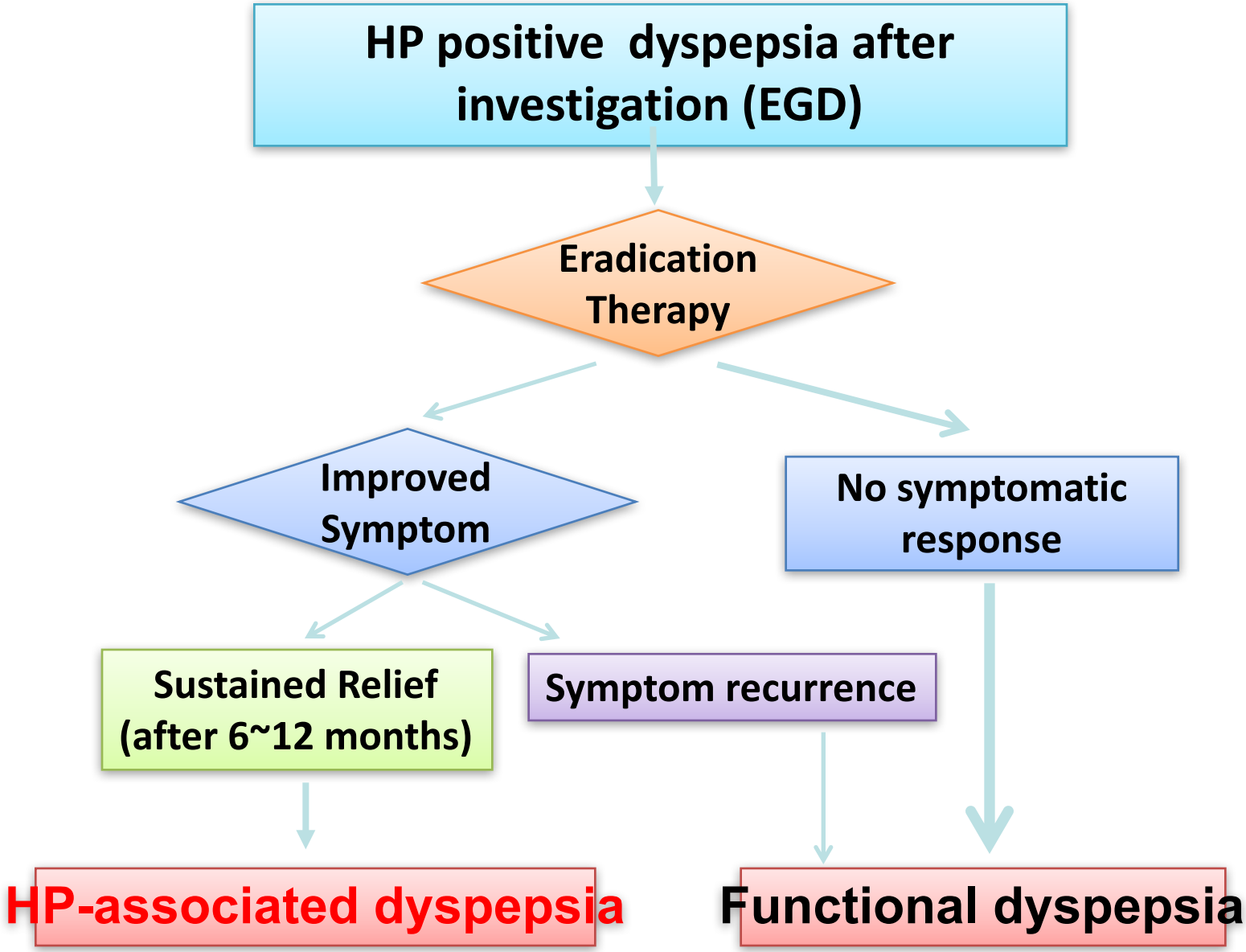
-*H. pylori*- Gastritis is an infectious disease

-H.pylori gastritis specific entity of dyspepsia

-High definition endoscopy with virtual chromoendoscopy to be implemented

-H.pylori eradication before the development of preneoplastic lesions

Algorithm of diagnosing *H. pylori*-associated dyspepsia



Sugano et al Gut 2015

Update on H.pylori managment

Maastricht V/ Florence

Gut 2017, Jan

Statement

H. pylori gastritis is a distinct entity and causes dyspeptic symptoms in some patients.

H. pylori eradication produces long-term relief of dyspepsia in about 10% of patients

(= 10 %more than with any comparator drug).

Level of Evidence: 1A (high) **Grade of Recommendation: strong**

Agree	**95%**	**39**
Rather agree	2%	1
Indecisive	0%	0
Rather disagree	0%	0
Disagree	2%	1

Statement 2

A test-and-treat strategy is appropriate for uninvestigated dyspepsia.

This approach is **subject to regional H. pylori prevalence** and cost-benefit considerations. It is not applicable to patients with alarm symptoms or older patients

Level of Evidence: 1A (high) **Grade of Recommendation: A (high)**

Agree	**95%**	**38**
Rather agree	2%	1
Indecisive	0%	0
Rather disagree	2%	1
Disagree	0%	0

H.pylori gastritis
Specific entity of Dyspepsia
But > 80 % remain asymptomatic!

Indikationen zur H.-pylori-Eradikation
DGVS Leitlinien 2016

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Magenkarzinomprophylaxe (bei Risikopersonen)			X	
Asymptomatische Gastritis		X		

Empfehlung/Statement 4.4

Patienten mit **asymptomatischer H. pylori-Gastritis**
sollte eine
Eradikationsbehandlung angeboten werden.

Konsensusstärke:
starker Konsens – Empfehlung

Fischbach et al. Z Gastroenterol 2016:54;327-363

DGVS Empfehlung/Statement 4.4

Patienten mit asymptomatischer H. pylori-Gastritis sollte eine Eradikationsbehandlung angeboten werden.

Konsensusstärke: starker Konsens

Fischbach et al. Z Gastroenterol 2016:54 327-363

GUT

Management of *Helicobacter pylori* infection ––the Maastricht V/Florence Consensus Report

P Malfertheiner, F Megraud, C A O'Morain, J P Gisbert, E J Kuipers, A T Axon, F Bazzoli, A Gasbarrini, J Atherton, D Y Graham, R Hunt, P Moayyedi, T Rokkas, M Rugge, M Selgrad, S Suerbaum, K Sugano and E M El-Omar

Gut published online October 5, 2016

Maastricht V- Florence

I **Indications/Associations**

Which are the clinical scenarios requiring treatment beyond established indications in the previous Maastricht consensus report?

II **Diagnosis**

Where is the progress in diagnostic methods/tests?

III **Treatment**

What is new? How to overcome resistance?

IV **Prevention/Public Health**

Should general H. pylori testing and treating become integrated in general medical strategy?

