CYP2D6 Variant Analysis for Drug Response

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

<table>
<thead>
<tr>
<th>Procedures addressed by this guideline</th>
<th>Procedure codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6 Genotyping for Drug Response</td>
<td>81226</td>
</tr>
<tr>
<td>CYP2D6 Common Variants and Copy Number, Mayo Clinic</td>
<td>0070U</td>
</tr>
<tr>
<td>CYP2D6 Full Gene Sequencing, Mayo Clinic</td>
<td>0071U</td>
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<tr>
<td>CYP2D6-2D7 Hybrid Gene Targeted Sequence Analysis, Mayo Clinic</td>
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<tr>
<td>CYP2D6 3’ gene duplication/ multiplication targeted sequence analysis, Mayo Clinic</td>
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</table>

What is CYP2D6 testing

Definition

The cytochrome P450 2D6 (CYP2D6) enzyme is involved in metabolizing many medications, including tamoxifen, tetrabenazine, deutetetabenazine and eliglustat.  

- Studies suggest that certain variations (polymorphisms) in the CYP2D6 gene result in reduced or absent enzyme function, which may lead to lower levels of active tamoxifen metabolites and reduced treatment efficacy.
• CYP2D6 testing has, therefore, been proposed to guide adjuvant therapy decisions in some circumstances.
  
o Tamoxifen users:
  
  ▪ Postmenopausal women considering tamoxifen have a choice between tamoxifen and aromatase inhibitors. Results of CYP2D6 testing could influence that decision, although data about the utility of testing has been mixed (see Guidelines/Evidence below for details).
  
  ▪ Testing is not indicated for perimenopausal and premenopausal women with hormone-positive breast cancer. Tamoxifen is the current standard of care for these patients, and no alternative treatment plans have been approved.
  
  ▪ Testing is not recommended for patients considering tamoxifen in the preventative setting.
  
  o Tetrabenazine (Xenazine) users:
  
  ▪ Tetrabenazine is a “vesicular monoamine transporter 2 (VMAT) inhibitor indicated for the treatment of chorea associated with Huntington’s disease.”
  
  ▪ CYP2D6 testing is used to help guide tetrabenazine dosage in patients that are being considered for a tetrabenazine dose greater than 50mg.
  
  ▪ For extensive and intermediate metabolizers, “the maximum recommended daily dose is 100 mg and the maximum recommended single dose is 37.5 mg.”
  
  ▪ “In poor metabolizers, the initial dose and titration is similar to extensive metabolizers except that the recommended maximum single dose is 25 mg, and the recommended daily dose should not exceed a maximum of 50 mg.”
  
  o Deutetrabenazine (Austedo) users:
  
  ▪ Deutetrabenazine is a “reversible depletor of monoamines (such as dopamine, serotonin, norepinephrine, and histamine) from nerve terminals”. Metabolites of deutetrabenazine, are reversible vesicular monoamine transporter 2 (VMAT) inhibitors.
  
  ▪ Deutetrabenazine is indicated for the treatment of chorea associated with Huntington’s disease.
  
  ▪ Maximum recommended daily dosage of deutetrabenazine is 48 mg. In patients who are poor CYP2D6 metabolizers, however, the total daily dosage should not exceed 36 mg (with a maximum single dose of 18 mg).
  
  o Eliglustat (Cerdelga) users:
  
  ▪ Eliglustat is a “glucosylceramide synthase inhibitor indicated for the long-term treatment of adult patients with Gaucher disease type 1 who are
CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IM), or poor metabolizers (PM) as detected by an FDA-cleared test.³

- CYP2D6 intermediate metabolizers and extensive metabolizers are recommended to take a dose of 84 mg twice daily. This dosage requirement is decreased to 84 mg once a day for CYP2D6 poor metabolizers.³

### Test information

- CYP2D6 testing is usually performed on a buccal swab or blood sample using polymerase chain reaction (PCR) to look for certain common variants.
- Genotype results are generally assigned a metabolizer phenotype:

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genotype(s)¹¹</th>
</tr>
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<tbody>
<tr>
<td>Poor Metabolizer (PM)</td>
<td>Two CYP2D6 inactive variants</td>
</tr>
<tr>
<td>Intermediate Metabolizer (IM)</td>
<td>One normal and one inactive variant, One inactive and one reduced-activity variant, Two reduced-activity variants</td>
</tr>
<tr>
<td>Extensive Metabolizer (EM)</td>
<td>Two normal CYP2D6 alleles</td>
</tr>
<tr>
<td>Ultrarapid Metabolizer (UM)</td>
<td>More than two copies of the normal CYP2D6 allele</td>
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</tbody>
</table>

