Anthem

Medical Policy

Subject:	Panel and other Multi-Gene Testing for ~~Genetic~~ Polymorphisms to Determine Drug-Metabolizer Status		
Document #:	GENE.00010	**Publish Date:**	~~09/25/2019~~07/01/2020
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Description/Scope

This document addresses the use of panel and multi-gene tests for ~~genetic~~ polymorphisms to determine drug-metabolizer status. ~~Testing for polymorphisms can identify variants of specific genes associated with abnormal and normal drug metabolism. The use of such testing is based on the theory that individuals with certain gene variants may potentially be able to receive higher or lower doses of some drugs, or should avoid some drugs altogether, to improve the likelihood of achieving clinical goals as well as lessening the risk of adverse drug effects. A number of proprietary panel tests have been developed to assess multiple variants and alleles across genes involved in drug metabolism.~~

Note: For additional information regarding single (individual) gene tests for polymorphisms~~pharmacogenomics~~, please see:

- CG-GENE-11 Genotype Testing for Individual Genetic Polymorphisms to Determine Drug-Metabolizer Status

Note: For additional information regarding panel tests please see:

- GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling

Position Statement

Investigational and Not Medically Necessary:

The use of panel and multi-gene tests for ~~genetic~~ polymorphisms to determine drug-metabolizer status is considered **investigational and not medically necessary.**

Rationale

Testing for polymorphisms can identify variants of specific genes associated with abnormal and normal drug metabolism. The use of such testing is based on the theory that individuals with certain gene variants may potentially be able to receive higher or lower doses of some drugs, or should avoid some drugs altogether, to improve the likelihood of achieving clinical goals as well as lessening the risk of adverse drug effects. A number of proprietary panels and multi-gene tests have been developed to assess multiple variants and alleles across genes involved in drug metabolism.

Several commercial laboratories market multi-gene ~~test~~ panels for genetic polymorphisms related to drug metabolizer status. While the use of some individual tests included in these ~~test~~ panels may be reasonable under specific circumstances, analysis ~~the use~~ of multiple genes~~tests~~ within a panel should be justified in that there is clinical evidence that ~~panel~~ testing each gene provides information that leads to meaningful impact on treatment. Many genetic and pharmacogenetic association studies have not been reproducible or replicated by independent (non-industry) sponsored studies. Replication of results from genome-wide association studies requires identification of a large and appropriate sample. Furthermore, various pharmacogenetic profiles have not been compared to each other, and thus, testing concordance remains unknown; in other words, it is possible for different proprietary tests to produce conflicting results for the same individual. At this time, the available published evidence addressing the use of such multi-gene tests and panels is limited to a few multi-gene tests and panels- and condition-specific studies (Altar, 2015; Hall-Flavin, 2012, 2013; Winner, 2013a, 2013b). The results of these studies are limited by the study designs utilized by the investigators, with each having some combination of no blinding, small study population, retrospective methodology, selection bias, short follow-up periods, and subjective study outcomes. The data from these studies is weakly supported, and further investigation is warranted using better designed, larger study samples and double-blind randomized controlled methodology.

In 2018 Bradley and others reported the results of a randomized controlled trial involving 685 subjects with depression or anxiety treated with either standard of care (n=333) or guided by the results of the NeuroIDgenetix® panel test (n=352). Subjects were evaluated at 4, 8 and 12 weeks post-initiation of therapy. The authors reported that subjects with depression had significantly higher response rates (p=0.001; OR, 4.72) and remission rates (p=0.02; OR, 3.54) vs. control subjects at 12 weeks. They also reported that experimental group subjects diagnosed with anxiety showed a meaningful improvement in Hamilton Rating Scale for Anxiety scores at both 8 and 12 weeks (p=0.02 and p=0.02, respectively) as well as higher response rates (p=0.04; OR, 1.76). These results are promising. However, the follow-up time of the study was short, and the authors reported a significant loss~~t~~ to follow-up (15.5%). Additionally, there were numerous medication changes reported throughout the study, which makes it difficult to determine the true clinical utility of this test. Finally, the reported results do not appear to be an intent to treat analysis, which may lead to selection bias, as dropped subjects are typically thought to be at risk of being failures or developed troubling side effects. Further investigation into the potential benefits of this test would be welcome.

