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

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*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 microbiologically-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.

**Conflict of Interest:** None

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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.

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### 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.

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