Appendix

Appendix A: Additional Methods
We reviewed the following coded policies: Aetna Pharmacogenetic and Pharmacodynamic Testing, Anthem Genotype Testing for Genetic Polymorphisms to Determine Drug Metabolizer Status, Cigna Pharmacogenetic Testing, and United Healthcare Genetic Testing, HCSC Cytochrome p450 (CYP450) Genotyping, and HCSC Genetic Testing for Mental Health Conditions.

For each policy, we opened the Excel Registry Master Coding File and compared and matched column A (Policy Source Unique ID) in the Policies TABLE to the number from the Policy Source Information Table. In the Policies TABLE, we counted how many panels were coded, and in each policy, we looked for and read the previously highlighted portions and rationalized why each test or panel was or was not coded and for panels, why they were considered panels. We then searched test or panel names on Google to find out how many genes they tested for, and if a panel was not covered, we scrolled through each policy to find rationale for no coverage and matched that to the coding in the Policies TABLE.

On the Registry Pharmacogenomics tab, we copied payers, policies, and effective and review dates onto a new Excel file named 2016 Pharmacogenomics Policies. Then, we Google searched each payer and policy name except for HCSC, where we directly went to the HCSC website, to the What We Do tab, to the Medical Policies, to the All Active Policies, and searched in an alphabetically sorted list for two policies. We matched the policy number to the existing one and checked for a more recent review date than the previous one listed in the Registry. Finally, we added links and the most recent review and effective dates of updated policies to the 2016 Pharmacogenomics Policies file. HCSC did not have updates.

To follow, we checked each updated policy for United Healthcare and Wellpoint Anthem BC and for HCSC, the 2015 policy, for next review dates, and added these into the 2016 Pharmacogenomics Policies file. These policies did not list next review dates, and after checking the websites directly we were still unable to find these dates.

Next, we opened, coded, and updated Wellpoint Anthem BC, Aetna, United Healthcare, and Cigna pharmacogenomics policies one at a time side by side along with Registry. Since the HCSC pharmacogenomics policies had not been updated yet, we did not look at those. We highlighted and coded the same components in the updated Wellpoint Anthem BC, Aetna, United Healthcare, and Cigna policies with the same methodology as in the existing coded policies.

Based on the above criteria, relevant policies were highlighted to include in the full list on the Excel spreadsheet titled New policy search compilation. We checked the highlighted policies in the “new policy search compilation” Excel file for duplicates from the coded updated PGx policies. Policies were narrowed down to six policies for entry into the Registry spreadsheet: HCSC Cytochrome p450 (CYP450) Genotyping, HCSC Genetic Testing for Mental Health Conditions, HCSC Genetic Testing for Warfarin Dose, HCSC Pharmacogenetic Testing for Pain Management, Aetna Genetic Testing, and Aetna Inflammatory Bowel Disease: Serologic Markers and Pharmacogenomic and Metabolic Assessment of Thiopurine Therapy. The relevant information for Registry entry was highlighted, and after double checking, we found that the HCSC Cytochrome p450 (CYP450) Genotyping and Genetic Testing for Mental Health Conditions were already coded from last year, and these policies were not updated on the HCSC website. Aetna Genetic Testing policy had an update, but we found that no PGx tests were in the policy. In summary, we narrowed down the policies we found to three new ones for coding into the Registry spreadsheet: HCSC Genetic Testing for Warfarin Dose, HCSC Pharmacogenetic Testing for Pain Management, and Aetna Inflammatory Bowel Disease: Serologic Markers and Pharmacogenomic and Metabolic Assessment of Thiopurine Therapy.
# Appendix Table B: CYP2C19 Genetic Testing Literature Search Results

