Payer Coverage Policies of CYP450 single gene and panel tests: Clinical and Economic Evidence

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Abstract

Objective: The purpose of this study is to analyze payer coverage of panel-based pharmacogenomics (PGx) genetic testing across the top five commercial payers to determine coverage variations and evaluate the evidence differences that resulted in payer coverage differences for the clopidogrel CYP2C19 test.

Methods: We utilized the TRANSPERS Payer Coverage Policy Registry© containing PGx testing policies from 2015 and updated it with 2016 PGx testing policies. In addition, we also searched for new 2016 PGx policies using previously used inclusion and exclusion criteria. We compared the 2015 and updated 2016 PGx policies noting language and coverage decisions and then analyzed the evidence used to make coverage decisions.

Results: Our findings identified six policies with 35 PGx tests. Updates to four out of the six policies and three new PGx policies have been identified, covering seven policies total. When comparing the 2015 and updated 2016 policies, we found 2 out of 3 payers covered single gene CYP2C19 testing but none covered CYP450 panels. We compared the evidence that the two payers used to make the coverage decision, and found 22 references but only 3 overlapped in each coverage policy.

Conclusion: Coverage and payer evidence cited are not consistent and coverage decisions are not always transparent for single gene CYP2C19 PGx testing for clopidogrel. A more standardized approach between payers and healthcare professionals is necessary to provide more transparent and robust evidence on both single gene PGx testing and CYP450 panel and link payer coverage decisions to available information in the literature.

Introduction

In recent years, PGx testing needs have increased as providers recognize its positive impact in improving outcomes. As clinicians rely more and more on PGx testing, coverage has become a concern for patients and providers alike as to how and if payers will cover the tests. Panel-based PGx genetic testing coverage and policies can change every year, shifting the tests that are covered for patients based on differing PGx analysis methods. For example, looking at changes in 2011 and 2012, PGx policies have brought many coverage additions and removals as well as coverage differences amongst different payers¹². For example, some payers cover CYP450 testing for clopidogrel, while others do not, and individual CYP2C19 testing for clopidogrel and CYP2D6 testing for tetrabenazine are covered, but the panels containing these genes are not covered.¹ These changes can influence patient testing decisions and thus, patient outcomes.

The objective of this study was to analyze coverage of panel-based PGx testing across the top five commercial payers, determine any coverage variations, and deduce differences in evidence analyses that may have resulted in payer coverage differences. Due to the inconsistency in PGx testing coverage, we compared and contrasted the coverage of panel-based PGx across the top five commercial payers in order to determine any coverage variations and linkage between payer coverage decision outcome and evidence analyzed. We specifically used the example of payer coverage for the clopidogrel CYP2C19 test individually and in a CYP450 panel. Our
ultimate goal was to compare the types of evidence that the payers used to make their coverage decisions in order to rationalize those decisions.

**Methods**

*The University of California – San Francisco (UCSF) Center for Translational and Policy Research (TRANS Perez) Payer Coverage Policy Registry©* was a collaborative effort between UCSF, Tufts Medical Center, American Institutes for Research, and Center for Business Models in Healthcare to address the need for transparent payer coverage and policies. The registry includes information on the multigene tests that are included in payer policies, which tests are covered and not covered, the rationale behind the coverage decision, and evidence cited in coverage decisions for multiple disease states and conditions. We define multigene tests as tests that analyze multiple genes by next generation sequencing or chromosomal microarray analysis. In this study, we used the PGx portion of this registry to analyze coverage decisions and rationales.

Based on the *The University of California – San Francisco (UCSF) Center for Translational and Policy Research (TRANS Perez) Payer Coverage Policy Registry©* coded PGx policies, we searched each payer and policy name for updated versions to those policies and coded them. We then searched for new PGx policies by going onto the top five payers’ websites and searching for policies using the terms “Genetic Test”, “Sequencing”, and “Panel” to identify applicable policies. Policy titles were screened for applicable terms and the knowledge of possible types of genetic testing that may be found in the policy to determine if they met criteria for inclusion in the database. The inclusion criteria were that coverage policy must be from the top five payers initially and must specifically address multi-gene panels or tests or sequencing of complete exomes or genomes (WGS, WES) by methods such as next-generation sequencing. Exclusion criteria were if the coverage policy was not from the top 5 payers initially, addressed single gene testing or single gene sequencing only, and contained gene expression profiling and testing done by FISH or Z-band karyotyping. We narrowed down the policies we found to three new ones for coding. Full details of the methods can be found in section A of the Appendix.

