Protocol

Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing

(20493)

Medical Benefit		**Effective Date**: 01/01/14	**Next Review Date**: 09/17
Preauthorization	No	**Review Dates**: 09/13, 09/14, 09/15, 09/16	

This Protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With a personal and/or family history suggesting an inherited cancer syndrome	Interventions of interest are: • Next-generation sequencing panels	Comparators of interest are: • Individual mutation testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity

Description

Numerous genetic mutations are associated with inherited cancer syndromes. Patients may have a personal and/or family history of cancer that suggests that the cancer is syndrome-related. Some patients may meet clinical criteria for one or more hereditary cancer syndromes, and it has been proposed that mutation testing using next-generation sequencing technology to analyze multiple genes at one time (panel testing) can optimize testing in these patients compared to testing for individual mutations.

Summary of Evidence

For individuals who have a personal and/or family history suggesting an inherited cancer syndrome who receive testing with a next-generation sequencing panel, the evidence includes mainly reports describing the frequency of detecting mutations in patients referred for panel testing. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Published data on analytic validity is lacking, but it has been reported to be high, approaching that of direct sequencing of individual genes. Clinical validity studies have generally reported the results of the frequency with which mutations are identified using large panels, and occasionally have reported the variant of unknown significance rate. Published data on clinical utility is lacking, and it is unknown whether use of these panels improves health outcomes. Many panels include mutations that are considered to be of moderate or low penetrance, and management guidelines are not well-defined in these patients, leading to the potential for harm in identifying one of these nonhighly penetrant mutations. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy

Genetic cancer susceptibility panels using next generation sequencing are considered **investigational**.

Policy Guidelines

Although genetic cancer susceptibility panels using next-generation sequencing are considered investigational, there may be individual components of the panel that are medically necessary.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Medicare Advantage

Note: For information on the use of genomic sequential analysis panels as they relate to non-small-cell-lung cancer under Medicare Advantage, please see the Molecular Analysis for Targeted Therapy of Non-Small-Cell-Lung Cancer Protocol.

Background

Genetic testing for cancer susceptibility may be approached by a focused method that involves testing for well-characterized mutations based on a clinical suspicion of which gene(s) may be the cause of the familial cancer. Panel testing involves testing for multiple mutations in multiple genes at one time.

Several companies, including Ambry Genetics and GeneDx, offer genetic testing panels that use next- generation sequencing (NGS) methods for hereditary cancers. NGS refers to one of several methods that use massively parallel platforms to allow the sequencing of large stretches of DNA. Panel testing is potentially associated with greater efficiencies in the evaluation of genetic diseases; however, it may provide information on genetic mutations of unclear clinical significance or which would not lead to changes in patient management. Currently available panels do not include all genes associated with hereditary cancer syndromes. In addition, these panels do not test for variants (i.e., single-nucleotide polymorphisms [SNPs]), which may be associated with a low, but increased cancer risk.

NGS Cancer Panels

A list of the genes that are included in these panels is given in Tables 1 and 2, followed by a brief description of each gene.

Table 1. Ambry Genetics Hereditary Cancer Panel Tests

Gene Tested	BRCAplus	GYNplus	BreastNext	OvaNext	ColoNext	PancNext	PGLNext	RenalNext	CancerNext
BRCA1	X	X	X	X		X			X
BRCA2	X	X	X	X		X			X
ATM			X	X		X			X