<table>
<thead>
<tr>
<th>PubMed Search Terms</th>
<th>Relevant Sections</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19 testing (keyword search)</td>
<td>Meta-analyses show no clinical benefit for testing patients with lower clinical risks (e.g., clopidogrel use in atrial fibrillation)</td>
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<tr>
<td></td>
<td>CPIC guidance limits genotype-guided dosing recommendations to patients undergoing percutaneous coronary intervention for acute coronary syndromes (excluding medical management of acute coronary syndromes, stroke, and peripheral artery disease). 9</td>
</tr>
<tr>
<td></td>
<td>ACCF/AHA guidelines state that genotyping may be considered in patients with unstable angina/non-ST segment elevation myocardial infarction (or after percutaneous coronary intervention for acute coronary syndromes) if test results could alter management.</td>
</tr>
<tr>
<td></td>
<td>Although availability varies, CYP2D6, CYP2C19, and other pharmacogenetic tests can be used as stand-alone tests or within broader pharmacogenomic panels. Further information on test availability and ordering is available through the National Institutes of Health Genetic Testing Registry (<a href="http://www.ncbi.nlm.nih.gov/gtr/">http://www.ncbi.nlm.nih.gov/gtr/</a>) and the Pharmacogenomics Knowledgebase (<a href="https://www.pharmgkb.org/">https://www.pharmgkb.org/</a>). Because clinical reimbursement rates vary, clinicians should consider contacting the laboratory or the patient's insurance provider for details before ordering.</td>
</tr>
<tr>
<td>CYP2C19 testing (keyword search)</td>
<td>Based upon our review of the current literature, we do not feel that there is support for the routine screening for CYP2C19 polymorphisms in patients being treated with clopidogrel; furthermore, the results of genetic testing may not be helpful in guiding therapeutic decisions. We recommend that decisions on the type of antiplatelet treatment be made based upon clinical evidence of potential differential outcomes associated with the use of these agents rather than on the basis of genetic testing.</td>
</tr>
<tr>
<td><a href="https://www.ncbi.nlm.nih.gov/pubmed">https://www.ncbi.nlm.nih.gov/pubmed</a></td>
<td>The ACCF and AHA responded to this “Boxed Warning” and convened a panel to create a clinical expert consensus document. 8 The consensus document was published in 2010 and concluded that “the role of genotyping in everyday practice remains unknown at this present time.” This group also noted that at the time of publication, there were “no prospective studies demonstrating a clinical benefit to personalizing antiplatelet therapy based on genotype analysis.” Advocates of genetic testing were present on the panel and argued that “given the magnitude of the potential clinical consequences of suboptimal platelet inhibition based on genetic variation, assessment of genotypes would be justifiable.”</td>
</tr>
<tr>
<td></td>
<td>However, an opposing opinion was also noted by panel members who stated there was no definitive proof that intervening on the basis of genotype would improve outcome…Opponents of testing also noted that the predictive performance of the presence of CYP2C19<em>2 and CYP2C19</em>3 allele variants was low, ranging only from 12–20% in predicting adverse clinical events. It was suggested that the state of knowledge was incomplete and that further studies would be useful to address these issues.</td>
</tr>
<tr>
<td></td>
<td>A review of the literature reveals that the findings of recent studies do not support the routine screening for CYP2C19 polymorphisms or targeted antiplatelet therapy based upon the results of genetic testing. Based upon our review we feel that decisions regarding conversion to newer antiplatelet agents such as ticagrelor or prasugrel should not be based upon genetic testing but on evidence of potentially improved clinical outcomes for patients treated with these newer agents but balanced against bleeding risks. With the end of the patent on clopidogrel and its current availability as a generic formulation, it is unlikely that a trial with a sample size of 20,000–30,000 patients, necessary to definitively study potential effects of genetic variation in CYP2C19 correlated with clinical outcomes would be funded or undertaken.</td>
</tr>
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<td></td>
<td>In 2010, an expert panel convened by the ACCF and AHA concluded that the routine testing for CYP2C19 polymorphisms in patients treated with clopidogrel was not warranted. 8 In our review of the published data since this recommendation and our overview of clinical trials on this subject registered by the NIH, we have not found any additional supporting evidence for tailored therapy based upon genetic testing.</td>
</tr>
<tr>
<td>CYP2C19 testing</td>
<td>Although there is good evidence for analytic, biological, and clinical validity of several phenotypic and genotypic biomarkers, the benefit of a management strategy that incorporates routine biomarker testing over standard of care</td>
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without such testing remains unproven. Appropriately designed, adequately powered trials are needed but face the challenges of feasibility, cost, and the progressive switch from clopidogrel to prasugrel or ticagrelor.

