BLUE CROSS OF NORTHEASTERN PA "BCNEPA" MEDICAL POLICY BULLETIN	**MANUAL:** MEDICAL POLICY
	REFERENCE NO.: MPO-490-0083
EFFECTIVE DATE October 1, 2014	**SUBJECT:** Genetic Testing

Blue Cross of Northeastern Pennsylvania ("BCNEPA") Medical Policy

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical policy and claims payment policy are applied. Policies are provided for informational purposes only and are developed to assist in administering plan benefits and do not constitute medical advice. Treating providers are solely responsible for medical advice and treatment. Policies are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and information are constantly changing and BCNEPA may review and revise its medical policies periodically. Also, due to the rapid pace of changing technology and the advent of new medical procedures, BCNEPA may not have a policy to address every procedure. In those cases, BCNEPA may review other sources of information including, but not limited to, current medical literature and other medical resources, such as Technology Evaluation Center Assessments (TEC) published by the Blue Cross Blue Shield Association. BCNEPA may also consult with health care providers possessing particular expertise in the services at issue.

I. DESCRIPTION:

Genetic testing is the analysis of human DNA, chromosomes, proteins, RNA and certain metabolites in order to detect hereditary diseases, mutations.

II. BENEFIT POLICY STATEMENT:

BCNEPA makes decisions on coverage based on Policy Bulletins, benefit plan documents, and the member's medical history and condition. Benefits may vary based on product line, group or contract, therefore, Member benefits must be verified. In the event of a conflict between the Member's benefit plan document and topics addressed in Medical Policy Bulletins (i.e., specific contract exclusions), the Member's benefit plan document always supersedes the information in the Medical Policy Bulletins. BCNEPA determines medical necessity only if the benefit exists and no contract exclusions are applicable.

Benefits are determined by the terms of the Member's specific benefit plan document [i.e., the Fully Insured policy, the Administrative Services Only (ASO) agreement applicable to the Self-Funded Plan Participant, or the Individual Policy] that is in effect at the time services are rendered.

III. MEDICAL POLICY STATEMENT:

Coverage is subject to the terms, conditions, and limitations of the member's contract.

Basic Coverage Criteria for Genetic Testing

A. BCNEPA will provide coverage for genetic testing of a member when medically necessary.

1. Genetic testing **(not discussed elsewhere in this policy)** may be considered medically necessary to establish a molecular diagnosis of an inheritable disease in a member when either of the following criteria is met:

a) The member has a family or personal history which indicates a significant risk for a genetic defect, **or**

b) The member demonstrates signs or symptoms of a genetically linked inheritable disease, **and**

c) All of the below criteria are met:

- Following completion of history, physical examination, pedigree analysis, genetic counseling, and conventional diagnostic studies, a definitive diagnosis remains uncertain, and
- The test is a proven method to identify a genetically linked inheritable disease, and
- There is sufficient scientific evidence to support that the test results will directly impact the management and treatment decisions of the condition, and
- The test will result in an improvement of the net health outcome

2. Genetic testing not meeting the above criteria is considered not medically necessary.

Alzheimer's Disease

B. BCNEPA will not provide coverage for genetic testing for the diagnosis or risk assessment of Alzheimer's disease as this is considered investigational. Genetic testing includes, but is not limited to testing for the apolipoprotein E, epsilon 4 allele, presenilin genes or amyloid precursor gene, or *TREM2*.

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer

C. BCNEPA will provide coverage for the use of the 21-gene RT-PCR assay (i.e., Oncotype DX™) for members when medically necessary.

