Helicobacter pylori-Induced Gastric Cancer in 2013: Where Are We Going?

Rick Peek
Vanderbilt University
Host responses to *H. pylori* virulence constituents influence carcinogenesis

Gastric inflammation

Decades

Distal gastric adenocarcinoma
Gastric Cancer
Adenocarcinoma of the Stomach

Second leading cause of cancer-related death worldwide

660,000 cases/year
Progression to Gastric Cancer

Non-colonized mucosa → Non-atrophic gastritis → Atrophic gastritis → Intestinal metaplasia → Dysplasia → Gastric adenocarcinoma
Analysis of Gastric Cancer Development with Respect to Treatment

Cumulative incidence (%)

Follow-up, months

Log-Rank $P = .33$

Wong et al., JAMA
Analysis of Gastric Cancer Development with Respect to Treatment in Patients without Premalignant Lesions

Cumulative incidence (%)

Follow-up, months

Wong et al., *JAMA*
Long-term follow-up of persons treated for *H. pylori* infection

![Graph showing the intensity of gastric premalignant lesions over years of follow-up for different groups: H. pylori-infected, untreated, H. pylori-infected, treatment failure, and H. pylori-infected, successful eradication.](image)

*CCR Biology Behind*

Mera et al., *Gut*
Design of Shandong Intervention Trial

- 4010 subjects
- 3599 endoscoped subjects invited to participate
- 3365 randomly assigned and eligible
- 2258 $H. pylori$-seropositive subjects
  - 2x2x2 factorial trial
  - Antibiotics, vitamins, and garlic
- Initial trial follow-up ended on May 1, 2003
- Extended follow-up ended on August 1, 2010
Estimated odds ratios for gastric cancer incidence for *H. pylori*-, garlic-, or vitamin-treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>OR</th>
<th>(95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. pylori</em></td>
<td>0.61</td>
<td>(0.38-0.96)</td>
<td>0.032</td>
</tr>
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<td>Garlic</td>
<td>0.80</td>
<td>(0.53-1.20)</td>
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<td>Vitamin</td>
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Ma et al., *JNCI*, 2012
Estimated odds ratios for gastric cancer incidence for *H. pylori*-, garlic-, or vitamin-treatment

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Ma et al., *JNCI*, 2012
### Combined analysis of *H. pylori* treatment effects on gastric cancer (GC) incidence in randomized trials

<table>
<thead>
<tr>
<th>First author</th>
<th>No. of patients <em>H. pylori</em> treatment</th>
<th>No. of patients placebo</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Correa, 2000</td>
<td>3/491</td>
<td>2/485</td>
<td>RR 0.66</td>
</tr>
<tr>
<td>Wong, 2004</td>
<td>7/817</td>
<td>11/813</td>
<td></td>
</tr>
<tr>
<td>Saito, 2005</td>
<td>2/379</td>
<td>52/1128</td>
<td>95% CI 0.42-0.81</td>
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<tr>
<td>Ma, 2012</td>
<td>34/2817</td>
<td>68/2739</td>
<td></td>
</tr>
</tbody>
</table>

Ma et al., *JNCI*, 2012
Host responses to *H. pylori* virulence constituents influence carcinogenesis.

Gastric inflammation

Decades

Distal gastric adenocarcinoma (1-3%)
Determinants which may influence occurrence of disease among *H. pylori*-colonized persons

- Strain variation
- Host genotypes
- Environmental co-factors
- Topography of gastric colonization
Determinants which may influence occurrence of disease among *H. pylori*-colonized persons

**Strain variation**

Host genotypes

Environmental co-factors

Topography of gastric colonization
Phylogeography of *H. pylori*

Linz et al., *Nature*
Molecular signaling alterations induced by intracellular CagA
Determinants which may influence occurrence of disease in *H. pylori*-colonized persons

- Strain variation
- **Host genotypes**
- Environmental co-factors
- Topography of gastric colonization
Determinants which may influence occurrence of disease in \textit{H. pylori}-colonized persons

Strain variation

\textbf{Host genotypes}

Environmental co-factors

\textbf{Topography of gastric colonization}
Pathophysiologic outcomes of chronic *H. pylori* infection