Gene Tested	BRCAplus	GYNplus	BreastNext	OvaNext	ColoNext	PancNext	PGLNext	RenalNext	CancerNext
BARD1			X	X					X
BRIP1			X	X					X
MRE11A			X	X					X
NBN			X	X					X
RAD50			X	X					X
RAD51C			X	X					X
PALB2			X	X		X			X
STK11	X		X	X	X	X			X
CHEK2			X	X	X				X
PTEN	X	X	X	X	X			X	X
TP53	X	X	X	X	X	X		X	X
CDH1	X		X	X	X				X
MUTYH			X	X	X				X
MLH1		X		X	X	X		X	X
MSH2		X		X	X	X		X	X
MSH6		X		X	X	X		X	X
EPCAM		X		X	X	X		X	X
PMS2		X		X	X	X		X	X
APC					X	X			X
BMPR1A					X				X
SMAD4					X				X
NF1			X	X			X		X
RAD51D			X	X					X
CDK4									X
CDKN2A						X			X
RET							X		
SDHA							X	X	
SDHAF2							X		
SDHB							X	X	
SDHC							X	X	
SDHD							X	X	
TMEM127							X		
VHL							X	X	
FH								X	
FLCN								X	
MET								X	
MITF								X	
TSC1								X	
TSC2								X	

Table 2. GeneDx Hereditary Cancer Panel Tests

Gene Tested	Breast/Ovarian Cancer Panel	Breast Cancer High-Risk Panel	Endometrial Cancer Panel	Lynch/Colorectal Cancer High-Risk Panel	Colorectal Cancer Panel	Pancreatic Cancer Panel	Comprehensive Cancer Panel
BRCA1	X	X	X			X	X
BRCA2	X	X	X			X	X
ATM	X				X	X	X
BARD1	X						X
BRIP1	X						X
MRE11A							

Gene Tested	Breast/Ovarian Cancer Panel	Breast Cancer High-Risk Panel	Endometrial Cancer Panel	Lynch/Colorectal Cancer High-Risk Panel	Colorectal Cancer Panel	Pancreatic Cancer Panel	Comprehensive Cancer Panel
NBN	X						
RAD50							
RAD51C	X						X
PALB2	X		X			X	X
STK11	X	X			X	X	X
CHEK2	X		X		X		X
PTEN	X	X	X		X		X
TP53	X	X	X		X	X	X
CDH1	X	X			X		X
MUTYH			X	X	X		X
MLH1	X		X	X	X	X	X
MSH2	X		X	X	X	X	X
MSH6	X		X	X	X	X	X
EPCAM	X		X	X	X	X	X
PMS2	X		X	X	X	X	X
APC				X	X	X	
BMPR1A					X		X
SMAD4					X		X
RAD51D	X						X
CDK4						X	X
CDKN2A						X	X
VHL						X	X
XRCC2	X				X	X	X
FANCC							X
AXIN2					X		X

Mayo Clinic also offers a hereditary colon cancer multigene panel analysis, which includes the genes in the Ambry Genetics ColoNext, with the addition of two other low-risk genes (*MLH3*, *AXIN2*). The University of Washington offers the BROCA Cancer Risk Panel, which is a NGS panel that includes the following mutations: *AKT1*, *APC*, *ATM*, *ATR*, *BAP1*, *BARD1*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDK4*, *CDKN2A*, *CHEK1*, *CHEK2*, *CTNNA1*, *FAM175A*, *GALNT12*, *GEN1*, *GREM1*, *HOXB13*, *MEN1*, *MLH1*, *MRE11A*, *MSH2* (+*EPCAM*), *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PIK3CA*, *PPM1D*, *PMS2*, *POLD1*, *POLE*, *PRSS1*, *PTEN*, *RAD50*, *RAD51*, *RAD51C*, *RAD51D*, *RET*, *SDHB*, *SDHC*, *SDHD*, *SMAD4*, *STK11*, *TP53*, *TP53BP1*, *VHL*, and *XRCC2*.[1] The University of Washington also offers the ColoSeq™ gene panel, which includes 19 genes associated with Lynch syndrome (hereditary nonpolyposis colorectal cancer), familial adenomatous polyposis (FAP), *MUTYH*-associated polyposis, hereditary diffuse gastric cancer, Cowden syndrome (CS), Li-Fraumeni syndrome (LFS), Peutz-Jeghers syndrome (PJS), Muir-Torre syndrome, Turcot syndrome, and juvenile polyposis syndrome (JPS): *AKT1*, *APC*, *BMPR1A*, *CDH1*, *EPCAM*, *GALNT12*, *GREM1*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *PIK3CA*, *PMS2*, *POLE*, *POLD1*, *PTEN*, *SMAD4*, *STK11*, and *TP53*.[2]

Myriad Genetics (Salt Lake City, UT) offers the myRisk™ NGS panel, which includes testing for the following genes: *APC*, *ATM*, *BARD1*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDK4*, *CDKN2A* (p16INK4a and p14ARF), *CHEK2*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PMS2*, *PTEN*, *RAD51C*, *RAD51D*, *SMAD4*, *STK11*, and *TP53*.