V **H. pylori, other Helicobacter, relationship with gut microbiota**

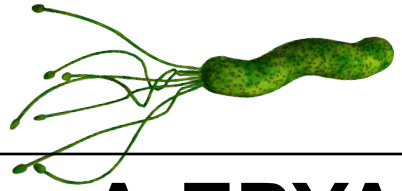
H. pylori and impact on gut microbiota,role of probiotics

H. pylori Infektion und Magenkarzinom

Die „Challenge“

H. pylori and gastric carcinogenesis

Bacterial virulence factors



Cag A-EPYA

Vac A-allelotypes

Host factors

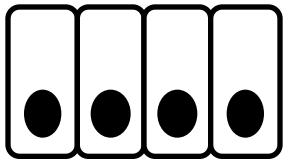
Environmental

Tobacco

Diet

Polymorphisms of inflammatory cytokines

Correa-Kaskade – Magenkarzinogese beim intestinalen Typ



Normales Gewebe

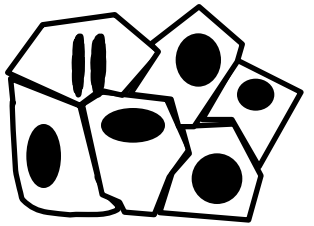
H.pylori Infektion

Chronische aktive Gastritis

Atrophische Gastritis

Intestinale Metaplasie

Dysplasie

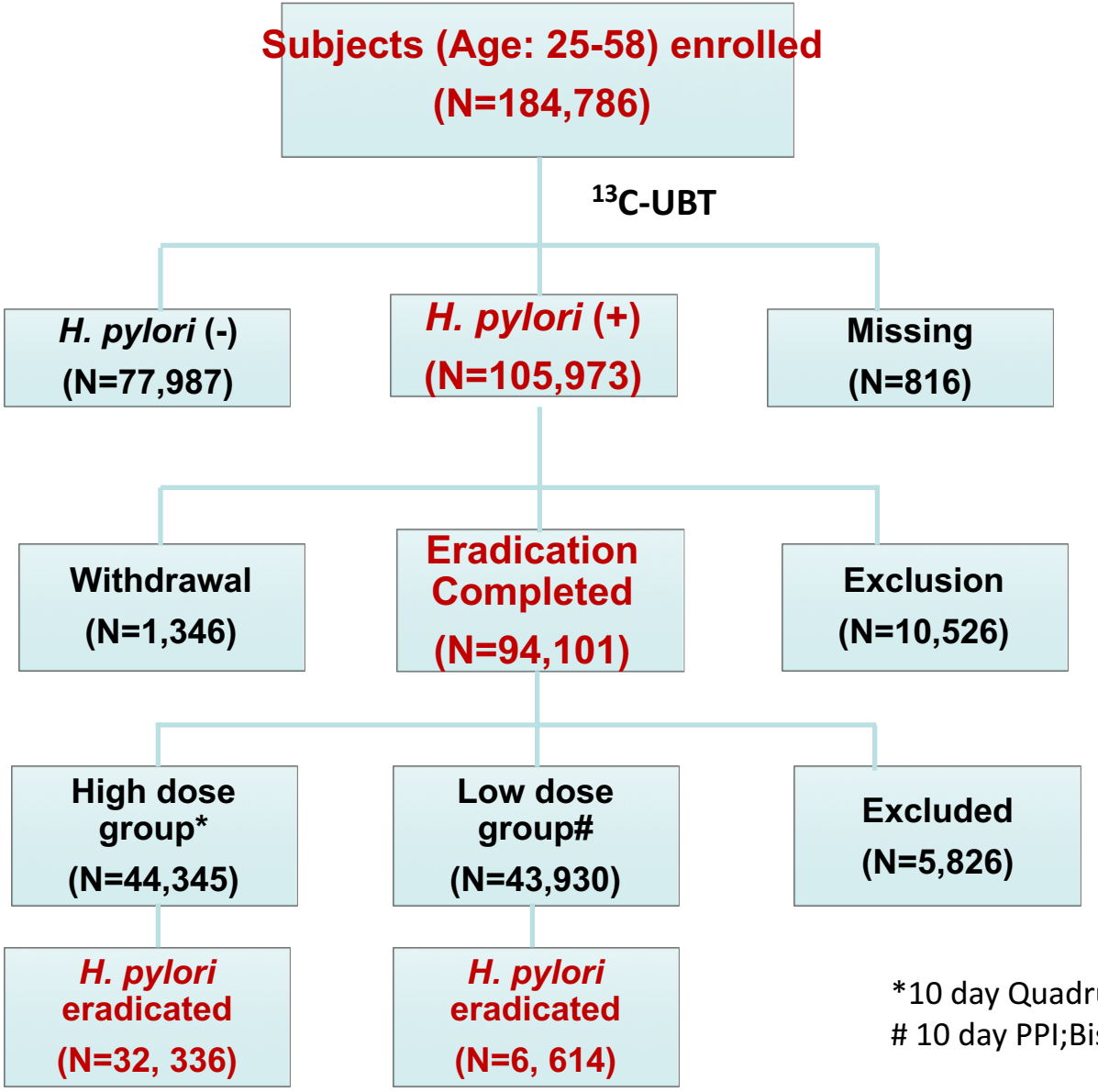


Magenkarzinom

Mod. Correa, Cancer Research 1992
Malfertheiner et al. Nat Rev Gastroenterol Hepat 2014

Gastric cancer prevention

A Large-scale Population-based Trial in China



Linqu County
F/U: 7 years

*10 day Quadruple
10 day PPI;Bismuth

Pan K et al. Gut. 2015 May 18. pii: gutjnl-2015-309197. doi: 10.1136/gutjnl-2015-309197. [Epub ahead of print]

A large randomised controlled intervention trial to prevent gastric cancer by eradication of *Helicobacter pylori* in Linqu County, China: baseline results and factors affecting the eradication

Pan K-Feng and Lian Zhang et al. Gut 2015;0:1–10.

- **A total of 184 786 residents aged 25–54 years** were enrolled in this trial and received 13C-urea breath test.
- **H. pylori positive participants were assigned into two groups, either receiving a 10-day quadruple anti- H. pylori treatment or look-alike placebos together with a single dosage of omeprazole and bismuth**.
- **H.pylori prevalence.was 57.6%.**
- **A total of 94 101 subjects completed the treatment.**
- **The overall H. pylori eradication rate was 72.9% in the active group.**

Screen and treat in low risk countries?