1. The use of the 21-gene RT-PCR assay (i.e., Oncotype DX™) to determine recurrence risk for deciding whether or not to undergo adjuvant chemotherapy may be considered medically necessary in women with primary breast cancer meeting the following characteristics:

   a) Unilateral, non-fixed tumor;

   b) Hormone-receptor-positive (estrogen receptor (ER) or progesterone receptor (PR));

   c) HER2-negative;

   d) Tumor size 0.6cm-1cm with moderate/poor differentiation or unfavorable features OR tumor size > 1 cm;

   e) Node-negative (lymph nodes with micrometastases (less than 2 mm in size) are considered node negative for this policy statement);

   f) Member will be treated with adjuvant endocrine therapy (e.g., tamoxifen or aromatase inhibitors); and

   g) When the test result will aid the patient in making the decision regarding chemotherapy (i.e., when chemotherapy is a therapeutic option); and

   h) When ordered within six months following diagnosis, since the value of the test for making decisions regarding delayed chemotherapy is unknown.

2. Other Related Guidelines:

   a) The 21-gene RT-PCR assay Oncotype DX™ should only be ordered on a tissue specimen obtained during surgical removal of the tumor and after subsequent pathology examination of the tumor has been completed and determined to meet the above criteria (i.e., the test should not be ordered on a preliminary core biopsy).

   b) The test should be ordered in the context of a physician-patient discussion regarding risk preferences when the test result will aid in making decisions regarding chemotherapy.

   c) For patients who otherwise meet the above characteristics but who have multiple ipsilateral primaries, a specimen from the tumor with the most aggressive histological characteristics should be submitted for testing, as this is how prognosis is clinically determined. It is not necessary to conduct Oncotype DX™ testing on each tumor.

D. BCNEPA will not provide coverage for the 21-gene RT-PCR assay (i.e., Oncotype DX™) for the following indications as they are considered investigational and, therefore, not covered because the safety and effectiveness of these services cannot be established by review of the available published peer-reviewed literature:

1. Determination of recurrence risk in breast cancer patients who are lymph node-positive or patients with bilateral disease.

2. The use of a subset of genes from the 21-gene RT-PCR assay for predicting recurrence risk in patients with noninvasive ductal carcinoma in situ (i.e., Oncotype DX DCIS) to inform treatment planning following excisional surgery.

3. The use of other gene expression assays (e.g., MammaPrint 70-gene signature, Mammostrat Breast Cancer Test, the Breast Cancer Index, the BreastOncPx, NexCourse Breast IHC4, or PAM50 Breast Cancer Intrinsic Classifier).

4. All other indications not identified above as medically necessary.

BRAF Gene Mutation Testing To Select Melanoma Patients for BRAF Inhibitor Targeted Therapy

E. BCNEPA will provide coverage for testing for the $BRAF^{V600}$ gene mutation when medically necessary.

1. Testing for the $BRAF^{V600}$ mutation in tumor tissue of patients with stage IIIC or IV melanoma may be considered medically necessary to select patients for treatment with FDA-approved BRAF inhibitors. (Currently only vemurafenib has FDA approval for treatment of advanced melanoma).

2. Testing for the $BRAF^{V600}$ mutation for all other patients with melanoma, including but not limited to, use in patients with lesser stage melanoma, is considered investigational.

Cystic Fibrosis

F. BCNEPA will provide coverage for genetic testing of the CFTR gene for cystic Fibrosis (CF) using the American College of Medical Genetics (ACMG) recommended mutation core panel (ACMG-23) when medically necessary.

1. Genetic **carrier** testing for CF may be considered medically necessary for any of the following indications:

a) Couples seeking prenatal care; or

b) Couples who are planning a pregnancy; or

c) Persons with a family history of CF; or

d) Persons with a first degree relative identified as a CF carrier; or

e) Reproductive partners of persons with CF.

2. Genetic testing for the **diagnosis** of CF may be considered medically necessary for any of the following indications:

   a) An individual who has one or more characteristic phenotypic features of CF, but negative/equivocal sweat chloride values; or

   b) An infant who has a meconium ileus or other symptoms indicative of CF, but who is too young to produce adequate volumes of sweat; or

   c) A male with congenital absence of the vas deferens (CAVD).

