Subject: Genetic Testing for Cancer Susceptibility  
Policy #: GENE.00001  
Current Effective Date: 08/01/2017  
Status: Revised  
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Description/Scope

This document addresses genetic testing to determine whether an individual is at risk for the development of cancer based on a genetic test. This document includes criteria which may be used to evaluate the medical necessity of a specific genetic test when there is no other more specific document.

Note: For additional information on genetic testing for malignant conditions, please refer to:

- GENE.00028 Genetic Testing for Colorectal Cancer Susceptibility
- GENE.00029 Genetic Testing for Breast and/or Ovarian Cancer Syndrome
- GENE.00030 Genetic Testing for Endocrine Gland Cancer Susceptibility
- GENE.00031 Genetic Testing for PTEN Hamartoma Tumor Syndrome
- GENE.00035 Genetic Testing for TP53 Mutations
- GENE.00043 Genetic Testing of an Individual's Genome for Inherited Diseases

Position Statement

Medically Necessary:

Genetic testing for susceptibility to malignant diseases is considered medically necessary when all of the following criteria are met:

1. The genetic disorder is associated with a potentially significant cancer; and
2. The risk of the significant cancer from the genetic disorder cannot be identified through biochemical or other testing; and
3. A specific mutation, or set of mutations, has been established in the scientific literature to be reliably associated with the risk of developing malignancy; and
4. The results of the genetic test may impact the medical management of the individual; and
5. The use of the genetic test in directing therapy decisions will likely result in an improvement in net health outcomes; and
6. Genetic counseling, which encompasses all of the following components, has been performed:
   a. Interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; and
   b. Education about inheritance, genetic testing, disease management, prevention and resources; and
   c. Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; and
   d. Counseling for the psychological aspects of genetic testing

Investigational and Not Medically Necessary:

Genetic testing for cancer susceptibility is considered investigational and not medically necessary in individuals not meeting any of the criteria above.

Genetic testing for cancer susceptibility using panels of genes (with or without next generation sequencing), including, but not limited to CancerNext™, is considered investigational and not medically necessary unless all components of the panel have been determined to be medically necessary based on the criteria above. However, individual components of a panel may be considered medically necessary when criteria above are met.

Note: When a component of a genetic panel is separately identified, but a specific medical necessity statement is not in another document, the criteria above may be used to determine medical necessity.

Rationale

Genetic Testing for Cancer Susceptibility

Genetic testing for cancer susceptibility is useful to predict an individual's risk of cancer development in the future and to identify carriers (individuals who do not have the cancer but have a copy of a gene which has been associated with the development of cancer). It has been estimated that approximately 5-10% of all cancers are considered to be hereditary (the result of inherited genetic susceptibility).

Genetic testing for cancer susceptibility (a form of predictive genetic testing) is generally carried out in asymptomatic individuals who are considered to be at high risk for developing cancer due to a strong family medical history of the disease, or other factors. Predictive genetic testing can be further divided into two categories: presymptomatic and predispositional. Presymptomatic predictive genetic testing confirms or denies the development of the disease in those at risk as the condition's gene mutation is highly penetrant and there is little or no variable expression. Predispositional predictive genetic tests provide information about an individual's risk of developing a specific disorder in the future. Predispositional predictive genetic testing is generally carried out for incompletely penetrant conditions and the results are not indicative of the inevitable occurrence of a condition or disease, nor are they a guarantee that a disease will not develop in the future.

One of the limitations of predictive genetic testing is the challenge in interpreting positive test results. Some individuals who test positive for a disease-associated mutation may never develop the disease. In order to be useful in the clinical setting, the results of predictive genetic testing should have a high positive predictive value and evidence should

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demonstrate that such results improve either disease prevention or management as compared with care without genetic testing. Please refer to GENE.00043 Genetic Testing of an Individual’s Genome for Inherited Diseases for more information on the specific types of genetic tests, including but not limited to predictive genetic testing.

A position statement published by the American Society of Clinical Oncology (ASCO) indicates that genetic testing for cancer susceptibility is appropriate when the:

1) Individual has personal or family history features suggestive of a genetic cancer susceptibility condition, 2) the genetic test can be adequately interpreted, and 3) the test results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer (ASCO, 2003).

ASCO also recommends that genetic testing only be provided in the setting of pre- and post-test counseling, which should include a discussion of the risks and benefits of cancer early detection and prevention modalities (ASCO, 2003).