Risiko für Entwicklung eines Magenkarzinoms innerhalb von 20 Jahren

„niedrig Risikoland“

405.172 Patienten mit Biopsie

↳ 1599 Patienten mit Magenkarzinom

bei normaler Mukosa	1: 256
- Gastritis	1: 85
- atrophische Gastritis	1: 50
- intestinale Metaplasie	1: 39
- Dysplasie	1: 19

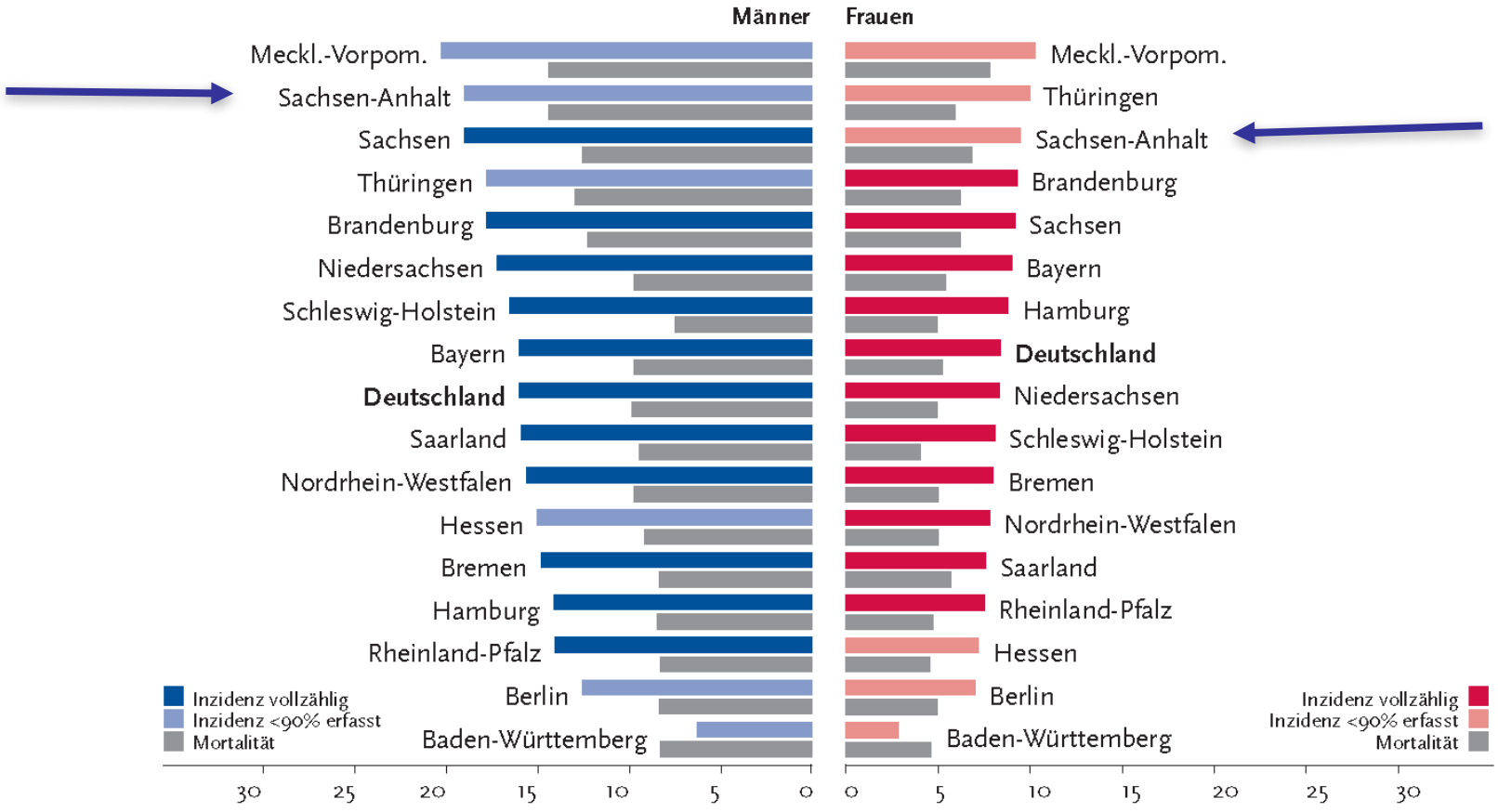
Song et al. BMJ. 2015 Jul 27;351:h3867

H. pylori gastritis defined as a precancerous lesion

Early Precancerous Lesions	**Gastritis**	**Stage* O**
		Stage* I
		Stage* II
		Stage* III
		Stage* IV
Advanced Precancerous Lesions	**Intra-epithelial Neoplasia (IEN)#**	**IEN Low Grade**
		IEN High Grade

Rugge M et al. Gut. 2016 Feb 29. pii: gutjnl-2015-310846

Inzidenz Magenkrebs nach Bundesländern



Krebs in Deutschland 2009/ 2013
RKI 9. Ausgabe

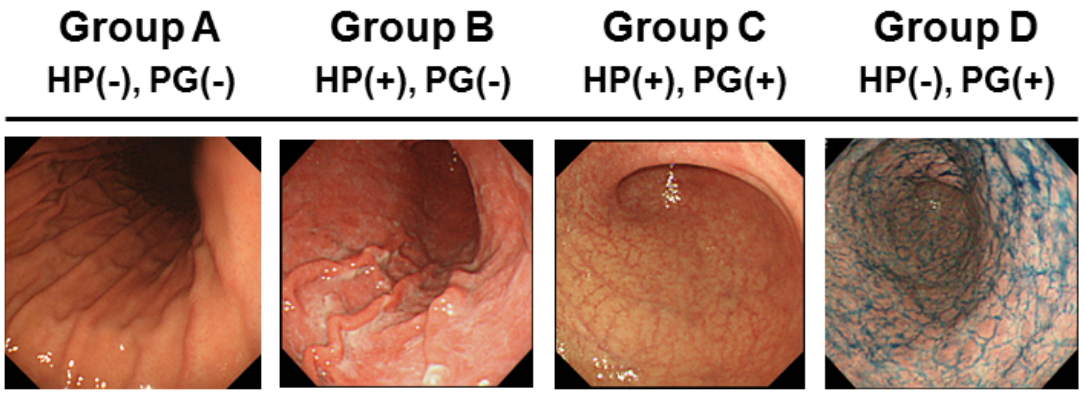
Gastric cancer 5-year age-standardised survival

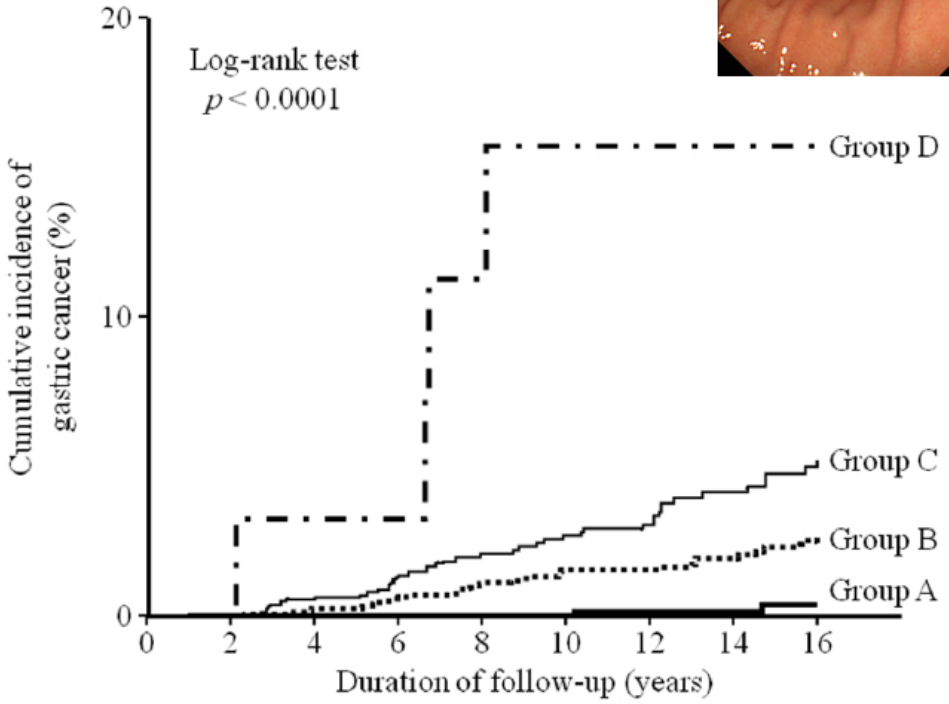
	Stomach cancer
European mean	**25·1 (24·8–25·4)**
Northern Europe	21·9 (21·2–22·6)
Denmark	16·0 (14·7–17·4)
Iceland	34·5 (27·8–41·3)
UK and Ireland	17·2 (16·8–17·5)
Central Europe	28·1 (27·6–28·5)
Austria	31·0 (29·9–32·2)
Germany	31·3 (30·6–32·0)
Netherlands	20·4 (19·7–21·2)

