Quartz

Pharmacogenetic Testing

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Policy

The Medical Management Department reviews referral requests for authorization of pharmacogenetic testing.

This Medical Policy does not constitute medical advice. When deciding coverage, the enrollee's specific plan document must be referenced. The terms of an enrollee's plan document (Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ from this Medical Policy. In the event of a conflict, the enrollee's specific benefit plan document supersedes this Medical Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements, and the plan benefit coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. Quartz reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary.

Procedure

A. Documentation Required:

In order to facilitate the authorization process, referral requests must include **ALL** the following:

1. Documentation of specific genetic test to be ordered and which drug the provider is considering.
2. Statement about how the results of the testing will lead to specific changes in the patient's management.
3. Statement reflecting the expected improvement in patient outcomes based on the requested test.

B. Criteria for Medical Necessity:

1. General Criteria

MM Department considers the decision for coverage of pharmacogenetic testing (e.g., genotyping, mutation analysis) as medically necessary when **ONE** of the following criteria is met:

a. Meets **ALL** of the following:

i. The patient is a candidate for a targeted drug therapy associated with a specific gene biomarker or gene mutation; **AND**

ii. The results of the pharmacogenetic test will directly impact clinical decision-making and clinical outcome for the patient; **AND**

iii. The testing method is considered to be scientifically valid to identify the specific gene biomarker or gene mutation; **AND**

iv. Use of the testing method has been scientifically proven to improve the patient's care.

OR

b. The U.S. Food and Drug Administration (FDA)-approved prescribing label states that the identification of a specific gene biomarker is either required or recommended prior to initiating therapy with the targeted drug.

Nurse reviewers can use the FDA websites below to search for a particular drug label:
http://www.accessdata.fda.gov/scripts/cder/daf/ **OR**
https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm

2. Test/ Drug-Specific Criteria

The following genetic tests are considered **MEDICALLY NECESSARY** for the following indications:

a. **ALK gene rearrangements**

Patients with inflammatory myofibroblastic tumor before commencing treatment with crizotinib (Xalkori).

Patients with non-squamous, non-small cell lung cancer (NSCLC) or NSCLC not otherwise specified (NOS) before commencing treatment with alectinib (Alecensa), brentuximab, brigatinib, ceritinib (Zykadia), crizotinib (Xalkori), lorlatinib (Lorbrena)..

b. **BCR-ABL (Blood Sample)**

Patients with chronic myelogenous leukemia (CML) or acute lymphoblastic leukemia (ALL) with Ph+ (Philadelphia chromosome positive) before commencing treatment with dasatinib (Sprycel), blinatumomab, bosutinib, busulfan, imatinib mesylate (Gleevac), nilotinib, ponatinib, or omacetaxine.

c. **BRAF V600E**

- Patients with non-small cell lung cancer before commencing treatment with dabrafenib (Tafinlar) in combination with trametinib (Mekinist).
- Patients with Erdheim Chester Disease (non-Langerhans histiocytosis) before initiating treatment with Vemurafenib (Zelboraf).

d. **BRAF V600E/MEK mutation (Tissue Sample)**

Patients with metastatic melanoma who are being considered for targeted therapy with BRAF/MEK inhibition therapy including binimetinib (Mektovi), cobimetinib (Cotellic), dabrafenib (Tafinlar), encorafenib (Braftovi), nivolumab (Opdivo), pembrolizumab (Keytruda), trametinib (Mekinist), vemurafenib (Zelboraf).

e. **BRCA 1 & BRCA 2 gene sequence analysis followed by deletion and duplication testing**

Patients with HER-2 negative locally advanced or metastatic breast cancer who are being considered for treatment with olaparib (Lynparza), niraparib (Zejula), talazoparib (Talzenna).

Patients with ovarian cancer who are being considered for treatment with rucaparib (Rubraca).

Patients with prostate cancer who are being considered for platinum therapy.

f. **CD20 (B lymphocyte antigen CD20)**

Patients being considered for treatment with anti-CD20 treatment with rituximab.

g. **CFTR (Blood Sample)**

Patients with cystic fibrosis before commencing treatment with ivacaftor and ivacaftor/lumacaftor (Orkambi), tezacaftor/ivacaftor (Symdeko).

h. **CLL FISH Probe**

Patients with B-cell chronic lymphocytic leukemia before commencing treatment with venetoclax (Venclexta).

i. **CXCR4 mutation analysis**

Patients with lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia before commencing treatment with ibrutinib.

j. **CYP2D6 polymorphisms**

Patients with Huntington's chorea who have been prescribed doses of tetrabenazine greater than 50mg per day.