Genes Included in NGS Panels

The following is a summary of the function and disease association of major genes included in NGS panels. This summary is not meant to be a comprehensive list of all genes included in all panels.

BRCA1 and *BRCA2* Mutations

BRCA1 and *BRCA2* germline mutations are associated with hereditary breast and ovarian cancer (HBOC) syndrome, which are associated most strongly with increased susceptibility to breast cancer at an early age, bilateral breast cancer, male breast cancer, ovarian cancer, cancer of the fallopian tube, and primary peritoneal cancer. *BRCA1* and *BRCA2* mutations are also associated with increased risk of other cancers, including prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer.

APC Mutations

APC germline mutations are associated with FAP and attenuated FAP. FAP is an autosomal dominant colon cancer predisposition syndrome characterized by hundreds to thousands of colorectal adenomatous polyps, and accounts for about 1% of all colorectal cancers (CRCs).

ATM Mutations

ATM is associated with the autosomal recessive condition ataxia-telangiectasia. This condition is characterized by progressive cerebellar ataxia with onset between the ages of one and four years, telangiectasias of the conjunctivae, oculomotor apraxia, immune defects, and cancer predisposition, particularly leukemia and lymphoma.

BARD1, BRIP1, MRE11A, NBN, RAD50, and RAD51C Mutations

BARD1, *BRIP1*, *MRE11A*, *NBN*, *RAD50*, and *RAD51C* are genes in the Fanconi anemia/*BRCA* pathway. Mutations in these genes are estimated to confer up to a four-fold increase in the risk for breast cancer.

BMPR1A and SMAD4 Mutations

BMPR1A and *SMAD4* are genes mutated in JPS and account for 45% to 60% of cases of JPS. JPS is an autosomal dominant disorder that predisposes to the development of polyps in the gastrointestinal tract. Malignant transformation can occur, and the risk of gastrointestinal cancer has been estimated from 9% to 50%.

CHEK2 Mutations

CHEK2 gene mutations confer an increased risk of developing several different types of cancer, including breast, prostate, colon, thyroid, and kidney. *CHEK2* regulates the function of BRCA1 protein in DNA repair and has been associated with familial breast cancers.

CDH1 Mutations

CDH1 germline mutations are associated with lobular breast cancer in women and with hereditary diffuse gastric cancer. The estimated cumulative risk of gastric cancer for *CDH1* mutation carriers by age 80 years is 67% for men and 83% for women. *CDH1* mutations are associated with a lifetime risk of 39% to 52% of lobular breast cancer.

EPCAM, MLH1, MSH2, MSH6, and PMS2 Mutations

EPCAM, *MLH1*, *MSH2*, *MSH6*, and *PMS2* are mismatch repair genes associated with LS (HNPCC). LS is estimated to cause 2% to 5% of all colon cancers. Lynch syndrome is associated with a significantly increased risk of several types of cancer—colon cancer (60%-80% lifetime risk), uterine/endometrial cancer (20%-60% lifetime risk), gastric cancer (11%-19% lifetime risk) and ovarian cancer (4%-13% lifetime risk). The risks of other types of cancer, including small intestine, hepatobiliary tract, upper urinary tract, and brain, are also elevated.

MUTYH Mutations

MUTYH germline mutations are associated with an autosomal recessive form of hereditary polyposis. It has been

reported that 33% and 57% of patients with clinical FAP and attenuated FAP, respectively, who are negative for mutations in the *APC* gene, have *MUTYH* mutations.

