A proposed staging system and stage-specific interventions for familial adenomatous polyposis

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Background and Aims: It is not possible to accurately count adenomas in many patients with familial adenomatous polyposis (FAP). Nevertheless, polyp counts are critical in evaluating each patient's response to interventions. However, the U.S. Food and Drug Administration no longer recognizes the decrease in polyp burden as a sufficient chemoprevention trial treatment endpoint requiring a measure of "clinical benefit." To develop endpoints for future industry-sponsored chemopreventive trials, the International Society for Gastrointestinal Hereditary Tumors (InSIGHT) developed an FAP staging and intervention classification scheme for lower-GI tract polyposis.

Methods: Twenty-four colonoscopy or sigmoidoscopy videos were reviewed by 26 clinicians familiar with diagnosis and treatment of FAP. The reviewers independently assigned a stage to a case by using the proposed system and chose a stage-specific intervention for each case. Our endpoint was the degree of concordance among reviewers staging and intervention assessments.

Results: The staging and intervention ratings of the 26 reviewers were highly concordant ($\rho = 0.710$; 95% credible interval, 0.651-0.759). Sixty-two percent of reviewers agreed on the FAP stage, and 90% of scores were within ± 1 stage of the mode. Sixty percent of reviewers agreed on the intervention, and 86% chose an intervention within ± 1 level of the mode.

Conclusions: The proposed FAP colon polyposis staging system and stage-specific intervention are based on a high degree of agreement on the part of experts in the review of individual cases of polyposis. Therefore, reliable and clinically relevant means for measuring trial outcomes can be developed. Outlier cases showing wide scatter in stage assignment call for individualized attention and may be inappropriate for enrollment in clinical trials for this reason. (Gastrointest Endosc 2016;84:115-25.)

Abbreviations: FAP, familial adenomatous polyposis; FDA, Food and Drug Administration; InSiGHT, International Society for Gastrointestinal Hereditary Tumors; ICC, intraclass correlation coefficient; IPSS, InSiGHT polyposis staging system.

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It is virtually impossible to accurately count adenomas during endoscopy in many patients with familial adenomatous polyposis (FAP). Nevertheless, polyp counts are critical in evaluating a patient's response to chemopreventive agents. However, there has been virtually no guidance for endoscopists and surgeons in determining when surgery should be performed. More pointedly, the determination of the U.S. Food and Drug Administration (FDA) that approval of new chemopreventive agents must meet a higher standard of clinical benefit has left the FAP community speculating as to what such a standard really calls for. Members of the International Society for Gastrointestinal Hereditary Tumors (InSiGHT) undertook the described study in order to develop a staging and staged intervention system that would provide an acceptable measure of clinical benefit in future industry-sponsored chemoprevention trials and other interventions in FAP.

In 1989, Spigelman et al[1] proposed a staging system for duodenal adenomas in patients with FAP. This system has enabled clinicians to monitor patients more effectively and has guided clinical interventions. Unfortunately, no corresponding staging system exists for adenomas in the colon and rectum in either the pre- or postoperative setting, perhaps because some perform colectomy or proctocolectomy soon after diagnosis of colorectal adenomas, regardless of severity. But many clinicians use the extent of "polyp burden" and clinical judgment to determine the timing of colectomy, both of which are subjective and individual based, thus indicating a need for standardization.

A diagnosis of FAP is typically established on the basis of adenomatous polyposis coli gene testing, and adenomas can be found in patients as young as age 10 or 12.[2,3] Although it is a normal practice to operate at an early point in the evolution of FAP, there has been a tendency to defer surgery in these young patients. Improvements in endoscopes and better, safer anesthesia for pediatric use have made full colonoscopy a very acceptable procedure in children. There is also value in waiting for the rectum to "declare itself" insofar as the development of adenoma burden is concerned, so that surgeons can better select the appropriate operation: colectomy or proctocolectomy.[4] Conversely, much older patients with attenuated FAP and mutY homolog (*MUTY*)-associated polyposis may initially be diagnosed with a very mild adenoma burden at age 50 or later.[5,6] An unknown but small fraction of such patients can be managed conservatively, with periodic multiple polypectomies without surgery.

This emerging diversity in FAP presentation, diagnosis, and treatment has not, of itself, been enough to stimulate the development of a colorectal polyposis staging system. However, in 2011, in a letter, the FDA stated that it would no longer approve, much less accelerate approval of, chemopreventive agents for the treatment of premalignant conditions such as FAP on the basis of a reduction in polyp number and size alone; a clearer demonstration of clinical benefit would be required (E L. Memorandum of meeting minutes pre-IND/pre-NDA for eicosapentaenoic acid [free fatty acid] [EPA-FFA]. In: Services DoHH, editor, Q8 2011:1-20).[7] In 2011, Meyskens and colleagues highlighted the need to develop effective biomarkers and true clinical endpoints for cancer chemoprevention trials.[8] At the 2011 meeting of InSiGHT, a group of FAP experts met with pharmaceutical leaders interested in responding to the FDA's clinical benefit challenge. The experts agreed that demonstrating clinical benefit would require the development of clinically relevant signposts of FAP progression that would also serve as primary endpoints for clinical trials of chemopreventive therapies. Also, treatment response or progression would have to be couched in oncological meaningful terms, despite the fact that FAP-related mortality is uncommon in patients with FAP because of current intensive endoscopic surveillance and surgical prophylaxis. To be clinically meaningful, the progressive disease stage would need to be linked to progressively more aggressive interventions. A staging system for colorectal polyposis akin to the Spigelman et al[1] staging system for duodenal polyposis might thus provide objective and clinically relevant measures of time to disease progression as well as disease regression. As a subgroup of the FAP experts who met in 2011, we undertook the development and testing of such a staging system.

As detailed in the following, we created a scale that divides colorectal polyposis into 5 progressive stages based on adenoma number and size. The degree of dysplasia, age, and desmoid disease were not considered in developing the InSiGHT polyposis staging system (IPSS). We then created a corresponding scale specifying the endoscopic, surgical, and/or chemopreventive interventions considered appropriate to the adenoma burden. Recognizing that clinical staging and interventions are based on expert opinion, we convened a panel of experts—endoscopists and surgeons—to review videos of edited colonoscopies or sigmoidoscopies (in cases of prior colectomy or proctocolectomy). Our endpoint was to discern the degree of agreement among the experts in assigning a given video to one of the 5 predefined InSiGHT polyposis staging system (IPSS) stages and, further, in proposing appropriate interventions for the stages they assigned.

METHODS

Development of the IPSS. At the 2011 annual InSiGHT meeting, the need for a staging system for colorectal polyposis was recognized in response to the FDA position requiring a measure of clinical benefit for new drug approval. Therefore, we developed an arbitrary classification system for progressive categories of colorectal polyposis severity and a means for validating that classification. The categories were developed by the