In a 2019 study by Greden and colleagues, the authors presented data from the Genomics Used to Improve DEpression Decisions (GUIDED) trial. A total of 1167 participants diagnosed with major depressive disorder were included and were randomized to treatment as usual or guided care. Active treatment guided by pharmacogenomic panel testing (GeneSight® Psychotropic, Assurex Health, Inc.) was compared to unguided active treatment in participants who had failed to respond to at least one adequate prior medication trial. GeneSight Psychotropic is a proprietary test that assesses the genotypes of 59 alleles and variants across 8 genes (CYP1A2, CYP2C9, CYP2C19, CYP3A4, CYP2B6, CYP2D6, HTR2A, SLC6A4) by a pharmacogenomic algorithm. Symptom improvement, response, and remission were monitored over 24 weeks with the primary endpoint at week 8. A total of 1167 participants completed the study through the blinded week 8 endpoint (607 participants in treatment as usual, 560 participants in the guided-care arm). Prior to treatment, 79.4% (456/574) of participants in the guided-care arm and 77.5% (476/614) of participants in the treatment as usual arm were prescribed medications that were congruent with the pharmacogenomics test report; at week 8 the proportion increased to 91.2% (508/557) for the guided-care arm and remained relatively unchanged in the treatment as usual arm. Symptom improvement (change in 17-item Hamilton Depression Rating Scale [HAM-D17]) was the primary outcome at week 8; secondary

outcomes were response (≥ 50% decrease in HAM-D17) and remission (HAM-D17 ≤ 7) at week 8. For those in the guided-care arm, there was a 27.2% decrease in HAM-D17 scores at the 8 week visit compared to a 24.4% decrease in the treatment as usual arm (non-significant: p=0.107). In the guided-care arm response rate was 146/560 (26.0%) at week 8 compared to 121/607 (19.9%) in the treatment as usual arm and the rate of remission for participants in the guided-care arm was 86/560 (15.3%) compared to 61/607 (10.1%) in the treatment as usual group (both statistically significant: p=0.013 and p=0.007 respectively). As noted by the authors, overall improvement of symptom improvement, response and remission was modest. The authors note that larger, controlled studies still need to be performed for those receiving their initial treatment. Limitations of this study include failure to meet the primary outcome, a short follow-up period (unblinded assessments in participants did not exceed week 8, not long enough to assess sustained remission), inadequate blinding (the treating clinician was not blinded to study arm), participant homogeneity (the majority of the participants were Caucasian), and a study population that only included participants with moderate to severe major depressive disorder. The long-term incremental clinical significance of pharmacogenomics testing remains unproven. Furthermore, it is unclear how pharmacogenetics testing influences long-term depression outcomes as compared to usual care, which ultimately relies upon symptom improvement and clinical response to a medication, irrespective of pharmacogenetics status.

In October 2018, 23andMe received Food and Drug Administration (FDA) approval as a direct-to-consumer test to provide information regarding genetic variants that can be associated with medication metabolism. The FDA authorization notes that consumers should not use this test to make treatment decisions on their own. Any medical decisions should be made only after discussing the results with a licensed health care provider and results have been confirmed using clinical pharmacogenetic testing.

A number of proprietary multi-gene and panel tests have been developed to assess multiple variants and alleles across genes involved in drug metabolism; some examples and uses are addressed here.

~~According to manufacturer reports from American International Biotechnology (AIBioTech®), pharmacogenetic testing panels are compliant with the Clinical Laboratory Improvement Amendments (CLIA). AIBioTech testing panels for CardioloGene, Pain Management Panel, PsychiaGene Genetic Panel, and Urologene Panel aim to assist in reducing the risk of adverse drug events by identifying metabolic profiles when considering options for drug therapy. There is currently no peer-reviewed published data available to assess the CardioloGene, Pain Management, PsychiaGene or Urologene panels.~~

~~DrugMEt was developed by Jurilab and Nanogen. The pharmacogenetics test is designed to detect up to 27 variations in eight genes encoding major drug-metabolizing enzymes. There is currently no peer-reviewed published data available to assess DrugMEt.~~

