PRIMERS IN CLINICAL AND TRANSLATIONAL RESEARCH

Advantages and Some Remaining Challenges in Hereditary Gastrointestinal Cancer Panel Testing

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Colorectal cancer affects 1 in 20 men and women in their lifetime. About 30% of these cases have been shown to be familial while only about 5% are associated with a highly penetrant hereditary colon cancer syndrome. In many familial cases, however, no mutation in the commonly implicated CRC genes is found. With the development of next-generation sequencing, testing laboratories are now able to offer hereditary gastrointestinal panel testing, which allows for the simultaneous sequencing of a much broader set of genes associated with CRC. We discuss the advantages and disadvantages of such testing to inform best clinical practice.

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INTRODUCTION

As early as the beginning of the 20th century, clinicians began to document hereditary predispositions for intestinal cancer, consistent with Lynch syndrome.1 In recent decades, advances in genetic technology and research have allowed for molecular identification of mutations in these hereditary cancer families and the implementation of prevention strategies for earlier diagnoses and even prolonged survival.2 Today, consensus guidelines indicate that patients with personal or family history of early onset, multiple, or more rare forms of intestinal cancers or polyps are suspicious for a hereditary cancer syndrome. Thus, these patients should be offered genetic evaluations for consideration of molecular testing by their providers or a genetic specialist.3 Historically, when a genetic evaluation determined the need for molecular testing it was primarily conducted as single gene testing. Yet, in this process, many families with striking cancer histories did not have a mutation in the gene interrogated.4

More recently, molecular testing technologies have evolved to incorporate next-generation sequencing (NGS). NGS allows for the parallel testing of multiple genes by sequencing millions of small DNA fragments simultaneously compared to Sanger sequencing which is only able to sequence one fragment of DNA per reaction. This significant increase in throughput allows for a much cheaper alternative and broader scope in genetic testing since it allows for multiple closely related syndromes of varied risk or penetrance to be offered in a single test.5 The recent implementation of this new technology has resulted in a wider variety of testing options including single gene testing, broader cancer-site specific panel testing (such as colon versus breast), or pancancer panel testing.5

Types of genetic testing available for hereditary GI cancer syndromes. Current testing options include single gene testing, cancer-site specific panel testing, or pancancer panel testing. Complete single gene testing should provide sequencing, deletion, and duplication testing for a single gene indicated by the provider. In contrast, a cancer-site specific panel test would provide testing for a broad group of genes all connected by risk for a specific cancer type. One example is the ColoNext panel testing available through Ambry Genetics. The ColoNext panel includes 17 genes currently clinically associated with increased colon or intestinal cancer risks. Finally, a pancancer panel test would include a larger group of genes related to multiple types of hereditary cancers, unspecific to a particular organ or organ system. The myRisk panel test from Myriad Genetics is an example of a pancancer panel test and includes genes involved in risks for multiple organ systems. Table 1 summarizes genetic panels currently offered by a variety of genetic testing companies.

Advantages and disadvantages of cancer gene panel testing compared to single syndrome testing. Both the New England Journal of Medicine (NEJM) and the American Society of Clinical Oncology (ASCO) released statements agreeing that multiple factors should be used to guide what type of genetic test to order.3,4 Patient specific factors to consider include but are not limited to the clarity of the patient’s personal or familial characteristics or lack thereof, the patient’s preference and tolerance regarding the possibility of ambiguous or incidental findings, the time in which results may be needed to guide surgical decisions and lastly consideration of insurance coverage.4,6,7 Panel testing can be beneficial for patients as long as providers and patients are aware of its limitations. There are several advantages and disadvantages of single syndrome versus panel testing (Table 2).

Some common advantages of panel testing include higher diagnostic yield (more comprehensive), less dependent on a
### Table 1: Commercially available genetic testing panels and included genes

