Commentary

# Screening colonoscopy intervals in familial colorectal cancer

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Colorectal cancer (CRC) is one of the top causes of cancer death throughout the world, but it is also one of the most preventable through early detection and removal of premalignant polyps. CRC arises via various genetic and epigenetic changes which alter normal mucosa giving rise to polyps and eventual cancers. This has been well characterized for both the adenoma-to-carcinoma sequence (1) and the serrated polyp oncogenic pathway (2). There is strong evidence that regular colonoscopy and removal of premalignant polyps reduces the incidence of and death from CRC in the average risk population (3) and in hereditary conditions such as Lynch syndrome (4,5). CRC screening guidelines are well established for average risk populations, and for high-risk population such as those associated with hereditary syndromes. However, there is an intermediate risk group with family history of CRC, but without a defined syndrome, that is not as well characterized.

This group, often called familial CRC, is variably defined, but often refers to people without CRC who have a first-degree relative affected with CRC before the age of 50 or 60 years, or have two second-degree relatives affected with CRC at any age. It is estimated that about 2% of the general population between ages 45–70 have a family history that meets criteria for the definition of familial CRC using age 50 as the cutoff for first degree relatives (6), thus making this a significant population at risk. The CRC risk ranges between 2–6 fold compared to the general population, and varies for each person according to the number of individuals affected and the age of cancer onset in the family. The National Comprehensive Cancer Network and the United States Multi-society Task Force recommend patients with either a first-degree relative with CRC before age 60 or two second-degree relatives with CRC at any age undergo colonoscopy every 5 years starting at age 40 or 10 years younger than the youngest age at CRC diagnosis (7,8). Although clinically logical, there is scarce data to support this interval.

Hennink *et al.* from the Netherlands recently reported results from the Familial Colorectal Cancer Surveillance (FACTS) study, which attempts to address this conundrum (9). The study is a multicenter, prospectively randomized trial evaluating colonoscopy screening intervals for people with a family history of CRC. Familial CRC was defined as having a single first-degree relative with CRC before the age of 50, or two first-degree relatives with CRC at any age. The objective was to compare the rates of advanced adenomatous polyps (AAP) in patients under surveillance every 3 years compared to those at a single interval of 6 years. Patients between ages 45–65 years were included after baseline colonoscopy. Patients with none, one, or two adenomas were randomized to undergo a single repeat colonoscopy at 6 years (group A), or two scheduled colonoscopies, one at 3 years and another at 6 years (group B). The primary endpoint was AAP detection, defined by adenomas with of high-grade dysplasia, villous histology, or size >1 cm. Patients with three or more adenomas of any size at baseline were excluded because they are recommended to undergo repeat examination in 3 years. Two hundred and sixty-two patients in group A and 266 patients in group B were analyzed.

On intention-to-treat analysis, there was no significant difference in the proportion of patients found to have AAPs at the first surveillance exam (6.9% group A *vs.* 3.5% group B). The rate of AAP detection at 6 years was also not statistically different between groups (6.9% for group A;

3.4% for group B), suggesting that a 6-year interval may provide adequate surveillance. Importantly, at baseline colonoscopy, a higher proportion of patients in group B had AAP compared to those in group A. Thus, the authors adjusted their analysis using bivariable logistic regression modeling. After correction for differences in AAPs at baseline colonoscopy, a higher proportion of patients in group B (first surveillance at 6 years) were found to have AAPs compared to screening at 3 years (adjusted OR 2.44, 95% CI, 1.02–5.78, P=0.044). This difference was also significant at the 6-year exam for both groups with an adjusted OR 2.61 (95% CI, 1.06–6.45, P=0.038). The authors analyzed risk factors for development of AAPs including sex, age, type of family history, and AAPs at baseline. The only significant predictor for the presence of an AAP at follow-up colonoscopy was the presence of an AAP at baseline colonoscopy. Patients with an AAP at baseline were 5.21 times more likely to have AAPs at the follow-up exam compared to those without AAP at baseline (P=0.006). They acknowledge that the group with baseline AAPs may not be appropriate for the longer intervals, but overall, the authors propose that a 6-year colonoscopic surveillance interval can be recommended for people with familial CRC risk.