For the 2015 and updated 2016 PGx policies, we compared the PGx test coverage and language. Upon comparing the updated PGx policies to the previous year’s policies. In addition, we analyzed the studies included in the payers’ coverage decisions regarding CYP2C19 PGx testing. We also performed a non-systematic literature search to identify clinical utility and reimbursement studies of CYP2C19 genotyping for clopidogrel to understand what the literature used in the coverage decision vs. what evidence is available in peer-reviewed literature. See Appendix Table B for literature search results.

**Results**

Our TRANS Perez Payer Coverage Policy Registry© identified six policies from 2015 with 35 PGx tests. Updates to four of the six policies and three new PGx policies have been identified, covering seven policies total. We found payer coverage differences for the single gene CYP2C19 testing for clopidogrel, with the additions and deletions that changed for the three policies shown in Appendix Table C.

For the two payers, we found a total of 22 studies that were evaluated that both payers cited to conclude their coverage decisions for CYP2C19 genetic testing. As shown in Table 1 the types of evidence for CYP2C19 testing consists of clinical studies, clinical guidelines, systematic reviews, and meta-analyses, and then a summary conclusion of each piece of evidence is provided.

| Table 1: Types of Evidence used in Payer Coverage Policies |
|-----------------|-----------------|------------------|-----------------|-----------------|-----------------|-----------------|
| **Payer**        | **CYP450 Applicable References** | **CYP2C19 / Clopidogrel References** | **Clinical Study** | **Clinical Guideline** | **Systematic Review or Meta-analysis** | **Summary Conclusions** |
|                  |                  |                  |                  |                  |                  |                  |


Three of the nine studies have conclusions that suggest genotyping, two of the nine studies have conclusions that recommend against routine genotyping, and four of the nine studies addressed genotyping in the context of other disease states, treatments, or genes or did not address CYP2C19 genotyping.

For Anthem, out of 13 studies were determined to be relevant, 10 studies have conclusions that suggest genotyping, two studies have conclusions that suggest against genotyping, and one study does not discuss the relationship between CYP2C19 genotyping and cardiovascular events.

Table 2: Relevant Evidence and Primary Outcomes Payers Cited

<table>
<thead>
<tr>
<th>Payer 1 (Aetna) References</th>
<th>Primary Outcome</th>
<th>Evidence Type</th>
<th>Payer 2 (Anthem) References</th>
<th>Result/Outcome</th>
<th>Evidence Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simon T, Verstuyft C, Mary-Krause M, et al; French Registry of Acute ST-Elevation and</td>
<td>Carrying CYP2C19 loss-of-function alleles had a higher rate of subsequent</td>
<td>CS</td>
<td>Simon T, Verstuyft C, Mary-Krause M, et al.; French Registry of Acute ST-Elevation</td>
<td>Carrying CYP2C19 loss-of-function alleles had a higher rate of subsequent cardiovascular events than</td>
<td>CS</td>
</tr>
</tbody>
</table>

Of the 22 studies, only 3 overlapped between the two payers, and due to this inconsistency, we further analyzed the evidence that four payers cited to conclude coverage for CYP2C19 testing for clopidogrel, and the results are summarized in Table 2. We did not include two of the four payers because the reference cited for one was unavailable, and the other payer did not mention CYP450 testing altogether.
<table>
<thead>
<tr>
<th>Citation</th>
<th>Summary</th>
<th>Reference</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-ST Elevation Myocardial Infarction (FAST-MI) Investigators. Genetic determinants of response to clopidogrel and cardiovascular events. NEJM. 2009;360(4):363-375</td>
<td>Cardiovascular events than those who were not. This effect was particularly marked among the patients undergoing percutaneous coronary intervention</td>
<td>and Non-ST Elevation Myocardial Infarction (FASTMI) Investigators. Genetic determinants of response to clopidogrel and cardiovascular events. N Engl J Med. 2009;360(4):363-375.</td>
<td>those who were not. This effect was particularly marked among the patients undergoing percutaneous coronary intervention</td>
</tr>
<tr>
<td>Holmes DR Jr, Dehmer GJ, Kaul S, et al. ACCF/AHA Clopidogrel Clinical Alert: Approaches to the FDA &quot;Boxed Warning&quot;. A Report of Evidence base insufficient to recommend routine genetic or platelet function testing. Use clinical judgment to see whether patient</td>
<td></td>
<td>Holmes MV, Perel P, Shah T, et al. CYP2C19 genotype clopidogrel metabolism, platelet function, and cardiovascular events:</td>
<td>Link between CYP2C19 genotype and responsiveness but no link between genotype and CV events</td>
</tr>
</tbody>
</table>

