YALE CRITERIA FOR GENETIC TESTING IN CASES OF SUSPECTED HEREDITARY DIFFUSE GASTRIC CANCER (HDGC) ARE MORE SENSITIVE THAN IGCLC AND ERN-GENTURIS CRITERIA IN A LARGE AMERICAN COHORT

Authors:

Benjamin A. Lerner, MD, MHS
Mar Giner-Calabuig, PhD
Cassidy Carraway
Marcy Richardson
Karl Krahn
Lisa Susswein
Brandie Leach
Rachid Karam
Rosa M. Xicola, PhD
Xavier Llor, MD, PhD

Background: Hereditary diffuse gastric cancer (HDGC) is an autosomal-dominant syndrome characterized by early-onset diffuse gastric cancer (DGC) and lobular breast cancer (LBC). This syndrome is most often caused by pathogenic variants in the *CDH1* gene. The International Gastric Cancer Linkage Consortium (IGCLC) developed clinical criteria for genetic testing in cases of suspected HDGC and updated them most recently in 2020. Our group previously showed these criteria to have poor sensitivity and proposed our own simpler and more sensitive Yale criteria. The European Reference Network on Genetic Tumour Risk Syndromes (ERN GENTURIS) subsequently proposed expanding the IGCLC criteria and showed its "lobular breast cancer-expanded" criteria to be more sensitive than the IGCLC criteria in a European cohort of *CDH1* mutation carriers. The purpose of this study was to compare performance of the ERN GENTURIS criteria with the IGCLC's and our Yale criteria in a large American cohort of *CDH1* mutation carriers.

Methods: Medical histories of 860 *CDH1* mutation carriers, identified predominantly by multigene panel testing at three US commercial laboratories, and their 4993 family members were reviewed. The percentage of subjects fulfilling the IGCLC criteria, the ERN GENTURIS criteria, and our Yale criteria were calculated. We made these calculations under two different conditions: first making no assumptions about unavailable pathology, then assuming gastric cancers in probands with confirmed *CDH1* mutations to be diffuse when pathology was unavailable.

Results: When making no assumptions about unavailable pathology, the Yale criteria had a sensitivity of 68.6% for *CDH1* pathogenic variants, compared with 15.0% and 27.1% for the IGCLC and ERN GENTURIS criteria, respectively. When assuming gastric cancers in probands with confirmed *CDH1* mutations to be diffuse, sensitivities were 72.2%, 21.6%, and 33.6% for the Yale, IGCLC, and ERN GENTURIS criteria, respectively.

Conclusions: In our cohort, which is the largest reported to date, the IGCLC and ERN GENTURIS criteria only called for genetic testing in a small minority of *CDH1* pathogenic variant carriers, while the Yale criteria detected a large majority. Identifying these individuals is important, as current guidelines call for prophylactic total gastrectomy or annual gastric surveillance in all *CDH1* mutation carriers. Capturing the full phenotypic spectrum of *CDH1* pathogenic variants is also crucial for developing appropriate guidance for patients with this condition. In addition to having superior sensitivity, our Yale criteria have the major advantages of not relying heavily on pathology information from family members (as it is

rarely available) and taking into consideration recommendations generated by other cancer genetics guidelines, addressing important practical issues encountered in cancer genetics clinics.

IGCLC criteria, 2020

Family criteria (FDR or SDR)

≥2 cases of gastric cancer in family, with ≥1 DGC
≥1 case of DGC at any age and ≥1 case of LBC at age <70 years, in different family members
≥2 cases of LBC in family members <50 years of age

Individual criteria

DGC at age <50 years
DGC at any age in individuals of Māori ethnicity
DGC at any age in individuals with a personal or family history (FDR) of cleft lip or cleft palate
History of DGC and LBC in same individual, both diagnosed at age <70 years
Bilateral LBC, diagnosed at age <70 years
Gastric in situ SRC or pagetoid spread of SRC in individuals <50 years of age

ERN-GENTURIS (LBC-expanded) criteria, 2023

Family criteria (FDR or SDR)

≥2 cases of gastric cancer in family, with ≥1 DGC
≥1 case of DGC at any age and ≥1 case of LBC at age <70 years, in different family members
≥2 cases of LBC in family members <50 years of age
≥2 cases of breast cancer, 1 case confirmed LBC
History of gastric cancer and breast cancer, 1 confirmed LBC regardless of age

Individual criteria

DGC at age <50 years
DGC at any age in individuals of Māori ethnicity
DGC at any age in individuals with a personal or family history (FDR) of cleft lip or cleft palate
History of DGC and LBC in same individual, both diagnosed at age <70 years
Bilateral LBC, diagnosed at age <70 years
Gastric in situ SRC or pagetoid spread of SRC in individuals <50 years of age
Isolated LBC in individual aged <55 years

Yale criteria

NCCN criteria for high-penetrance breast cancer susceptibility genes, version 2.2024

Breast cancer at age ≤50 years
Triple-negative breast cancer
Multiple primary breast cancers (in same individual)
LBC with personal or family history of DGC
Male breast cancer
Breast cancer + Ashkenazi Jewish ancestry
Breast cancer + 1st, 2nd, or 3rd degree relative with breast cancer ≤50
Breast cancer + 1st, 2nd, or 3rd degree relative with male breast cancer
Breast cancer + 1st, 2nd, or 3rd degree relative with ovarian cancer
Breast cancer + 1st, 2nd, or 3rd degree relative with pancreatic cancer
Breast cancer + 1st, 2nd, or 3rd degree relative with metastatic (or high- or very-high-risk group) prostate cancer
Breast cancer + ≥2 additional diagnoses of breast and/or prostate cancer (any grade) on same side of the family

Significant gastric cancer history

DGC at any age in proband, FDR, or SDR
≥2 cases gastric cancer in FDR or SDR, ≥1 diagnosed at age ≤50 years

Figure 1. Hereditary diffuse gastric cancer (HDGC) genetic testing criteria. DGC, diffuse gastric cancer; ERN GENTURIS, European Reference Network on Genetic Tumour Risk Syndromes; FDR, first- degree relative; IGCLC, International Gastric Cancer Linkage Consortium; LBC, lobular breast cancer; NCCN, National Comprehensive Cancer Network; SDR, second-degree relative; SRC, signet ring cells.