GENETIC TESTING FOR INHERITED MUTATIONS OR SUSCEPTIBILITY TO CANCER OR OTHER CONDITIONS
MED207.110

COVERAGE:

Pre- and post-genetic test counseling may be eligible for coverage in addition to the genetic testing itself if the testing is covered. See criteria below.

BREAST and/or OVARIAN CANCER (Inherited BRCA1 or BRCA2 Mutations):

- Genetic Testing may be eligible for coverage under either of the following circumstances;
  - Individuals who have breast or ovarian cancer and are from families with a high risk of BRCA1 or BRCA2 mutations. Families at high risk for harboring a BRCA1 or BRCA2 mutation are those in which the incidence of breast or ovarian cancer in first- or second-degree relatives suggests an autosomal dominant inheritance, i.e., about half the family members are affected. This criterion may not adequately cover the possibility of paternal transmission of a BRCA1 or BRCA2 mutation. Men rarely develop breast cancer and thus there may not be an affected first-degree relative. The size of the family may not permit analysis of possible autosomal dominant inheritance.
  - Unaffected individuals (male or female) who come from families with a known BRCA1 or BRCA2 mutation. These unaffected family members should be tested only after finding a mutation in an affected first- or second-degree relative. In this situation, the DNA from the unaffected family member can be tested specifically for the same mutation of the affected family member without having to sequence the entire gene. Testing an unaffected family member without knowing the genetic status of the family may lead to difficulties in interpreting the test results.

- Genetic Testing is considered investigational and is not eligible for coverage for the following circumstances;
  - Unaffected family members in the absence of a known BRCA1 or BRCA2 mutation in the family, unless the family history reveals at least four (4) first- and/or second-degree relatives with breast, ovarian, or colon cancer AND there is NO AFFECTED family member available for testing. Once the BRCA mutation is detected in an affected family member, the unaffected family member may be approved for testing,
  - Unaffected individuals of potentially high-risk populations (e.g., Ashkenazi Jewish descent) with no significant family
MEDULLARY CARCINOMA of the THYROID (Germline Mutations of the 'RET' Proto-Oncogene):

- Genetic Testing for 'RET' proto-oncogene point mutations may be eligible for coverage in family members;
  - Symptomatic patients with defined 'RET' gene mutations;
  - Patients known to be affected by inherited medullary thyroid cancer, but not previously evaluated for 'RET' mutations; and
  - Patients with medullary thyroid cancer with no family history of such cancer (sporadic incidence).

COLON CANCER (Germline Mutations FAP or HNPCC Genes):

- Genetic Testing to determine carrier status of the adenosis polyposis coli gene (APC) may be eligible for coverage in -
  - Patients with greater than 20 colonic polyps, OR
  - First-degree relatives (i.e., siblings, parents, offspring) of patients diagnosed with familial adenomatous polyposis (FAP).
- Genetic Testing to determine the presence of the gene for hereditary nonpolyposis colorectal cancer (HNPCC) may be eligible for coverage in patients who meet the Amsterdam or Bethesda criteria, as described below -
  - Amsterdam criteria (patients must meet ALL of the following):
    1. Have three or more relatives with a histology verified colorectal cancer, one of whom is a first-degree relative of the other two; AND
    2. History of colorectal cancer involving at least two generations; AND
    3. Have one or more colorectal cancers diagnosed before 50 years of age.
  - Bethesda criteria (patients may meet ANY of the following):
    1. Have individuals with 2 HNPCC-related cancers, including synchronous and metachronous colorectal cancers or associated extracolonic cancers; OR
    2. Have individuals with colorectal cancer and a first-degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and/or a colorectal...
adenoma; with one of the cancers diagnosed at less than 45 years of age, and the adenoma at less than 40 years of age; OR

3. Have individuals with colorectal cancer or endometrial cancer diagnosed at less than 45 years of age; OR

4. Have individuals with right-sided colorectal cancer with an undifferentiated pattern of histopathology diagnosed at less than 45 years of age; OR

5. Have individuals with signet ring cell type colorectal cancer diagnosed at less than 45 years of age; OR

6. Have individuals with adenomas diagnosed at less than 40 years of age.

• Genetic Testing is considered investigational and is not eligible for coverage for the following –
  ▪ Identification specifically for I1307K mutation; and
  ▪ Identifying which patients should undergo HNPCC genetic testing by using the replication error (RER) phenotype test, also referred to as the micro-satellite instability (MSI) test.