PALB2 Mutations

PALB2 germline mutations are associated with an increased risk of pancreatic and breast cancer. Familial pancreatic and/or breast cancer due to *PALB2* mutations is inherited in an autosomal dominant pattern.

PTEN Mutations

PTEN mutations are associated with *PTEN* hamartoma tumor syndrome (PHTS), which includes CS, Bannayan-Riley-Ruvalcaba syndrome, and Proteus syndrome. CS is characterized by a high risk of developing tumors of the thyroid, breast, and endometrium. Affected persons have a lifetime risk of up to 50% for breast cancer, 10% for thyroid cancer, and 5% to 10% for endometrial cancer.

STK11 Mutations

STK11 germline mutations are associated with PJS, an autosomal dominant disorder, with a 57% to 81% risk of developing cancer by age 70, of which gastrointestinal and breast cancers are the most common.

TP53 Mutations

TP53 are associated with LFS. People with *TP53* mutations have a 50% risk of developing any of the associated cancers by age 30 and a lifetime risk up to 90%, including sarcomas, breast cancer, brain tumors, and adrenal gland cancers.

NF1 Mutations

Neurofibromin 1 (NF1) encodes a negative regulator in the *ras* signal transduction pathway. Mutations in the *NF1* gene have been associated with neurofibromatosis type 1, juvenile myelomonocytic leukemia, and Watson syndrome.

RAD51D Mutations

RAD51D germline mutations are associated with familial breast and ovarian cancers.

CDK4 Mutations

Cyclin-dependent kinase-4 (CDK4) is a protein-serine kinase involved in cell cycle regulation. Mutations in this gene are associated with a variety of cancers, particularly cutaneous melanoma.

CDKN2A Mutations

Cyclin-dependent kinase inhibitor 2A (*CDKN2A*) encodes proteins that act as multiple tumor suppressors through their involvement in two cell cycle regulatory pathways: the p53 pathway and the *RB1* pathway. Mutations or deletions in *CDKN2A* are frequently found in multiple types of tumor cells. Germline mutations in *CDKN2A* have been associated with risk of melanoma, along with pancreatic and central nervous system cancers.

RET Mutations

RET encodes a receptor tyrosine kinase; mutations in this gene are associated with multiple endocrine neoplasia syndromes (types IIA and IIB) and medullary thyroid carcinoma.

SDHA, SDHB, SDHC, SDHD, and SDHAF2 Mutations

SDHA, *SDHB*, *SDHC*, *SDHD*, and *SDHAF2* gene products are involved in the assembly and function of one component of the mitochondrial respiratory chain. Germline mutations in these genes are associated with the development of paragangliomas, pheochromocytomas, gastrointestinal stromal tumors, and a *PTEN*-negative CS (Cowden-like syndrome).

TMEM127 Mutations

Transmembrane protein 127 (*TMEM127*) germline mutations are associated with risk of pheochromocytomas.

VHL Mutations

VHL germline mutations are associated with Hippel-Lindau syndrome, an autosomal dominant familial cancer syndrome. This syndrome is associated with a variety of malignant and benign tumors, including central nervous system tumors, renal cancers, pheochromocytomas, and pancreatic neuroendocrine tumors.

FH Mutations

Fumarate hydratase (*FH*) mutations are associated with renal cell and uterine cancers.

FLCN Mutations

Folliculin (*FLCN*) acts as a tumor suppressor gene; mutations in this gene are associated with the autosomal dominant Birt-Hogg-Dube syndrome, which is characterized by hair follicle hamartomas, kidney tumors, and CRC.

MET Mutations

MET is a proto-oncogene that acts as the hepatocyte growth factor receptor. *MET* mutations are associated with hepatocellular carcinoma and papillary renal cell carcinoma.

