*Annals of Gastroenterology* (2021) **34,** 451-452

# Merging *Helicobacter pylori* eradication and family history-based genetic counseling in patients with gastric cancer: towards an overarching approach in clinical practice

**Alexios-Fotios A. Mentis[a], Theodore Rokkas[b]**

Hellenic Pasteur Institute; Henry Dunant Hospital, Athens, Greece

*Helicobacter pylori* (*H. pylori*) represents the prototype chronic infection of the gastric and potentially the gastrointestinal system, and it is a key model for studying microbially-induced oncogenesis in humans [1,2]. *H. pylori* is now a well-established risk factor for gastric cancer [3], especially through the action of certain microbial genes, such as CagA [4], whereas its eradication has been robustly linked to gastric cancer reduction, especially for those harboring non-atrophic or atrophic gastritis as precancerous lesions [5]. Although perhaps not oft-discussed in daily practice, a family history of gastric cancer is also a major contributing factor [6].

A recent study by Choi *et al* assessed whether *H. pylori* eradication can reduce the risk for gastric cancer in individuals with a family history of this cancer type in first-degree relatives [7]. The study built upon previous systematic findings that first-degree relatives of patients with gastric cancer present with a higher risk of developing gastric cancer themselves, as evidenced both by *H. pylori* prevalence rates *per se* and by markers of gastric atrophy and intestinal metaplasia [8]. In that novel study, the authors showed a statistically significant difference in the proportion of patients developing gastric cancer between those treated for *H. pylori* and those who did not receive any treatment (1.2% vs. 2.7%, hazard ratio 0.45, 95% confidence interval 0.21-0.94; P=0.03) [7]. These results imply that the risk posed by having a family history of gastric cancer can be mitigated by addressing an environmental (in this case, microbial) factor [7]. Nonetheless, they should be interpreted with caution, especially upon considering some methodological caveats in this study, which diminish their broader clinical usefulness (as observed in other *H. pylori*-related studies [9]). Specifically, the family history of gastric cancer was defined as *having at least one first-degree relative with gastric cancer whose diagnosis had been histologically confirmed* [7]. However, no search for variants in well-established oncogenes and tumor suppressor genes and, in turn, no stratification based on such genetic biomarkers (e.g., *E-cadherin* or *ARID1A*) were performed in that study. Doing so would have allowed a more robust genetic confirmation of gastric cancer predisposition [10-12].

Moving forward, a broader question arises, important for clinical practice and clinical cancer genetics counseling: is having a first-degree relative with gastric cancer a sufficient criterion for family history? This question is crucial, not only from a clinical, cancer genetics viewpoint, but also when viewed in the context of *H. pylori*. In many family settings, previous studies have observed the intrafamilial presence of phylogenetically identical *H. pylori* strains (as assessed by rRNA gene patterns, called *ribopatterns*) [13]. Regardless of whether these findings are explained by person-to-person transmission or, alternatively, by the presence of a common source of infection, they collectively highlight the potential for intrafamilial transmission of *H. pylori* [13]. Mother-to-child and sibling-to-sibling transmission have also been reported [14]. Therefore, could this intrafamilial transmission of *H. pylori* strains contribute to the family history of gastric cancer?

On this basis, future studies considering the ties between a family history of gastric cancer and *H. pylori* eradication should also assess the molecular subtypes (e.g., analysis of CagA and the CagA-associated EPIYA polymorphisms [15]) and potential clonality of *H. pylori* strains, both in the examined individuals and in their first-degree affected relatives. Such study designs could ultimately contribute to a *precision oncomicrobiology* approach (for further description, see [1]) and could have far-reaching implications.

*H. pylori* infection is a communicable disorder (i.e., an infectious disease), whereas gastric cancer is considered a chronic, non-communicable disease. Thus, the suggestion that intrafamilial transmission of *H. pylori* contributes to shared strain-induced common gastric cancer needs to be validated in independent settings before concrete clinical guidelines are formulated; nevertheless, the *margins* between the notion of *communicable* and *non-communicable* diseases would become looser if that scenario is validated. Besides, the idea that non-communicable diseases may in fact be *communicable* is not novel; this notion has been previously suggested in different contexts and settings [16,17].