**Legend:**
- **CG:** Case report
- **CS:** Cross-sectional study
- **SR/MA:** Systematic review and meta-analysis
<table>
<thead>
<tr>
<th>Task Force/Association</th>
<th>Reference</th>
<th>Study Details</th>
<th>Outcome/Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wallentin L, James S, Storey RF, et al.; for the PLATO investigators. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: A genetic substudy of the PLATO trial. Lancet. 2010;376(9749):1320-1328.</td>
<td>Ticagrelor more efficacious than clopidogrel, irrespective of CYP2C19 polymorphisms for preventing composite of MI, CV death, and stroke</td>
<td>CS</td>
<td>CYP2C19*2 carrier status is significantly associated with an increased risk of adverse cardiovascular events</td>
</tr>
<tr>
<td>Mega JL, Close SL, Wiviott SD, et al. Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: A pharmacogenetic analysis. Lancet. 2010;376(9749):1312-1319.</td>
<td>Looking at ABCB1 and CYP2C19</td>
<td>CS</td>
<td>Tripling maintenance clopidogrel dose from 75 mg to 225 mg in CYP2C19<em>2 heterozygotes achieved levels of platelet reactivity similar to 75 mg in noncarriers. In CYP2C19</em>2 homozygotes, doses of up to 300 mg not comparable degree of platelet inhibition</td>
</tr>
<tr>
<td>Sibbing D, Koch W, Gebhard D, et al. Cytochrome 2C19<em>17 allelic variant, platelet aggregation, bleeding events, and stent thrombosis in clopidogrel treated patients with coronary CYP2C19</em>17 carrier status is significantly associated with enhanced response to clopidogrel and an increased risk of bleeding in patients taking clopidogrel and undergoing PCI</td>
<td></td>
<td>CS</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Summary</td>
<td>Category</td>
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• For clopidogrel indications other than PCI, there is little evidence to support association between carriage of a CYP2C19 allele and increased risk of adverse cardiovascular outcomes.  
• Predominantly white participants using clopidogrel for PCI report a modest increase in risk of adverse cardiovascular outcomes associated with CYP2C19 LoF allele carriage. Studies in Asian (mainly Chinese and Korean) populations report a increase in the risk of adverse cardiovascular outcomes associated with carriage of a CYP2C19 LoF allele. | CS |

*United payer policy reference unable to be found
**Cigna 2016 policy does not specifically mention CYP2C19
Notes: Clinical study = CS, Clinical guideline = CG, Systematic review/meta-analysis= SR/MA; shading indicates overlapping references between the two policies.
The non-systematic literature search on clinical utility and reimbursement for CYP2C19 testing and summarized our findings into Table 3. The search identified and we reviewed the clinical utility and reimbursement of clopidogrel CYP2C19 testing for rationalizing pharmacogenetic testing guideline recommendations, we found a total of 2 guidelines and 16 peer reviewed articles. Regarding clinical utility and benefit, some sources recommend testing and others do not since clinical utility and benefit evidence does not obviously suggest one or the other. No general consensus is currently established. Regarding CYP2C19 testing for clopidogrel reimbursement, we found a total of 9 articles. Although all articles stated reimbursement of some percentage of PGx testing, reimbursement rates differed and were not standardized among different payers and care settings. For cost-effectiveness of CYP2C19 testing for clopidogrel, we found 7 articles. Most articles stated that genotyping before treatment is more cost-effectiveness than not genotyping.

Table 3: CYP2C19 testing for clopidogrel clinical utility and reimbursement evidence table