De Angelis et al. Lancet Oncol. 2014 Jan;15(1):23-34

Was machen wir dagegen?

Serologische Risiko-Evaluation





Yoshida et al. Int J Canc 2013

Gastric adenocarcinoma screening and prevention in the era of new biomarker and endoscopic technologies: a cost-effectiveness analysis

Jennifer M Yeh,[1] Chin Hur,[2] Zachary Ward,[1] Deborah Schrag,[3] Sue J Goldie[1]

Gut. 2016 ,Apr (4),563-74

Screening the general population at age 50 years reduced the lifetime intestinal-type NCGA risk (0.24%)

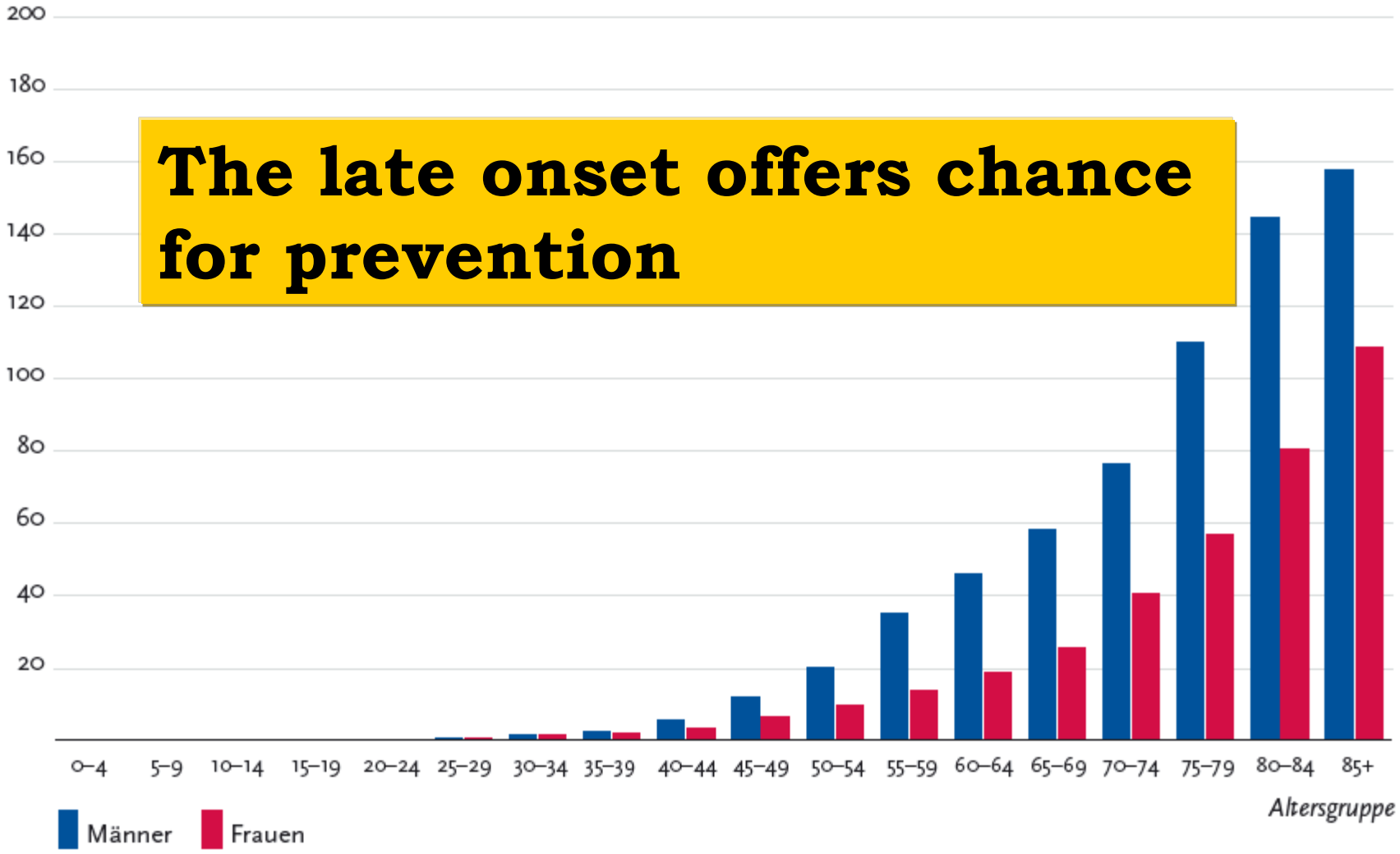
by 26.4% with serum pepsinogen screening,

21.2% with endoscopy and EMR

only 0.2% with H. pylori screening/treatment

Serum pepsinogen screening was more effective and more costeffective than all other strategies, although its ICER varied from $76 000/QALY (current smokers) to $105 400/QALY (general population)

Gastric cancer disease of the aged
ICD-10 C16, Deutschland, 2007 – 2008
je 100.000