Familial Alzheimer's Disease (AD):

Genetic Testing is considered investigational and is not eligible for coverage for the diagnosis or risk assessment of Familial Alzheimer's Disease (AD). This includes, but is not limited to, testing for:

• apolipoprotein E epsilon 4 allele,
  • presenilin genes (1 or 2), or
  • amyloid precursor genes.

Genetic Testing is considered investigational and is not eligible for coverage for the diagnosis and risk of Sporadic AD. This includes, but is not limited to, testing for:

• apolipoprotein E epsilon 4 allele,
  • presenilin genes (1 or 2),
  • amyloid precursor genes, or
  • low density lipoprotein receptor-related protein (LPR) genes.

Genetic Testing for OTHER CONDITIONS, including but not limited to, prostate cancer, lung cancer, retinoblastoma, scleroderma, cystic fibrosis, Huntington's disease, heart disease, diabetes, Parkinson's
Learning the secrets of the human gene is revolutionizing our understanding of the genetic basis of disease. Certain genetic mutations determine the development of specific diseases. Therefore, Genetic Testing has dramatically expanded the ability to predict, diagnose, and treat these diseases. Many of the tests are moving quickly from the research setting to the marketplace without the benefit of FDA review. These tests have the potential to reshape disease prevention and treatment by identifying inherited mutations and/or susceptibility to cancer.

This policy addresses genetic testing for Breast and/or Ovarian Cancer, Medullary Carcinoma of the Thyroid, Colon Cancer, and Alzheimer's Disease.

- **Genetic Testing for Breast and/or Ovarian Cancer (Inherited BRCA1 or BRCA2 Mutations):**
  
  Alterations in two genes, BRCA1 and BRCA2 (Breast Cancer, BRCA), are associated with an increased risk of breast and ovarian cancer. Families suspected of having hereditary breast and/or ovarian cancer are characterized by cancer occurring at an early age, in multiple generations, and often bilaterally and in a pattern suggesting an autosomal dominant pattern of inheritance. The susceptibility may be transmitted through the maternal or paternal side of the family. The identification of BRCA1 and BRCA2, makes it possible to test for abnormalities in these genes and gain information on the future risk of cancer. When faced with the risk of inheriting the susceptibility to cancer, patients with a positive test may consider management options, such as prophylactic surgery. Those with a negative test may be relieved over genetic risk and can make choices about hormone use, marriage, and childbearing.

- **Genetic Testing for Medullary Carcinoma of the Thyroid (Germline Mutations of the 'RET' Proto-Oncogene):**
  
  Mutations of specific points of the 'RET' gene sequence are associated with the inheritance of Multiple Endocrine Neoplasia (MEN) 2A and 2B and Familial Medullary Thyroid Carcinoma (FMTC). 90-95% of the inherited medullary thyroid carcinoma can be attributed to specific 'RET' point mutations. Genetic assays for 'RET' mutations are used as an alternative to biochemical monitoring (identification of patients with the inherited disease before it progresses beyond the earliest stages) to test individuals from families affected by MEN 2A, MEN 2B, or FMTC for inheritance of the disease-causing gene mutation. Genetic assays are also used to determine if new cases of medullary thyroid carcinoma exist in individuals with no family history of the disease. Patients who test positive may undergo immediate thyroidectomy or postpone thyroidectomy until biochemical tests suggest evolving medullary cancer.
• Genetic Testing for Colon Cancer (Germline Mutations FAP or HNPCC Genes):

The susceptibility genes for Familial Adenomatous polyposis (FAP) and Hereditary Nonpolyposis Colorectal Cancer (HNPCC) are dominantly inherited. Germline mutations in the adenomatous polyposis coli gene, located on chromosome 5, are responsible for FAP. Mutations in one of four different genes, located on chromosome 2, 3, or 7 are associated with HNPCC. Genetic testing is used to detect mutations in both FAP and HNPCC genes, both as a method to detect which patients with a known diagnosis of colon cancer are affected with a hereditary syndrome, and to identify currently unaffected members of a family at high risk for either FAP or HNPCC. Patients with known mutations may consider increased screening for colon or other cancers, or a prophylactic total colectomy.

