PATHOLOGY ARTICLE

Establishing a clinical and molecular diagnosis for hereditary colorectal cancer syndromes: Present tense, future perfect? CME

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With increasing diagnostic capabilities, the demand for germline testing for hereditary colorectal cancer syndromes has increased steadily in recent years, and with colorectal endoscopy screening programs detecting more patients at an earlier stage, the demand for testing is expected to increase further. Positive diagnostic genetic testing results allow patients to undergo tailored surveillance and relatives to opt for predictive testing. Yet, uncertainty remains in a significant number of patients who fit clinical diagnostic categories, but do not show positive germline testing results. Novel genetic techniques that evaluate many genes at once may allow this group of patients that is at present unclassified to shrink in years ahead. These novel testing strategies can also uncover unexpected pathogenic mutations or genetic variants of which the pathogenicity is uncertain, complicating genetic counseling and follow-up strategies. The wider application of DNA-based diagnostics reveals that germline mutation carriers can express a much wider clinical phenotype than thus far appreciated. We discuss here several of the major hereditary colorectal cancer syndromes and the implications of current genetic testing strategies. Further international integration of testing results could improve risk stratification and counseling for individual patients. Proper data management and patient education are key to maintaining our patients' consent and confidence.

HANDLING GERMLINE MUTATION SCREENING IN 2014: BIGGER, BETTER?

Clinical testing for germline mutations in colorectal cancer (CRC) has progressed rapidly in the past few years, and the cost of next-generation sequencing (NGS) has dropped precipitously. It is now possible to sequence all 400 driver genes implicated in CRC in 1 panel for a cost comparable to that of traditional Sanger sequencing of 1 gene. However, data analysis is complex for NGS and requires significant bioinformatics input beyond that called for in traditional clinical medicine.[1,2] The amount of data generated is massive, and major effort is required for variant identification and classification. In this age of "big data," combining existing medical databases to spot epidemiological patterns currently hidden from clinical observation appears all-too alluring. Clinical records are rightly stored in digital data files to compare treatment outcomes between different institutions. Data showing that greater hospital volume improves patient outcome ("practice makes perfect") for complex oncological care, such as pancreatic or esophageal cancer, have led to major infrastructural changes in health care organization. However, further linking of patient data means that inevitably patterns appear that reveal personal information about individual patients. In a commendable attempt to cut public spending, the United Kingdom's National Health Service Care.data program was set to start uploading data to a data storage site maintained by the Health and Social Care Information Centre based in Leeds from early spring 2014 onward. The Health and Social Care Information Centre would create one of the world's most comprehensive health care databases by uploading hospital records and medical data. However, the program was broadly criticized in the lay press and by key British organizations (such as the British Medical Association and the Royal

Abbreviations: AFAP, attenuated familial adenomatous polyposis; CRC, colorectal cancer; FAP, familial adenomatous polyposis; IHC, immunohistochemistry; LS, Lynch syndrome; MAP, MUTYH-associated polyposis; MMR, mismatch repair; MSI, microsatellite instability; MSS, microsatellite stable; NGS, next-generation sequencing; PCR, polymerase chain reaction.

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College of General Practitioners) for obscuring patients' rights to opt out and for threatening the confidential nature of the health service. The public's dismay of the Care.-data program led to its postponement for at least 6 months, and the kickoff is now planned for August 2014. These issues are extra thorny at a time when there is broadly felt discomfort with population-wide data storage after the Snowden revelations, leading some to remark that "we now trust no one with our private data, not even our doctors" (*The Guardian*, January 31, 2014).