Per the manufacturer's website (Genomind®), Genecept assay (also referred to as Genomind Professional PGx™) is a genetic test which aims to identify specific genetic markers to assist with decision making for mental disorders. The test aims to guide treatment for several psychiatric conditions including major depression, anxiety disorder, obsessive compulsive disorder, bipolar disorder, and schizophrenia. In a naturalistic unblinded study by Brennan and colleagues (2015), the purpose was to collect data from participants using the Genecept Assay to determine the effectiveness of the test based on clinician-rated and participant-rated measures and assess the influence on treatment decisions. The deoxyribonucleic acid (DNA) sample was collected via saliva and then participants completed online questionnaires at baseline, 1~~one~~ month and 3~~three~~ months. There were 137 participants who also

had corresponding clinician assessments. Diagnoses included primary mood disorder, attention-deficit disorder, schizophrenia, cognitive disorder, substance-related disorder, developmental disorders, and personality disorders. The surveyed physicians reported that the assay results influenced medication decisions for 93% of participants and the physicians made a change to the medication regimen congruent with the assay report in 94% of participants. The participant surveys demonstrated decreases in depression and anxiety symptoms, decreased side effect of medications, and increased quality of life. However, while there was overall improvement following pharmacogenetics testing, without a control group the results cannot be attributed to a specific benefit of testing. With a short follow-up period, lack of heterogeneity of participants, and lack of control group, further studies of randomized controlled designs are needed to fully ascertain the magnitude of clinical utility of genetic testing.

GeneSight has developed several pharmacogenomic tests. GeneSight Analgesic aims to analyze how genes might affect an individual's response to opioids and muscle relaxants. GeneSight ADHD aims to help identify and avoid ADHD medications which are likely to cause side effects based on genetics. The GeneSight Psychotropic panel, according to the manufacturer website, uses an algorithm to analyze different genes to ascertain an individual's response to different psychotropic medications. As noted in the GUIDED study, there were several limitations including failure to meet the primary outcome, short follow-up period, inadequate blinding and participant homogeneity.

According to the Millennium Health website, the Millennium Pharmacogenetic Testing (PGT) is a test that aims to help identify how genetic variations in enzymes can affect an individual's response to certain medications prescribed for chronic pain. There is currently no peer-reviewed published data available to assess the Millennium test.

The NeuroIDgenetix test, according to the AltheaDx website, is a neuropsychiatric test that uses a panel of genetic tests reported to analyze variants of receptor and transporter genes associated with response to psychiatric medications. Studies are underway to assess the use of these genetic panel tests, however as noted above in the Bradley 2018 study, there were several methodological issues which led to difficulty determining the true clinical utility of the test.

The SureGene Test for Antipsychotic and Antidepressant Response (STA2R)~~,~~ aims to use genetic information to assist with behavioral health medication decisions. A genetic variant in the sulfotransferase 4A1 haplotype 1 (SULT4A1-1) gene has been reported to be a predictor of risk of hospitalization for individuals with schizophrenia who are treated with olanzapine or who might be switched to olanzapine. Genetic variation in the SULT4A1-1 gene is associated with severity of clinical symptoms and response to antipsychotic treatment. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study has looked at genetic studies of antipsychotic treatment response and prediction of individual difference in treatment outcomes for those with schizophrenia. Liu and colleagues (2012) looked at the CATIE data to see if there is influence of SULT4A1-1 haplotype status on hospitalization due to exacerbation of schizophrenia. Using a Kaplan-Meier survival analysis of the CATIE data, the authors found that participants with negative SULT4A1-1 had a higher risk of hospitalization than participants with positive SULT4A1-1. In this industry-sponsored study, the number of participants who were positive SULT4A1-1 was low as well as the overall number of hospitalizations. Prospective studies are necessary with larger participant population and heterogeneity to replicate clinical significance.

The RightMed® comprehensive test, marketed by OneOme, claims to analyze multiple genes involved in drug metabolism, drug targets, drug receptors and drug transports to categorize more than 300 medications into four recommendations: "major gene-drug interaction", "moderate gene-drug interactions", "minimal gene-drug interactions", and "limited pharmacogenetics impact." According to the manufacturer, the RightMed test was developed using proprietary algorithms based on available clinical evidence from scientific literature and public and private databases; however, the test has not been evaluated in a prospective, controlled study to assess the benefits and potential harms of using the test report to guide medication use. Currently published evidence is limited to several feasibility studies; as well, a number of clinical trials appear ongoing. To this end, evidence of clinical utility and net health benefit are lacking.

Evidence evaluating the clinical utility of pharmacogenetic multi-gene testsing panels for ~~genetic~~ polymorphisms for the purpose of guiding drug treatment remains limited and additional data is required to demonstrate that multi-gene panel testing results in improved net health outcomes.