3. Genetic testing for **prenatal (fetus) diagnosis** of CF may be considered medically necessary for any of the following indications:

   a) A fetus when both parents have an combination of a diagnosis of CF, or is a known carrier of a CFTR mutation, or has a family history of CF; or

   b) A fetus when both parents are CFTR mutation carriers and an echogenic bowel is identified on ultrasound.

4. Genetic testing for CF is considered not medically necessary for any of the following indications:

   a) Carrier screening in the general population; or

   b) Persons who have previously been tested; or

   c) Routine genetic screening for CF in newborns; or

   d) CFTR gene sequence analysis or extended mutation panels (i.e., beyond the ACMG-23 standard mutation panel).

Cytochrome p450 Genotyping

G. BCNEPA will provide coverage for CYP450 genotyping when medically necessary.

1. CYP450 genotyping for the purpose of aiding in the choice of clopidogrel versus alternative anti-platelet agents, or in decisions on the optimal dosing for clopidogrel, may be considered medically necessary.

2. CYP450 genotyping for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity for all other drugs is considered investigational. This includes, but is not limited to, CYP450 genotyping for the following applications:

   a) Selection or dose of selective serotonin reuptake inhibitor (SSRI);

   b) Selection or dose of antipsychotics;

   c) Deciding whether to prescribe codeine for nursing mothers;

   d) Selection and dosing of selective norepinephrine reuptake inhibitors;

e) Selection and dosing of tricyclic antidepressants;

f) Dose of efavirenz (common component of highly active antiretroviral therapy for HIV infection);

g) Dose of immunosuppressant for organ transplantation;

h) Selection or dose of beta blockers (e.g., metoprolol); and

i) Dosing and management of anti-tuberculosis medications.

H. BCNEPA will not provide coverage for genotyping to determine cytochrome p450 (CYP2C19) genetic polymorphisms for the purpose of managing the treatment of H-pylori infection as this is considered investigational.

I. BCNEPA will not provide coverage for genotyping to determine cytochrome p450 (CYP2D6) genetic polymorphisms for the purpose of managing treatment with Tamoxifen for women at high risk for or with breast cancer as this is considered investigational.

DNA-Based Testing for Adolescent Idiopathic Scoliosis

J. BCNEPA will not provide coverage for DNA-based prognostic testing for adolescent idiopathic scoliosis as this is considered investigational.

Factor V Leiden

K. BCNEPA will not provide coverage for genetic testing for inherited thrombophilia, including testing for factor V Leiden mutations, prothrombin gene mutations, and mutations in the MTHFR gene, as this is considered investigational.

FMR 1 Mutations (including Fragile X Syndrome)

L. BCNEPA will provide coverage for genetic testing for FMR 1 mutations when medically necessary.

1. Genetic testing for FMR 1 mutations may be considered medically necessary for the following patient populations:

a) Individuals of either sex with mental retardation, developmental delay, or autism spectrum disorder,

b) Individuals seeking reproductive counseling who have a family history of fragile X syndrome or a family history of undiagnosed mental retardation,

c) Prenatal testing of fetuses of known carrier mothers,

d) Affected individuals or their relatives who have had a positive cytogenetic fragile X test result, who are seeking further counseling related to the risk of carrier status among themselves or their relatives.

2. Genetic testing for FMR 1 mutations is considered not medically necessary for all other patient populations.

Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

M. BCNEPA will not provide coverage for genetic cancer susceptibility panels using next generation sequencing (i.e., BreastNext, OvaNext, ColoNext, and CancerNext) as these are considered investigational.

Genetic Testing for Alpha Thalassemia

N. BCNEPA will provide coverage for genetic testing for alpha thalassemia when medically necessary.

1. Preconception (carrier) testing for alpha thalassemia in prospective parents may be considered medically necessary when both parents have evidence of alpha thalassemia based on biochemical testing.

a) Biochemical testing to determine whether alpha thalassemia is present should be the first step in evaluating the presence of the condition.

b) Biochemical testing consists of complete blood count, microscopic examination of the peripheral smear, and Hgb electrophoresis.