In assessing the value of a specific genetic test for susceptibility to a particular malignant condition, consideration should be given to the peer-reviewed, published literature addressing the analytical validity, clinical validity, and clinical utility of the test. Each genetic test must be evaluated to determine whether or not the identified genetic mutation reliably identifies a specific type of cancer, and that the results of the genetic test, whether affirmative or negative, will impact the clinical management of the individual (for example, guide treatment decisions, surveillance recommendations or preventive strategies). The results of genetic testing are also expected to improve net health outcomes, (that is, the anticipated health benefits of the interventions outweigh any harmful effects [medical or psychological] of the intervention).

**Genetic Testing Using Panels of Genes**

Until recently, genetic testing for cancer susceptibility was generally carried out by direct sequencing which analyzes a specific gene for a particular mutation. However, next generation sequencing, (including but not limited to massively parallel sequencing, and microarray testing) has made it possible to conduct panel testing which involves the analysis of multiple genes for multiple mutations simultaneously. Panel testing has the potential benefit of analyzing multiple genes more rapidly and thereby providing the results of the genetic work-up in a more timely fashion. However, the newer sequencing techniques may be associated with a higher error rate and lower diagnostic accuracy than direct sequencing which could affect the clinical validity of testing. Another potential drawback of the newer technologies is that they may provide information on genetic mutations which is of uncertain clinical significance (it is unclear if the gene mutations increase an individual’s risk for cancer susceptibility substantially or even at all).

Discussion among professional societies regarding the clinical utility and the ethical implications of genetic testing for cancer susceptibility continues. In 2013, the American College of Medical Genetics and Genomics issued a recommendation that a panel of inherited mutations with strong associations to human diseases should be universally tested whenever a genetic sequencing test is ordered, regardless of the original clinical context for which a test was ordered. The majority of the genes recommended for testing were associated with cancer susceptibility. The American College of Medical Genetics and Genomics indicated that additional genes would be added on an ongoing basis. A concern with this recommendation is the fact that, if implemented, both the individual being tested and the ordering physician may receive more information than they are requesting. In those instances when the disease under consideration is not malignant, information may be provided related to genetic mutations associated with cancer susceptibility. Conversely, when a test is ordered for a non-cancer-related indication, genetic testing results may provide information which indicate increased risks for malignant conditions for which the individual is not currently diagnosed and which were not being considered (Green, 2013).

The 2015 update of American Society of Clinical Oncology (ASCO) statement on Genetic and Genomic Testing for Cancer Susceptibility discusses the impact of advances in genetic testing on oncology practices. With regard to massively parallel sequencing (next-generation sequencing) and cancer susceptibility testing, the ASCO document states the following:

ASCO recognizes that concurrent multigene testing (ie, panel testing) may be efficient in circumstances that require evaluation of multiple high-penetration genes of established clinical utility as possible explanations for a patient's personal or family history of cancer. Depending on the specific genes included on the panel employed, panel testing may also identify mutations in genes associated with moderate or low cancer risks and mutations in high-penetration genes that would not have been evaluated on the basis of the presenting personal or family history. Multigene panel testing will also identify variants of uncertain significance (VUSs) in a substantial proportion of patient cases, simply as a result of the multiplicity of genes tested. ASCO affirms that it is sufficient for cancer risk assessment to evaluate genes of established clinical utility that are suggested by the patient's personal and/or family history (Robson, 2015).

In an acknowledgement that the field of genetic testing is continuously evolving and guidelines and recommendations will need to be updated periodically, the ASCO publication also states the following:

There remains an urgent need for more research into the implications of unexpected mutations in high-penetration genes and mutations in moderate-penetration genes. Continued research is also necessary to resolve VUSs. There is a dearth of literature regarding how to best counsel patients who may be appropriate candidates for panel testing, and it is important to study the most effective counseling techniques. Until these questions are resolved, it remains appropriate to conduct limited testing for mutations in genes of established clinical utility suggested by the patient's history (Robson, 2015).

In summary, when assessing the value of a specific genetic testing panel for susceptibility to a particular malignant condition, consideration should be given to the peer-reviewed, published literature addressing the analytical validity, clinical validity, and clinical utility of each component of the panel.

**Gene Mutations**

**Notes:** Provided below is a brief definition of some of the genes being investigated for cancer susceptibility. This information should not be construed to be an all-inclusive list of all applicable cancer susceptibility genes. Please refer to the Position Statement section above to determine if the requested genetic test meets the medically necessary criteria.