*H. pylori* infection

**Simple gastritis phenotype**
Majority of subjects
Mixed mild gastritis

**Duodenal ulcer phenotype**
Antral predominant gastritis
High gastrin & acid secretion

**Gastric cancer phenotype**
Corpus predominant gastritis
High gastrin
Hypochlorhydria

PPI
Host factors and *H. pylori*-induced carcinogenesis

*H. pylori*

Gastric acidity

Inflammation
IL-1β and *H. pylori*-induced carcinogenesis
Relationship between IL-1 polymorphisms and IL-1β production

IL-1β -31 C
IL-1β -511 T
IL-1RN 2/2 → IL-1β production

IL-1β -31 T
IL-1β -511 C
IL-1RN 1/1 → IL-1β production
IL-1 genotype frequencies in *H. pylori*-infected gastric cancer patients and controls

<table>
<thead>
<tr>
<th>Locus</th>
<th>Genotype</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1  -31</td>
<td>T/T</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>C/T</td>
<td>1.8 (1.3-2.4)</td>
</tr>
<tr>
<td></td>
<td>C/C</td>
<td>2.5 (1.6-3.8)</td>
</tr>
<tr>
<td>IL-1  -511</td>
<td>C/C</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>C/T</td>
<td>1.8 (1.3-2.4)</td>
</tr>
<tr>
<td></td>
<td>T/T</td>
<td>2.6 (1.7-3.9)</td>
</tr>
<tr>
<td>IL-1RN</td>
<td>1/1</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>1/2</td>
<td>1.2 (0.9-1.6)</td>
</tr>
<tr>
<td></td>
<td>2/2</td>
<td>3.7 (2.4-5.7)</td>
</tr>
</tbody>
</table>

El-Omar et al., *Nature*
Odds ratios from studies examining the association between *IL-1B-511* and gastric cancer

Wang et al., *Int. J. Cancer*
Association of *H. pylori* virulence and host *IL-1β* genotypes with gastric cancer

<table>
<thead>
<tr>
<th><em>H. pylori</em> and <em>IL-1</em> –511 genotypes</th>
<th>Gastritis alone (n)</th>
<th>Gastric cancer (n)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>cagA</em>–/CC</td>
<td>35</td>
<td>4</td>
<td>1 (referent)</td>
</tr>
<tr>
<td><em>cagA</em>–/T</td>
<td>46</td>
<td>8</td>
<td>1.5 (0.4-5.5)</td>
</tr>
<tr>
<td><em>cagA</em>+/CC</td>
<td>26</td>
<td>38</td>
<td>13 (4.1-40)*</td>
</tr>
<tr>
<td><em>cagA</em>+/T</td>
<td>28</td>
<td>80</td>
<td>25 (8.2-77)*</td>
</tr>
<tr>
<td><em>vacA</em> s2/CC</td>
<td>27</td>
<td>1</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td><em>vacA</em> s2/T</td>
<td>35</td>
<td>8</td>
<td>6.2 (0.7-52)</td>
</tr>
<tr>
<td><em>vacA</em> s1/CC</td>
<td>17</td>
<td>27</td>
<td>43 (5.3-345)*</td>
</tr>
<tr>
<td><em>vacA</em> s1/T</td>
<td>22</td>
<td>71</td>
<td>87 (11-679)*</td>
</tr>
</tbody>
</table>

*Figueiredo et al., JNCI*
Significance of association for SNPs and anti-\textit{H. pylori} seropositivity

Mayerle \textit{et al.}, \textit{JAMA}, 2013
TLR1 expression levels corresponding to rs10004195 TLR1 SNP

Residual mRNA expression level

Population
- Germany
- The Netherlands

Mayerle et al., JAMA, 2013
Determinants which may influence occurrence of disease in *H. pylori*-colonized persons

- Strain variation
- Host genotypes
- Environmental co-factors → salt
- Topography of gastric colonization
Salt regulates expression of *H. pylori* CagA.
Iron deficiency increases the risk for gastric carcinogenesis

Iron regulates microbial virulence and contributes to disease

*H. pylori* infection is associated with iron deficiency

Iron deficiency is associated with a high incidence of Preneoplastic gastric lesions

Gastric adenocarcinoma
Dietary iron depletion increases gastric dysplasia and cancer in rodents
Iron depletion augments assembly of the cag type IV secretion system
Iron deficiency parallels the severity of *H. pylori*-induced premalignant lesions in human populations.
*H. pylori* isolated from patients with low ferritin levels induce increased levels of pro-inflammatory cytokines.

