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# Hereditary Cancer Panel Ordering Trends: a Review of Lynch Specimens Submitted to LabCorp between 8/1/2015 and 12/1/2017

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## I. Background

### Hereditary colon cancer and Lynch syndrome

As the third most commonly diagnosed cancer, colorectal cancer (CRC) in the United States accounted for 50,260 deaths and 135,430 newly diagnosed cases in 2017 (Siegel et al.). Of these diagnosed cases, an estimated 5% of CRC etiologies are attributed to the inheritance of a gene with a known increased susceptibility for cancer development (Byrne and Tsikitis). Several genes are well established in their association with colorectal cancer and sometimes as comorbidity with other cancers (Byrne and Tsikitis).

Approximately half of cases of hereditary colorectal cancer are thought to be associated with Lynch syndrome (Byrne and Tsikitis). Lynch syndrome is a hereditary cancer condition caused by germline pathogenic variants in one of four distinct mismatch repair genes or less commonly, the gene *EPCAM*. In addition to colorectal cancer, patients with Lynch syndrome are also at risk for uterine, ovarian, stomach, small intestine, and other cancers. The remaining half of hereditary colorectal cancer is due to other, less common but well established conditions such as familial adenomatous polyposis, juvenile polyposis syndrome, and *MUTYH*-associated polyposis (Byrne and Tsikitis). Additionally, with the advent of next generation sequencing (NGS), newly emerging risk genes such as *POLE* and *POLD1* can be considered in a work-up for a family history of colorectal cancer.

Full gene sequencing and deletion/duplication analysis enables the simultaneous testing of multiple genes with speed, accuracy, and reduced cost compared to previous technologies. Hereditary multi-gene panels that focus on specific cancers, like CRC, or broadly screen for a variety of different types of cancers are offered by LabCorp. The panels are available in several different menu configurations for patients with concerns regarding their hereditary cancer risks for one or multiple cancer types.

## II. Introduction

LabCorp genetic counselors (GC) review all incoming hereditary cancer test orders. LabCorp's germline Lynch syndrome testing has been offered since October 2014 and includes comprehensive, deletion/duplication, and targeted sequence analysis for the *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* genes. In all, there are 16 distinct test codes from which an ordering provider may choose. Since mid-2015, LabCorp genetic counselors review each order for appropriateness and indication of testing. The genetic counselor will contact the ordering provider if the indication for Lynch syndrome testing is unclear or the patient may benefit from a more comprehensive test.

The option to update to more comprehensive testing became available when LabCorp launched the VistaSeq® Hereditary Cancer Panel (27 genes) on 8/24/2015, VistaSeq Hereditary Cancer Panel Without *BRCA* (25 genes) on 3/28/2016, and 10 additional clinically targeted panels on 5/1/2017.

This study explored the difference in the number of Lynch syndrome orders updated to a hereditary cancer panel in the time period after each addition of new panel options. Any test order using one or more Lynch test codes was included. Medically actionable results stemming from these test updates were reviewed.

## III. Methods

Specimens submitted to LabCorp between 8/1/2015 and 12/1/2017 and ordered for Lynch testing were reviewed for any test updates to a hereditary cancer panel facilitated by a LabCorp GC. Further, testing outcomes and results were recorded for each specimen. These data were analyzed for differences in number of tests updated depending on panel options available, differences in rates of medically actionable results, and the cancer association of the gene in specimens with medically actionable results. To improve future ordering, the specialty of ordering provider was recorded.

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## IV. Results

This dataset spanned all three VistaSeq panel test launches and compared conversion rates. Lynch test orders were converted at a rate of 5% (n=20) to the original expanded hereditary cancer test, VistaSeq 27 gene panel. Later, the conversion rate increased to 13% (n=86) after the second panel, VistaSeq without *BRCA* (25 genes) launched. Following the introduction of smaller, more targeted panel options, the Lynch-VistaSeq panel conversion rate increased again to 19% (n=73). Of the 179 total specimens converted and tracked through final reporting, 95 completed insurance preauthorization and proceeded to testing (53%). Of those 95 specimens tested, 10 patients (11%) had medically actionable results and 9 (90%) of these patients had findings in genes not associated with Lynch syndrome. None of these 10 specimens originally ordered for Lynch testing were submitted by a genetics professional.

