Primary Care Implications of the Expanded National Guidelines for Germline Testing of Patients Previously Diagnosed with Colorectal Cancer

Steven Sorscher, MD

Colorectal cancer (CRC) is among the most common cancers diagnosed in the United States. Most patients are cured, have completed their routine surveillance in oncology clinics, and are being followed by primary care clinicians (PCCs). Those providers are tasked with discussing with these patients genetic testing for inherited cancer-predisposing genes that are called PGVs.

Recently, the National Comprehensive Cancer Network (NCCN) Hereditary/Familial High-Risk Assessment: Colorectal Guidelines expert panel updated their recommendations for genetic testing. It is now recommended that all patients diagnosed with CRC before age 50 be tested and patients diagnosed at age 50 or older be considered for multigene panel testing (MGPT) for inherited cancer-predisposing PGVs.

Here, I discuss the basis for the NCCN expanded genetic testing recommendations and highlight the salient controversies related to genetic testing. I also review the literature that suggests that PCCs identified more training as the measure needed before they are comfortable having complex discussions related to genetic testing with their patients. (J Am Board Fam Med 2023;36:360–365.)

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The Expanded National Comprehensive Cancer Network Guidelines for Genetic Testing

It is estimated that 150,000 Americans are diagnosed with colorectal cancer (CRC) every year.[1] Of the estimated 1.5 million CRC survivors, roughly 940,000 patients are greater than 5 years from their time of diagnosis.[2] After 5 years, it is not recommended that these patients continue follow-up in oncology clinics.[3] Instead, these patients often are receiving their ongoing care, including initial discussions about predictive genetic testing, from primary care clinicians (PCCs).

The National Comprehensive Cancer Network (NCCN)–published guidelines[4] are "the recognized standard for clinical direction and policy in cancer care."[5,6] The NCCN Hereditary/Familial High-Risk Assessment: Colorectal Guidelines panel is responsible for recommending which CRC patients undergo multigene panel testing (MGPT) for inherited cancer-predisposing genes called PGVs.[4]

For years, NCCN panels have recommended testing for all patients diagnosed with pancreas and ovary cancers and for a large proportion of patients diagnosed with breast and prostate cancers. Until recently, the panel only endorsed MGPT for patients diagnosed with CRC who have personal or family histories suggesting high pretest probabilities of having inherited a PGV. However, updated guidelines now recommend that all patients diagnosed before age 50 undergo MGPT, and for patients diagnosed at age 50 or older, MGPT should be considered.[4]

Evidence Supporting the Expanded Guidelines

Multiple factors led to the expanded recommendations for germline testing in patients diagnosed with CRC. Technological advances have made

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Corresponding author: Steven Sorscher, MD, Winston-Salem, NC 27104 (E-mail: ssorscher1@gmail.com).

MGPT testing highly sensitive and specific for detecting PGVs.[7,8] The penetrance of the cancers associated with nearly all common PGVs or likely PGVs identified by MGPT has been established.[9] In addition, MPGT is now considerably less expensive than previously, and currently the cost ranges between $249 and $6040.[8]

Roughly 10% of CRCs are caused by inherited cancer-predisposing PGVs, most commonly[10,11] the mismatch repair (MMR) and adenomatous polyposis coli (APC) gene PGVs, which are the basis for the Lynch and familial adenomatous polyposis syndromes, respectively.[10–12] MMR and APC PGVs account for only a small percentage (5% to 6%) of CRCs. NCCN guideline recommendations for patients found to carry an MMR PGV, for example, include preventive hysterectomies, proven to reduce uterine cancer risk, and daily aspirin, which has been shown to reduce CRC mortality in Lynch syndrome patients.[1,13]

However, the basis for the recommendation that all patients under age 50 diagnosed with CRC undergo MGPT and all patients diagnosed age 50 and over be considered for testing was primarily related to reports that showed that when MPGT was done based solely on a diagnosis of CRC, between 7.8% and 16% of CRC patients were identified as carrying a PGV that typically was a non-CRC-predisposing gene.[14,15]

In fact, most of these PGVs would not have been uncovered had the current guidelines criteria for MPGT, based on "risk-assessment" for carrying those genes, been the basis for ordering the genetic testing.[14–17] For example, in one cited study, PGVs were identified in 15.5% of patients, although MMR PGVs were only identified in 3.1% of patients.[16] Using the new criteria for genetic testing (CRC diagnosed under age 50 and consider in patients with CRC diagnosed age 50 and over) represents a biomarker for eligibility for testing that is far simpler to remember than the myriad of risk-assessment criteria previously endorsed to identify the non-MMR, non-APC PGVs carried by CRC patients.