Background/Overview

Drug efficacy and toxicity vary substantially between individuals. Because drugs and doses are typically adjusted to meet individual requirements as needed by using trial and error, clinical consequences may include a prolonged time to optimal therapy and serious adverse events. It has been found that inherited DNA sequence variation (polymorphisms) in genes for drug-metabolizing enzymes may have a significant effect on the efficacy or toxicity of a drug. This field of research is referred to as pharmacogenomics.

It has been proposed that testing for certain genes to detect polymorphisms will allow physicians to predict side effects to drugs and to tailor a drug regimen based on an individual's genetic make-up. It may be that this testing will improve the choice of drug, or the dose of the drug, when the drug in question has a narrow therapeutic dose range, when the consequences of treatment failure are severe, and/or when serious adverse reactions are more likely in individuals with certain polymorphisms.

Critical elements of assessing the effectiveness of such genetic tests include: (1) analytic (diagnostic) validity; (2) clinical validity; and (3) clinical utility. Analytic validity measures the technical performance of the test, in terms of accurately identifying the genetic markers to be measured. Clinical validity measures the strength of association between genetic test results and clinical parameters such as dose, therapeutic efficacy, or adverse events. Clinical utility, the ultimate goal of genetic testing, measures the ability of the test to improve clinical outcomes, such as whether prescribing or dosing based on information from genetic testing improves therapeutic efficacy or adverse event rate as compared with treatment without genetic testing.

Therefore, when considering whether or not a test to determine drug metabolizer status is appropriate in the treatment of individuals prescribed certain medications, specific issues need to be evaluated, including:

- A specific mutation, or set of mutations, has been established in the scientific literature to be reliably associated with drug metabolism status; AND
- A biochemical or other non-genetic test is identified but the results are indeterminate, or the genetic status cannot be identified through such biochemical or other non-genetic testing; AND
- The results of the genetic test could impact the medical management of the individual with a resulting improvement in health outcomes.

Multi-gene panel testing has been proposed to guide treatment, member evaluations and decisions based on the ability to predict response to treatment in particular clinical contexts. Pharmacogenetic tests intend to assess how a drug is metabolized, including evaluation of variation in genes that encode drug-metabolizing enzymes, drug transporters, and drugs targets, as well as other genes involved in the drug's mechanism of action. Next generation sequencing, (including but not limited to massively parallel sequencing, and microarray testing) has made it possible to conduct multi-gene panel testing which involves the analysis of multiple genes for multiple mutations simultaneously. Multi-gene ~~P~~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.

The impact of polymorphisms has been the focus of study with a wide variety of drugs~~ and for many diseases and conditions~~. ~~-~~The use of this type of science is just starting to be investigated, and its impact on actual medical practice is not yet fully understood.

Definitions

Metabolize: Refers to breaking down a drug so that it is no longer clinically active.

Polymorphisms: Refers to genetic variation between individuals resulting in differences in gene expression, in this case differing activity of various enzymes.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When Services are Investigational and Not Medically Necessary:

CPT	
81479	Unlisted molecular pathology procedure [when specified as a multi-gene ~~panel of~~ test~~s~~ for drug metabolism]
0029U	Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (ie, *CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1* and rs12777823) Focused Pharmacogenomics Panel; Mayo Clinic
0030U	Drug metabolism (warfarin drug response), targeted sequence analysis (ie, *CYP2C9, CYP4F2, VKORC1*, rs12777823) Warfarin Response Genotype; Mayo Clinic
0078U	Pain management (opioid-use disorder) genotyping panel, 16 common variants (ie, *ABCB1, COMT, DAT1, DBH, DOR, DRD1, DRD2, DRD4, GABA, GAL, HTR2A,*

	HTTLPR, MTHFR, MUOR, OPRK1, OPRM1), buccal swab or other germline tissue sample, algorithm reported as positive or negative risk of opioid-use disorder INFINITI® Neural Response Panel, PersonalizeDx Labs, AutoGenomics Inc
0173U	Psychiatry (ie, depression, anxiety), genomic analysis panel, includes variant analysis of 14 genes Psych HealthPGx Panel, RPRD Diagnostics, RPRD Diagnostics
0175U	Psychiatry (eg, depression, anxiety), genomic analysis panel, variant analysis of 15 genes Genomind® Professional PGx Express™ CORE, Genomind, Inc, Genomind, Inc