- The frequency of the CYP2D6 metabolizer phenotypes varies with ethnicity. About 5-10% of Caucasians are poor metabolizers, while the frequency is much lower in Africans and Asians.¹⁰

### Guidelines and evidence

- Tetrabenazine, deutetrabenazine, and eliglustat:
  - CYP2D6 is listed as an FDA-approved biomarker for both tetrabenazine and eliglustat.¹²
  - Product labeling for tetrabenazine, deutetrabenazine, and eliglustat address CYP2D6 testing.²,³,⁴
- Tamoxifen
○ Evidence-based guidelines from the National Comprehensive Cancer Network (NCCN, 2016) state: “At this time, based on current data the [NCCN Breast Cancer] panel recommends against CYP2D6 gene testing for women being considered for tamoxifen therapy.” (category 2A: The recommendation is based on lower level evidence and there is uniform NCCN consensus)

○ Practice guidelines from the American Society of Clinical Oncologists (ASCO, 2009) state: “Given the limited evidence, CYP2D6 testing is currently not recommended in the preventive setting.”

○ Two important large clinical trials have most directly addressed clinical utility of CYP2D6 testing for tamoxifen response. Both found that CYP2D6 genotype did not predict long-term outcome among tamoxifen users.

  ▪ Regan et al. performed CYP2D6 variant testing on tumor tissue from 4393 patients enrolled in the BIG 1-98 trial and evaluated the association with breast cancer recurrence. BIG 1-98 was an international, randomized double-blind trial that compared tamoxifen monotherapy, letrozole (an aromatase inhibitor) monotherapy, and sequential therapy (2 years of one and 3 years of another). Patients were mostly Caucasian and all had postmenopausal, hormone receptor-positive, operable breast cancer. Results found a non-statistically significant association between metabolizer phenotype and recurrence (poor metabolizer vs. extensive metabolizer HR = 0.58, 95% CI = 0.28 to 1.21). The authors concluded “The results of this study do not support using the presence or absence of hot flushes or the pharmacogenetic testing of CYP2D6 to determine whether to treat postmenopausal breast cancer patients with tamoxifen.”

  ▪ Similarly, Rae et al. found no association between CYP2D6 genotype and breast cancer recurrence in people treated with tamoxifen from the randomized double-blind Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial (n=1203; poor metabolizer vs. extensive metabolizer HR = 1.25, 95% CI = 0.55 to 3.15). The authors conclude “The results do not support the hypothesis that CYP2D6 genotype predicts clinical benefit of adjuvant tamoxifen treatment among postmenopausal breast cancer patients.”

• The Clinical Pharmacogenomics Implementation Consortium (CPI, 2018) has evaluated outcomes using CYP2D6 genotyping to guide tamoxifen treatment for breast cancer. Because of wide variability of breast cancer types where tamoxifen is administered (breast cancer prevention, ductal carcinoma in situ, metastatic breast cancer, etc.) the guideline focused only on the use of CYP2D6 genotyping in estrogen-receptor positive (ER+) breast cancer. Using this narrow focus, there was moderate evidence to support improvements in breast cancer recurrence or event-free survival for patients treated with tamoxifen who were poor metabolizers (PM). However, there was weak evidence to support improvements in breast cancer-specific-survival and overall survival in this same PM group. The evidence regarding potential improvements in outcomes for patients treated with tamoxifen who were intermediate metabolizers (IM), normal metabolizers (NM) [also called...
extensive metabolizers (EM)] and ultra-rapid metabolizers (UM) was also judged to be weak.\textsuperscript{15}

Criteria
CYP2D6 testing will be granted when the following criteria are met:

Testing for Tetrabenazine Response
- No previous CYP2D6 testing performed, AND
- Member has a diagnosis of Huntington’s disease, AND
- Treatment with tetrabenazine is being considered in a dosage greater than 50mg per day, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Testing for Deutetetrabenazine Response
- No previous CYP2D6 testing performed, AND
- Member has a diagnosis of Huntington’s disease, AND
- Treatment with deutetetrabenazine is being considered in a dosage greater than 36mg per day, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Testing for Eliglustat Response
- No previous CYP2D6 testing performed, AND
- Member has a diagnosis of Gaucher disease, AND
- Treatment with eliglustat is being considered, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Exclusions and other considerations
- CYP2D6 testing for tamoxifen response is considered investigational/experimental and, therefore, not eligible for reimbursement.
- CYP2D6 testing for all other indications is considered investigational/experimental and, therefore, not eligible for reimbursement.
- Additional CYP2D6 tests, denoted by CPT codes 0071U–0076U, are typically not medically necessary. Requests for these tests will be reviewed on a case by case basis.
References


12. FDA. Table of valid genomic biomarkers in the context of approved drug labels. Available at http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm.
