



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 or to determine response to treatment with dasatinib (Sprycel), blinatumomab, bosutinib, busulfan, imatinib mesylate (Gleevac), nilotinib, ponatinib, or omacetaxine.

NOTE: The authorization for quantitative BCR-ABL testing to determine response to treatment includes 12 tests within 12 months for patients in active treatment.

- 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 and homologous recombination deficiency testing (tissue and blood)**

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 fallopian tube cancer, ovarian cancer, or primary peritoneal cancer who are being considered for treatment with niraparib (Zejula), olaparib (Lynparza) or rucaparib (Rubraca).

Patients with pancreatic cancer who are being considered for treatment with olaparib (Lynparza).

Patients with prostate cancer who are being considered for platinum therapy, olaparib (Lynparza), or rucaparib (Rubraca).

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. **CYP2C9 polymorphisms**

Patients with relapsing forms of multiple sclerosis including clinically isolated syndrome, relapsing-remitting, and active secondary progress disease who are being considered for therapy with siponimod (Mayzent).

k. **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).

l. **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 (Erbix), dacomitinib (Vizimpro), erlotinib (Tarceva), gefitinib (Iressa), osimertinib (Tagrisso), panitumumab, or ramucirumab (Cyramza).

m. **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.

n. **ERB B2 (HER2)**

Patients with breast cancer before commencing treatment with abemaciclib, ado-trastuzumab emtansine (Kadcyla), everolimus, lapatinib, neratinib, palbociclib, pertuzumab (Perjeta), ribociclib 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 esophageal or esophagogastric junction cancers, gastric or gastroesophageal cancers, or salivary gland cancer, before commencing treatment with trastuzumab (Herceptin).

o. **FLT3 (FMS-like Tyrosine kinase 3) Mutation**

Patients with acute myeloid leukemia before commencing therapy with midostaurin (Rydapt), gilteritinib (Xospata).

p. **FGFR1, FGFR2 and FGFR3 fusion/rearrangements (fibroblast growth factor receptor)**

Patients with stage 3b or 4 bladder cancer to predict response to erdafitinib.

Patients with cholangiocarcinoma to predict response to pemigatinib (Pemazyre).

Patients with myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase fusion genes to predict response to pemigatinib (Pemazyre).

q. **HLA-B* 1502**

Patients of Asian ancestry before commencing treatment with carbamazepine.

r. **HLA-B* 5701**

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

s. **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.

t. **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 or cholangiocarcinoma before commencing treatment with ivosidenib (Tibsovo).

u. **KIT D816V Mutation detection by PCR**

Patients with aggressive systemic mastocytosis before commencing therapy with imatinib mesylate (Gleevac).

v. **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 (Erbix) and panitumumab (Vectibix).

w. **MET exon14 skipping mutation**

Patients with metastatic non-small cell lung cancer to predict response to capmatinib (Tabrecta).

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

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

Patients with adrenocortical tumors, biliary tract cancer, cervical, esophageal or esophagogastric junction cancers, fallopian tube cancer, gallbladder cancer, gastric cancer, occult primary tumors, ovarian cancer, penile cancer, poorly differentiated neuroendocrine carcinoma/large or small cell, primary peritoneal cancer, or testicular cancer to predict response to pembrolizumab (Keytruda).

y. **MTHFR C677T genotyping**

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

z. **Neurotrophic receptor tyrosine kinase (NTRK) gene fusion**

Patients with metastatic cancer or cancer whereby surgical resection is likely to result in severe morbidity or who have no satisfactory alternative treatments or have progressed following treatment, especially anaplastic thyroid cancer, biliary tract, cervical, endometrial, esophageal or esophagogastric junction cancers, follicular and Hurthle cell thyroid carcinoma, gallbladder cancer, gastric cancers, hepatocellular cancer, metastatic salivary cancer, non-small cell lung, pancreatic, papillary thyroid, rectal, soft tissue sarcomas or vulvar cancers to predict response to treatment with larotrectinib (Vitrakvi) or entrectinib (Rozlytrek).

aa. **NUTD15 (Nudix hydroxylase 15) (Blood)**

Patients with lymphoblastic leukemia before commencing treatment with thiopurine therapy including azathioprine, mercaptopurine (6-MP) and thioguanine (6-TG) or if excessive toxicity arises with use.

bb. **PD-L1**

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

Patients with triple negative breast cancer, 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 atezolizumab, avelumab (Bavencio), durvalumab (Imfinzi), nivolumab (Opdivo), pembrolizumab (Keytruda).

Patients with locally advanced or metastatic bladder cancer to predict response to atezolizumab (Tecentriq) or pembrolizumab (Keytruda).

Patients with non-small cell lung cancer to predict response to nivolumab + ipilimumab (Opdivo + Yervoy) therapy.

cc. **PDGFRA exon 18 mutation (including D842V mutation)**

Patients with unresectable or metastatic gastrointestinal stromal tumor (GIST) to predict response to avapritinib (Ayvakit).

dd. **PDGFRB FISH**

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

ee. **PIK3CA (tumor tissue or blood)**

Patients with HR+/HER2 negative breast cancer to predict response to alpelisib.

ff. **PKD1 & PKD2**

Patients with suspected autosomal dominant polycystic kidney disease (ADPKD), e.g. multiple cysts on kidneys and who are considered high risk for rapid progression to end stage renal disease and are being considered for tolvaptan (Jynarque) therapy.

gg. **RET gene rearrangement or RET gene fusion mutation (tumor)**

Adult patients with metastatic non-small cell lung cancer, and adult and pediatric patients 12 years and older with advanced or metastatic thyroid cancer to predict response to selpercatinib (Retevmo).

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

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

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

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

jj. 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 thiopurine therapy including azathioprine, mercaptopurine (6-MP) and thioguanine (6-TG) or if excessive toxicity arises with use.

kk. Tumor Mutational Burden

Patients with anaplastic, follicular, Hurthle cell or medullary thyroid cancer; cervical cancer, endometrial cancer, poorly differentiated neuroendocrine carcinoma/large or small cell, uterine sarcoma or vulvar cancer before commencing therapy with pembrolizumab (Keytruda).

C. Indications Considered Not Medically Necessary: *(Not an all-inclusive list)*

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

D. Indications Considered Experimental & Investigational: *(Not an all-inclusive list)*

1. CYP2C19 polymorphism genotyping for determination of clopidogrel therapy;
2. VKORC1 polymorphism genotyping for determining warfarin dosing;
3. 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;
4. 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.
 - c. Patients to inform opioid prescribing;
5. Dopamine receptor and transporter testing, (e.g., DRD1, DRD2, DRD4, DAT1, SLC6A3, DBH) to inform prescribing;
6. SLCO1B1 genotyping to inform statin prescribing;

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

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