ICD-10 Diagnosis

All diagnoses

References

Peer Reviewed Publications:

1. Altar CA, Carhart JM, Allen JD, et al. Clinical validity: Combinatorial pharmacogenomics predicts antidepressant responses and healthcare utilizations better than single gene phenotypes. Pharmacogenomics J. 2015; 15(5):443-451.
2. Bradley P, Shiekh M, Mehra V, et al. Improved efficacy with targeted pharmacogenetic-guided treatment of patients with depression and anxiety: a~~A~~ randomized clinical trial demonstrating clinical utility. J Psychiatr Res. 2018; 96:100-107.
3. Brennan FX, Gardner KR, Lombard J, et al. A naturalistic study of the effectiveness of pharmacogenetic testing to guide treatment in psychiatric patients with mood and anxiety disorders. Prim Care Companion CNS Disord. 2015; 17(2):1-17.
4. Greden JF, Parikh SV, Rothschild AJ, et al. Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: a~~A~~ large, patient- and rater-blinded, randomized, controlled study. J Psychiatr Res. 2019; 111:59-67.
5. Hall-Flavin DK, Winner JG, Allen JD, et al. Using a pharmacogenomic algorithm to guide the treatment of depression. Transl Psychiatry. 2012; 2:e172.
6. Hall-Flavin DK, Winner JG, Allen JD, et al. Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. Pharmacogenet Genomics. 2013; 23(10):535-548.
7. Liu Q, Ramsey TL, Meltzer HY, et al. Sulfotransferase 4A1 haplotype 1 (SULT4A1-1) is associated with decreased hospitalization events in antipsychotic-treated patients with schizophrenia. Prim Care Companion CNS Disord. 2012; 14(3)~~. pii~~: PCC.11m01293.
8. Winner J, Allen JD, Altar CA, Spahic-Mihajlovic A. Psychiatric pharmacogenomics predicts health resource utilization of outpatients with anxiety and depression. Transl Psychiatry. 2013; 3:e242.
9. Winner JG, Carhart JM, Altar CA, et al. A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. Discov Med. 2013; 16(89):219-227.

Government Agency, Medical Society, and Other Authoritative Publications:

1. U.S. Food and Drug Administration (FDA). FDA News Release. FDA authorizes first direct-to-consumer test for detecting genetic variants that may be associated with medication metabolism. Last updated October 31, 2018. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm624753.htm. Accessed on March 18, 2020~~August 26, 2019~~.

Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Revised	05/14/2020	Medical Policy & Technology Assessment Committee (MPTAC) review. Title change to "Panel and other Multi-Gene Testing for Polymorphisms to Determine Drug-Metabolizer Status." Revision to INV/NMN statement; added "other multi-gene" and removed "genetic." Updated Description/Scope, Rationale and Index sections. Updated Coding section with 07/01/2020 CPT changes; added 0173U, 0175U.
	02/05/2020	Updated Rationale section.
Revised	08/22/2019	~~Medical Policy & Technology Assessment Committee (~~MPTAC~~)~~ review. Revised title. Clarified Position Statement by removing "genotype" and ~~-~~trade names. Updated Rationale, Background/Overview, Definitions, and Index sections.
Revised	06/06/2019	MPTAC review. Genotype testing for single polymorphisms of metabolizing enzymes for specific drugs was removed and moved into a separate clinical utilization management guideline (CG-GENE-11). Title changed. Updated