2. Genetic testing to confirm a diagnosis of alpha thalassemia is considered not medically necessary.

3. Genetic testing for alpha thalassemia in other clinical situations is considered investigational.

Genetic Testing for CHARGE Syndrome

O. BCNEPA will provide coverage for genetic testing for CHARGE Syndrome when medically necessary.

1. Genetic testing for CHARGE syndrome may be considered medically necessary to confirm a diagnosis in a patient with signs/symptoms of CHARGE syndrome when a definitive diagnosis cannot be made with clinical criteria.

a) A diagnosis of definite CHARGE syndrome can be made clinically in individuals with all four major characteristics or three major and three minor characteristics.

- Major characteristics include: ocular coloboma, choanal atresia or stenosis, cranial nerve abnormality, ear anomalies/deafness.

- Minor characteristics include: genital hypoplasia, hypogonadotrophic hypogonadism, developmental delays, cardiac malformations, short stature, cleft lip and/or cleft palate, tracheoesophageal fistula, distinctive CHARGE facial appearance, consisting of a prominent forehead and a prominent nasal bridge. Other, less frequent manifestations include kidney malformations, immunodeficiency, various limb abnormalities,

scoliosis, dental problems, omphalocele, brain malformations, attention deficit hyperactivity disorder (ADHD), and various behavioral problems.

b) In patients without the classical clinical criteria to diagnose CHARGE, in those with a milder phenotype, and/or in those with features that overlap with and cannot be distinguished from other syndromes, genetic testing may provide a definitive diagnosis.

2. Mutation testing for CHARGE syndrome is considered investigational in all other situations.

Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies

P. BCNEPA will not provide coverage for genetic testing for the diagnosis of inherited peripheral neuropathies to confirm a clinical diagnosis, or for all other indications as this is considered investigational.

Genetic Testing for Facioscapulohumeral Muscular Dystrophy

Q. BCNEPA will provide coverage for genetic testing for facioscapulohumeral muscular dystrophy (FSHD) when medically necessary.

1. Genetic testing for facioscapulohumeral muscular dystrophy may be considered medically necessary to confirm a diagnosis in a patient with clinical signs of the disease.

a) FSHD is typically suspected in an individual with the following:

- weakness that predominantly involves the facial, scapular stabilizer, and foot dorsiflexor muscles without associated ocular or bulbar muscle weakness, and
- age of onset usually by 20 years of age (although mildly affected individuals show signs at a later age and some remain asymptomatic).

2. Genetic testing for facioscapulohumeral muscular dystrophy is considered investigational for all other indications.

Genetic Testing for Hereditary Pancreatitis

R. BCNEPA will not provide coverage for genetic testing for hereditary pancreatitis as this is considered investigational.

Genetic Testing for Lipoprotein(a) Variant(s) as a Decision Aid for Aspirin Treatment

S. BCNEPA will not provide coverage for the use of genetic testing for the rs3798220 allele (LPA-Aspirin Check®) as this is considered investigational in patients who are being considered for treatment with aspirin to reduce risk of cardiovascular events.

Genetic Testing for Nonsyndromic Hearing Loss

T. BCNEPA will provide coverage for genetic testing for nonsyndromic hearing loss (NSHL) when medically necessary.

NOTE: NSHL is defined as hearing loss that is not associated with other physical signs or symptoms. For NSHL, it is more difficult to determine whether the etiology is hereditary or acquired, since by definition there are no other clinical manifestations. Autosomal recessive patterns of inheritance predominate and account for 80% of congenital NSHL. The majority of the remaining 20% of patients have an autosomal dominant inheritance pattern, with a small number having X-linked or mitochondrial inheritance.

- Genetic testing for NSHL mutations (GJB2, GJB6 and other NSHL-related mutations) may be considered medically necessary in individuals with NSHL to confirm the diagnosis of hereditary NSHL.