MITF Mutations

Microphthalmia-associated transcription factor (*MITF*) is a transcription factor involved in melanocyte differentiation. *MITF* mutations lead to several auditory-pigmentary syndromes, including Waardenburg syndrome type 2 and Tietze syndrome. *MITF* variants are also associated with melanoma and renal cell carcinoma.

TSC1 Mutations

Tuberous sclerosis 1 (*TSC1*) and tuberous sclerosis 2 (*TSC2*) encode the proteins hamartin and tuberin, which are involved in cell growth, differentiation, and proliferation. Mutations in these genes are associated with the development of tuberous sclerosis complex, an autosomal dominant syndrome characterized by skin abnormalities, developmental delay, seizures, and multiple types of cancers, including central nervous system tumors, renal tumors (including angiomyolipomas, renal cell carcinomas), and cardiac rhabdomyomas.

XRCC2 Mutations

XRCC2 encodes proteins thought to be related to the RAD51 protein product that is involved in DNA double-stranded breaks. Variants may be associated with Fanconi anemia and breast cancer.

FANCC Mutations

*F*anconi-anemia complementation group C (*FANCC*) is one of several DNA repair genes that mutate in Fanconi anemia, which is characterized by bone marrow failure and a high predisposition to multiple types of cancer.

AXIN2 Mutations

AXIN2 mutations are associated with familial adenomatous polyposis syndrome, although the phenotypes associated with *AXIN2* mutations do not appear to be well characterized.

Hereditary Cancer and Cancer Syndromes

Hereditary Breast Cancer

Breast cancer can be classified as sporadic, familial, or hereditary. Sporadic breast cancer accounts for 70% to 75% of cases and is thought to be due to nonhereditary causes. Familial breast cancer, in which there are more

cases within a family than statistically expected, but with no specific pattern of inheritance, accounts for 15% to 25% of cases. Hereditary breast cancer accounts for 5% to 10% of cases and is characterized by well-known susceptibility genes with apparently autosomal dominant transmission.

The "classic" inherited breast cancer syndrome is HBOC syndrome, most of which are due to mutations in the *BRCA1* and *BRCA2* genes. Other hereditary cancer syndromes such as LFS (associated with *TP53* mutations), CS (associated with *PTEN* mutations), PJS (associated with *STK11* mutations), hereditary diffuse gastric cancer, and, possibly, Lynch syndrome also predispose patients to varying degrees of risk for breast cancer. Other mutations and SNPs are associated with increased risk of breast cancer.

Mutations associated with breast cancer vary in their penetrance. Highly penetrant mutations in the *BRCA1*, *BRCA2*, *TP53*, and *PTEN* genes may be associated with a lifetime breast cancer risk ranging from 40% to 85%. Only about 5% to 10% of all cases of breast cancer are attributable to a highly penetrant cancer predisposition gene. In addition to breast cancer, mutations in these genes may also confer a higher risk for other cancers.[3]

Other mutations may be associated with intermediate penetrance and a lifetime breast cancer risk of 20% to 40% (e.g., *CHEK2*, *APC*, *CDH1*). Low-penetrance mutations discovered in genome-wide association studies (e.g., SNPs), are generally common and confer a modest increase in risk, although penetrance can vary based on environmental and lifestyle factors.

An accurate and comprehensive family history of cancer is essential for identifying people who may be at risk for inherited breast cancer and should include a 3-generation family history with information on both maternal and paternal lineages. Focus should be on both people with malignancies and family members without a personal history of cancer. It is also important to document the presence of nonmalignant findings in the proband and the family, because some inherited cancer syndromes are also associated with other nonmalignant physical characteristics (e.g., benign skin tumors in CS).

Further discussion on the diagnostic criteria of HBOC will not be addressed in this Protocol. Criteria for a presumptive clinical diagnosis of LFS and CS have been established.

Li-Fraumeni Syndrome

LFS has been estimated to be involved in approximately 1% of hereditary breast cancer cases. LFS is a highly penetrant cancer syndrome associated with a high lifetime risk of cancer. People with LFS often present with certain cancers (soft tissue sarcomas, brain tumors, adrenocortical carcinomas) in early childhood and have an increased risk of developing multiple primary cancers during their lifetime.