Uncovering a non-MMR, non-APC gene has important implications. For example, *BRCA2* PGVs were among the most common PGVs identified in NCCN cited studies.[14,15] Carrying a *BRCA2* PGV is an indication of proven measures to mitigate the risk of developing and for detecting early breast, ovary, and other cancers. For instance, bilateral salpingo-oophorectomy is recommended in patients with *BRCA2* PGVs to prevent ovarian cancers, and magnetic resonance imaging (MRI) is recommended to screen for breast cancer. With bilateral salpingo-oophorectomy, the risk of dying of ovarian cancer will be reduced by more than 90%.[18,19]

Still, it is important to recognize that for some identified PGVs there are not proven measures to reduce mortality from associated cancers. For example, although *BRCA2* PGVs are the most common variants predisposing to pancreatic cancer, and although screening MRIs, per the NCCN guidelines, are to be "considered" to detect pancreatic cancer early in *BRCA2* carriers, there is not yet proof that MRIs reduce pancreatic cancer mortality even in this high-risk group.[20]

The NCCN guidelines were also expanded because patients wish to know if they carry PGVs.[21] In the primary care clinic setting, Duenas et al[21] reported that surveyed patients wished to have testing to learn of their future risk (81%), particularly if the information might help family members (58%) and advance research (34%). In fact, Halverson et al[22] reported that 67% of patients who initially declined testing at the time of the initial evaluation said either they would or had changed their mind about testing if/when the clinicians "mentioned it again."

Challenges for PCCs Related to the Expanded Guidelines

The expansion of the guidelines to recommend testing for more patients diagnosed with CRC has presented a number of challenges.

Along with the NCCN CRC guideline expansion, the Cancer Moonshot version 2.0 recommended that all patients diagnosed with cancer be offered evaluation for eligibility for germline testing in part because there are marked racial, ethnic, and socioeconomic disparities in patients diagnosed with cancer who undergo genetic counseling to determine eligibility for testing.[23,24]

Currently, if patients wish to undergo evaluation for germline testing, they are most often referred to a genetic counselor. However, there is already an enormous shortage of genetic counselors.[25] If the broadened NCCN and Moonshot recommendations are adopted, there will be an increase in the number of CRC patients being offered evaluation

for eligibility and testing for PGVs, and the shortage of providers trained in genetics to meet this demand could potentially be overwhelming.

In addition, there will likely be a widening gap between socioeconomic groups for those who undergo testing if the Moonshot recommendations are adopted because, despite the expanded guidelines, the vast majority of patients do not meet NCCN eligibility for testing, and payers seldom cover testing for those not meeting eligibility criteria.[18] Thus, among those who wish to be tested but do not meet eligibility, those who can afford to pay out of pocket will continue to be tested at a higher rate than those who cannot.

To mitigate the anticipated supply, demand, and disparity issues, Moonshot and the NCCN recommended that more PCCs be trained in genetics. Although Luctkar-Flude et al[26] reported a willingness among primary care providers to be involved in the care of cancer patients, the providers reported knowledge and experience gaps that they felt would hamper their effectiveness in this area.

Another challenge with expanded testing guidelines involves the concept of "genetic exceptionalism," which is the belief that genetic information and testing results are unique and should therefore be handled and reported differently than other medical information. However, in a landmark commentary, the bioethicists Green and Botkin[27] concluded "no clear, significant distinction between genetic and nongenetic tests justifies a different approach by clinicians." Still, genetic exceptionalists believe that the uncertainties and implications associated with predictive genetic tests are fundamentally more complicated compared with the results of other predictive laboratory tests (eg, lipid profile testing to predict risk of developing atherosclerotic disease) and only clinicians thoroughly trained in genetics should be involved in genetic testing.[18]

For example, with MGPT, between 13% and 47% will have 1 or more variants of uncertain significance (VUSs) detected and reported.[28] Many geneticists and genetic counselors maintain that only those with extensive and ongoing specialty training in genetics could possibly keep up with the evolving information related to particular VUSs.[18,28] Incorrect interpretation of risk associated with VUSs can have drastic effects on patient outcomes in populations already subject to health care disparities.

Because the expanded guidelines include patients with low pretest probabilities of carrying a PGV associated with CRC risk, more patients will be identified as carrying VUSs. Many geneticists and the NCCN panels have recommended that PCCs receive training in genetics and explaining the implications of possible outcomes of specific test results including VUSs, true negatives, uninformative negatives, true positives, and mosaic results. In the meantime, the NCCN and Moonshot believe that trained PCCs could evaluate patients and order genetic testing, but for any uncertainty related to a result, referral to a clinical geneticist or genetic counselor should follow.

Identifying PGV carriers suggests cascade testing of family members. Hoskins and Gotlieb[25] concluded that "lack of knowledge on the part of physicians and patients and process issues represent the major barriers" to uptake of testing patients diagnosed with cancer and cascade testing of family members but also stated that "in institutions with motivated individuals, these barriers have been fixed with simple process modifications."