There is good evidence for analytical validity of the genetic test for LOF polymorphisms.45 There is also good evidence that LOF polymorphisms are associated with reduced levels of the active clopidogrel metabolite and with reduced on-treatment inhibition of ADP-induced platelet activation… Evidence for clinical utility of CYP2C19 genotyping as a predictive biomarker is limited to subgroup analyses with inconclusive findings.

Despite the variable effects of clopidogrel on ADP-mediated platelet activation, the benefit of a management strategy that incorporates routine biomarker testing remains unproven.

We suggest that routine phenotypic or genetic testing should not be recommended until an appropriately designed clinical trial shows that such testing provides clinical benefit to patients.

The lack of large-scale, prospective, randomized study data demonstrating that modifying antiplatelet therapy based on PFT or GT has a meaningful impact on clinical outcomes have led guideline recommendations to be poorly supportive of their use in clinical practice.

Genotyping for a CYP2C19 loss of function variant in patients with UA/NSTEMI (or, after ACS and with PCI) on clopidogrel therapy might be considered if results of testing may alter management. (Level of Evidence: C)

Genetic testing might be considered to identify whether a patient at high risk for poor clinical outcomes is predisposed to inadequate platelet inhibition with clopidogrel. (Level of Evidence: C)

The routine clinical use of genetic testing to screen patients treated with clopidogrel who are undergoing PCI is not recommended. (Level of Evidence: C)

Genotyping and/or platelet function testing may be considered in selected cases when clopidogrel is used. (Level of Evidence: B)

It is unlikely that functional testing may provide useful information to guide clinical decision-making in most individual patients for the prevention of ischemic events. Such limited incremental clinical utility is also in line with the modest increase in predictive accuracy of adding results of PFT and GT to other established predictors of poor outcomes currently available evidence cannot support the routine clinical use of PFT and GT, as is also reflected in practice guidelines 1, 2 and 3, suggesting the need for more studies before these tests can be recommended to guide antiplatelet therapy.

Their clinical use should be limited to patients at high risk for poor clinical outcomes (e.g., scenarios in which a thrombotic event may be catastrophic or lethal such as in unprotected left main, bifurcating left main, last patent coronary vessel) and only if this will result in a change in therapy

There was evidence supporting the cost effectiveness of testing for HLA-B*57:01 (prior to abacavir), HLA-B*15:02 and HLA-A*31:01 (prior to carbamazepine), HLA-B*58:01 (prior to allopurinol) and CYP2C19 (prior to clopidogrel treatment)

Three studies compared three strategies: clopidogrel for all patients, prasugrel for all patients, genetic testing with clopidogrel for those who tested negative and prasugrel for those who tested positive. All found genotyping to dominate [55–57]. The fourth study considered ticagrelor as a comparator [58]. Genotyping was cost effective versus universal clopidogrel, but universal ticagrelor may be more cost effective than genotyping, depending on the cost-effectiveness threshold, with the incremental cost-effectiveness ratio (ICER) being reported as 'generally within what is considered acceptable'. Genetic testing prior to clopidogrel is recommended by the FDA, with actionable pharmacogenetic information noted by the EMA, PMDA and HCSC

We recommend to genotype for CYP2C19 loss-of-function alleles in patients with CAD who are to undergo percutaneous coronary intervention and stenting, and to adjust the antiplatelet treatment based on the genotyping results

The FDA more specifically mentions that genotyping can be used as an aid in determining a therapeutic strategy and to consider alternative treatment in PM