BARD1 (BRCA1 associated RING domain 1) protein interacts with the BRCA1 gene protein. The two proteins working together act as tumor suppressors. The role of BARD1 mutations in cancer risk is unclear, although some research
studies suggest that changes in the BARD1 gene may influence an individual's risk of developing breast cancer.

BMPR1A (bone morphogenetic protein receptor, type IA) and SMAD4 gene mutations are associated with juvenile polyposis syndrome (JPS). JPS is inherited in an autosomal dominant manner and confers an increased risk of developing gastrointestinal cancer.

BRIP1 (BRCAl interacting protein C-terminal helicase 1) protein interacts with the BRCA1 protein. The two proteins working together act as tumor suppressors. Some research studies suggest certain inherited mutations in the BRIP1 gene are associated with an increased risk of developing breast cancer. Fanconi anemia type J (FA-J) is caused by two mutated copies of the BRIP1 gene in each cell.

CDH1 (cadherin 1, type 1, E-cadherin [epithelial]) germ line mutations are characterized by a high risk for stomach and lobular breast cancer. CDH1 is an autosomal dominant disorder. The average age of onset of gastric cancer in affected individuals is 38 years old. The lifetime risk of developing gastric cancer by age 80 is approximately 67% for men and 83% for women. Inherited mutations in the CDH1 gene increase a woman's risk of developing lobular breast cancer.

CHEK2 (checkpoint Kinase 2) gene mutations confer an increased risk of developing several different types of cancer, including breast, ovarian, prostate, colon, kidney and thyroid. CHEK2 mutations have also been associated with Li-Fraumeni syndrome.

MRE11A (meiotic recombination 11 homolog A) mutations may cause nephronophthisis-related ciliopathies (NPHP-RC), a group of recessive diseases that affect the kidney, retina and brain. A homozygous truncating mutation MRE11A has been found in individuals with cerebellar vermis hypoplasia, ataxia and dysarthria.

NBN (nibrin) mutations may be associated with an increased risk of developing several cancers including breast, prostate, ovarian, melanoma and leukemia.

RAD50 (RAD50 homolog) gene mutations have been associated with the development of breast cancer.

RAD51C (RAD51 paralog C) gene mutations have been associated with the development of breast cancer.

STK11 (serine/threonine kinase 11) germ line mutations have been associated with Peutz-Jegher syndrome (PJS). Individuals with PJS have an increased risk for the development of noncancerous growths (hamartomatous polyps) in the gastrointestinal tract and an elevated risk of developing certain types of cancer.

Genetic Testing Using Panels of Genes

Next-generation sequencing addresses any of the technologies that allow rapid sequencing of large numbers of segments of DNA, up to and including entire genomes. Next-generation sequencing is not a specific sequencing technology or a test in itself. Instead, the term emphasizes the difference between the earlier testing methods that involved the sequencing of one DNA strand at a time. Next generation sequencing includes but is not limited to massively parallel sequencing and microarray analysis.

Next generation sequencing has led to the development of genetic testing incorporating panels which analyze multiple genes for multiple mutations simultaneously. Researchers are investigating genetic testing using panels of genes as a means to identify genetic mutations that may contribute to the development of hereditary cancers.

Genetic Counseling

According to the National Society of Genetic Counselors (NSGC), genetic counseling is the process of assisting individuals to understand and adapt to the medical, psychological and familial ramifications of a genetic disease. This process typically includes the guidance of a specially trained professional who:

1. Integrates the interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; and
2. Provides education about inheritance, genetic testing, disease management, prevention and resources; and
3. Provides counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; and
4. Provides counseling for the psychological aspects of genetic testing (NSGC, 2006).

Definitions

Analytical validity: The accuracy with which a test identifies the presence or absence of a particular gene or genetic change (mutation).

Clinical utility: Results of a test provide clinically relevant information about diagnosis, treatment, management, or prevention of a particular disease. As a result of the test, changes in medical management lead to clinically useful improvements in health outcomes.

Clinical validity: The accuracy with which a test identifies or predicts an individual's clinical status.

Genetic testing: A type of test that is used to determine the presence or absence of a specific gene or set of genes to help diagnose a disease, screen for specific health conditions, and for other purposes.

Genotype: All or part of the genetic constitution of an individual or group, inherited from parents.

Mutation: A change in DNA sequence.

Next-generation sequencing: Any of the technologies that allow rapid sequencing of large numbers of segments of DNA, up to and including entire genomes. This technology includes but is not limited to massively parallel sequencing and microarray analysis.

