To Test or Not To Test: Colon Cancer Pharmacogenetics and Predisposition Genetics

Leslie Cole Manace

Department of Genetics, Kaiser Permanente Oakland Medical Center, Department of Medicine, University of California, San Francisco, USA

The challenge in pharmacogenetics is not only finding good markers, but also if and when to use them. In the case of colon cancer management, there are well-established genomic, proteomic and pharmacogenetic markers predicting efficacy of medical therapy and informing prognosis. The question before physicians and health care organizations is whether this testing has sufficient clinical utility—which is to say what individuals are appropriate to test, whether the testing is cost-effective, and if there is ultimately improved clinical outcome.

There is currently debate over the adoption of genetic tools in colorectal cancer (CRC) evaluation and management. There are two well-established genomic and proteomic tests available for evaluation of the DNA “mismatch repair” (MMR) system, a crucial pathway involved in CRC development. Deficient MMR function leads to accumulation of mutations and carcinogenesis. CRC tumors can be studied by microsatellite instability (MSI) analysis to assess for genomic aberrations, and immunohistochemistry (IHC) to evaluate for proteomic findings. MSI refers expansion (or, “instability” in size) of tracks of repetitive DNA (termed “microsatellites”), which occurs when there is a defective mismatch DNA repair system. IHC examines for absence of MMR protein subtypes (such as MLH1 and MSH2), which implies that the corresponding MMR gene has a pathogenic mutation in it, disrupting protein production. A combination of MSI and IHC can be used with high sensitivity and specificity to detect the approximately 5% of cases of CRC caused by the underlying inherited cancer predisposition Lynch syndrome. Lynch syndrome, or hereditary non-polyposis colon cancer (HNPPC), is caused by inherited, germline mutation (present in every cell of an individual) in genes involved in the MMR pathway, leading to frequent and younger colon, endometrial, and other cancers in an autosomal dominant pattern in families [1]. A patient’s personal medical history, family history, and tumor IHC and MSI results are combined to determine if the diagnosis of Lynch syndrome is appropriate. Specific surveillance and at-risk family member counseling is recommended for individuals with Lynch syndrome. In the much more frequent (~95%) cases of sporadic CRC not due to an inherited germline mutation, IHC and MSI results are also proving to be useful in prognosis and management [2]. It has recently been proposed that all CRC samples, regardless of patient’s age at diagnosis or family history, be tested for MMR deficiency and MSI to detect the rare Lynch syndrome cases [3], which may also aid in prognosis and management for the general population with CRC.

Management of CRC is also increasingly being informed by pharmacogenetic analysis. One of the most well-supported pharmacogenetic correlatations today involves CRC and the oncogene KRAS. KRAS was originally characterized from a colon cancer line and is a member of the RAS family of intracellular signal transducers. In wild-type form, KRAS contributes to tissue signaling and cell proliferation, differentiation, and senescence, and when mutated acts as a potent oncogene in many human cancers. More recently, a role for KRAS in drug response has been uncovered. Metastatic colorectal cancer tumors with KRAS mutations do not respond to specific anti-epidermal growth factor receptor (EGFR) monoclonal antibodies [5,6]. The hypothesized biologic basis for this strong pharmacogenetic association is that in the case of a gain-of-function KRAS mutation, the epidermal growth factor pathway is overactivated downstream of the EGFR receptor, bypassing any dampening of this pathway by EGFR-targeted antibody therapies [7]. Therefore, patients with advanced CRC harboring KRAS mutation will be expected to derive no benefit from anti-EGFR therapy, while losing valuable time in starting other more effective treatment and being exposed to potential adverse effects [8].

The proto-oncogene BRAF is another important player in colon cancer genetics. BRAF functions in the MAP kinase/ERK pathway, regulating cell differentiation and division [9]. The Val600-to-Glu (V600E) mutation in BRF, due to 1797T-A transversion in the gene, is commonly found in malignant melanoma, gastric and colorectal carcinoma, and other cancers [10]. Interestingly, this typical V600E BRAF mutation has not been identified in tumors with mutations in the KRAS gene, implying that BRAF and KRAS mutations exert equivalent effects in tumorigenesis after tumor initiation but before malignant conversion [11-13]. There is also a striking connection between BRAF and carcinogenesis in Lynch syndrome. The V600E BRAF mutation is almost always found in cancer mismatch repair-deficient cancers. Adding BRAF V600E mutation analysis is helpful in differentiating the hereditary Lynch syndrome cases: if the MMR protein MLH1, for instance, is absent on IHC, and the V600E BRAF mutation is present, the CRC is likely a sporadic case not representing underlying Lynch syndrome [14]. However, if MLH1 is absent and V600E BRAF mutation is absent, the case more likely reflects Lynch syndrome, and molecular genetic analysis of MLH1 is indicated along with appropriate counseling of the patient and at risk family members. In effect, BRAF testing is used as an exclusion criterion for Lynch syndrome diagnosis. New research indicates BRAF analysis may also have a role in advanced melanoma management for determining optimal therapy.

Use of pharmacogenetic testing and mismatch repair pathway analysis in CRC is currently institution-and-provider-dependent. The author’s primary institution offers testing for MMR, KRAS, and BRAF in-house. Molecular genetic testing of KRAS and BRAF is available on a case-by-case basis when appropriate, and a pilot program is being considered to test all colorectal cancer samples routinely for MMR protein expression. The experience with this practice, and other clinical studies, will provide needed data on the outcomes of pharmacogenetic and genomic testing in colon cancer management, and whether more widespread adoption will improve outcomes.

*Corresponding author: Leslie Cole Manace, MD MPhil, Department of Genetics, Kaiser Permanente Oakland Medical Center, Department of Medicine, University of California, San Francisco, USA, E-mail: leslie.c.manace@kp.org

Received March 15, 2011; Accepted March 17, 2011; Published March 19, 2011

Citation: Manace LC (2011) To Test or Not To Test: Colon Cancer Pharmacogenetics and Predisposition Genetics. J Pharmacogenom Pharmacoproteomics 2:e101. doi:10.4172/2153-0645.1000e101

Copyright: © 2011 Manace LC. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Journal of Pharmacogenomics & Pharmacoproteomics

Volume 1 • Issue 1 • 1000101

ISSN: 2153-0645 JPP, an open access journal
References