They suggested considering genetic testing of patients at moderate- or high-risk for poor outcomes.
| C19+testing+ guidelines | genotype-guided treatment was more cost effective compared with treating all patients with either clopidogrel or prasugrel without genotyping.  
Genotyping for the CYP2C19 LOF allele can differentiate between those patients who will derive benefit from clopidogrel with good efficacy and a lower cost, and those patients who will derive benefit more from the newer antiplatelets with better efficacy, such as prasugrel and ticagrelor. |
<table>
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<tbody>
<tr>
<td>CYP2C19 testing guidelines (keyword search) <a href="https://www.ncbi.nlm.nih.gov/pubmed/?term=CYP2C19+testing+guidelines">https://www.ncbi.nlm.nih.gov/pubmed/?term=CYP2C19+testing+guidelines</a></td>
<td>Evidence supports an effect of CYP2C19 genotype on protection from major adverse cardiovascular outcomes for acute coronary syndrome/percutaneous coronary intervention, but not for lower-risk conditions [98]. Therefore, despite the large number of studies published, guiding clopidogrel dosing on the basis of CYP2C19 genotype is still a matter of debate.</td>
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</table>
| CYP2C19 testing utility (keyword search) https://www.ncbi.nlm.nih.gov/pubmed/?term=CYP2C19+testing+utility | However, the clinical utility of clopidogrel and warfarin is still limited.  
In 2010, the American College of Cardiology (ACC) and American Heart Association (AHA) issued a consensus statement that, in the absence of prospective randomized clinical trials, ‘the evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time.’  
Recently, the clinical pharmacogenetics implementation consortium (CPIC) recommended guidelines for the use of CYP2C19 genetic information to guide clopidogrel therapy in ACS/PCI patients if CYP2C19 genetic testing results are available. |
| Julie A. Johnson [Author] (keyword search) | Seven different third party payers, including Medicare, reimbursed for the test during the first month of billing, with an 85% reimbursement rate for outpatient claims that were submitted in the first month.  
Billing for CYP2C19 genotyping began in June 2013, when the Department of Pathology, Immunology and Laboratory Medicine began billing third party payers and the hospital for outpatient and inpatient tests, respectively. During the first month of billing, seven different third party payers (including Medicare) and the hospital reimbursed for the test. Reimbursement was received for 85% of outpatient claims for CYP2C19 genotyping billed in the first month.  
Once billing for the CYP2C19 genotype was initiated, a decision was made by the interventional cardiologists to transition to ordering the test only in patients undergoing a successful PCI. This strategy to select the patients most likely to benefit from genotyping was a logical one as it would lead to a lower absolute cost of genotyping. However, as genomic medicine initiatives transition from grant- or institutional-supported enterprises to full clinical programs, balancing the financial implications, especially reimbursement for preemptive testing, against the potential future benefits of using genotype data in clinical care will remain important challenges. |
| Julie A. Johnson [Author] (keyword search) | On the basis of the above assessment, we have argued that the clinical relevance of CYP2C19 pharmacogenetics with clopidogrel is indication specific, meaning that the greatest clinical value of genetic testing is in patients undergoing PCI (Johnson et al., 2012b). It is these patients who obtain the greatest benefit from treatment, who are at risk for stent thrombosis, and thus are at greatest risk from loss of CYP2C19 function. |
| Julie A. Johnson [Author] (keyword search) | Although robust GWAS evidence exists linking common variants to complex CVD, studies are not yet available to inform the clinical benefit of providing such genetic information to patients.  
Many commentators agree that any test to be covered should satisfy a test of clinical utility; however, no consensus exists as to what constitutes clinical utility, and there is a lack of clear guidance as to what the appropriate level of evidence should be. |
| "Cytochrome P-450 CYP2C19 genetics"[Mesh] | CYP2C19 metabolizer status is not associated with the composite outcome of cardiovascular death, MI, or stroke in medically managed ACS patients treated with clopidogrel or prasugrel. Our findings do not support routine CYP2C19 genetic testing in this population. |
No CYP2C19*2 carriers treated with 10 mg prasugrel daily in the rapid genotyping group had HTPR at day 7, compared to 30% given standard treatment (75 mg clopidogrel daily) (p = 0.0092).

Among carriers of at-risk genotypes, treatment with prasugrel was superior to an augmented dosing strategy of clopidogrel in reducing HTPR.

Tailored antiplatelet therapy according to point-of-care genetic and phenotypic testing reduced HTPR after 30 days.

Personalized antiplatelet therapy according to CYP2C19 genotype after PCI can significantly decrease the incidence of MACE and the risk of 180-day ST in Chinese population.

CYP2C19 genotype-directed antiplatelet therapy post-PCI may reduce ischemic events at 1 year.