| Company              | Panel name          | Testing category                  | Genes included on panel                                                                 |
|----------------------|---------------------|-----------------------------------|-----------------------------------------------------------------------------------------|
| Myriad Genetics      | COLARIS             | Single gene/syndrome panel        | MLH1, MSH2, EPCAM, MSH6, PMS2, and MYH                                                 |
|                      | COLARIS AP          | Cancer-site specific panel        | APC and MYH, BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, EPCAM, APC, MSH6, MSH2, PMS2,        |
|                      | MyRisk              | Pancancer panel                   |                                           |
|                      |                     |                                   |                                          |
| GeneDx               | Lynch colorectal    | Cancer-site Specific Panel        | APC, EPCAM, MLH1, MSH2, MSH6, MUTYH, and PMS2                                         |
|                      | high risk           | (high risk only)                  |                                           |
|                      | Colo rectal cancer  | Cancer-site Specific Panel        | APC, ATM, AXIN2, BMPR1A, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2, POLD1,    |
|                      |                    |                                   |                                           |
|                      | Comprehensive       | Pancancer panel                   | APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, GEM1, |
|                      | cancer panel        |                                   |                                           |
|                      |                     |                                   |                                           |
| Ambry Genetics       | Lynch panel         | Single gene/syndrome test         | APC, BMPR1A, CDH1, CHEK2, EPCAM, GEM1, MLH1, MSH2, MSH6, MUTYH, PMS2, POLD1, POLE,     |
|                      | ColoNext            | Cancer-site specific panel        |                                           |
|                      | CancerNext          | Pancancer panel                   | APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, GEM1, |
|                      |                    |                                   |                                           |
|                      | Invitae             | Colorectal cancer                 | APC, ATM, AXIN2, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, GEM1, |
|                      |                    | Cancer-site specific panel        |                                           |
|                      | VistaSeq            | Pancancer panel                   | APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, GEM1, |
|                      |                    |                                   |                                           |
|                      | Integrated Genetics (Lap Corp) | VistaSeq Pancancer panel test |                                           |
|                      | Quest Diagnostics   | Common hereditary cancer          | APC, ATM, AXIN2, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, GEM1, |
|                      | Glantage            | Pancancer panel                   |                                           |
|                      | MYvantage           | Pancancer panel test              | APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, (p14ARF and p16),   |
|                      |                    |                                   |                                           |

VUS, variants of unknown significance.

### Table 2: Advantages and disadvantages of single/limited gene testing compared to larger panel testing

| Single/limited gene testing | Hereditary colon/intestinal cancer panel testing | Pancancer testing |
|-----------------------------|-----------------------------------------------|-------------------|
| Advantages                  | Comprehensive test but specific for hereditary colon cancer  | Most comprehensive hereditary cancer test |
|                            | Low change of incidental findings              | Some overlap between breast and colon cancer syndromes |
|                            | More time and cost effective than single/limited gene testing |                              |
| Disadvantages               | Higher change of VUS                           | High chance of Incidental finding and/or VUS |
| Best for                    | Personal and family histories suggestive of a hereditary colon cancer syndrome but either suggestive of 2 or more syndromes or with limited information on polyps | Personal and family histories of multiple cancer types including but not limited to colon, breast and gynecological cancers |
|                            | Personal and family history strongly suggestive of a single syndrome | Cases where insurance may only cover one test |

Absent/limited family history
The patient presented with limited family history and limited definitive pathology on polyps. The patient reported limited extended family history. Genetic counseling due to more than 20 nonspecific hyperplastic polyps was completed. Results returned showing a pathogenic mutation in a gene called SMAD4, indicating a molecular hereditary cancer diagnosis of Juvenile Polyposis Syndrome and possibly Hereditary Hemorrhagic Telangiectasia. Either diagnosis is important in knowing the appropriate medical management for the patient and his affected family members.

The most recognized disadvantage of panel testing compared to single syndrome testing is a higher rate of ambiguous results. This can include variants of unknown significance (VUS) or mutations in genes with limited medical management. Both of these findings can lead to a lack of clear guidance in patient care. An example of this is highlighted in the case of a 33-year old Hispanic male who was tested using a colon specific panel test due to his young colon cancer. The testing identified a VUS in a gene called CDH1. A pathogenic mutation in this gene causes Hereditary Diffuse Gastric Cancer Syndrome, a rare hereditary gastric syndrome, for which the medical recommendation is to have a prophylactic gastrostomy. We discussed with the patient since there is limited information it is medically recommended to treat this variant as a negative result. While at this time we do not believe this particular variant is related to our patient’s personal history it is an ambiguous result that will need to be followed. One way to mitigate this potential limitation of panel testing is to pre-counsel patients regarding the three possible results they could receive from genetic testing (positive, negative, and VUS) and better prepare patients for the possibility of unclear results (Figure 1).

CONCLUSION

In general, single gene/limited testing is most appropriate when a clinical diagnosis already exists or one specific condition is indicated based on patient or family history. Whereas panels can function when pedigrees are suggestive of multiple syndromes or clear indications are lacking. While the discussion above provides a general road map to guide non-genetics providers, it is vital in the context of the evolving complex nature of cancer genetics, to recognize that a multitude of considerations exist when determining the most appropriate test for a patient. Professional organizations including ASCO and the National Comprehensive Cancer Network agree that the pre and post-test traditional counseling model including a complete family history is valuable for all suspected hereditary patients regardless of what type of genetic testing occurs. Therefore many providers may wish to refer suspected hereditary patients directly to a genetic professional. Accordingly, NCCN clinical guidelines provide annual updates with specific recommendations for when and whom to refer to genetics. The most basic guidelines for referral of hereditary risk include but are not limited to gastrointestinal malignancy diagnosed; under 50 years of age, with rarer pathologies, with multiple affected relatives, or when more than 10 polyps are recognized.

Figure 1 Clinical management recommendations based on the three possible results from genetic testing.

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CONFLICT OF INTEREST

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