![Bar chart showing IL-8 protein levels in high and low ferritin groups](chart.png)

- **High ferritin**
  - IL-8 protein (fold over control): 4

- **Low ferritin**
  - IL-8 protein (fold over control): 6

**P < 0.005**
H. pylori-induced gastric cancer: an axis of evil

- Microbial constituents
- Host effectors
- Environmental co-factors
## Estimated odds ratios for gastric cancer incidence for *H. pylori*-treatment, garlic-, or vitamin-treatment

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<tr>
<th>Treatment</th>
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<td>Vitamin</td>
<td>0.81 (0.54-1.22)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Ma et al., *JNCI*, 2012
Shandong Intervention Trial

Efficacy of *H. pylori* eradication therapy at 15 years of follow-up: 47%
What are the roles of non-\textit{H. pylori} constituents of the gastric microbiota in disease outcome?
Compositional differences in the gastric microbiome with and without *H. pylori*

Gastric microbiota in *H. pylori*-infected and uninfected mice

Lofgren et al., *Gastroenterology*, 2011

% of total bacterial sequences

- Actinobacteria
- Bacteroidetes
- Cyanobacteria
- Proteobacteria
- Firmicutes

Controls vs. Infected
Gastric intraepithelial neoplasia (GIN) in conventionally housed (SPF) versus germ-free mice

Incidence %

- H. pylori + SPF
- H. pylori + Germ Free

Lofgren et al., *Gastroenterology*, 2011
Experimental design for altering the microbiota with and without *H. pylori* challenge

<table>
<thead>
<tr>
<th>Control</th>
<th>8 days Pen/Strep</th>
<th>4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>+/- <em>H. pylori</em></td>
<td>+/- <em>H. pylori</em></td>
<td>+/- <em>H. pylori</em></td>
</tr>
</tbody>
</table>

Rolf et al., *Infect Immun*, 2013
T-cell responses to *H. pylori* in the presence or absence of antibiotics

Rolig et al., *Infect Immun*, 2013

% of total

<table>
<thead>
<tr>
<th></th>
<th>CD4</th>
<th>CD8</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. pylori +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics -</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reconstituted -</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Total gastric mRNA expression of \( \text{Ifn} \gamma \)

\[
\begin{array}{c|c|c|c}
H. pylori & + & + & + \\
\text{Antibiotics} & - & + & + \\
\text{Reconstituted} & - & - & + \\
\end{array}
\]

\( \text{Ifn} \gamma \) fold increase

\( * \)
Distribution of operational taxonomic units (OTUs) from bacterial DNA integrations in gastric adenocarcinoma

% reads from bacterial OTUs

Riley et al., PLoS Comp Bio, 2013
Multi-decade development of gastric adenocarcinoma initiated by *H. pylori*

Plottel and Blaser, *Cell Host and Microbe*, 2013
Is there a role for extragastric microbiome influences on \( H. pylori \)-induced host responses with carcinogenic potential?
Concurrent intestinal *Helicobacter* infection attenuates gastric injury induced by *H. pylori*

Lemke et al., *Infect Immun*
Species-specific effect of concurrent enterohepatic *Helicobacter* infection on *H. pylori*-induced gastric injury

Ge et al., *Infection and Immunity*, 2011
Are there additional reasons that mitigate against widespread test and treat strategies for *H. pylori*?
Complications of Gastroesophageal Reflux Disease

- Gastroesophageal Reflux Disease
- Barrett’s Esophagus
- Dysplasia
- CA

↑ Severity
↓ Frequency
## Association of Barrett’s metaplasia with *H. pylori* status and associated conditions