Penetrance: The likelihood that a clinical condition will occur when a particular genotype exists.

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81404

Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) [when specified as the following]:

- STK11 (serine/threonine kinase 11) (eg, Peutz-Jeghers syndrome), duplication/deletion analysis

81405

Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) [when specified as the following]:

- SMAD4 (SMAD family member 4) (eg, hemorrhagic telangiectasia syndrome, juvenile polyposis), duplication/deletion analysis
- STK11 (serine/threonine kinase 11) (eg, Peutz-Jeghers syndrome), full gene sequence

81406

Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) [when specified as the following]:

- CDH1 (cadherin 1, type 1, E-cadherin [epithelial]) (eg, hereditary diffuse gastric cancer), full gene sequence
- SMAD4 (SMAD family member 4) (eg, hemorrhagic telangiectasia syndrome, juvenile polyposis), full gene sequence

81479

Unlisted molecular pathology procedure [when specified as the following: BARD1, BMPR1A, BRIP1, CHEK2, MRE11A, NBN, RAD50, RAD51C]

ICD-10 Diagnosis

All malignancy-related diagnoses, including but not limited to

C00.0-C06.9 Malignant neoplasms
Z15.01-Z15.09 Genetic susceptibility to malignant neoplasm
Z00.0-Z08.9 Family history of primary malignant neoplasm
Z85.0-Z85.9 Personal history of malignant neoplasm

When services are Investigational and Not Medically Necessary:

For genetic susceptibility testing when criteria are not met

When services are also Investigational and Not Medically Necessary:

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81437 Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TME1M127, and VHL

81438 Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL

81445 Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CEBPA, DNMT3A, EZH2, FLT3, ID1, IDH2, JAK2, KRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed

81450 Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed

81455 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CEBPA, DNMT3A, EZH2, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed

81479 Unlisted molecular pathology procedure [when specified as testing for cancer susceptibility using panels of genes (with or without next generation sequencing), including, but not limited to CancerNext]

0013U Oncology (solid organ neoplasm), gene rearrangement detection by whole genome next-generation sequencing, DNA, fresh or frozen tissue or cells, report of specific gene rearrangement(s)
MatePair Targeted Rearrangements, Oncology, Mayo Clinic

0014U Hematology (hematolymphoid neoplasm), gene rearrangement detection by whole genome next-generation sequencing, DNA, whole blood or bone marrow, report of specific gene rearrangement(s)
MatePair Targeted Rearrangements, Hematologic, Mayo Clinic

ICD-10 Diagnosis

All diagnoses

References


Websites for Additional Information


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Document History

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<tr>
<td>Revised</td>
<td>08/08/2013</td>
<td>MPTAC review.</td>
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<tr>
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<td>07/11/2013</td>
<td>Hematology/Oncology Subcommittee review. Added investigational and not medically necessary Position Statement addressing genetic testing for cancer susceptibility using panels of genes (with or without next generation sequencing). Updated Rationale, Background and Overview, Coding References and Index sections of the document.</td>
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<td>Revised</td>
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<td>05/08/2013</td>
<td>Hematology/Oncology Subcommittee review. Expanded the medically necessary criteria for BRCA1 / 2. Clarified that &quot;close blood relatives&quot; now defined as first-, second- and third-degree relatives on same side of family. In the section on Lynch Syndrome, removed criterion that the individual has a first- or second-degree relative with a right-sided colorectal cancer with an undifferentiated pattern on histopathology diagnosed prior to age 45; and the individual has a first- or second-degree relative with a signet ring cell type colorectal cancer diagnosed prior to age 45. Modified medically necessary statement for MYH (Human MutY homolog)-associated Polyposis (MAP) to clarify that MYH is also known as MUTYH. Updated rationale and references.</td>
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<td>06/27/2012</td>
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<td>06/19/2012</td>
<td>Hematology/Oncology Subcommittee review. Expanded the medically necessary criteria to include large genomic rearrangement testing (BART) when criteria are met and to modify the investigational and not medically necessary language to clarify BART is not covered when criteria are not met. Clarified BRCA1/2 medically necessary criteria related to &quot;individual with a family history of 3 or more first-, second- or third-degree relatives...&quot;. Expanded the medically necessary criteria for HNPPC (Lynch syndrome) for individuals with a family member who would meet criteria for testing, but that family member is not available.</td>
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<td>Hematology/Oncology Subcommittee review. In the medically necessary section for BRCA1 and BRCA2, the word &quot;premenopausal&quot; was changed to &quot;prior to age 50&quot; and the word &quot;epithelial&quot; was removed from the criteria. Deleted Criterion stating &quot;Individuals with a personal history of breast cancer, and diagnosed age less than 50 years with a limited family history.&quot; Updated review date, Description/Scope, Rationale, Definitions, Coding, References and History sections of the document. Modified language in medical necessity criteria to provide clarity.</td>
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<td>04/01/2012</td>
<td>Updated Coding section with 04/01/2012 HCPCS changes; removed codes S3818, S3819, S3820, S3822, S3823, S3828, S3829, S3830, S3831 deleted 03/31/2012.</td>
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<td>Hematology/Oncology Subcommittee review. Updated review date, References and History sections. In the selection criteria for BRCA1 and BRCA2, revised the first bullet by removing the word &quot;especially&quot; from the criteria. Added bullets 6 – 9 under the BRCA1 and BRCA2 criteria.</td>
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Revised 10/4/2017 GENE.00001 Genetic Testing for Cancer Susceptibility