The late onset offers chance for prevention

Krebs in Deutschland 2007/2008, 8. Ausgabe 2012

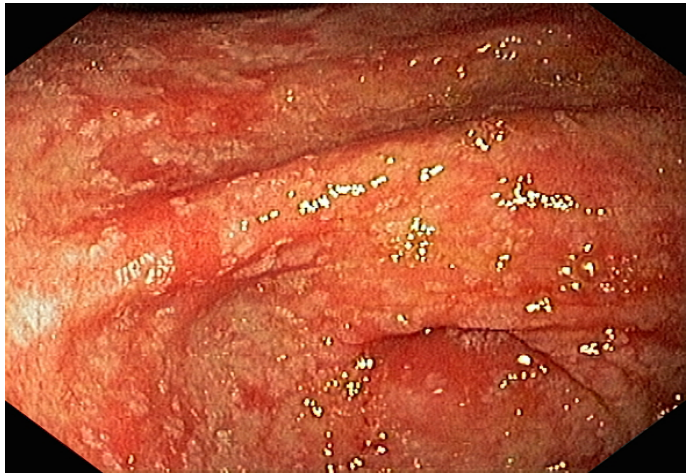
Screening auf „Präneoplasie“ des Magens

Gastrin 17

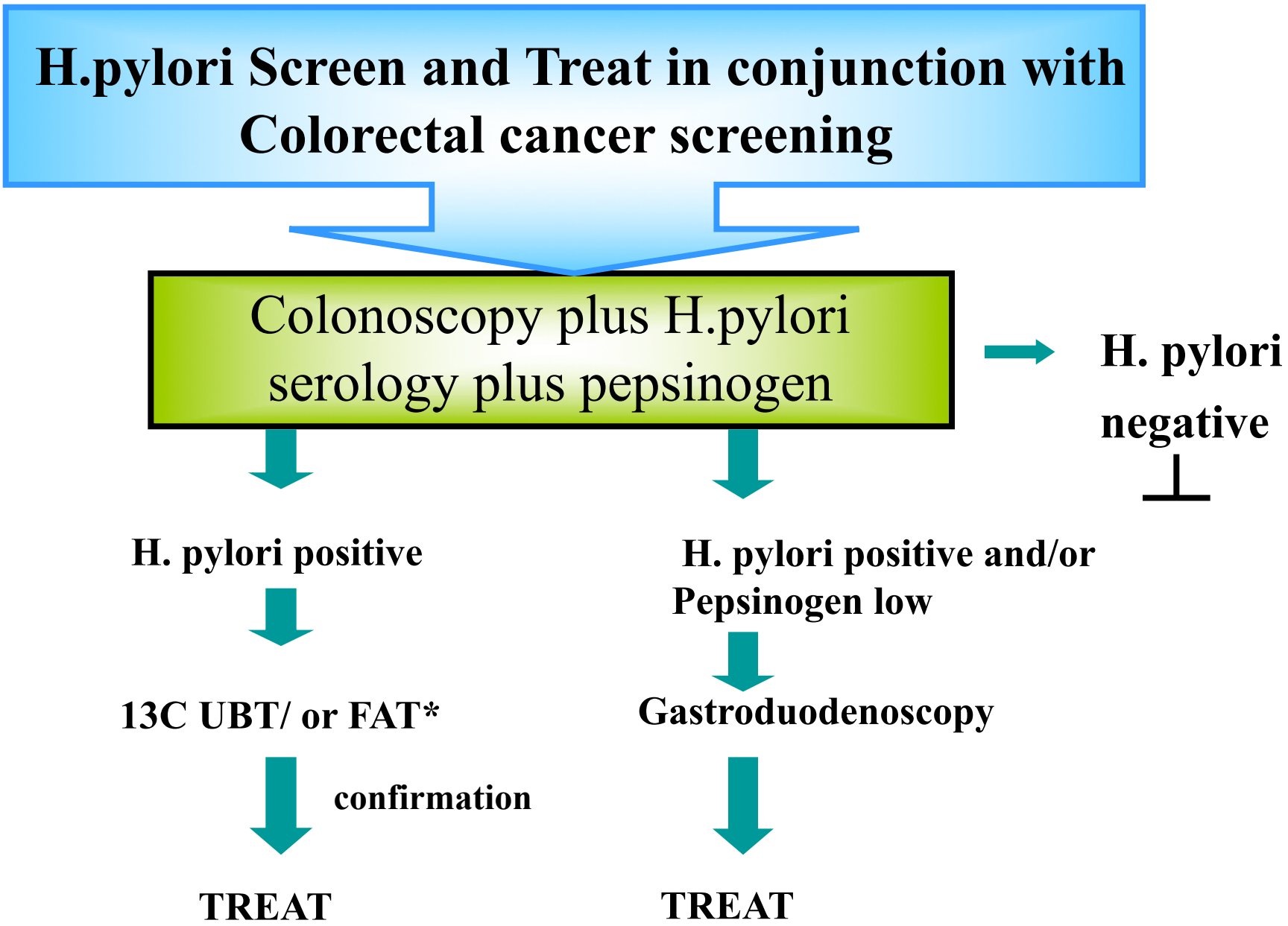
Pepsinogen I + II
PI/II-Ratio

H.pylori-AK

„Gastropanel“



H.pylori Screen and Treat in conjunction with Colorectal cancer screening



* FAT = Fecal Antigen Test

Helicobacter pylori as risk factor for colonic neoplasms in 2013 and 2014

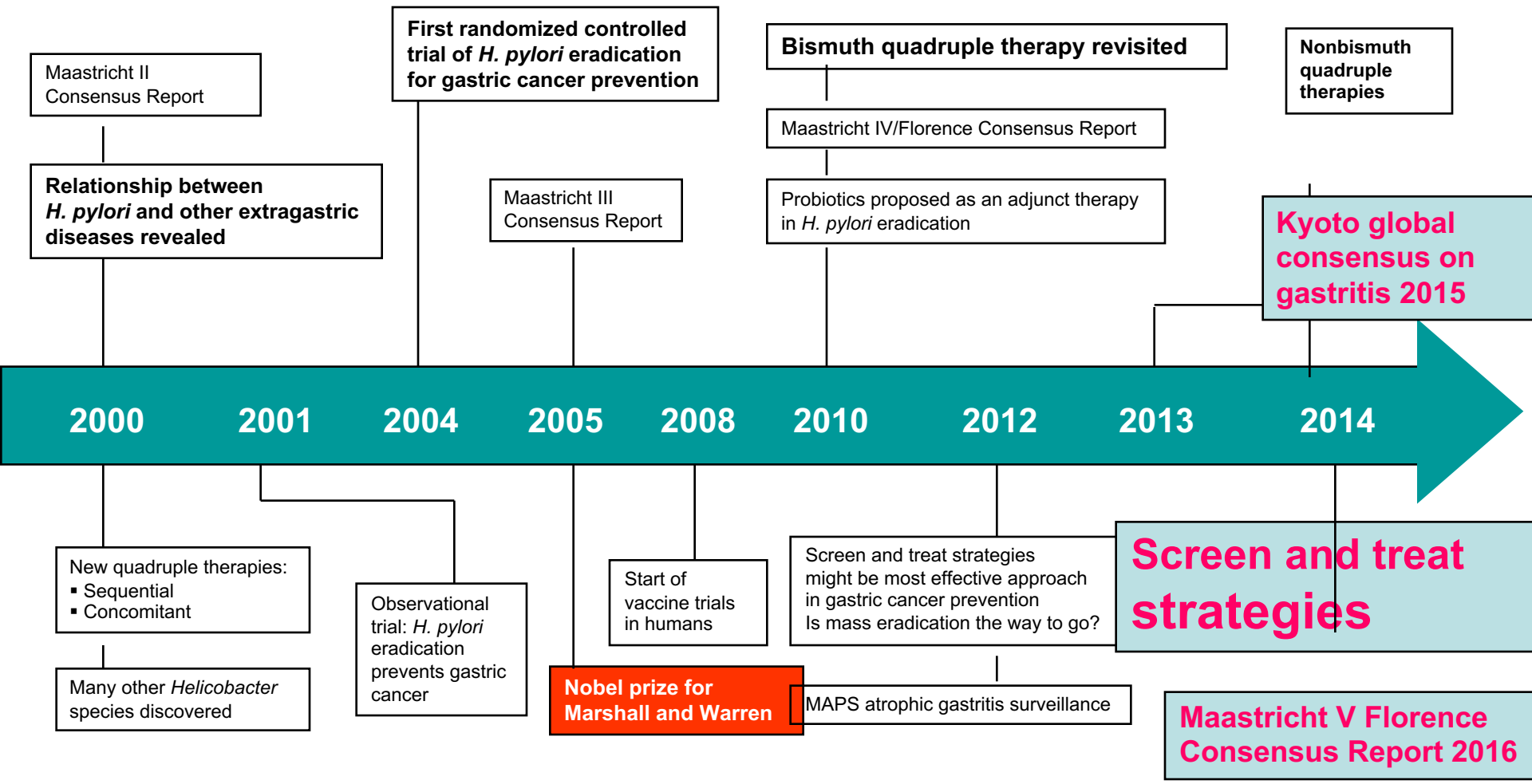
Colonic neoplasm	OR	Reference
Hyperplastic polyps:	(OR=1.24, 95% CI: 1.18–1.30)	Sonnenberg and Genta [46]
Adenomatous polyps:	(OR=1.52, 95% CI: 1.46–1.57)	
Advanced adenomas:	(OR=1.80, 95% CI: 1.69–1.92)	
Adenomas high-grade dysplasia:	(OR=1.97, 95% CI: 1.82–2.14)	
Adenocarcinoma:	(OR=2.35, 95% CI: 1.98–2.80)	
Colonic neoplasm overall:	**(OR=2.73, 95% CI: 1.76–4.24)**	Selgrad et al. [45]
Hyperplastic polyps:	(OR=2.66, 95% CI: 1.23–5.74)	
Low-grade IEN polyp:	(OR=1.85, 95% CI: 1.14–2.99)	
Colonic polyps:	(OR=1.5, 95% CI: 1.26–1.79)	Rokkas et al. [44&]
Colon cancer:	(OR=1.3, 95% CI: 1.07–1.59)	