A recent proposed draft for local coverage determination by the Centers for Medicare and Medicaid Services (CMS; Palmetto GBA, Virginia) determined that CYP2C19 genetic testing (CPT 81225) is medically necessary for patients with ACS undergoing PCI initiating or reinitiating clopidogrel therapy, but not for medical management of ACS without PCI, stroke or PAD.

Cost-effectiveness studies on CYP2C19-guided antiplatelet therapy have been inconclusive, but have suggested that this strategy may be a more cost-effective approach.

Cost-effectiveness studies have also been inconclusive with respect to pharmacogenetic-guided antiplatelet therapy, and cardiology society guidelines do not currently recommend routine CYP2C19 genotyping, together ultimately leaving the decision to test ACS/PCI patients up to the individual clinician when clopidogrel is being considered.

When all possible patients are genotyped, these numbers double, saving $444,852 annually.

Tailoring antiplatelet therapy regimens according to CYP2C19 genotype can reduce costs associated with preventable adverse outcomes.

Genotype-guided use of prasugrel, versus universal use of clopidogrel or prasugrel, was consistently found to be the cost-effective (or generate net benefits) option for ACS patients in four decision-analytic modeling studies, all including non-fatal MI, nonfatal stroke, fatal/non-fatal bleeding and cardiovascular death as target clinical outcomes.

Five of the seven reviewed studies found genotype-guided therapy to be cost-effective or gained net benefit when compared with universal treatment for ACS patients, mostly with PCI.

Cost-effectiveness analyses have demonstrated that substantial cost savings could be achieved with a genotype-based strategy compared with empirical use of the newer P2Y₁₂ inhibitors for all patients after PCI to overcome 'genetic clopidogrel resistance'.

According to one study, compared with prasugrel use in all patients, the use of prasugrel and clopidogrel in a genotype-guided strategy resulted in an incremental cost-effectiveness ratio of US$30,200 per quality-adjusted life year.

### Appendix Table C: 2016 Updates to Pharmacogenomics Policy Coverage and Wording

<table>
<thead>
<tr>
<th>PGx Policies</th>
<th>Updated Policy?</th>
<th>Changes to Policy?</th>
<th>Previous Policy Language</th>
<th>Current Policy Language</th>
<th>Difference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Payer 1</td>
<td>Yes</td>
<td>No</td>
<td>Aetna considers genotyping for other cytochrome P450 polymorphisms (diagnostic tests to identify specific genetic variations that</td>
<td>No change</td>
<td>No change</td>
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</table>
may be linked to reduced/enhanced effect or severe side effects of drugs metabolized by the cytochrome P450 system including opioid analgesics, warfarin, tamoxifen, proton pump inhibitors, antipsychotic medications, and selective serotonin reuptake inhibitors) experimental and investigational because the clinical value of this type of genetic testing has not been established.

Aetna considers CYP2D6 genotyping experimental and investigational for predicting response to beta blockers.

Aetna considers CYP2D6 genotyping experimental and investigational for identifying individuals with Alzheimer's disease with different clinical response to donepezil (Aricept) because its clinical value has not been established.

Aetna considers GeneSightRx testing for the management of individuals treated with antidepressant and/or anti-psychotic medications experimental and investigational because its clinical value has not been established.

Aetna considers the Genecept Assay (Genomind) experimental and investigational for managing psychiatric conditions.

Aetna considers the Millennium PGT (Millennium Laboratories) experimental and investigational for management of medications for chronic pain and for all other indications.

Aetna considers the PersonaGene Genetic Panels (AlBioTech) experimental and investigational for making medication adjustments and for all other indications.