Patients with type 1 Gaucher disease before commencing treatment with eliglustat (Cerdelga).

k. **EGFR exon 19 deletions and EGFR exon 21 L858R alterations**

Patients with NSCLC or NSCLC not otherwise specified before commencing treatment with EGFR tyrosine kinase inhibitor therapy including afatinib (Gilotrif), cetuximab (Erbitux), dacomitinib (Vizimpro), erlotinib (Tarceva), gefitinib (Iressa), osimertinib (Tagrisso) or panitumumab.

l. **EGFR exon 20 T790M alterations**

Patients with NSCLC or NSCLC not otherwise specified before commencing treatment with osimertinib (Tagrisso).

Patients with NSCLC or NSCLC who have been previously tested and treated with an EGFR TKI to look for developing resistance.

m. **ERB B2 (HER2)**

Patients with breast cancer before commencing treatment with abemaciclib, ado-trastuzumab emtansine (Kadcyla), everolimus, lapatinib, neratinib, palbociclib, pertuzumab (Perjeta), ribobiclib or trastuzumab (Herceptin) .

Patients with NSCLC or NSCLC who have been previously tested and treated with an EGFR TKI after EGFR exon 20 T790M testing is performed and is negative to look for additional therapy targets.

Patients with gastric or gastroesophageal cancers before commencing treatment with trastuzumab (Herceptin).

n. **FLT3 (FMS-like Tyrosine kinase 3) Mutation**
Patients with acute myeloid leukemia before commencing therapy with midostaurin (Rydapt), gilteritinib (Xospata).

o. **HLA-B* 1502**

Patients of Asian ancestry before commencing treatment with carbamazepine.

p. **HLA-B* 5701**

Patients infected with HIV-1 before commencing treatment with abacavir.

q. **HLA-B*5801**

Patients with gout from a high-risk population (e.g. Asian racial ethnic group such as Han Chinese, Taiwanese, Korean or Thai); or chronic renal insufficiency; prior to commencing treatment with allopurinol.

r. **IDH1 and IDH2 (isocitrate dehydrogenase)**

IDH2 - Patients with acute myeloid leukemia before commencing treatment with enasidenib (Idhifa).

IDH1 - Patients with relapsed or refractory acute myeloid leukemia before commencing treatment with ivosidenib (Tibsovo).

s. **KIT D816V Mutation detection by PCR**
Patients with aggressive systemic mastocytosis before commencing therapy with imatinib mesylate (Gleevac).

t. **KRAS mutation analysis with BRAF reflex testing** (tumor tissue or blood)

Patients with non-small cell lung cancer to predict non-response to erlotinib (Tarceva) treatment.

Patients with metastatic colon cancer, anal adenocarcinoma and small bowel adenocarcinoma to predict non-response to cetuximab (Erbitux) and panitumumab (Vectibix).

u. **Mismatch repair/microsatellite instability testing**

Patients with metastatic colorectal cancer to predict response to ipilimumab (Yervoy), nivolumab (Opdivo), pembrolizumab (Keytruda).

v. **MTHFR C677T genotyping**

Patients with premature cardiovascular disease or hypertension to support genotype directed supplemental treatment of hypertension with riboflavin.

w. **PD-L1**

Patients with non-small cell lung cancer, cervical cancer, urothelial carcinoma, gastric adenocarcinoma, and gastroesophageal junction adenocarcinoma to predict response to pembrolizumab (Keytruda).

Patients with non-small cell lung cancer and urothelial cancer to predict response to atezolizumab (Tecentriq).