In conclusion, the study by Choi *et al* highlights that *H. pylori* eradication is of merit even in the presence of a family history of cancer; however, the methodological criteria implemented in this study should be viewed with caution

[a]Public Health Laboratories, Hellenic Pasteur Institute (Alexios-Fotios A. Mentis); [b]Gastroenterology Clinic, Henry Dunant Hospital (Theodore Rokkas), Athens, Greece

Conflict of Interest: None

Correspondence to: Dr. Alexios-Fotios A. Mentis, MD, MPH, PgCert, Public Health Laboratories, Hellenic Pasteur Institute, Athens, Greece, e-mail: amentis1@jhu.edu

Received 15 November 2020; accepted 23 November 2020; published online

DOI: https://doi.org/10.20524/aog.2021.0589

before conclusive clinical guidelines are established. More importantly, clinical gastroenterologists should work closely with both clinical molecular geneticists and clinical molecular microbiologists to offer an *overarching* approach in clinical practice, by concurrently considering: (a) the family's genetic predisposition to gastric cancer; and (b) oncogenesis-related microbial genetic features of *H. pylori* strains isolated from these patients.

## References


1. Mentis AA, Boziki M, Grigoriadis N, Papavassiliou AG. *Helicobacter pylori* infection and gastric cancer biology: tempering a double-edged sword. *Cell Mol Life Sci* 2019;**76**:2477-2486.
2. Sgouras D, Tegtmeyer N, Wessler S. Activity and functional importance of *Helicobacter pylori* virulence factors. *Adv Exp Med Biol* 2019;**1149**:35-56.
3. Uemura N, Okamoto S, Yamamoto S, et al. *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med* 2001;**345**:784-789.
4. Yamaoka Y, El-Zimaity HM, Gutierrez O, et al. Relationship between the cagA 3' repeat region of *Helicobacter pylori*, gastric histology, and susceptibility to low pH. *Gastroenterology* 1999;**117**:342-349.
5. Rokkas T, Rokka A, Portincasa P. A systematic review and meta-analysis of the role of *Helicobacter pylori* eradication in preventing gastric cancer. *Ann Gastroenterol* 2017;**30**:414-423.
6. Yaghoobi M, Bijarchi R, Narod SA. Family history and the risk of gastric cancer. *Br J Cancer* 2010;**102**:237-242.
7. Choi IJ, Kim CG, Lee JY, et al. Family history of gastric cancer and *Helicobacter pylori* treatment. *N Engl J Med* 2020;**382**:427-436.
8. Rokkas T, Sechopoulos P, Pistiolas D, Margantinis G, Koukoulis G. *Helicobacter pylori* infection and gastric histology in first-degree relatives of gastric cancer patients: a meta-analysis. *Eur J Gastroenterol Hepatol* 2010;**22**:1128-1133.
9. Mentis AA, Dardiotis E. *Helicobacter pylori* eradication for metachronous gastric cancer: an unsuitable methodology impeding broader clinical usage. *Front Oncol* 2019;**9**:90.
10. Wang K, Kan J, Yuen ST, et al. Exome sequencing identifies frequent mutation of ARID1A in molecular subtypes of gastric cancer. *Nat Genet* 2011;**43**:1219-1223.
11. Hansford S, Kaurah P, Li-Chang H, et al. Hereditary diffuse gastric cancer syndrome: CDH1 mutations and beyond. *JAMA Oncol* 2015;**1**:23-32.
12. Guilford P, Hopkins J, Harraway J, et al. E-cadherin germline mutations in familial gastric cancer. *Nature* 1998;**392**:402-405.
13. Georgopoulos SD, Mentis AF, Spiliadis CA, et al. *Helicobacter pylori* infection in spouses of patients with duodenal ulcers and comparison of ribosomal RNA gene patterns. *Gut* 1996;**39**:634-638.
14. Kivi M, Tindberg Y, Sörberg M, et al. Concordance of *Helicobacter pylori* strains within families. *J Clin Microbiol* 2003;**41**:5604-5608.
15. Sougleri IS, Papadakos KS, Zadik MP, Mavri-Vavagianni M, Mentis AF, Sgouras DN. *Helicobacter pylori* CagA protein induces factors involved in the epithelial to mesenchymal transition (EMT) in infected gastric epithelial cells in an EPIYA-phosphorylation-dependent manner. *FEBS J* 2016;**283**:206-220.
16. Wainberg ML, Helpman L, Duarte CS, et al. Curtailing the communicability of psychiatric disorders. *Lancet Psychiatry* 2018;**5**:940-944.
17. Christakis NA, Fowler JH. The collective dynamics of smoking in a large social network. *N Engl J Med* 2008;**358**:2249-2258.


# Erratum

In the article *Koutri et al*, "*Distribution of eosinophils in the gastrointestinal tract of children with no organic disease*" *Ann Gastroenterol 2020 Sep-Oct;33(5):508-515. doi: 10.20524/aog.2020.0518*, the authors made unintentional errors in the reported areas of high power fields of the microscopes used for the assessment of eosinophil density of the GI tract: the correct numbers were 0.306 eos/mm$^2$ for the Madrid and Rome centers and 0.196 eos/mm$^2$ for the Athens center. The article has been corrected online.

DOI: https://doi.org/10.20524/aog.2021.0627