Other findings included 31 specimens with variants of uncertain significance of which 15 were found in non-Lynch genes. The remaining 54 specimens tested negative for the hereditary cancer gene panels.

Of the 95 tested specimens, 63 Lynch syndrome orders were updated to clinically non-specific hereditary cancer panels (VistaSeq 27 or 25). Medically actionable results were identified in 5 patients, while variants of uncertain significance were found in 25 patients. The remaining 33 specimens had negative results.

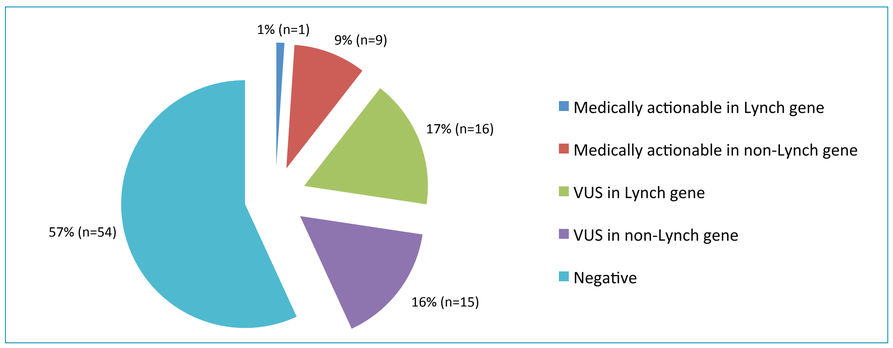
Of the 95 tested specimens, 32 specimens were updated to clinically targeted hereditary cancer panels. Medically actionable results were identified in 5 patients while variants of uncertain significance were found in 6 patients. The remaining 21 specimens had negative results.

### Table 1. 10 specimens with medically actionable results, 9 of which (90%) were in non-Lynch related genes

| Specimen | Original Order | Clinical Indication | Updated Order | Medically Actionable Result | Classification |
|---|---|---|---|---|---|
| 1 | MLH1/MSH2 | Mother with uterine cancer at 35y | VistaSeq 27 gene | *NBN* c.2071-1G>A | Likely pathogenic |
| 2 | MLH1/MSH2/ MSH6/PMS2/ EPCAM and BRCA1/2 | Personal hx of ovarian cancer at 80y | VistaSeq 27 gene | *BRIP1* c.2392C>T | Pathogenic |
| 3 | MLH1/MSH2/ MSH6 | Personal hx of CRC in late 30s | VistaSeq 25 gene | *CHEK2* c.1100delC | Pathogenic |
| 4 | MLH1 deletion/ duplication | Reported familial *CHEK2* variant | VistaSeq 25 gene | *CHEK2* c.1100delC | Pathogenic |
| 5* | MLH1/MSH2/ MSH6/PMS2 | Personal hx of uterine cancer at 43y. Fam hx of early onset CRC and uterine cancer. Reported family member positive for Lynch syndrome.* | VistaSeq 25 gene | *MLH1* c.1852_1854delAAG | Pathogenic |
| 6 | EPCAM | Mother with ovarian cancer at 26y, grandfather with CRC at 80y | VistaSeq Breast/ GYN, 25 gene | *BRCA1* c.68_69delAG | Pathogenic |
| 7 | MLH1 targeted sequencing | Two sisters with CRC at 48y and 51y | VistaSeq High Risk Colorectal, 7 gene | *MUTYH* c.1187G>A | Pathogenic |
| 8 | MLH1/MSH2/ MSH6/PMS2 | Family hx polyposis | VistaSeq Colorectal, 22 genes | *APC* 2161_2170delG GAAGTGCTG | Pathogenic |
| 9 | MSH2 | Personal and family hx of CRC and adenomatous polyposis | VistaSeq High Risk Colorectal, 7 gene | *APC* c.1958+1_1958+2 dupGT | Likely Pathogenic |
| 10 | MLH1/MSH2/ MSH6/PMS2 | Family hx of CRC | VistaSeq High Risk Colorectal, 7 gene | *APC* c.677delA | Likely Pathogenic |