- Preconception genetic testing (carrier testing) for NSHL mutations (*GJB2, GJB6* and other NSHL-related mutations) in parents may be considered medically necessary when at least one of the following conditions has been met:

  a) Offspring with hereditary NSHL; *OR*

  b) One or both parents with suspected NSHL; *OR*

  c) First- or second-degree relative affected with hereditary NSHL; *OR*

  d) First-degree relative with offspring who is affected with hereditary NSHL.

- Genetic testing for nonsyndromic hearing loss mutations is considered investigational for all other situations.

Genetic Testing for Rett Syndrome

U. BCNEPA will provide coverage for genetic testing for Rett Syndrome when medically necessary.

1. Mutation testing for Rett syndrome may be considered medically necessary to confirm a diagnosis of Rett syndrome in a female child with developmental delay and signs/symptoms of Rett syndrome, but when there is uncertainty in the clinical diagnosis**.**

1. All other indications for mutation testing for Rett syndrome, including prenatal screening and testing of family members, are considered investigational.

Genetic Testing for Statin-Induced Myopathy

V. BCNEPA will not provide coverage for genetic testing for the presence of variants in the *SLCO1B1* gene for the purpose of identifying patients at risk of statin-induced myopathy

as this is considered not medically necessary.

In Vitro Companion Diagnostic Devices

W. BCNEPA will provide coverage for In Vitro Companion Diagnostic Devices (IVD) when medically necessary.

1. IVD, e.g. diagnostic molecular tests may be considered medically necessary when all of the following criteria are met:

   a) The IVD was approved through the FDA In Vitro Companion Diagnostic Devices process; and

   b) The Associated Therapeutic Product (ATP), e.g. pharmaceutical or biologic treatment, would be considered medically necessary for the diagnosis and specific clinical situation under review; and

   c) The IVD is being used to determine whether the associated ATP would be a medically necessary therapy.

   d) Examples include but are not limited to:

   - Therascreen® EGFR RGQ PCR Kit for Gilotrif in the treatment of NSCLC;
   - THxID™ BRAF Kit for Mekinist or Tafinlar int the treatment of malignant melanoma;
   - VYSIS ALK Break Apart FISH Probe Kit for Xalkori in the treatment of NSCLC.

2. The use of an IVD not meeting above criteria is considered investigational.

Lactase Insufficiency

X. BCNEPA will not provide coverage for the use of targeted mutation analysis of -13910 C>T for the prediction of lactase insufficiency as this is considered investigational.

Measurement of TPMT

Y. BCNEPA will provide coverage for genotypic analysis for Thiopurine Methyltransferase (TPMT) when medically necessary.

1. Genotypic analysis of Thiopurine Methyltransferase (TPMT) may be considered medically necessary on a one-time basis in the following situations:

   a) Prior to initiation of AZA/6-MP therapy; or

   b) In patients known to have developed elevated liver function tests or leucopenia during previous therapy with these drugs; or

   c) In patients receiving AZA/6-MP with an abnormal complete blood count results that do not respond to dose reduction.

2. Analysis of the 6-TG and 6-MMP metabolite markers of AZA/6-MP levels may be considered medically necessary in patients whom standard dosing of AZA/6-MP fails to produce a therapeutic response. (Rationale: low or non-detectable levels may support a clinical suspicion of non-compliance and detectable levels may suggest preferential metabolism toward 6-MMP suggesting alternative immunomodulators may be required.)

3. Genotypic analysis of TPMT or analysis of the 6-TG and 6-MMP metabolite markers not meeting the criteria outlined above is considered not medically necessary.

Melanoma

Z. BCNEPA will not provide coverage for genetic testing for mutations associated with familial cutaneous malignant melanoma or associated with susceptibility to cutaneous malignant melanoma as this is considered investigational.

Microarray-Based Gene Expression Profile Testing for Multiple Myeloma Risk Stratification

AA. BCNEPA will not provide coverage for microarray-based gene expression profile testing (i.e., MyPRS™/MyPRS *Plus*™ GEP70 test from Signal Genetics LLC, Little Rock, AR) for multiple myeloma as it is considered investigational for all indications.