Revised 11/18/2010 MPTAC review.
Revised 11/17/2010 Hematology/Oncology Subcommittee review. Re-organized position statements. Medically necessary criteria for BRCA1/BRCA2 and HNPCC revised based on NCCN guidelines in clinical oncology. Added general medical necessity criteria for genetic testing for malignant diseases. Revised investigational/not medically necessary criteria to read “Genetic testing for cancer susceptibility is considered investigational and not medically necessary in individuals not meeting any of the criteria in sections I and II above, including but not limited to the BRACAnalysis® Rearrangement Test [BART].” Updated review date, Definitions, Coding, References and History sections.

Revised 11/19/2009 MPTAC review.
Revised 11/18/2009 Hematology/Oncology Subcommittee review. Added new position statement stating “Genetic testing for large rearrangements in BRCA1 and BRCA2 genes (BRACAnalysis Rearrangement Test [BART]) is considered investigational and not medically necessary.” Updated review date, Rationale, Coding, Background/Overview, References, Index and History sections.

Revised 05/21/2009 MPTAC review.
Revised 05/20/2009 Hematology/Oncology Subcommittee review. Revised patient selection criteria to reflect more recent recommendations from the American College of Obstetricians and Gynecologists (ACOG) and the National Comprehensive Cancer Network (NCCN). (1) Medical necessity criteria for BRCA1/2 expanded to allow genetic testing for individuals with ovarian cancer, primary peritoneal cancer, or fallopian tube cancer (without having to meet any additional criteria); (2) In bullet #1 under the medically necessary section for MYH-associated Polyposis (MAP), removed the words "at one time" from the patient selection criteria; (3) In bullet #3 under the medically necessary criteria for HNPPCC, changed the age limit from less than 45 years to less than 50 years. Updated review date, Definitions, and History sections of the document.

Revised 05/15/2008 MPTAC review.
Revised 05/14/2008 Hematology/Oncology Subcommittee review. Modified patient selection criteria based on feedback from external consultants, peer-reviewed scientific literature and professional society guidelines, including, but not limited to the NCCN guidelines. Updated review date, Background/Overview, References and History sections.

Revised 02/21/2008 MPTAC review. Document revised to have GENE.0001 only address genetic testing for cancer susceptibility. Title changed to Genetic Testing for Cancer Susceptibility. Prenatal genetic testing moved to GENE.00012 (Preconceptional or Prenatal Genetic Testing of Parents or Prospective Parents) and diagnostic genetic testing moved to GENE.00013 (Diagnostic Genetic Testing of a Potentially Affected Patient (Adult or Child). Updated review date, Background/Overview, References and History sections.

Revised 11/29/2007 MPTAC review. Revised patient selection criteria, rationale, coding and background/overview sections to clarify that genetic testing for ALS is considered INV and NMN. Updated review date, Description, Definitions, and History sections. Added index section. The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary."

Reviewed 12/07/2006 MPTAC review. Updated review date, Coding, Definitions, and History sections.
01/01/2007 Updated Coding section with 01/01/2007 CPT/HCPCS changes.
01/01/2006 Updated Coding section with 01/01/2006 CPT/HCPCS changes.

Revised 12/01/2005 MPTAC review. Addition of attachment A medical review worksheet to policy.
Revised 09/22/2005 MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations

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