4. Sidhu R, Wilson P, Wright A *et al.* Faecal lactoferrin—a novel test to differentiate between the irritable and inflamed bowel? Aliment Phamacol Ther 2010;31:1365–70.
5. Schröder O, Naumann M, Shastri Y *et al.* Prospective evaluation of faecal neutrophil-derived proteins in identifying intestinal inflammation: combination of parameters does not improve diagnostic accuracy of calprotectin. Aliment Phamacol Ther 2007;26:1035–42.
6. Hastie T, Tibshirani R, Friedman J. The elements of statistical learning: data mining, inference, and prediction, 2nd (edn). Springer: New York, 2003.

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Response to Sorrentino *et al.*

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To the Editor: We thank Sorrentino *et al.* (1) for their interest in our article (2), and appreciate their comments about our published paper. We do acknowledge that there are other ways in which our meta-analysis could have been performed. However, with our analysis, we cannot make a conclusion based on the available body of data on fecal lactoferrin in irritable bowel syndrome (IBS) patients. We had acknowledged this in our discussion with the following statement: "little data is available to make a judgment on the utility of fecal lactoferrin in excluding IBD" in IBS points. This is a very different issue than assessing disease activity and monitoring in patients with IBD for which fecal lactoferrin is an excellent test.

REFERENCE

1. Menees SB, Powell C, Kurlander J *et al.* A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. Am J Gastroenterol 2015;110:444–54.
2. Sorrentino D, Franck C. Utility of fecal markers to diagnose and monitor inflammatory bowel diseases. Am J Gastroenterol 2015;110:1732 (this issue).

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ACG Guidelines on Management of *PTEN*-Hamartoma Tumor Syndrome: Does the Evidence Support so Much so Young?

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To the Editor: The recently published American College of Gastroenterology guidelines "Genetic testing and management of hereditary gastrointestinal cancer syndromes" is comprehensive and addresses the diagnosis, cancer risks, management, and surveillance recommendations for patients with many hereditary gastrointestinal (GI) cancer syndromes (1). The *PTEN*-hamartoma tumor syndrome (PHTS) is a rare hereditary cancer syndromes caused by germline mutations in *PTEN*. PHTS is an umbrella term encompassing at least two syndromes, Cowden and Bannayan–Riley–Ruvalcaba syndrome. The management recommendations for patients with PHTS by Syngal *et al.* (1) include colonoscopy and esophagogastroduodenoscopy (EGD) beginning at age 15 and repeated every 2 and 2–3 years, respectively. It appears that these recommendations are based on a report from Schreibman *et al.* (2) in 2005, where up to 60% Cowden syndrome patients had GI and colorectal polyps, predominantly hamartomas. The association between PHTS and GI cancer was not confirmed at that time and therefore, Schreibman *et al.* (2) advised "a vigorous screening protocol" until further data becomes available.

In recent years, data regarding the GI manifestations in PHTS have been independently reported from several centers around the world. Collectively, it has been shown that up to 92% of individuals with PHTS who undergo colonoscopy have colorectal polyps, ranging from a few to innumerable polyps comprising a variety of histologies including hamartomas, adenomas, ganglioneuromas, serrated polyps, juvenile polyps, inflammatory polyps, lymphoid aggregates, and normal colonic mucosa (3,4). The mean age when polyps were detected was 37 years (3,4). Individuals with *PTEN* mutations have also been found to be at an increased risk of colorectal cancer, which is estimated to be twofold to threefold above the general population, or a 9–18% lifetime risk (3,4). Among the groups from the United States, Israel, and France, the average age of colorectal cancer diagnosis was 46.7 years, while a European group found an average age at diagnosis of 57 years (3,4). The youngest reported patient with a *PTEN* mutation developing colorectal cancer is a 28-year-old reported by Kersseboom *et al.* (5).

Upper GI polyps have been observed in 68–90% of patients with a mix of polyps with histologies similar to that observed in the colorectum (3,6,7). Upper GI tract cancers, including gastric (ages at diagnoses, 52 years and late 60s) and esophageal (ages, 33 and 41 years), are more rarely reported (6,8,9).

On the basis of this contemporary body of literature, the available evidence would support a less aggressive recommendation for colorectal cancer (CRC) screening with colonoscopy beginning between ages 35 and 40 or 5 and 10 years earlier than the youngest age of CRC diagnosis in the family, whichever is earlier (3,4,6,10). The interval for repeat colonoscopy should be based on endoscopic findings, with consideration of

every 1–2 years with removal of all polyps, >5 mm for patients with polyposis or every 3–5 if there is a low adenoma burden and/or no polyps (4). While more data are needed to establish the true upper GI cancer risks, it is the opinion of these authors that a baseline EGD should be done at the time of first colonoscopy with a follow-up EGD based on findings or every 5 years if normal.

Given the impact of professional society guidelines on clinical practice, we believe it is important for Syngal *et al.* to revise their PHTS surveillance recommendations in light of the most current data.