<table>
<thead>
<tr>
<th></th>
<th>Barrett’s</th>
<th></th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>76,475</td>
<td>2510</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><em>H. pylori</em> (-)</td>
<td>67,119</td>
<td>2366</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td><em>H. pylori</em> (+)</td>
<td>9356</td>
<td>144</td>
<td>0.42</td>
<td>0.35-0.49</td>
</tr>
<tr>
<td>Gastritis (-)</td>
<td>65,521</td>
<td>2317</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Gastritis (+)</td>
<td>10,954</td>
<td>193</td>
<td>0.47</td>
<td>0.41-0.55</td>
</tr>
</tbody>
</table>

Sonnenberg, et al., *Gastroenterology*, 2010
Association of esophageal adenocarcinoma with carriage of *H. pylori*, by *cagA* status

<table>
<thead>
<tr>
<th>Subject status</th>
<th>Number of controls</th>
<th>Number of cancer cases</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>- -</td>
<td>138</td>
<td>91</td>
<td>1.0</td>
<td>-</td>
</tr>
<tr>
<td>+ -</td>
<td>40</td>
<td>26</td>
<td>1.1</td>
<td>0.6-2.1</td>
</tr>
<tr>
<td>+ +</td>
<td>46</td>
<td>12</td>
<td>0.4</td>
<td>0.2-0.9</td>
</tr>
</tbody>
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Chow et al., *JNCI*
Association between *H. pylori* and esophageal adenocarcinoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oberg</td>
<td>0.95 (0.35, 2.65)</td>
</tr>
<tr>
<td>Peek</td>
<td>0.81 (0.32, 2.07)</td>
</tr>
<tr>
<td>Vieth</td>
<td>0.48 (0.33, 0.69)</td>
</tr>
<tr>
<td>Weston</td>
<td>0.22 (0.06, 0.78)</td>
</tr>
<tr>
<td>El Omar</td>
<td>0.72 (0.44, 1.17)</td>
</tr>
<tr>
<td>Wu</td>
<td>0.87 (0.53, 1.43)</td>
</tr>
<tr>
<td>Ye</td>
<td>0.35 (0.20, 0.60)</td>
</tr>
<tr>
<td>de Martel</td>
<td>0.61 (0.32, 1.17)</td>
</tr>
<tr>
<td>Anandasabapathy</td>
<td>0.38 (0.10, 1.41)</td>
</tr>
<tr>
<td>Siman</td>
<td>0.48 (0.13, 1.81)</td>
</tr>
<tr>
<td>Anderson</td>
<td>0.49 (0.32, 0.77)</td>
</tr>
<tr>
<td>Derakhshan</td>
<td>0.32 (0.10, 1.02)</td>
</tr>
<tr>
<td>Fruh</td>
<td>0.76 (0.43, 1.34)</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td><strong>0.56 (0.46, 0.68)</strong></td>
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</table>

Islami et al., *Cancer Prev Res*
Association between *H. pylori* and esophageal squamous cell carcinoma

<table>
<thead>
<tr>
<th>Author</th>
<th>Odds Ratio (95% CI)</th>
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<tbody>
<tr>
<td>Talley</td>
<td>1.55 (0.80, 3.00)</td>
</tr>
<tr>
<td>El Omar</td>
<td>2.11 (1.15, 3.90)</td>
</tr>
<tr>
<td>Wang KX</td>
<td>1.25 (0.73, 2.15)</td>
</tr>
<tr>
<td>Ye</td>
<td>0.92 (0.57, 1.47)</td>
</tr>
<tr>
<td>Wu</td>
<td>0.37 (0.22, 0.62)</td>
</tr>
<tr>
<td>Wang Z</td>
<td>1.97 (1.11, 3.51)</td>
</tr>
<tr>
<td>Itijima</td>
<td>1.40 (0.62, 3.15)</td>
</tr>
<tr>
<td>Kamangar</td>
<td>1.11 (0.85, 1.45)</td>
</tr>
<tr>
<td>Siman</td>
<td>0.61 (0.29, 1.45)</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>1.10 (0.78, 1.55)</td>
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Islami et al., *Cancer Prev Res*
Association between CagA$^+$ *H. pylori* and esophageal adenocarcinoma