Other barriers to adoption of the new guidelines include legal protections related to employment discrimination and insurability and confidentiality, reliability of results from direct-to-consumer genetic testing, and the recommended need for confirmatory tests from Clinical Laboratory Improvement Amendments–certified laboratories when a patient is identified as carrying a PGV with direct-to-consumer testing and the confidential use of their results for future reclassifying of variants.[18]

Finally, it is somewhat unclear whether PCCs believe cancer survivorship, which includes expertise in genetic testing, should be part of their practices. Crabtree et al[29] suggested that primary care providers reported an "identity crisis" in considering their role in managing cancer survivors and that "it remains unclear how follow-up needs of survivors should be prioritized and/or integrated into primary care." They wrote that the unclear definition of "survivor" creates a "nebulous situation as to when primary care should resume responsibility for these patients."

Solutions to Challenges Related to the Expanded Guidelines

The role of PCCs in discussing and offering genetic testing to their patients has resulted from the

explosion in interest in genetic testing and the recognition of the benefits of identifying patients who carry PGVs. Education of PCCs in genetics seems to be the most often cited solution to the anticipated need for more PCC involvement in germline genetic testing.

In 2004, Burke[30] suggested that targeted educational efforts, computerized prompts, and electronic patient decision tools to gather family history information could all be useful to primary care providers as they discuss genetic testing with their patients.

In 2009 Hong et al[31] discussed the American Board of Internal Medicine's 2007 proposal for credentialling "Comprehensive Care Internists" with responsibilities that would include addressing the growing unmet need of cancer survivors who voiced concerns, such as the value of genetic testing, but were no longer being followed by oncology. The authors noted the importance of this specialty given the screening recommendations that were either already recommended or emerging for PGV carriers.

Nekhlyudov and Greenfield[32] wrote that there is an increasing population of cancer survivors who are no longer followed by oncologists and "there are essentially no medical education or residency training curricula focusing on concerns of cancer survivors."

In 2015, a commission that included primary care and public health experts suggested that carefully crafted clinical guidelines and care plan measures would empower PCCs with the tools they need to manage the concerns of cancer survivors, 1 of which was the clinical utility of genetic testing.[33]

Crabtree et al[29] surveyed primary care providers (PCPs) practicing at 14 sites and more than 10,000 patients who were offered genetic testing at an annual preventive care visit, regardless of their pretest probability of carrying a PGV. The authors concluded that "to increase physician training in care of patients with a history of cancer, family medicine and internal medicine certification boards and professional organizations need to create new educational pieces and continuing medical education (CME) content in support of cancer survivorship care" for that majority of survivors no longer being followed in oncology clinics.

From their investigation of the barriers and solutions to involving PCPs in genetic testing, Lemke et al[34] found that PCPs reported "low confidence with tasks related to ordering, interpreting and managing the results of genetic tests and identified the need for additional education." In fact, 42.9% of PCPs surveyed somewhat or strongly agreed that they feel confident explaining genetic test results related to cancer with their patients. Nonetheless, 77% of PCPs "somewhat or strongly agreed that the genetic testing program is useful to change their current management of patients' care."

PCPs underscored the need for education related to management options, clinical testing guidelines, and data privacy. In decreasing order of frequency, PCPs suggested patient education handouts, physician reference sheets, CME events, in-office education, and online courses.[34]

In particular, nongenetics providers were concerned regarding their ability to advise patients related to privacy and discrimination against those identified as carrying PGVs (despite protections offered by the US Genetic Information Nondiscrimination Act).

In their study, Lemke et al[34] recognized that PCPs are likely unaware of how best to discuss the issue of VUSs with patients, the genetic reports issued all included a statement about VUSs, and patients were given options to further explore identified VUSs. The authors concluded that "as PCPs are the foundation of preventive medicine, it is important they be engaged in the integration process to realize the potential of genomics in health care and reduce the risk of disease.

In another study involving 488 primary care providers, the authors concluded from survey responses that "enhanced training, guidelines, clinical tools, and awareness of patient protections might support the effective adoption of genomic medicine by primary care providers."[35]

Conclusions

William Osler, the father of medical education in this country, said, "It is more important to understand what sort of patient has a disease than what sort of disease a patient has."[36] Genetic testing has emerged as a powerful tool in terms of appreciating what cancers a patient is at particularly high risk of developing.

In the United States, providers and payers defer to the NCCN Hereditary/Familial High Risk Assessment: Colorectal Cancer panel as the authoritative source that determines the standard of care for MGPT. For all patients diagnosed with CRC

before age 50, MGPT is now recommended and is to be considered in all patients diagnosed at age 50 and over.

PCPs often lack the experience or training in genetics needed to discuss with patients the profound ramifications related to genetic tests. Cancer Moonshot recommends evaluation for eligibility for testing for all patients diagnosed with CRCs and suggests educating more PCCs in genetics in part due to a shortage in genetics counselors, to mitigate disparities in providing this potentially life-saving service to patients, and because most patients diagnosed with CRC are beyond follow-up with their oncologists.

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