Genetic testing for familial cancer syndromes is at the heart of this debate. With clinical genetic screening rapidly coming of age, regulatory policies lag behind our technological capabilities. Obviously, casting a wider net both in terms of the number of patients tested and the number of variants interrogated will result in more by-catch. Currently, little consensus exists on the approach to these issues. Given the previous example of a hasty introduction of the Care.-data program in the United Kingdom, patients must not opt out of genetic testing because of fear of highly personal data falling into the hands of insurance and other commercial companies. In a study published in *Science* in 2013,[3] Massachusetts Institute of Technology researchers "cracked the system" and showed that by combining freely available online data in public sequencing projects with genealogy registries, the identity of study participants in genome studies could be triangulated.[1-3] Transparent communication to the public of the goals and expected results of genetic analysis studies (whether these are large-scale tumor genome studies or targeted germline analyses) is essential in maintaining our patients' trust in clinical care and the public's continued support of basic research. It is a fundamental human right that people determine how personal medical data are used, and this right extends to genetic data. Exercising this right requires health-literate patients, especially because genetic testing often affects relatives. Indeed, regulatory bodies should proactively inform the public of the current (exciting) genetic research possibilities, lest we lose our patients' confidence when discussing genetic analysis.

SCOPE OF THIS PAPER

GI tumor predisposition syndromes provide a benchmark for understanding the mechanism of stepwise sporadic tumor formation. We review the current state of affairs of genetic testing for hereditary CRC syndromes, focusing on familial adenomatous polyposis (FAP), *MUTYH*-associated polyposis (MAP), and Lynch syndrome (LS). Because we await the unraveling of the genetics of serrated polyposis, this important condition is not covered here. Nonetheless, many patients with a mixture of adenomatous and serrated polyps currently testing negative may later be shown to fall into this category. The rarer so-called hamartomatous polyposis syndromes (juvenile polyposis syndrome, Peutz-Jeghers syndrome, and *PTEN* hamartoma tumor syndrome [previously called Cowden syndrome]) are not covered.[4] We discuss novel testing strategies, in particular with regard to the large group of patients with uncharacterized familial CRC predisposition.

FAMILIAL ADENOMATOUS POLYPOSIS

FAP is the prototype of the hereditary CRC syndromes. It is caused by germline mutations in the *APC* gene and often manifests as extensive colorectal adenomatous polyposis, by definition 100 or more adenomatous polyps for classic FAP. FAP is inherited in an autosomal dominant manner and has an impressive clinical picture with hundreds to thousands of adenomas developing in severely affected individuals by 16 years of age and, by extension, a nearly 100% cancer risk if left untreated by early colectomy (Fig. 1). This syndrome is a favored model system for understanding sporadic CRC formation.[3,5] FAP accounts for 1% of all CRC, which is less than the population CRC burden attributed to LS (see later). Variable extracolonic features of FAP include duodenal polyps, dental abnormalities, congenital hypertrophy of the retinal pigment epithelium, and desmoid tumors. Attenuated FAP (AFAP) is characterized by fewer colonic polyps, by definition fewer than 100, with an average of 30 adenomas, occurring at a later age. Colorectal adenomatous polyposis can also be attributed to biallelic mutations in the *MUTYH* gene. This condition has an autosomal recessive inheritance pattern and is discussed in the following section.

Clinical context

In patients with profuse colorectal adenomatous polyposis, the workup is straightforward, and genetic testing is geared toward identifying either germline *APC* or biallelic *MUTYH* mutations. Demonstration of a pathogenic germline mutation will not usually affect patient management in most cases, but will serve as a basis for predictive testing in at-risk relatives. The number of polyps at diagnosis is a strong predictor of the outcome of genetic testing. Whereas *MUTYH* mutations are (rarely) found in patients with more than 1000 polyps, these severely affected patients are 40 times more likely to carry a pathogenic *APC* mutation. Both a higher number of polyps and a younger age at diagnosis predict a higher likelihood that a pathogenic *APC* germline mutation is present. For example, a 20-year old patient without a family history of CRC demonstrating more than 1000 colorectal adenomatous polyps has a calculated 97% chance of an underlying *APC* germline mutation. Conversely, a 50-year-old patient with CRC, lacking a family history of CRC, with 10 to 19 adenomas has a 2% chance of an *APC* mutation, but a 6% chance of biallelic *MUTYH* mutations.[6,7] Mutational testing is, therefore, more likely to be diagnostic in classic FAP than in AFAP, with *APC* mutation detection ranging from 56% in those with