El Omar 0.33 (0.12, 0.87)
Wu 0.70 (0.36, 1.38)
Ye 0.26 (0.14, 0.49)
de Martel 0.49 (0.21, 1.11)
Siman 0.41 (0.10, 1.76)
Overall (95% CI) 0.41 (0.28, 0.62)

Islami et al., *Cancer Prev Res*
Association between CagA- *H. pylori* and esophageal adenocarcinoma

<table>
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<tr>
<th>Study</th>
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<tbody>
<tr>
<td>El Omar</td>
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<tr>
<td>Wu</td>
<td>0.97 (0.56, 1.66)</td>
</tr>
<tr>
<td>Ye</td>
<td>1.73 (0.58, 5.13)</td>
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<tr>
<td>de Martel</td>
<td>0.79 (0.33, 1.87)</td>
</tr>
<tr>
<td>Siman</td>
<td>0.96 (0.09, 10.58)</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>1.10 (0.78, 1.55)</td>
</tr>
</tbody>
</table>

Islami et al., *Cancer Prev Res*
Association of *H. pylori* status with asthma

<table>
<thead>
<tr>
<th><em>H. pylori/CagA</em></th>
<th>Asthma status</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never (n)</td>
<td>Current (n)</td>
</tr>
<tr>
<td>-/-</td>
<td>3613</td>
<td>296</td>
</tr>
<tr>
<td>+/-</td>
<td>1330</td>
<td>98</td>
</tr>
<tr>
<td>+/+</td>
<td>2115</td>
<td>131</td>
</tr>
</tbody>
</table>

Chen and Blaser, *Arch Int Med*
## Association of *H. pylori* status with asthma, stratified by age

Chen and Blaser, *Arch Int Med*

<table>
<thead>
<tr>
<th><em>H. pylori/CagA</em></th>
<th>Age at Onset ≤15 yrs</th>
<th></th>
<th>Age at Onset &gt;15 yrs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n OR (95% CI)</td>
<td>n OR (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-/-</td>
<td>149 1</td>
<td>129 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+/-</td>
<td>34 0.97 (0.65-1.45)</td>
<td>57 0.95 (0.68-1.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+/+</td>
<td>38 0.63 (0.43-0.93)</td>
<td>86 0.97 (0.72-1.32)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Reciprocity between \textit{H. pylori} colonization and disease states

- Childhood diarrheal diseases
- Tuberculosis
- Obesity
- Stroke mortality
Who should be tested and treated for *H. pylori*?
Indications among *H. pylori*-infected persons for antimicrobial therapy

Peptic ulcer disease
Gastric MALToma
Family history of gastric cancer
Hypertrophic gastritis (Menetrier’s)
Prior to long-term NSAID use
Non-ulcer dyspepsia
Prior to long-term PPI use
Atrophy/intestinal metaplasia/dysplasia
Conclusions

Complex human diseases such as gastric cancer are multifactorial, and their pathogenesis combines effects of microbial, host and environmental factors
Conclusions

Test and treat strategies for the indiscriminant elimination of *H. pylori* in the United States are not supported by current data unless a defined risk factor is present.
Distribution of bacterial OTUs from the microbiome and bacterial DNA integrations in stomach adenocarcinoma

Riley et al., PLoS Comp Bio, 2013
Distribution of bacterial OTUs from the microbiome and bacterial DNA integrations in stomach adenocarcinoma

Riley et al., PLoS Comp Bio, 2013
Atrophy in relation to $IL-1B-511$ genotype in Japanese patients

Furuta et al., Gastroenterology
Median gastric juice pH stratified by *IL-1B* genotype

![Bar chart showing gastric juice pH for C/C, C/T, and T/T genotypes.](image-url)
Phylotype frequencies of clones from gastric specimens (n=23 patients)

Bik et al., PNAS
Characterization of esophageal microbiome by populations

Yang et al., *Gastroenterology*, 2009
# H. pylori and gastric cancer: Key statements for prevention strategies

