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Establishing a center of excellence for hereditary diffuse gastric cancer syndrome

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Gastric adenocarcinoma, although rare in the United States, is quite common worldwide. While most cases appear sporadically and are attributed to both environmental and host factors, approximately 1% to 3% of incident cases are due to a heritable cancer syndrome. The most common inherited gastric cancer syndrome is caused by a germline mutation in the *CDH1* tumor suppressor gene, which encodes for the cell adhesion molecule E-cadherin.[1] The resulting autosomal dominant pattern of increased gastric and lobular breast cancer risk has been termed hereditary diffuse gastric cancer (HDGC) syndrome. Current consensus guidelines suggest that patients with a personal or family history of diffuse gastric cancer and/or lobular breast cancer undergo genetic testing.[2] If a pathogenic germline *CDH1* mutation is detected, patients are recommended to undergo risk-reducing total gastrectomy due to the 56% to 70% cumulative lifetime risk of developing gastric cancer.[3] For many newly diagnosed patients, the next step in their medical care can be uncertain.

Cancer care is disease based, not discipline based. Therefore, an integrated multidisciplinary team of experts is considered the *sine qua non* of cancer treatment. Although guidelines exist for cancer screening and risk-reducing surgery in HDGC syndrome,[2] there is little guidance for patients or their physicians. Since clinical decision making in this syndrome centers around cancer risk-reduction, many patients search first for a surgeon. The American

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College of Surgeons (ACS), through their quality programs platform, has partnered with accrediting bodies in a variety of medical specialties to create care standards, assist with treatment infrastructure, and collect outcomes data for quality improvement.[4] Such programs include the National Accreditation Program for Rectal Cancer and the National Accreditation Program for Breast Centers. However, national or even international recognition and oversight is not practical for a rare cancer syndrome. Although accreditation for rare cancer syndromes is not practical, it may be helpful to achieve consensus, as with clinical guidelines,[2] on the attributes of excellence in the multidisciplinary care and study of patients with HDGC.

The authors have established an innovative gastric cancer research program to care for and study patients with HDGC and other inherited forms of stomach cancer. The program is not centered around surgery (ie, total gastrectomy), but rather comprehensive, high-quality medical care, and dedication to clinical and basic science research in gastric cancer. The components of patient-centered care is critical for maintaining excellence include genetic counseling, gastroenterology, dietetics, surgical oncology, pathology, breast oncology, clinical pharmacy, psychosocial support, nursing coordination, cancer research, and community engagement. Although no uniform standards exist to define the optimal care setting for patients with HDGC, the program described herein may serve as a model for comprehensive, high-quality care.

Certified genetics healthcare providers with expertise in hereditary cancer risk assessment are essential members of any care team. Genetic counseling and testing for HDGC are offered based on stringent criteria focused on personal and/or family history of diffuse gastric cancer.[2] However, in the era of readily available cancer gene panel testing, many patients receive germline testing without adequate genetic counseling. Genetic counselors not only obtain a comprehensive family history, but also are integral to shared decision making with patients as they grapple with the risks, benefits, costs, and timing of personalized management strategies. Genetic counselors are necessary to provide ongoing genetics education, cancer family history updates, and diagnosis of HDGC in at-risk relatives through *CDH1* cascade genetic testing. A meta-analysis of families with a hereditary gastrointestinal cancer syndrome found that only 34% to 52% of at-risk relatives underwent cascade genetic testing. Comparatively, the frequency of genetic testing among those who received genetic counseling increased to 95% in the same study,[5] indicating that genetic counseling plays a vital role in the cascade testing decision-making process.

After the diagnosis of a pathogenic germline *CDH1* mutation, adult patients are recommended to undergo a screening upper endoscopy (esophagogastroduodenoscopy [EGD]) to evaluate the stomach, irrespective of their decision to have risk-reducing gastrectomy. It is imperative that the endoscopist understands the occult nature of HDGC and the recommendation for a systematic approach to gastroscopy and biopsies. Gastroenterologists caring for these patients in centers of excellence are intimately familiar with and perform over two-dozen individual gastric mapping procedures annually. Along with the initial endoscopic evaluation, many patients have questions about diet and nutrition, relating either to specific symptoms or to concerns over an impending total gastrectomy. A registered dietitian with first-hand knowledge of preoperative nutritional assessment and

postgastrectomy sequelae is vitally important to the success of any planned operation. Additionally, a dietitian should be a permanent member of the care team as longitudinal care is a hallmark of caring for patients with HDGC.

Total gastrectomy is an uncommon procedure in the United States. Most general surgeons rarely perform the operation, leading many patients to larger medical centers. While the mortality rate after gastrectomy is low, postoperative morbidity can be high, especially in low-volume centers.[6] No set minimum for annual gastrectomy operations exists, however, evidence suggests that mortality rates after total gastrectomy decrease an annual case volume exceeds thirteen.[6] Patients should consider not only the frequency with which a surgeon performs total gastrectomy, but also a surgeon's knowledge of clinical guidelines for HDGC. Preoperative counseling should include a specific plan for postgastrectomy care as all patients should receive long-term dietary counseling, nutritional assessment, and general medical follow-up. Both inpatient recovery and outpatient care schedules are essential to successful recovery following total gastrectomy. Patients should be provided easy and frequent access to their care team, including the surgeon and dietitian, during the first 12 months postgastrectomy.

Pathologic assessment of the gastrectomy specimen may be overlooked, yet it constitutes a critical aspect of clinical care and a significant opportunity for research and improved understanding of HDGC. Guidelines for pathologic assessment after gastrectomy include the need for an expert surgical pathologist and meticulous examination of a much larger area of the stomach that would normally be performed. In accordance with consensus guidelines, the entire gastrectomy specimen is fixed, photographed, and mapped following resection. Procurement of fresh tissue for research in the operating theater is also highly recommended when available. Paraffin-embedded tissue blocks are generated from the grid-like map that is created. Thorough examination and reporting of pathologic findings should acknowledge that results are attributed based on the fullest extent of specimen analysis. All pathologic findings should be reviewed by expert pathologists along with members of the research team. Gastrectomy specimens are a valuable resource for understanding HDGC, thus fresh, frozen, and fixed tissue should all be utilized to support hereditary gastric cancer research.

Longitudinal care after total gastrectomy is critical to the health and well-being of patients with HDGC. Early and frequent postoperative evaluations with nutritional assessment are performed at regular intervals. Bone density loss can be a problem related to both calcium homeostasis and normal aging, thus bone density testing may be warranted. Female patients require annual breast MRI and mammography alternating every 6 months.[2] Additional, age-appropriate cancer screening should be offered and may provide insight into other health problems potentially related to HDGC. Quality of life, not only related to total gastrectomy, but also the diagnosis of HDGC, should be considered as an important outcome measure. Programs should offer patients and families access to psychosocial and spiritual care provided by a team dedicated to the well-being of those affected by cancer and rare diseases.

While no set of standards exist to identify centers of excellence for the treatment and study of patients with HDGC syndrome, the elements described herein can serve as a model for comprehensive, quality care. Patients should seek treatment at centers that demonstrate

expertise, high-quality surgical care in tandem with the requisite clinical expertise essential for HDGC patients well-beyond total gastrectomy. Furthermore, integrated translational and basic science research are crucial components of excellence for which patients and advocates of HDGC should consider obligatory for future success in treating this rare cancer syndrome.

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