Comprehensive Inherited Cancer Panel Including Confirmation For Lynch Syndrome

Introduction

Comprehensive Inherited Cancer Panel Including Confirmation for Lynch Syndrome is designed for patients who have been diagnosed with colorectal cancer, endometrial cancer or ovarian cancer and demonstrated to have MMR protein deficiency by Immunohistochemistry IHC and/or Microsatellite Instability MSI. The panel evaluates 39 genes linked to Breast, Ovarian, Endometrial, Colorectal, Lynch Syndrome, Gastric, Melanoma, Pancreatic, Polyposis, Prostate, Renal, Thyroid/Parathyroid and Uterine, and Other Major Syndromic Cancers in conjunction with confirming the presence of germline mutations in the MMR genes MLH1, MSH2, MSH6 and PMS2 and deletions in ECAMP to establish the diagnosis of Lynch Syndrome.

Until recently, most testing for cancer genetic risk involved traditional exon-by-exon Sanger sequencing of each candidate gene. In contrast, the advent of Next Generation Sequencing allows parallel sequencing of millions of short pieces of DNA simultaneously. Prior to Next Generation Sequencing, genetic testing usually started with the most commonly involved genes and proceeded to less likely genes only when clinical suspicion was very high. However, cancer panels allow testing of all genes in parallel without substantially increasing the cost, leading to a different clinical algorithm in which all known contributing genes can be assayed at first evaluation.


"Approximately 15% of all ovarian cancers are attributable to a BRCA1 or BRCA2 mutation. An additional 5-6% of ovarian cancers have gene mutations in other genes including the Lynch syndrome genes (MLH1, MSH2, MSH6, PMS2), and BRIP1, RAD51D, RAD51C, PALB2, BARD1, and TP53".

“Advantages of cancer gene panels include decreased cost and improved efficiency of cancer genetic testing by decreasing the time involved, number of patient visits, and number of tests sent. A negative genetic test is more reassuring at eliminating the likelihood of inherited risk when all known genes for that phenotype have been assayed.”

Data confirms the benefits of multigene panel testing among patients at risk for hereditary ovarian cancer.

Data presented at American Society for Clinical Oncology ASCO in June 2014 by Lucy R. Langer, MD, from Compass Oncology and U.S. Oncology illustrated that in 648 patients with ovarian cancer, 34% of the pathogenic mutations identified were outside of BRCA1/2 and the genes associated with Lynch syndrome. This means that 42 patients with cancer-causing mutations would have been missed if they were simply tested for BRCA1/2 or Lynch syndrome mutations and there would not have been an opportunity to optimize patient care based on hereditary cancer status.

n = 648
Lynch Syndrome (LS) is an autosomal dominant familial cancer syndrome caused by mutations in multiple susceptibility genes. Current literature suggests Lynch syndrome affects 28,000 individuals annually. It is estimated that 1 in 35 colorectal carcinomas is associated with Lynch Syndrome. The hallmark of Lynch syndrome associated cancers is the presence of DNA mismatch repair (MMR) protein deficiency in the MLH1, MSH2, MSH6, PMS2, or deletions in EPCAM (also known as TACSTD1) genes. These mutations are associated with an increased lifetime risk for colorectal cancer (CRC) and other malignancies within the tumor spectrum including at least endometrial, ovarian, gastric, small bowel, urothelial, hepatobiliary tract, sebaceous and pancreatic cancers.

Professional Medical Societies endorse the emergence of universal screening for Lynch syndrome along with the ability of immunohistochemistry (IHC) to identify DNA MMR protein deficiency on tumor tissue. Greater than 90% of LS tumors are MSI-H and/or lack expression of at least one of the MMR (mismatch repair) proteins by IHC. 10-15% of sporadic colon cancers exhibit abnormal IHC and are MSI-H due to abnormal methylation of the MLH1 gene promoter rather than due to Lynch Syndrome. Mutant BRAFV600E is found in the majority of sporadic MSI-H CRC and is rarely found in Lynch syndrome related CRC. Thus the presence of an abnormal IHC test increases the possibly of LS, but does not make a definitive diagnosis. When DNA MMR loss of protein expression is identified by IHC on tumor tissue, genetic testing must be performed to confirm germline mutation. Using the most advanced sequencing technology, Otogenetics Inherited Cancer Panel Testing is to confirm the presence of germline mutation(s) in MMR genes MLH1, MSH2, MSH6, PMS2 and deletions in EPCAM genes in a single test. Individuals with a germline mutation are then confirmed as Lynch Syndrome patients.

In individuals with Lynch syndrome, the lifetime risk of colon cancer may be as high as 75% by the age of 70 years, with an average age onset of 45 years in MLH1 and MSH2 mutation carriers. Mutations in MLH1 and MSH2 account for 70-90% of families with Lynch Syndrome. The risk of colon and endometrial cancer is less in MSH6 and PMS2 mutation carriers, although the cancer risk may not be lower for MSH6 carriers if one takes the data out to age 80. While individuals with a single MLH1, MSH2, MSH6 and PMS2 mutation develop cancers in mid-life, individuals with biallelic MLH1, MSH2, MSH6 and PMS2 mutations have a distinctive phenotype and tumor spectrum, and often develop cancer as early as the first decade of life. First-degree relatives of mutation carriers have a 50% probability of having the same germ-line mutation. Families of Lynch syndrome patients can benefit from genetic screening and counseling.

In addition to being a confirmatory test for Lynch Syndrome, the panel evaluates 39 genes Linked to Breast, Ovarian, Endometrial, Colorectal, Lynch Syndrome, Gastric, Melanoma, Pancreatic, Polyposis, Prostate, Renal, Thyroid/Parathyroid and Uterine, and Other Major Syndromic Cancers.