<table>
<thead>
<tr>
<th>Statement</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A screen-and-treat strategy of <em>H. pylori</em> should be explored in communities with a <strong>significant burden of gastric cancer</strong></td>
<td><strong>A</strong></td>
</tr>
<tr>
<td><em>H. pylori</em> eradication to prevent gastric cancer should be undertaken in <strong>populations at high risk</strong></td>
<td><strong>A</strong></td>
</tr>
</tbody>
</table>

Malfertheiner et al., *Gut*, 2012
### H. pylori and gastric cancer: Key statements for prevention strategies

<table>
<thead>
<tr>
<th>Statement</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. pylori</em> eradication for gastric cancer prevention is cost-effective in certain communities with a <strong>high risk for gastric cancer</strong></td>
<td>B</td>
</tr>
<tr>
<td><em>H. pylori</em> eradication offers additional clinical and financial benefits in addition to gastric cancer prevention</td>
<td>A</td>
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</tbody>
</table>

Malfertheiner et al., *Gut*, 2012
Distribution of bacterial OTUs from the bacterial DNA integrations in gastric adenocarcinoma

Riley et al., PLoS Comp Bio, 2013

- 83% Proteobacteria
- 17% Unassigned bacteria
- 4% Non-Proteobacterial species
Comparison of three fully sequenced *H. pylori* strains

<table>
<thead>
<tr>
<th>Feature</th>
<th>Strain</th>
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<tbody>
<tr>
<td></td>
<td>26695</td>
</tr>
<tr>
<td>Size (Mb)</td>
<td>1.7</td>
</tr>
<tr>
<td>Predicted # of ORFs</td>
<td>1590</td>
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<td>Strain-specific ORFs</td>
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</table>
Genetic heterogeneity among *H. pylori* strains

56 *H. pylori* strains

*H. pylori* DNA microarray

1150 genes (75%) "core" genome

381 genes (25%) "variable" genome

Gressman et al., *PLoS Genetics*
Chronology of *H. pylori* strain J99

**Year:**
- 1994: Original isolation
- 1999: Complete sequence published
- 2000: New isolates (n=30) harvested from source patient

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- 1994: Original isolation
- 1999: Complete sequence published
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**Genetic diversity:**
- RAPD PCR
- Sequence analysis
- *H. pylori* whole genome microarray

<table>
<thead>
<tr>
<th>Region</th>
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<tr>
<td>Cardia</td>
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<td>Corpus</td>
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<tr>
<td>Antrum</td>
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<tr>
<td>Duodenum</td>
<td>5</td>
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</table>
Microarray-generated cluster diagram of archival J99 and 13 recent J99 isolates

Israel and Peek, *PNAS*
\textit{H. pylori} eradication to prevent gastric cancer should be considered in the following:

First-degree relatives of family members with a diagnosis of gastric cancer

Patients with previous gastric neoplasia already treated by endoscopic or subtotal gastric resection

Patients with a risk of severe pan-gastritis, corpus-predominant gastritis, severe atrophy

Malfertheiner et al., \textit{Gut}, 2012
Cancer incidences in Japanese migrants to Hawaii

Kolonel et al., Nat Rev Cancer
*H. pylori* eradication to prevent gastric cancer should be considered in the following:

Patients on chronic gastric acid inhibition for more than 1 year

Patients with strong environmental risk factors for gastric cancer (heavy smoking, high exposure to dust, coal, quartz, cement and/or work in quarries)

*H. pylori*-positive patients with a fear of gastric cancer

Malfertheiner et al., *Gut*, 2012
H. pylori eradication to prevent gastric cancer should be considered in the following:

Possibly First Generation migrants from regions with a high incidence of gastric cancer
What factors dictate pathologic outcomes that develop within the context of *H. pylori* infection?
Gastric cancer mortality by geographic locale

Hatakeyama, *Nature*
Divergent IL-17 expression levels induced by *H. muridarum* versus *H. hepaticus*

*Ge et al., Infection and Immunity, 2011*
Factors to be considered for prevention strategies include:

The incidence of gastric cancer in the community to be targeted

Likely future trends in cancer incidence if intervention is not employed

The availability of primary care facilities and other logistics

Malfertheiner et al., *Gut*, 2012
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