• Genetic Testing for Familial Alzheimer's Disease:

Alzheimer's Disease (AD) is commonly associated with a family history; 40% of patients with AD have at least one other afflicted first-degree relative. At present, the following 4 genes have been associated with AD:

- Susceptibility Polymorphism at the Apolipoprotein E (ApoE) Gene (includes the Epsilon 2, 3, and 4 type of apolipoprotein allele) and
- Genetic Mutation;
  - amyloid AB precursor gene (APP),
  - presenilin 1 gene, and
  - presenilin 2 gene.

Genetic testing for the ApoE allele gene in patients with late onset AD and testing for mutations in the presenilin or amyloid precursor genes in the rare patient with onset AD have been investigated:

- as an aid in diagnosing for patients presenting with symptoms suggestive of AD, or
- as a technique for risk assessment in asymptomatic patients with a family history of AD.

Genetic testing using the ApoE gene has been investigated for determination of Sporadic risk in patients presenting with symptoms or for those asymptomatic individuals without a family history of AD.

Future developments in Genetic Testing can be expected for prostate cancer, lung cancer, retinoblastoma, scleroderma, cystic fibrosis, Huntington's disease, heart disease, diabetes, Parkinson's disease, and multiple sclerosis.

RATIONALE:

Diagnostic and predictive genetic testing through DNA probes are
entering community-based medical practice at a rapid rate. The BCBSA Technology Evaluation Criteria (TEC) has assessed genetic testing for breast and/or ovarian cancer, thyroid cancer, and colorectal cancer. These assessments were the basis of the decisions for allowance of testing strategy by defining the specific genetic mutation in an affected family member. Unaffected family members are then tested, when appropriate, to see if they have inherited the same genetic mutation.

The use of genetic testing for familial AD as a diagnostic adjunct in patients already presenting with dementia may prove useful, but it will not change the outcome of the disease and remains under investigation. Genetic testing in asymptomatic individuals is unwarranted and create potential misuse or interpretation of testing results.

As genetic research proceeds, many other conditions may appear in the marketplace without FDA review and government regulation. The ability to perform genetic tests to diagnose or predict disease often exists before the ability to prevent or treat disease. This is a risk in genetic testing for AD. Until laboratories are able to establish clinical validity or utility, genetic testing for common diseases such as cardiovascular disease, diabetes, neurodegenerative diseases, and some cancers are in the developmental/research stage. Important prerequisites in the future of genetic research are safe, effective testing and laboratories of assured quality, competent providers, assured privacy of genetic information, and informed consumers.

According the BCBSA's TEC Assessment, testing should not be offered to minors because of lack of effective interventions to be applied during childhood. This is in compliance with the recommendations of the American Society of Human Genetics regarding testing of children for adult-onset disorders.

PRICING:

Genetic testing for AD may be offered along with cerebrospinal fluid (CSF) levels of the Tau protein and AB-42 peptide. This group of tests may be collectively referred to as the Admark Profile, offered by Athena Diagnostics. Genetic testing for AD may be offered along with CSF levels or urinary levels of neural thread proteins. This group of test may be referred to as the AD7C test, as developed by Nymox Pharmaceutical Corporation. The Tau protein, AB-42 peptide, and/or neural thread proteins are being used as biomarkers to measure and support the clinical diagnosis of possible AD, probable AD, or definite AD.

DISCLAIMER:

State and federal law, as well as contract language, including definitions and specific inclusions/exclusions, takes precedence over Medical Policy and must be considered first in determining coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Any benefits are subject to the payment of premiums for the date on which services are rendered. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.
capitated IPA/medical group must contact the IPA/medical group for information regarding HMO claims/reimbursement information and other general polices and procedures.

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