

editorial Totally Unexpected: Nonsyndromic *CDH1* Mutations and Hereditary Diffuse Gastric Cancer Syndrome

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The amazingly rapid advances in next-generation DNA sequencing technologies and decrease in costs have affected all aspects of clinical medicine, but perhaps none so much as the approach to hereditary cancer susceptibility genetic testing. One of the most important areas of precision oncology, the determination of pathogenic germline cancer gene mutations, contributes to individual risk assessment and screening strategies, prevention, and therapeutic approaches to cancer.

However, the advent of and access to multigene panel testing has dramatically shifted the approach to genetic testing away from the focused testing of selected patients for specific high-risk cancer syndromes, to testing most patients simultaneously for multiple high-risk cancer syndromes as well as moderate-risk cancer-associated genes.¹ Although this has clearly resulted in significant increases in the identification of individuals at risk, it has also led to clinical conundrums regarding management of nonsyndromic carriers of an unexpected or unanticipated genetic mutation (UGM), as has been widely discussed.²

The poster child for an anxiety-inducing cancer UGM is *CDH1*, a gene which when found in families meeting criteria for hereditary diffuse gastric cancer (HDGC) confers a high risk for often incurable signet-ring gastric cancer at a young age, for which no demonstrated screening techniques exist, and for which the only effective clinical approach to prevention is a prophylactic total gastrectomy that, in nearly all published cases, has shown multifocal early diffuse gastric cancer.³ Because inherited *CDH1* mutations also predispose women to lobular breast cancer, it is now included on many multigene panels that are often ordered largely on the basis of a personal or family history of breast cancer.

Increasingly, individuals are found to be carriers of known pathogenic *CDH1* mutations but without a family history fitting the International Gastric Cancer Linkage Consortium (IGCLC)-accepted definition of HDGC.⁴ Therefore, the perfect

storm during a Friday afternoon genetics clinic is the question of what to advise for a healthy middle-aged woman with a family history of ductal breast cancer, who is now found to be a *CDH1* germline mutation carrier—a prophylactic gastrectomy, regular if ineffective endoscopic screening, or nothing? To answer this, it is critical to determine the actual risk of gastric cancer in *CDH1* carriers who do not meet IGCLC criteria for HDGC.

In the article accompanying this editorial, Lowstuter et al⁵ report the first published series of individuals with UGMs in *CDH1*. Their study is large and includes nearly 27,000 patients who underwent multigene panel testing (including *CDH1*) over a 2-year period at Ambry Genetics, an established commercial diagnostic laboratory, and > 300 patients who had panel testing through the University of Southern California high-risk cancer genetics clinic. Of these patients, 0.06% and 1.26%, respectively, were found to have pathogenic germline *CDH1* mutations, and more than half of mutation carriers from each group did not meet HDGC criteria, thus being UGMs.

An important strength of this study is the introduction of a formal classification for those cases that do not meet IGCLC HDGC criteria. These cases are divided into patients with IGCLC-partial phenotype, who exhibit some hint of HDGC in their family, such as individuals with gastric cancer, lobular breast cancer at older ages, or even lobular carcinoma in situ; and patients who are IGCLC-negative, who have no evidence of gastric cancer or lobular breast cancer in their family.

Using this nomenclature, one-quarter of both the laboratory- and clinic-based *CDH1* carriers were IGCLC-negative (although the results from the laboratory-based group must be considered preliminary, because the patients' family histories were obtained from the ordering form rather than through genetic counselor-derived pedigrees). At this point, none of these five individuals have

James M. Ford

Stanford University School of Medicine, Stanford, CA

Corresponding author: James M. Ford, MD, Clinical Cancer Genetics Program, Division of Oncology, Departments of Medicine and Genetics, Stanford University School of Medicine, Stanford, CA 94305-5151; e-mail: jmf@stanford.edu.

undergone a prophylactic gastrectomy nor have they reported having received a subsequent cancer diagnosis. Thus, we cannot speculate on their potential risk for early gastric cancer, despite their lack of a suggestive family history.

However, three of the 10 patients with IGCLC-partial phenotype underwent prophylactic gastrectomy procedures, and all had early gastric cancer (one patient as young as 39 years). Although this article does not fully answer what to do for the patient who was the subject of our Friday afternoon genetics clinic, it does provide important insights into how to approach these difficult decisions and what additional information we need to do so with greater confidence.

Certainly, those *CDH1* mutation carriers with any personal or family history of gastric or lobular breast cancer, even if they do not meet IGCLC criteria for HDGC, should at least consider a prophylactic gastrectomy. However,

for those individuals who are truly IGCLC-negative after a comprehensive family history is taken by a skilled genetic counselor, it is difficult to recommend such an invasive procedure. Both groups should definitely have regular endoscopic screening with blind biopsies, and proceed to gastrectomy if any malignant cells are identified.⁴

Finally, all of these recommendations go out the window if and when a case of a true IGCLC-negative *CDH1* carrier develops gastric cancer or has a prophylactic gastrectomy that identifies early gastric cancer. For this reason, it is critical that such UGM *CDH1* carriers are closely followed and that their clinical outcomes reported, gathered in registries, and published. We are totally committed to doing just that in *JCO Precision Oncology*.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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James M. Ford

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