CI, confidence interval; IEN, intraepithelial neoplasia; OR, odds ratio.

Malfertheiner and Selgrad Curr Opin Gastroenterol. 2014 Nov;30(6):589-95

Timeline

Key developments in *Helicobacter pylori* clinical research



Malfertheiner P. et al. Nat. Rev. Gastroenterol. Hepatol. 2014, vol 11,no10,628-638

H. pylori Infektion

Therapie erfolgt Resistenz- adaptiert

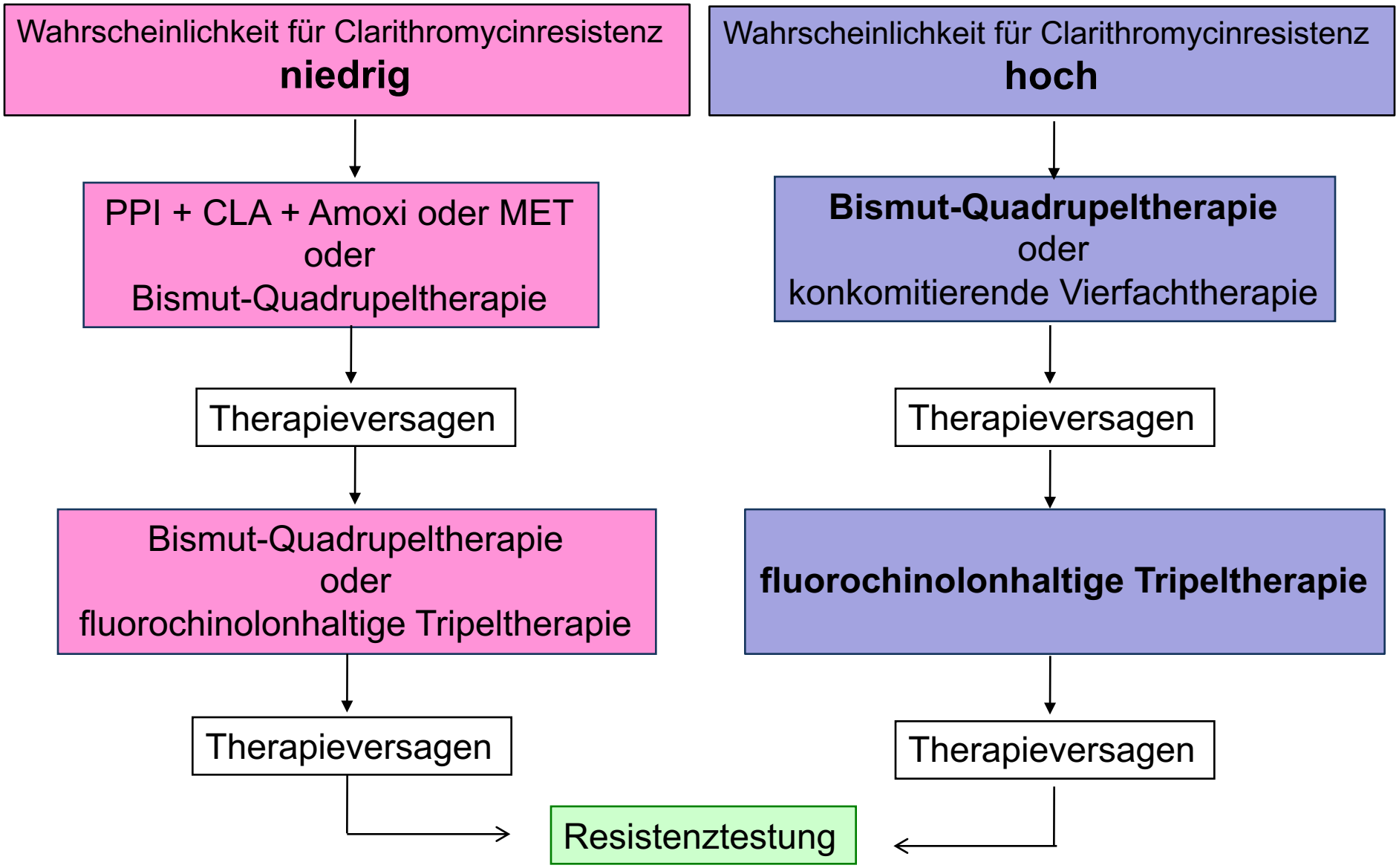
Review article: the global emergence of *Helicobacter pylori* antibiotic resistance

I. Thung*,[1], H. Aramin*,[1], V. Vavinskaya*, S. Gupta†, J. Y. Park‡, S. E. Crowe† & M. A. Valasek*

- **bacterial antibiotic resistance is regionally variable**
- **clarithromycin resistance** has been rapidly increasing in many countries over the past decade, with rates as high as approximately **30% in Japan and Italy, 50% in China and 40% in Turkey;**
- **resistance rates are much lower in Sweden and Taiwan, at approximately 15%; there are limited data in the USA**. Other antibiotics show similar trends, although less pronounced.