Classic LFS is defined by the following criteria:

- A proband with a sarcoma diagnosed before age 45 years AND
- A first-degree relative with any cancer before age 45 years AND
- A first- or second-degree relative with any cancer before age 45 years or a sarcoma at any age.

The 2009 Chompret criteria for LFS (*TP53*) testing are as follows:

- A proband who has:
    - A tumor belonging to the LFS tumor spectrum (soft tissue sarcoma, osteosarcoma, premenopausal breast cancer, brain tumor, adrenocortical carcinoma, leukemia, or lung bronchoalveolar cancer) before age 46 years AND
    - At least one first- or second-degree relative with an LFS tumor (except breast cancer if the proband has breast cancer) before age 56 years or with multiple tumors; OR

- A proband with multiple tumors (except multiple breast tumors), two of which belong to the LFS tumor spectrum and the first of which occurred before age 46 years; OR
- A proband who is diagnosed with adrenocortical carcinoma or choroid plexus tumor, irrespective of family history.

Classic criteria for LFS have been estimated to have a positive predictive value (PPV) of 56% and high specificity, although the sensitivity is low (≈ 40%).[4] The Chompret criteria have an estimated PPV of 20% to 35%, and when incorporated as part of *TP53* testing criteria in conjunction with classic LFS criteria, substantially improve the sensitivity of detecting LFS. When the Chompret criteria are added to the classic LFS criteria, the sensitivity for detected patients with *TP53* mutations is approximately 95%.

The National Comprehensive Cancer Network (NCCN) also considers women with early-onset breast cancer (age of diagnosis < 30 years), with or without a family history of the core tumor types found in LFS, as another group in whom *TP53* gene mutation testing may be considered. If the LFS testing criteria are met, NCCN guidelines recommend testing for the familial *TP53* mutation if it is known to be present in the family. If it is not known to be present, comprehensive *TP53* testing is recommended, (i.e., full sequencing of *TP53* and deletion/duplication analysis) of a patient with breast cancer. If the patient is unaffected, testing the family member with the highest likelihood of a *TP53* mutation is recommended. If a mutation is found, recommendations for management of LFS, include increased cancer surveillance and, at an earlier age, possible prophylactic surgical management, discussion of risk of relatives, and consideration of reproductive options. NCCN guidelines also state that in the situation where a person from a family with no known familial *TP53* mutation undergoes testing and no mutation is found, testing for other hereditary breast syndromes should be considered if testing criteria are met.

Cowden Syndrome

CS is a part of PHTS and is the only PHTS disorder associated with a documented predisposition to malignancies. Women with CS have a high risk of benign fibrocystic disease and a lifetime risk of breast cancer estimated at 25% to 50%, with an average age between 38 and 46 years at diagnosis. The *PTEN* mutation frequency in people meeting International Cowden Consortium criteria for CS has been estimated to be approximately 80%.[5] A presumptive diagnosis of PHTS is based on clinical findings; however, because of the phenotypic heterogeneity associated with the hamartoma syndromes, the diagnosis of PHTS is made only when a *PTEN* mutation is identified. Clinical management of breast cancer risk in patients with CS includes screening at an earlier age and possible risk-reducing surgery.

Hereditary Ovarian Cancer

The single greatest risk factor for ovarian cancer is a family history of disease. Breast and ovarian cancer are components of several autosomal dominant cancer syndromes. The syndromes most strongly associated with both cancers are the *BRCA1* or *BRCA2* mutation syndromes. Ovarian cancer has been associated with Lynch syndrome, basal cell nevus (Gorlin) syndrome, and multiple endocrine neoplasia.