<table>
<thead>
<tr>
<th>Payer 2</th>
<th>Yes</th>
<th>Yes</th>
<th>The clinical utility of the following genetic tests have not been established and therefore these tests are not medically necessary: Psychotropic medication pharmacogenetics (AmpliChip Panel; CYP450 Polymorphisms; BDNF, DRD, HTR, SLC6A4, and TPH1 Genes).</th>
</tr>
</thead>
<tbody>
<tr>
<td>United</td>
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<td>The clinical utility of the following genetic tests have not been established and therefore these tests are not medically necessary: Psychotropic medication pharmacogenetics - BDNF, COMT, DRD, HTR, SLC6A4, and TPH1 Genes. Psychotropic medication pharmacogenetics - CYP450 Polymorphisms and AmpliChip Panel. Psychotropic medication pharmacogenetics - Gene Panels. Psychotropic medication pharmacogenetics - HLA Typing.</td>
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<tr>
<td>Added</td>
<td></td>
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<td>COMT Psychotropic medication pharmacogenetics-gene panels Psychotropic medication pharmacogenetics-HLA typing</td>
</tr>
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<tr>
<th>Payer 3</th>
<th>Yes</th>
<th>Yes</th>
<th>The use of testing panels for genetic polymorphisms to determine drug metabolizer status is considered investigational and not The use of testing panels for genetic polymorphisms to determine drug metabolizer status is considered</th>
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<tr>
<td>Added</td>
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<td>DrugMEt</td>
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| Payer 4 (Cigna) | Yes | Yes | Cigna does not cover pharmacogenetic testing (e.g., genotyping, mutation analysis) to detect response to targeted drug therapy for EITHER of the following because it is experimental, investigational, or unproven (this list may not be all inclusive):

- ANY of the following genes or gene mutations, for ANY indication, including but not limited to the following:
  - CYP2C19 gene for ANY of the following drug targets:
    - Clopidogrel (Plavix) resistance or inhibition
    - Proton pump inhibitors
    - Antidepressants
    - Barbiturates
    - Mephenytoin
  - UGT1A1 or UGT1A1 gene for treatment with irinotecan (Camptosar)
  - CYP2C9 and VKORC1 genes for warfarin metabolism
  - CYP3A4 and CYP3A5 genes, including common variants *2, *3, *4, *5, or *6
  - Cigna does not cover drug metabolizing enzyme genotyping systems (e.g., AmpliChip Cytochrome P450 (CYP450) Genotyping Test; Invader UGT1A1 Molecular Assay)

| | | | Cigna does not cover pharmacogenetic screening in the general population because such testing is considered not medically necessary.

| | | | Cigna does not cover multigene pharmacogenetic genotyping assays because such assays are considered experimental, investigational or unproven.

| | | | Removed

| | | | Specific tests/genes | PHARMAchip

| | | | Removed some examples | Vysis ALK Break Apart FISH Probe Kit

| (Anthem) | medically necessary unless all components of the panel have been determined to be medically necessary based on the criteria above. Individual components of a panel may be considered medically necessary when criteria above are met. Examples of such panels include but are not limited to the following:

- AIBioTech® CardioloGene Genetic Panel
- AIBioTech® Pain Management Panel
- AIBioTech® PsychiaGene Genetic Panel
- AIBioTech® Urologene Panel

| Genecept™ Assay
| GeneSight® Analgesic
| GeneSight® Psychotropic
| GeneSight® ADHD

| Millennium PGTSM

| Proove® Drug Metabolism test panel
| Proove® Narcotic Risk test panel
| SureGene Test for Antipsychotic and Antidepressant Response (STA2R)
| Vysis ALK Break Apart FISH Probe Kit

| investigational and not medically necessary unless all components of the panel have been determined to be medically necessary based on the criteria above. Individual components of a panel may be considered medically necessary when criteria above are met. Examples of such panels include but are not limited to the following:

- AIBioTech® CardioloGene Genetic Panel
- AIBioTech® Pain Management Panel
- AIBioTech® PsychiaGene Genetic Panel
- AIBioTech® Urologene Panel
| DrugMEt™ Assay
| Genecept™ Assay
| GeneSight® Analgesic
| GeneSight® Psychotropic
| GeneSight® ADHD

| Millennium PGTSM

| PHARMAchip
| Proove® Drug Metabolism test panel
| Proove® Narcotic Risk test panel
| SureGene Test for Antipsychotic and Antidepressant Response (STA2R).

| Removed some examples | Vysis ALK Break Apart FISH Probe Kit

| • PHARMAchip

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| Specific tests/genes |
because such systems are considered experimental, investigational or unproven.

Cigna does not cover ANY of the following pharmacogenetic testing panels for any indication because they are experimental, investigational or unproven:

SureGene Test for Antipsychotic and Antidepressant Response (STA2R)
Genecept Assay
GeneSight Analgesic
GeneSight Psychotropic
GeneSight ADHD