Aliment Pharmacol Ther. 2016 Feb;43(4):514-33.

DGVS Leitlinien 2016
Therapiealgorithmus zur H.-pylori-Eradikation

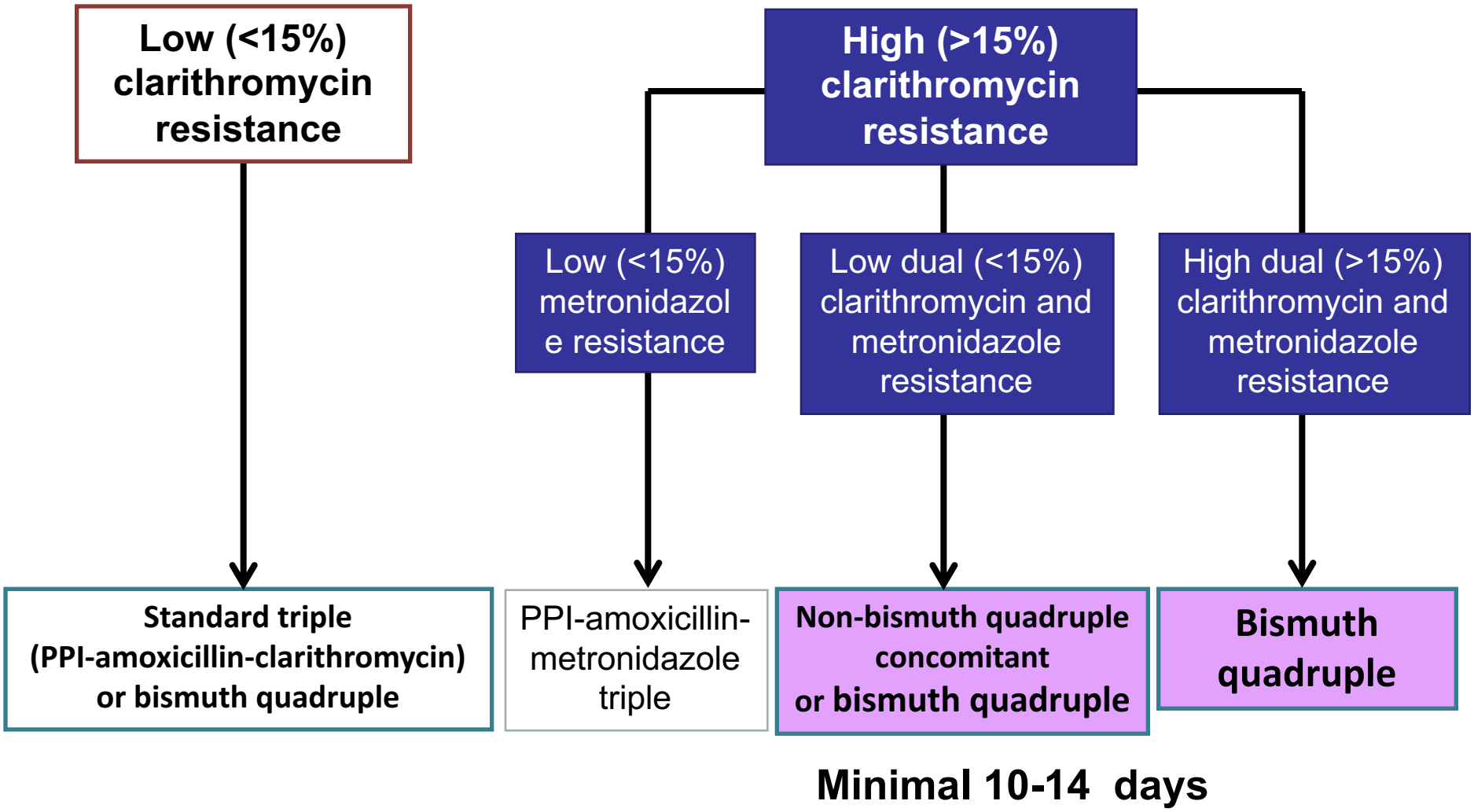


DGVS Empfehlung/Statement 5.12

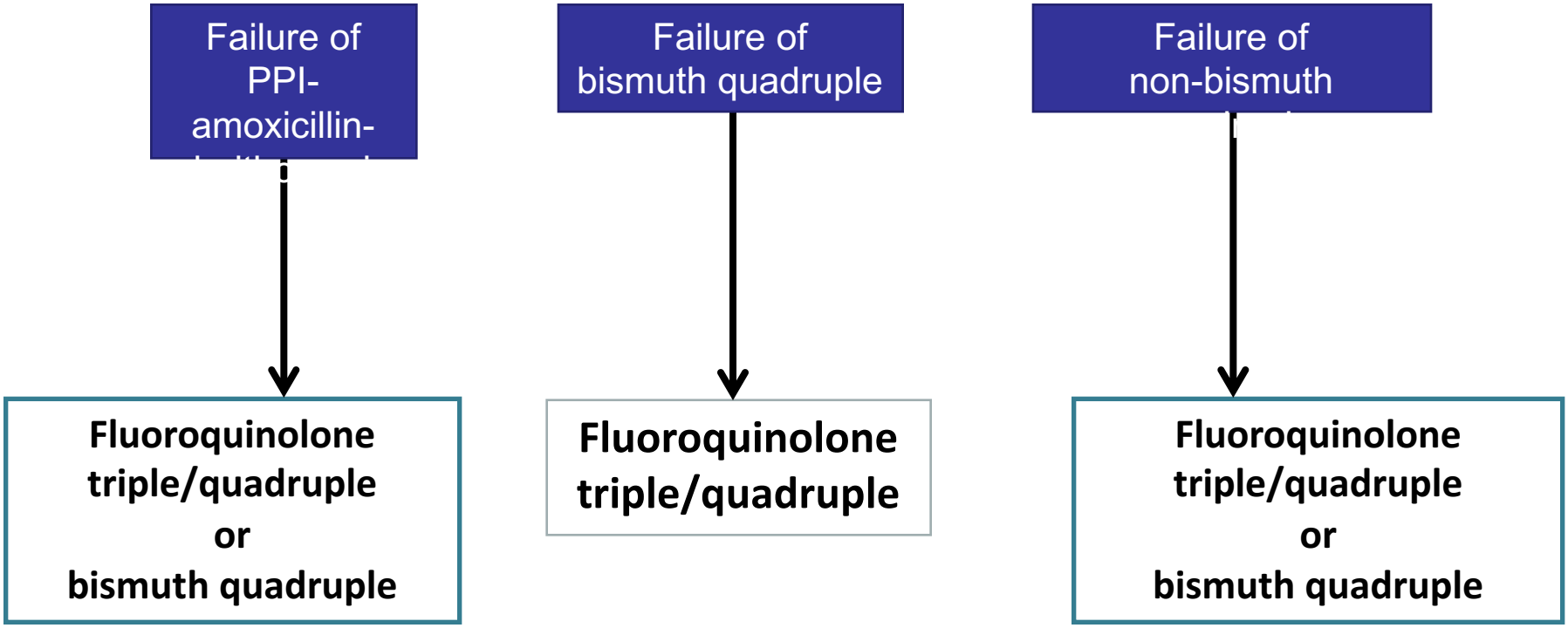
Bei niedriger Wahrscheinlichkeit für eine primäre Clarithromycin-Resistenz können in der Erstlinientherapie eine **Standard-Triple-Therapie** oder eine **Bismuth-basierte Quadrupeltherapie** eingesetzt werden.