*This specimen was updated to a multi-gene hereditary cancer panel for prior authorization reasons.

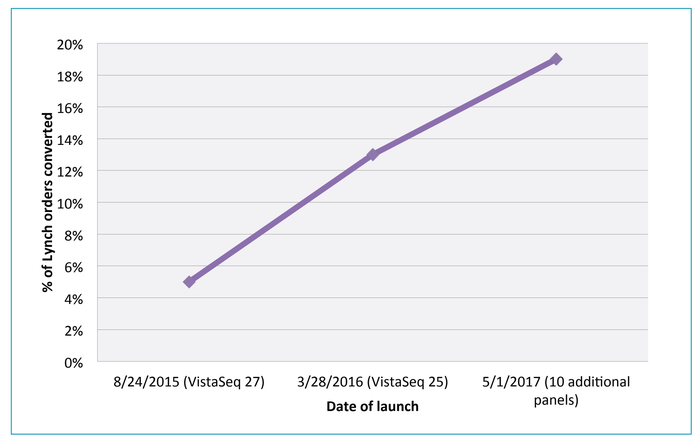
### Figure 2. Overview of types of results from converted orders (n=95)



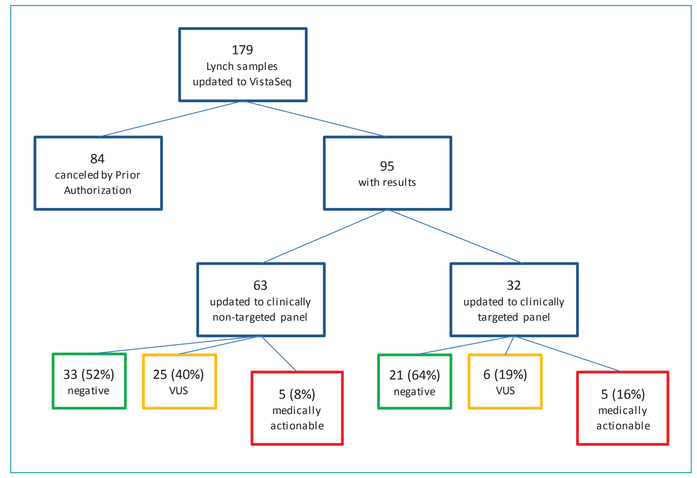

## V. Conclusions

The increase in conversion from a Lynch syndrome specific test to a hereditary cancer panel was significantly greater when more clinically targeted panel options were available. It is noted, however, that ordering physicians did not always choose the targeted panels even once the options became available. These data showed that large, multi-gene panels were able to return a larger than expected number of medically actionable results in genes that were not associated with Lynch syndrome. In some cases the medically actionable results were not related to the indication for testing or the known personal or family cancer history. This suggests that order review and client contact by laboratory genetic counselors can help identify medically actionable results in genes not otherwise considered for testing in patients. Additionally, these data highlight the complexity of the potential results from hereditary cancer testing and reaffirm the need for clinical genetic counseling before and/or after ordering genetic testing.

### Figure 1. % of Lynch orders converted after panel launches




### Figure 3. Flow Chart of Updated Lynch Testing Samples Through Reporting Process




## VI. Limitations

A consumer bias may have influenced providers to convert Lynch test orders to VistaSeq panels which include the five Lynch genes. Preauthorization services are performed for VistaSeq panels, but not for any of the Lynch test codes.

## VII. References

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