The current American College of Gastroenterology guideline "Genetic testing and management of hereditary gastrointestinal cancer syndromes" recommendations patients with PHTS undergo colonoscopy and EGD beginning at age 15 and repeated every 2 and 2–3 years, respectively.

It has been shown that up to 92% of individuals with PHTS who undergo colonoscopy have colorectal polyps, ranging from a few to innumerable polyps with the mean age when polyps were detected at 37 years.

The lifetime risk of developing colorectal cancer with PHTS is 9–18%, with an average age at diagnosis of 47–57 years.

Upper GI tract polyps have been observed in 68–90% of patients, with only rare case reports of gastric and esophageal cancers.

A less aggressive recommendation for GI screening for PHTS should be considered with colonoscopy beginning between ages 35 and 40 or 5 and 10 years earlier than the youngest age of CRC diagnosis in the family and a baseline EGD at the time of first colonoscopy. Follow-up is dependent on findings.

REFERENCES

1. Syngal S, Brand RE, Church JM *et al.* ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol 2015;110:223–62.
2. Schreibman IR, Baker M, Amos C *et al.* The hamartomatous polyposis syndromes: a clinical and molecular review. Am J Gastroenterol 2005;100:476–90.
3. Nieuwenhuis MH, Kets CM, Murphy-Ryan M *et al.* Is colorectal surveillance indicated in patients with PTEN mutations? Colorectal Dis 2012;14:e562–6.
4. Stanich PP, Pilarski R, Rock J *et al.* Colonic manifestations of PTEN hamartoma tumor syndrome: case series and systematic review. World J Gastroenterol 2014;20:1833–8.
5. Kersseboom R, Dubbink HJ, Corver WE *et al.* PTEN in colorectal cancer: a report on two Cowden syndrome patients. Clin Genet 2012;81:555–62.
6. Heald B, Mester J, Rybicki L *et al.* Frequent gastrointestinal polyps and colorectal adenocarcinomas in a prospective series of PTEN mutation carriers. Gastroenterology 2010;139:1927–33.
7. Levi Z, Baris HN, Kedar I *et al.* Upper and lower gastrointestinal findings in pTEN mutation-positive Cowden syndrome patients participating in an active surveillance program. Clin Transl Gastroenterol 2011;2:e5.
8. Marques M, Ramalho R, Baldaque-Silva F *et al.* Novel mutation identified in Cowden syndrome presenting as a gastric adenocarcinoma. Clin Res Hepatol Gastroenterol 2013;37:e131–2.
9. Sherman SK, Maxwell JE, Qian Q *et al.* Esophageal cancer in a family with hamartomatous tumors and germline PTEN frameshift and SMAD7 missense mutations. Cancer Genet 2015;208:41–6.
10. Network NCC. NCCN clinical practice guidelines in oncology genetic/familial high risk assessment: breast and ovarian version I. 2015, 2015.

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Response to Editorial of Peter D.R. Higgins (July 2015)

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To the Editor: We read with great interest the editorial by Higgins, "Miles To Go On The SCENIC Route: Should Chromoendoscopy Become The Standard Of Care In IBD Surveillance?" (1), regarding the SCENIC Consensus Statement (2). Dr. Higgins suggests that methods which improve detection of dysplasia in colonoscopic surveillance for inflammatory bowel disease (IBD) patients (e.g., chromoendoscopy and high-definition colonoscopy) should not be recommended and implemented in clinical practice without documentation that these methods also improve important clinical outcomes such as colorectal cancer, advanced colorectal cancer, and mortality (1). As authors of the SCENIC Consensus Statement, we indicated that lack of data on clinical outcomes was an issue and called for further research (2). However, direct documentation that surveillance for neoplasia in IBD patients reduces colorectal cancer incidence and mortality also is lacking. By Higgins' reasoning, we would not implement IBD surveillance pending appropriate studies of the impact of surveillance on these clinical outcomes.

In the SCENIC process, we accepted as a starting point the universal recommendation that surveillance to detect neoplasia be performed and our goal was to determine optimal practice for detection and management of neoplasia. Rigorous guideline development processes as prescribed by the Institute of Medicine, including systematic reviews, deliberations by a panel representing all stakeholders, and use of GRADE methodology, are widely accepted to produce more trustworthy recommendations than those that are authored by individuals and based on non-systematic narrative reviews. And higher-quality evidence generally is of greater importance in deliberations than lower-quality evidence such as the retrospective studies that were the subject of the editorial by Higgins (1). Recent guidelines from around the world are in agreement with the SCENIC recommendations (2).

Physicians and patients must make decisions every day in practice based on incomplete evidence. For this reason, guidelines commonly provide recommendations even in the absence of optimal evidence. Rigorous guidelines, including the SCENIC Consensus Statement, provide information regarding the quality of supporting evidence, the strength of recommendations, and the reasons for making recommendations, and allow physicians