Konsensusstärke:
starker Konsens – Empfehlung offen

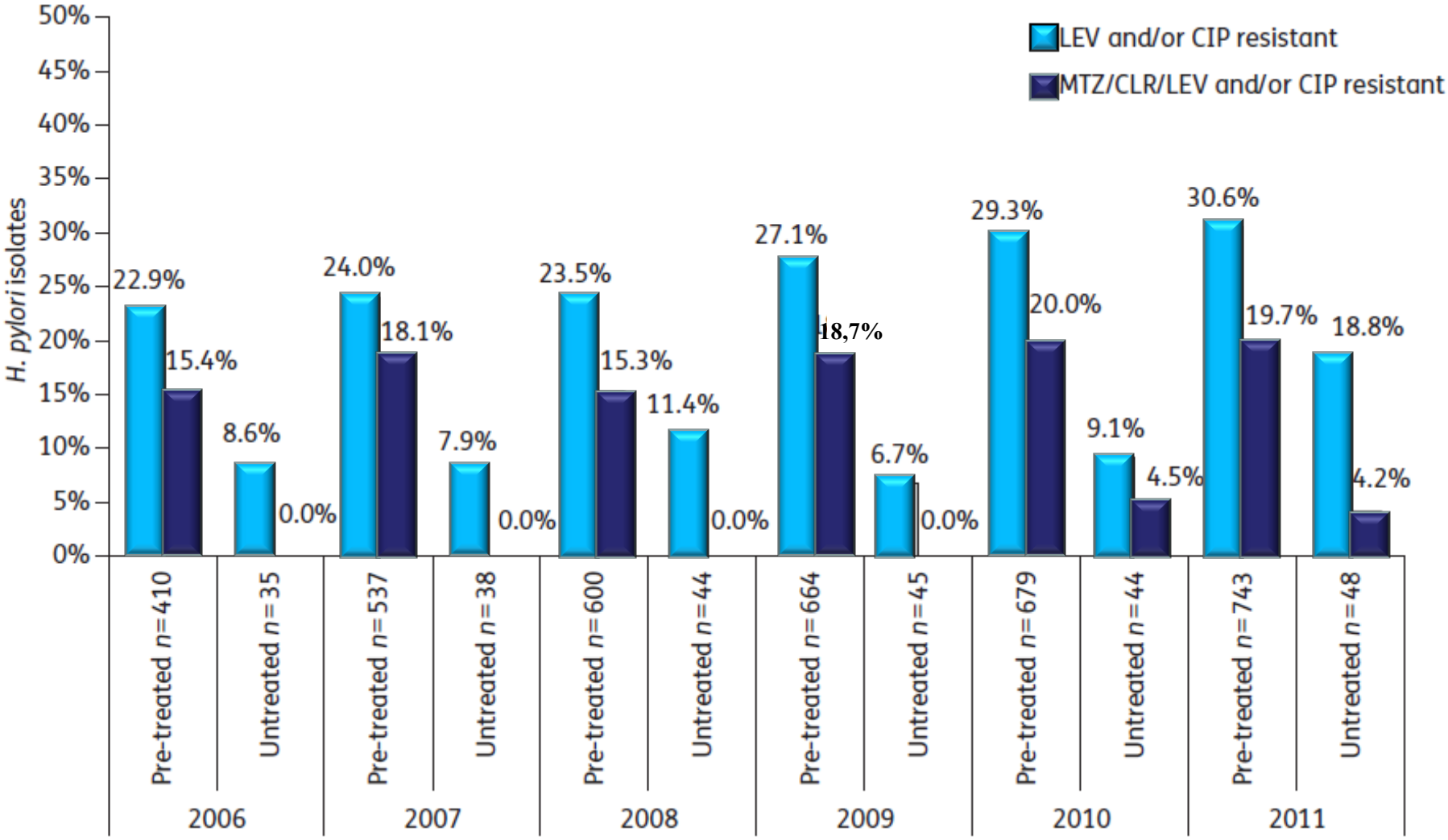
ALGORITHM FOR FIRST-LINE TREATMENT



ALGORITHM FOR SECOND-LINE TREATMENT (empirically)



Yearly percentages of quinolone and triple resistance and their dependence on prior eradication treatments.



Wueppenhorst et al. J Antimicrob Chemother 2013; 68: 1562–1566

Antimicrobial Susceptibility-Guided Therapy Versus Empirical Concomitant Therapy for Eradication of *Helicobacter pylori* in a Region with High Rate of Clarithromycin Resistance

Angel Cosme,* Jacobo Lizasoan,* Milagrosa Montes,† Esther Tamayo,† Horacio Alonso,* Usua Mendarte,* Maider Martos,* Maria Fernandez-Reyes,† Cristina Saraqueta‡ and Luis Bujanda*

Helicobacter 2016 Feb;21(1)29-34

- **Three hundred consecutive HP-infected patients received antimicrobial susceptibility-guided therapy or empirical concomitant therapy for 10 days.**

- Patients diagnosed by culture received one of three combinations of antibiotics based on susceptibility results:
- omeprazole, amoxicillin, and clarithromycin (OAC);
- omeprazole, amoxicillin, and levofloxacin (OAL);
- or omeprazole, amoxicillin, and metronidazole

Concomitant and antimicrobial susceptibility-guided eradication rates were, respectively, **87% and 94%** by intention-to-treat (p = .08) and **89% and 95%** (p = .08) per protocol per-protocol analysis.

Rifabutin Containing Triple Therapy and Rifabutin with Bismuth Containing Quadruple Therapy for Third-Line Treatment of *Helicobacter pylori* Infection: Two Pilot Studies

Antonio Francesco Ciccaglione,* Roberta Tavani,* Laurino Grossi,* Luigina Cellini,† Lamberto Manzoli‡ and Leonardo Marzio*

- Twenty-nine patients were recruited in the pantoprazole, amoxicillin, rifabutin group
- 30 in the pantoprazole, amoxicillin, rifabutin, and bismuth subcitrate group.
- H. pylori sensitivity to rifabutin and amoxicillin.
- 18/27 (66.7%, 95% CI: 47.7–85.7%) in the pantoprazole, amoxicillin, rifabutin group
- **28/29 (96.6%, 95% CI: 89.5–100.0%) in the pantoprazole, amoxicillin, rifabutin, and bismuth subcitrate group**

colloidal bismuth subcitrate → resulted in a 30% therapeutic gain

www.hsinitiative.org

H. pylori is the director of the Gut microbiota orchestra