Patients with metastatic urothelial cell carcinoma who have disease progression during **OR** following platinum containing chemotherapy **OR** within 12 months of neoadjuvant **OR** adjuvant therapy with platinum containing chemotherapy to predict response to durvalumab (Imfinzi), avelumab (Bavencio) or nivolumab (Opdivo).

x. **PDGFRB FISH**

Patients with myelodysplastic syndrome/myeloproliferative disease before commencing therapy with imatinib mesylate (Gleevac).

y. **ROS-1 rearrangement** (tumor tissue or blood)

Patients with non-small cell lung cancer to predict response to ceritinib or crizotinib (Xalkori) or lorlatinib (Lorbrena).

z. **SMN1, SMN2 testing (blood)**

Patients with suspected or known spinal muscular atrophy before commencing therapy with nusinersen (Spinraza) or onasemnogene abeparvovec (Zolgensma).

aa. **TPMT genotyping (Blood Sample)**

Patients with acute lymphoblastic leukemia, rheumatic disease, inflammatory bowel disease or solid organ transplant before commencing treatment with or escalating dose therapy with azathioprine, mercaptopurine (6-MP) or thioguanine.

C. Indications Considered Experimental, Investigational or not Medically Necessary: (*Not an all-inclusive list)*

The following genetic tests are considered experimental and investigational for the indications listed below because the clinical value of these tests have not been established:

1. CYP2C19 polymorphism genotyping for determination of clopidogrel therapy;

2. VKORC1 polymorphism genotyping for determining warfarin dosing;

3. EGFR testing before commencing treatment with cetuximab (Erbitux) or panitumumab (Vectibix) in colorectal cancer patients;

4. MTHFR C677T genotyping in:

    a. Patients with hypertension but no prior stroke, myocardial infarction or heart disease to support genotype-directed supplementation with vitamin or nutrient supplementation to improve symptoms or prevent complications;
    b. Pregnant patients to support genotype-directed supplementation with vitamin or nutrient supplementation to improve symptoms or prevent complications;
    c. Patients with schizophrenia or major depressive disorder to inform selection or dose of treatment medications;
    d. Patients with leukemia to determine therapeutic response to antifolate chemotherapy such as methotrexate;

5. Cytochrome P450 (CYP450) polymorphism testing (e.g., CYP1A2, CYP2D6, CYP2C19, CYP3A4, CYP3A5) to evaluate for potential reduced/enhanced effect or side effects of drugs in:
    a. Patients with depression, mood disorders, psychosis, anxiety, attention-deficit/hyperactivity disorder, or substance use disorder to inform the selection or dose of treatment medications;
    b. Patients with breast cancer before commencing treatment with tamoxifen.
    Patients to inform opioid prescribing;

6. Dopamine receptor and transporter testing, (e.g., DRD1, DRD2, DRD4, DAT1, SLC6A3, DBH) to inform prescribing;

7. SLCO1B1 genotyping to inform statin prescribing;

8. Genetic testing panels, whole genome sequencing or exome sequencing are not covered unless specifically outlined in the policy above;

References:

Booth R, Ansari M, Loit E, et.al. Assessment of Thiopurine S-Methyltransferase Activity in Patients Prescribed Thiopurines: A Systematic Review. Annals of Internal Medicine. 2011; 154:814-823.

Centers for Medicare and Medicaid Services. Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450N)
Published March 16, 2018. Available at: https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=290&bc=ACAAAAAAQAAA&#Top Accessed January 9, 2019.

Guyatt G, Akl E, Crowther M, et.al. Executive Summary. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST 2012; 141(2) (Suppl):7S – 47S.

Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2012;380(9839):358-365.

Hayes, Inc. Regulation of Genetic Testing in the United States, White Paper, 2011 Winfred S. Hayes, Inc.

Hayes, Inc. GTE Indication.

- Cytochrome P450 (CYP450) Genotyping to Predict Response to Antidepressant and Antipsychotic Medications. Published May 14. 2015. Accessed October 16, 2017.
- Genetic testing to predict allopurinol toxicity. GTE Indication. Published August 10. 2017. Accessed October 16, 2017.
- MTHFR Genetic Testing in Common Clinical Conditions. Published August 17, 2017. Accessed October 16, 2017.
- MTHFR Pharmacogenomic Genotyping for Altering Drug Treatments. Published March 23, 2017. Accessed October 16, 2017.
- Pharmacogenomic testing for selected psychiatric and behavioral conditions. Published May 18, 2017. Accessed October 16, 2017.
- SLCO1B1 genotyping to improve statin prescribing and patient adherence, and to avoid adverse outcomes such as myopathy. Published August 4, 2016. Accessed October 16, 2017.

Hayes, Inc. GTE Report. BRAF p.Val600Glu (V600E) and p.Val600Lys (V600K) Testing for Trametinib and Dabrafenib Combination Therapy in Melanoma. Published February 12, 2015. Accessed October 16, 2017.