Hereditary Colon Cancer

Hereditary colon cancer syndromes are thought to account for approximately 10% of all CRCs. Another 20% have a familial predilection for colorectal cancer without a clear hereditary syndrome identified.[6] The hereditary CRC syndromes can be divided into the polyposis and nonpolyposis syndromes. Although there may be polyps in the nonpolyposis syndromes, they are usually less numerous; the presence of 10 colonic polyps is used as a rough threshold when considering genetic testing for a polyposis syndrome.[7] The polyposis syndromes can be further subdivided by polyp histology, which includes the adenomatous (*FAP*, attenuated *FAP*, *MUTYH*-associated) and hamartomatous (JPS, PJS, PHTS) polyposis syndromes. The nonpolyposis syndromes include Lynch.

Identifying which patients should undergo genetic testing for an inherited colon cancer syndrome depends on family history and clinical manifestations. Clinical criteria are used to focus testing according to polyposis or non-polyposis syndromes, and for adenomatous or hamartomatous type within the polyposis syndromes. If a patient presents with multiple adenomatous polyps, testing in most circumstances focuses on *APC* and *MUTYH* mutations. Hamartomatous polyps could focus testing for mutations in the *STK11*/*LKB1*, *SMAD4*, *BMPR1A*, and/or *PTEN* genes.

Genetic testing to confirm the diagnosis of Lynch syndrome is usually performed on the basis of family history in those families meeting the Amsterdam criteria who have tumor microsatellite instability (MSI) by immunohisto-chemistry on tumor tissue.[8] Immunohistochemical testing helps identify which of the four *MMR* genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) most likely harbors a mutation. The presence of MSI in the tumor alone is not sufficient to diagnose Lynch because 10% to 15% of sporadic CRCs exhibit MSI.

MLH1 and *MSH2* germline mutations account for approximately 90% of mutations in families with Lynch syndrome; *MSH6* mutations in about 7% to 10%; and *PMS2* mutations in fewer than 5%. Genetic testing for Lynch is ideally performed in a stepwise manner: testing for *MMR* gene mutations is often limited to *MLH1* and *MSH2* and, if negative, then *MSH6* and *PMS2* testing.

Management of Polyposis Syndromes

FAP has a 100% penetrance, with polyps developing on average around the time of puberty, and the average CRC diagnosis before age 40. Endoscopic screening should begin around age 10 to 12 years, and operative intervention (colectomy) remains the definitive treatment. For attenuated *FAP*, colonoscopic surveillance is recommended to begin between ages 20 and 30 years, or 10 years sooner than the first polyp diagnosis in the family.[9] For *MUTYH*-associated polyposis, colonoscopic surveillance is recommended to start between ages 20 and 30 years.

Colonic surveillance in the hamartomatous polyposis syndromes includes a colonoscopy every two to three years, starting in the teens.

Management of Nonpolyposis Syndromes

People with Lynch syndrome have lifetime risks for cancer as follows: 52% to 82% for CRC (mean age at diagnosis, 44-61 years); 25% to 60% for endometrial cancer in women (mean age at diagnosis, 48-62 years); 6% to 13% for gastric cancer (mean age at diagnosis, 56 years); and 4% to 12% for ovarian cancer (mean age at diagnosis, 42.5 years; approximately one-third are diagnosed before age 40 years). The risk for other Lynch-related cancers is lower, although substantially increased over that of the general population. For hereditary nonpolyposis colorectal cancer or Lynch, colonoscopic screening should start between ages 20 and 25 years. Prophylactic colectomy is based on aggressive CRC penetrance in the family. Screening and treatment for the extracolonic malignancies in hereditary nonpolyposis colorectal cancer also are established.[10]

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Related Protocols

General Approach to Evaluating the Utility of Genetic Panels

Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome (BRCA1/BRCA2)

Genetic Testing for Li-Fraumeni Syndrome

Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Genetic Testing for PALB2 Mutations

Genetic Testing for PTEN Hamartoma Tumor Syndrome

Molecular Analysis for Targeted Therapy of Non-Small-Cell-Lung Cancer

Use of Common Genetic Variants (Single Nucleotide Polymorphisms) to Predict Risk of Nonfamilial Breast Cancer

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Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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