Multigene Expression Assay for Predicting Recurrence in Colon Cancer

BB. BCNEPA will not provide coverage for gene expression assays for determining the prognosis of stage II colon cancer following surgery (ColonPRS®, Coloprint®, Genefx Colon®, OncoDefender-CRC, and Oncotype DX®) as they are considered investigational.

Genetic Testing for CADASIL Syndrome

CC. BCNEPA will provide coverage for genetic testing for CADASIL Syndrome when medically necessary.

i. Genetic testing to confirm the diagnosis of CADASIL syndrome may be considered medically necessary under the following conditions:

1. Clinical signs, symptoms, and imaging results are consistent with CADASIL, indicating that the pre-test probability of CADSIL is at least in the moderate to high range.

NOTE: Pescini et al. published a study in 2013 that attempted to identify clinical factors that increase the likelihood of a pathologic mutation being present. The following table summarizes the pooled frequency of clinical and radiologic features, and the points assigned for each finding. The authors recommended that a total score of 14 be used to select patients for testing, as this score resulted in a high sensitivity (96.7%) and a moderately high specificity (74.2%).

	Number with NOTCH3 Mutation	% with NOTCH3 Mutation	Points
Clinical Features			
Migraine	239/463	52%	1
Migraine with aura	65/85	76%	3
TIA/stroke	380/526	72%	1 (2 if <50yo)
Psychiatric disturbance	106/380	28%	1
Cognitive decline	188/434	43%	3
Radiologic features			
Leukoencephalopathy (LE)	277/277	100%	3
LE extended to temporal pole	174/235	74%	1
LE extended to external capsule	228/303	75%	5
Subcortical infarcts	210/254	83%	2

b) The diagnosis of CADASIL is inconclusive following alternate methods of testing, including MRI and skin biopsy.

2. Genetic testing for CADASIL syndrome in all other situations, including but not limited to testing of asymptomatic patients who have a first or second degree relative with CADASIL, is considered investigational.

Preimplantation Genetic Testing

DD. BCNEPA will not provide coverage for preimplantation genetic screening (PGS) as an adjunct to in vitro fertilization (IVF) as it is considered investigational in members/couples who are undergoing IVF in all situations.

Provenance Errors

EE. BCNEPA will not provide coverage for genetic testing for control and documentation of the handling of samples (i.e. The KnowError® Test, Specimen Provenance Assay) to decrease specimen provenance errors (see Definitions) as this is considered not medically necessary.

Quantitative Assay for Measurement of HER2 Total Protein Expression and HER2 Dimers

FF. BCNEPA will not provide coverage for the assessment of HER2 status by quantitative total HER2 protein expression and HER2 homodimer measurement (i.e. HERmark Breast Cancer Assay) as this is considered investigational.

Sequencing-based Tests to Determine Trisomy 21 from Maternal Plasma DNA

GG. BCNEPA will provide coverage for nucleic acid sequencing-based testing of maternal plasma for trisomy 21 when medically necessary.

1. Nucleic acid sequencing-based testing of maternal plasma for trisomy 21 (e.g., MaterniT21™, verifi®, or Harmony™) may be considered medically necessary in women with high-risk singleton pregnancies undergoing screening for trisomy 21.

   NOTE: High-risk singleton pregnancies, as defined by the American College of Obstetricians and Gynecologists (ACOG) Committee Opinion, Number 454, December 2012 include women who meet at least one of the following criteria:

   - Maternal age 35 years or older at delivery;
   - Fetal ultrasonographic findings indicating increased risk of aneuploidy;
   - History of previous pregnancy with a trisomy;
   - Standard serum screening test positive for aneuploidy; or
   - Parental balanced robertsonian translocation with increased risk of fetal trisomy 13 or trisomy 21.

2. Nucleic acid sequencing-based testing of maternal plasma for trisomy 21 in women who do not meet the above criteria is considered not medically necessary.

3. Nucleic acid sequencing-based testing of maternal plasma for trisomy 21 is considered investigational in women with twin or multiple pregnancies.