Hayes, Inc. Prognosis overview. Rydapt (Midostaurin) for acute myeloid leukemia. Published January 22, 2018. Accessed June 25, 2018.

Holmes MV, Perel P, et.al. CYP2C19 genotype, Clopidogrel Metabolism, Platelet Function and Cardiovascular Events - A Systematic Review and Meta-analysis. JAMA. 2011;306:2704-14.

Holbrook A, Schulman S, Witt DM, et.al. Evidence-Based Management of Anticoagulant Therapy, CHEST, February 2012 Supplement.

Laboratory Analysis and Application of Pharmacogenetics to Clinical Practice, National Academy of Clinical Biochemistry 2010.

Lichtenstein G, Hanauer S, Sandborn W, et.al. Management of Crohn's Disease in Adults. ACG Guidelines. American Journal of Gastroenterology. 2009;104:465-483.

Mallal S, Phillips E, Carosi G, et.al. HLA-B*5701 Screening for Hypersensitivity to Abacavir, NEJM. 2008;358:568-79.

Mao L, Jian C, Changzhi L, et al. Cytochrome CYP2C19 polymorphism and risk of adverse clinical events in clopidogrel-treated patients: a meta-analysis based on 23,035 subjects. Arch Cardiovasc Dis. 2013;106(10):517-527.

McArthur GA, Chapman PB, Robert C, et al. Safety and efficacy of vemurafenib in BRAF (V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol. 2014;15(3):323-332.

Mehanna R, Hunter C, Davidson A, Jimenez-Shahed J, Jankovic J. Analysis of CYP2D6 genotype and response to tetrabenazine. Mov Disord. 2013;28(2):210-215.

NHS / National Institute for Health and Clinical Excellence. Crohn's Disease. Management in adults, children and young people. Issued: October 2012 / NICE clinical guideline 152.

National Comprehensive Cancer Network (NCCN), Clinical Practice Guidelines in Oncology, Available at NCCN.org.

- Acute Lymphoblastic Leukemia. V1.2018-March. Accessed October 10, 2018.
- Breast Cancer. V2.2018-October. Accessed October 10, 2018.
- Chronic Myeloid Leukemia, V1.2019-October. Accessed October 10, 2018.
- Colon Cancer. V3.2018-August. Accessed October 210 2018.
- Melanoma. V3.2018-July. Accessed October 24, 2018.
- Non-Small Cell Lung Cancer. V1.2019-October. Accessed October 24, 2018.
- Rectal Cancer. V3.2018-August. Accessed October 10, 2018.

O'Gara P, Kushner F, Ascheim D, et.al. 2013 ACCF / AHA Guideline for the Management of ST-Elevation Myocardial Infarction. A Report of the American College of Cardiology Foundation / American Heart Association Task Force on Practice Guidelines, Journal of the American College of Cardiology. 2013;61(4).

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed November 18, 2016.

Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med*. 2011;365(18):1663-1672.

Tangamornsuksan W, Chaiyakunapruk N, Somkrua R, Lohitnavy M, Tassaneeyakul W. Relationship between the HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *JAMA Dermatol*. 2013;149(9):1025-1032.

UpToDate® August 28, 2014, Overview of Pharmacogenomics, www.uptodate.com.

UpToDate® November 20, 2015, 6-mercaptopurine (6-MP) metabolite monitoring and TPMT testing in the treatment of inflammatory bowel disease with 6-MP or azathiopurine.

UpToDate® October 27, 2016, Molecularly targeted therapy for metastatic melanoma.

UpToDate® September 26, 2016, Anaplastic lymphoma kinase (ALK fusion oncogene positive non-small cell lung cancer.

UpToDate® November 15, 2016, Cystic fibrosis: overview of the treatment of lung disease.

UptoDate® June 30, 2016, Personalized, genotype-directed therapy for advanced non-small cell lung cancer.

US Food and Drug Administration. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). Last update December 13, 2018.

https://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm301431.htm Accessed January 9, 2019.

US Food and Drug Administration. Table of Pharmacogenomics Biomarkers in Drug Labels. Last update August 3, 2018. Available at: https://www.fda.gov/Drugs/ScienceResearch/ucm572698. Accessed January 9, 2019.

Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *N Engl J Med*. 2015;373(3):220-231.