Professor Vasen and the group from the Netherlands historically have made significant scientific contributions to the management of CRC surveillance in both average risk and high-risk populations. They are to be congratulated for tackling the issue of familial CRC, where the surveillance intervals have been proposed on expert opinion, but are not well-defined. This is the first randomized controlled trial evaluating different colonoscopy surveillance intervals in familial CRC. The FACTS study provides novel data and insight into the natural history of patients with increased CRC risk due to family history and identifies a subset of patients who likely can be safely surveyed at 6 years intervals.

It is important take these results with caution as they are derived with a specific patient population and are not widely applicable to all patients with family history of CRC. People with more than one first-degree relative or those meeting Amsterdam criteria have increased risk and were not included in this study and should be followed more closely. Also, the data from this study suggests that patients with familial CRC who have AAPs at baseline colonscopy should not have prolonged surveillance intervals. Thus, both family history and findings at initial colonoscopy should be considered when prescribing the next colonoscopy. Another consideration of this study is the lack of recognition of serrated polyps as a clinically relevant endpoint. Sessile serrated colorectal polyps have malignant potential at least similar to that of adenomas and should guide management intervals (2,10,11). Lastly, successful cancer prevention via colonoscopy depends on the quality of the bowel preparation, skill and experience of the endoscopist, and patient compliance. Patient management and compliance in this study were excellent as evidenced by skilled endoscopists, good quality bowel preparations, and 95% compliance with recommendations. It may be challenging to achieve similar results in other health care systems.

Another word of caution is evoked by the doubled detection rate of non-high-risk adenomas in the longer interval group (26% *vs.* 13%). Although not considered high-risk, we do not fully understand the rate of progression or natural history of adenomas in familial CRC and the results need to be confirmed in larger studies. This is underscored by the fact that one patient developed CRC even at the 3 years interval. Furthermore, although AAPs are a good surrogate for CRC, the study was not powered to detect differences in CRC incidence or mortality between the groups.

Despite these challenges of the study, Hennink *et al.* provide useful information regarding screening intervals for a narrowly-defined subset of individuals with a limited CRC family. Personalization of care and cost-effectiveness of screening procedures will continue to drive decisions in an increasingly economically challenging health care environment that stresses utilization of resources. Ultimately, the clinician must provide thoughtful recommendations to each patient based on the literature, individual personal and family history of adenomas and CRC, and the quality of the exam.

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## Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

## References

1. Vogelstein B, Fearon ER, Hamilton SR, et al. Genetic alterations during colorectal-tumor development. N Engl

 

J Med 1988;319:525-32.
2. Rex DK, Ahnen DJ, Baron JA, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. Am J Gastroenterol 2012;107:1315-29; quiz 1314, 1330.
3. Ransohoff DF. How much does colonoscopy reduce colon cancer mortality? Ann Intern Med 2009;150:50-2.
4. de Jong AE, Hendriks YM, Kleibeuker JH, et al. Decrease in mortality in Lynch syndrome families because of surveillance. Gastroenterology 2006;130:665-71.
5. Järvinen HJ, Aarnio M, Mustonen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 2000;118:829-34.
6. de Jong AE, Vasen HF. The frequency of a positive family history for colorectal cancer: a population-based study in the Netherlands. Neth J Med 2006;64:367-70.
7. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology 2008;134:1570-95.
8. National Comprehensive Cancer Network. Colorectal Cancer Screening, version 1. Available online: www.NCCN.org
9. Hennink SD, van der Meulen-de Jong AE, Wolterbeek R, et al. Randomized Comparison of Surveillance Intervals in Familial Colorectal Cancer. J Clin Oncol 2015;33:4188-93.
10. Kalady MF. Sessile serrated polyps: an important route to colorectal cancer. J Natl Compr Canc Netw 2013;11:1585-94.
11. Liang JJ, Bissett I, Kalady M, et al. Importance of serrated polyps in colorectal carcinogenesis. ANZ J Surg 2013;83:325-30.

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