Thyroid Cancer

HH. BCNEPA will provide coverage for genetic testing for members relating to medullary carcinoma of the thyroid when medically necessary.

1. Genetic testing for members for RET-proto-oncogene point mutations may be considered medically necessary in the following situations:

    a) Among symptomatic members of families with defined RET gene mutations;

    b) Among members of families known to be affected by inherited medullary thyroid cancer but not previously evaluated for RET mutations; and

    c) Among patients with sporadic medullary thyroid cancer.

2. Genetic testing for RET-proto-oncogene point mutations in situations not outlined above is considered not medically necessary.

Whole Exome Sequencing

II. BCNEPA will not provide coverage for whole exome sequencing as this is considered investigational for all indications.

IV. DEFINITIONS:

BRCA1 and BRCA2: genes that, when arterial, may place a family member at risk for developing breast, ovarian, and other cancers. BRCA1 was the first example of this type of gene to be isolated. BRCA1 is thought to account for about 50% of all inherited breast cancer. BRCA2 is thought to account for approximately 30-40% of all inherited breast cancer.

Cystic fibrosis of pancreas: hereditary disorder with wide spread dysfunction of exocrine glands, chronic pulmonary disease, pancreatic deficiency, high levels of electrolytes in sweat and sometimes biliary cirrhosis.

FAP: Familial Adenomatous Polyposis.

Gene: an individual unit of hereditary information that is located at a specific position within the chromosome. A gene provides coded information for a specific characteristic, trait or body function.

Genetics: a term for the scientific study of heredity. Heredity is studied by examining the characteristics of a family and the material carrying hereditary information.

Genetic Testing for Inherited BRCA1 or BRCA2 Mutations: Families suspected of having hereditary breast and/or ovarian 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. Germ-line alterations in two genes, BRCA1 and BRCA2, are associated with an increased risk of breast and ovarian cancer. Alterations in BRCA1 and BRCA2 explain much, but not all, of inherited forms of breast and ovarian cancer. With the identification of BRCA1 and BRCA2, it is now possible to test for abnormalities in these genes to provide information on future risk of cancer.

Qualified Laboratory: Clinical laboratories providing assays of BRCA1 and BRCA2 are certified by the Clinical Laboratory Improvement Amendments of 1988.

Genetic Testing for inherited Susceptibility to Colon Cancer: There are currently two well-defined types of hereditary colorectal cancer, familial adenomatous polyposis (FAP) and hereditary

nonpolyposis colorectal cancer (HNPCC). FAP is characterized by age 10. If left untreated, all affected individuals will go on to develop colorectal cancer. FAP accounts for 1% of colorectal cancer and may also be associated with osteomas of the jaw, skull, and limbs; sebaceous cysts; and pigmented spots on the retina, referred to as Gardner's syndrome. Individuals with HNPCC tend to have early-onset colorectal cancer, right-sided tumors, and often multiple cancers. HNPCC is estimated to account for 3% to 5% of colorectal cancer and is also associated with an increased risk of other cancers such as endometrial, ovarian, urinary tract, and biliary tract cancer. The lifetime risk of developing colorectal cancer in HNPCC is approximately 80%.

Hereditary hemochromatosis: iron overload disorder considered to be the most common inherited disease in Caucasians.

HNPCC: Hereditary Non-Polyposis Colon Cancer.

Lynch Syndrome: Formerly known as hereditary nonpolyposis colorectal cancer or HNPCC.

Medullary carcinoma of the thyroid: uncommon type of thyroid cancer that arises from the parafollicular or C cells thyroid, which produce the hormone calcitonin.

Adjuvant Chemotherapy: Chemotherapy given to kill any remaining cancer cells, usually after all detectable tumor is removed by surgery or radiotherapy.

Breast Cancer Gene Expression Ratio: Lab test developed to help physicians predict the risk of disease recurrence in woman with estrogen receptor (ER) positive, lymph node negative breast cancer.

Epidermal Growth Factor: A small protein that promotes cell growth and differentiation.