		Coding, Description/Scope, Rationale, Background/Overview, References and Index sections.
Revised	03/21/2019	MPTAC review. Added MN statement for individuals to be considered for treatment with allopurinol. Updated Rationale, References, and Index sections. Updated Coding section with additional diagnosis codes for testing for allopurinol.
Reviewed	01/24/2019	MPTAC review. Updated Rationale and References sections.
	09/20/2018	Updated Coding section with 10/01/2018 CPT changes; added 0070U-0076U, 0078U; removed 0028U deleted 09/30/2018.
Reviewed	01/25/2018	MPTAC review. Updated Rationale, References, Websites, and Index sections. Updated Coding section with additional diagnosis codes for testing for carbamazepine.
	12/27/2017	The document header wording updated from "Current Effective Date" to "Publish Date." Updated Coding section with 01/01/2018 CPT changes; added 81230, 81231, 81232, 81346 replacing Tier 2 codes, added 0028U, 0029U, 0030U, 0031U, 0033U; removed 0015U deleted 12/31/2017.
	08/01/2017	Updated Coding section with 08/01/2017 CPT PLA code changes.
Revised	02/02/2017	MPTAC review. Updated formatting in the Position Statement. Updated Rationale, Coding and Reference sections.
	01/01/2017	Updated Coding section; removed code 81291 now addressed in a separate document.
Revised	02/04/2016	MPTAC review. Added new tests to Investigational and Not Medically Necessary statement. Deleted the Vysis ALK Break Apart FISH Probe Kit from the Investigational and Not Medically Necessary statement. Updated Rationale and Reference sections.
	01/01/2016	Updated Coding section with 01/01/2016 CPT descriptor revision for code 81355; removed ICD-9 codes.
Revised	08/06/2015	MPTAC review. Added note regarding testing for thiopurine methyltransferase (TPMT) for individuals receiving treatment with azathioprine or 6-mercaptopurine therapy, and testing for NS3 Q80K for individuals being treated for Hepatitis C virus are NOT addressed on this document. Removed position statement addressing NS3 Q80K polymorphism testing in individuals with HCV genotype 1a. Updated Rationale, and References sections. Updated Coding section; removed CPT 87902 no longer addressed.
Revised	02/05/2015	MPTAC review. Added medically necessary statements for individuals who may be treated with eliglustat or tetrabenazine. Added investigational and not medically necessary statement for drugs mentioned in the medically necessary statement when criteria have not been met. Added investigational and not medically necessary statement for individuals who may be treated with simeprevir plus sofosbuvir. Added investigational and not medically necessary statement for individuals who may be treated with opioids and narcotics. Added several commercially available test panels to investigational and not medically necessary statement. Updated Rationale, Coding and References sections.

Revised	08/14/2014	MPTAC review. Added to medically necessary section: "Genotype testing for the presence of hepatitis C virus (HCV) genotype 1a with the NS3 Q80K polymorphism is considered medically necessary before beginning treatment with Olysio™ (simeprevir) plus peginterferon and ribavirin." Added investigational and not medically necessary statement regarding testing panels. Updated Coding, Rationale, Reference, and Index sections.
Reviewed	02/13/2014	MPTAC review. Updated Rationale and Reference sections.
Reviewed	02/14/2013	MPTAC review. Updated Rationale and Reference sections.
	01/01/2013	Updated Coding section with 01/01/2013 CPT changes; removed 88384-88386 deleted 12/31/2012.
Revised	02/16/2012	MPTAC review. Added medically necessary statement for genotype testing for Human Leukocyte Antigen B (HLA-B*5701) for persons infected with HIV-1 before starting treatment with abacavir. Updated Rationale, Coding and Reference sections.
	01/01/2012	Updated Coding section with 01/01/2012 CPT changes.
Reviewed	05/19/2011	MPTAC review. Updated Reference section.
Revised	05/13/2010	MPTAC review. Added testing for CYP2C19 variant of Cytochrome P450 as medically necessary for individuals receiving clopidogrel therapy and who have not been previously tested or those for whom clopidogrel therapy has been proposed. Updated Rationale, Coding, Reference and Index sections.
	01/01/2010	Updated Coding section with 01/01/2010 HCPCS changes.
Revised	05/21/2009	MPTAC review.
Revised	05/21/2009	Hematology/Oncology Subcommittee review. Added use of Human Leukocyte Antigen B*1502 (HLAB*1502) as medically necessary with criteria. Added Clopidogrel and HLAB*1502 to investigational and not medically necessary section. Updated Rationale, Coding, Reference and Index sections.
Reviewed	02/26/2009	MPTAC review. Updated Rationale and Reference sections.
Reviewed	02/21/2008	MPTAC review. Updated Rationale and Reference sections.
Revised	11/29/2007	MPTAC review. Altered title to replace "Cytochrome P450" with "Genetic." Revised the investigational/not medically necessary position statements to include all genetic polymorphism testing for drug metabolizer status. The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary." Updated Rationale, Background, Reference, and Index sections.
Revised	03/08/2007	MPTAC review. Added tamoxifen to investigational/not medically necessary section. References and Coding updated. Document number changed from LAB.00013 to GENE.00010.
Reviewed	03/23/2006	MPTAC review. References updated.
New	04/28/2005	MPTAC initial document development.