Epidermal Growth Factor Receptor: A protein found on the surface of cells to which epidermal growth factor binds.

Estrogen: Hormone secreted by the ovaries which affects many aspects of the female body, including a woman's menstrual cycle and normal sexual and reproductive development.

HER-2: Abbreviation for Human Epidermal Growth Factor Receptor-2. HER-2 is expressed by, and involved in the growth of, some cancer cells.

Hormonal Therapy: Treatment of breast cancer using hormone-blocking agents like Tamoxifen. This type of treatment is usually offered to patients who have hormone receptor positive tumor.

Hormone Receptor Positive Tumor: Breast cancer, which is dependant upon female hormones for its growth.

MammaPrint®: Gene expression profiling test that predicts the risk of metastasis in breast cancer patients.

Onco*type* DX™: A diagnostic test that quantifies the likelihood of disease recurrence in women with early-stage breast cancer and assesses the likely benefit from certain types of chemotherapy.

Progesterone: A hormone that prepares the uterus for the development of a fertilized egg.

First-Degree Relative: Any relative who is one meiosis away from a particular individual in a family (i.e., parent, sibling, offspring).

Second-Degree Relative: Any relative who is two meioses away from a particular individual in a pedigree; a relative with whom one quarter of an individual's genes is shared (i.e., grandparent, grandchild, uncle, aunt, nephew, niece, half-sibling).

Malformation: (from the American College of Medical Genetics Guideline, Evaluation of the Newborn with Single or Multiple Congenital Anomalies)

- A malformation refers to abnormal structural development.
- A major malformation is a structural defect that has a significant effect on function or social acceptability. Examples: ventricular septal defect or a cleft lip.
- A minor malformation is a structural abnormality that has minimal effect on function or societal acceptance. Examples: preauricular ear pit or partial syndactyly (fusion) of the second and third toes.
- A syndrome is a recognizable pattern of multiple malformations. Syndrome diagnoses are often relatively straightforward and common enough to be clinically recognized without specialized testing. Examples include Down syndrome, neural tube defects and achondroplasia. However, in the very young, or in the case of syndromes with variable presentation, confident identification may be difficult without additional testing.

Specimen Provenance Errors: Errors in assignment of tissue origin, which generally arise from human errors such as mislabeling, switching of specimens, contamination, etc.

CODING:

- **The identification of a code in this section does not denote coverage or separate reimbursement.**
- Covered procedure codes are dependent upon meeting criteria of the policy and appropriate diagnosis code.
- The following list of codes may not be all-inclusive, and are subject to change at any time.
- Benefits are determined by the terms of the Member's specific benefit plan document [i.e., the Fully Insured policy, the Administrative Services Only (ASO) agreement applicable to the Self-Funded Plan Participant, or the Individual Policy] that is in effect at the time services are rendered.

PROCEDURE CODES

0004M	81220	81244	81266	81297
0006M	81221	81245	81267	81298
0007M	81222	81250	81268	81299
0008M	81223	81251	81270	81300
81161	81224	81252	81275	81301
81200	81225	81253	81280	81302
81201	81226	81254	81281	81303
81202	81227	81255	81282	81304
81203	81228	81257	81290	81310
81205	81229	81260	81291	81315
81206	81235	81261	81292	81316
81207	81240	81262	81293	81317
81208	81241	81263	81294	81318
81209	81242	81264	81295	81319
81210	81243	81265	81296	81321

81322	81371	81400	81506	S3845
81323	81372	81401	81507	S3846
81324	81373	81402	81599	S3849
81325	81374	81403	82777	S3850
81326	81375	81404	88299	S3852
81330	81376	81405	88363	S3853
81331	81377	81406	G0452	S3854
81340	81378	81407	G9143	S3855
81341	81379	81408	S3800	S3861
81342	81380	81479	S3840	S3865
81350	81381	81500	S3841	S3866
81355	81382	81503	S3842	S3870
81370	81383	81504	S3844	