<table>
<thead>
<tr>
<th>Source and Link</th>
<th>Summary of Relevant Sections and Notes</th>
</tr>
</thead>
</table>
Testing considered for unstable angina/non-ST segment elevation MI (or after percutaneous coronary intervention for acute coronary syndromes) if testing changes management |
| Adnan M Bhopalwala. 2015. [http://europepmc.org/articles/PMC4300541;jsessionid=xP58KQMioGPl2fgM1v7L2](http://europepmc.org/articles/PMC4300541;jsessionid=xP58KQMioGPl2fgM1v7L2) | Not enough support for routine CYP2C19 screening for polymorphisms in patients being treated with clopidogrel  
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  
CYP2C19 testing does not have clinical benefit and not enough evidence for improving outcomes  
Need larger RCT and more evidence |
| Noel C. Chan. 2014. [http://www.bloodjournal.org/content/124/5/689.long?ssChecked=true](http://www.bloodjournal.org/content/124/5/689.long?ssChecked=true) | Testing clinical benefit is unproven  
Good analytical and clinical validity but inconclusive clinical utility  
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 |
Clinical use should be limited to individuals with high risk for poor outcomes  
The routine clinical use of genetic testing to screen patients treated with clopidogrel who are undergoing PCI is not recommended  
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  
Their clinical use should be limited to patients at high risk for poor clinical outcomes |
<table>
<thead>
<tr>
<th>Author</th>
<th>Title</th>
<th>Summary</th>
</tr>
</thead>
</table>
| Alfi Yasmina. 2014. | Testing recommended for patients with CAD undergoing percutaneous coronary intervention and stenting  
http://www.futuremedicine.com/doi/pdf/10.2217/pgs.14.16 | Testing should be considered for patients with moderate or high risk of poor outcomes  
Genotyping before treatment was more cost effective.                                                                                                                                                                                                                     |
| C.F. Samer. 2013.  | Evidence supports testing for percutaneous coronary intervention  
| Mohamed H.A. Shahin. 2013. | Limited evidence of CYP2C19 genetic testing clinical utility  
http://europepmc.org/articles/PMC3731766 | Conflicting evidence between ACC/AHA and CPIC  
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. |
| Kristin W. Weitzel. 2014. | Seven payers reimbursed for CYP2C19 testing within first month of billing  
| Julie A. Johnson. 2013. | CYP2C19 testing is of greatest clinical value for patients undergoing PCI  
http://pharmrev.aspetjournals.org/content/65/3/987.long#title21 | CYP2C19 genetic testing has limited clinical utility, and no consensus exists as to what clinical utility is  
Out of 12 payers examined, 3 mention CYP2C19 testing (1 covers; 2 do not).                                                                                                                                 |
| Euan A. Ashley. 2012. | CYP2C19 genetic testing for ACS (acute coronary syndromes) patients is not supported  
http://circ.ahajournals.org/content/126/1/142.long#sec-17 | RCTs for CYP2C19 genotype-directed antiplatelet therapy support genotyping directed therapy but these RCTs were not powered for actual clinical outcomes  
CYP2C19 testing covered for patients with acute coronary syndromes undergoing PCI or reinitiating clopidogrel therapy  
Cost-effectiveness studies are not conclusive, and cardiology society guidelines do not recommend routine CYP2C19 genotyping.                                                                                                                                 |
| Jacob A. Doll. 2016. | Through a budget impact model, CYP2C19 genotyping can reduce costs and adverse events.  
| Yao Yang. 2015. | Genotyping is more cost-effective than not genotyping, but genotype-guided use for prasugrel is more cost-effective than for clopidogrel.  
http://www.nature.com/nrcardio/journal/v12/n8/full/nrcardio.2015.64.html | Genotyping is more cost-effective than not genotyping, but genotype-guided use for prasugrel is more cost-effective than for clopidogrel.                                                                                                                                                                                                 |
| Samuel G. Johnson. 2015. | Genotype based strategy is more cost effective than no genotyping for clopidogrel  
| Minghuan Jiang. 2015. | Lab usually bills hospital for inpatient genotyping performed onsite and bill third party payers for outpatient genotyping  
http://www.tandfonline.com/doi/full/0.1517/17425255.2015.1068757 | Not enough cost-effectiveness data to support PGx testing  
Payers usually do not cover PGx testing, but sometimes may cover with PA.                                                                                                                                                                                                      |
| Naveen L. Pereira. 2015. | Lab usually bills hospital for inpatient genotyping performed onsite and bill third party payers for outpatient genotyping  
http://www.jmcp.org/doi/pdf/10.18553/jmcp.2015.21.7.552 | Not enough cost-effectiveness data to support PGx testing  
Payers usually do not cover PGx testing, but sometimes may cover with PA.                                                                                                                                                                                                      |

**Discussion**

In analyzing the payer policies for coverage of single gene CYP2C19 genetic testing and CYP450 panels, we analyzed the number and overlap of articles cited between two payers that covered CYP2C19 testing. Payer A cited 12 sources relevant to CYP2C19 testing with 9 directly relevant to clopidogrel and thrombosis while Payer B cited 11 sources relevant to CYP2C19 testing with 7 directly relevant to clopidogrel and thrombosis. The payer policies on CYP2C19 genotyping and the implications on clinical practice are discussed.
B cited 14 articles relevant to CYP2C19 testing with 13 directly relevant to clopidogrel and thrombosis. Between the two payers, three articles were cited for both. In addition, we wanted to compare the evidence payers used to make coverage decisions for CYP2C19 PGx testing for clopidogrel since Payers 1 and 2 covered the test and Payer 3 did not.

Of worth noting is that payers 1 and 2 were very transparent in citing the evidence that they used to make their coverage decisions, citing the studies and guidelines, while payer 3 was not transparent. Although payer 3 cited a clinical guideline, we were unable to find the guideline and its contents even through institutional and academic databases and thus unable to analyze and conclude how and why payer 3 was able to make its decision. The evidence source was not open access, and without the guideline, we are unable to conclude how and why payers 1 and 2 differed from payer 3 in terms of this decision-making. These coverage decisions should be transparent both to the payer and public since they can affect anyone that needs the genetic testing based on current guideline recommendations. The general consensus from current guidelines and studies shows that CYP2C19 PGx testing for clopidogrel can be cost-effective for acute coronary syndrome patients undergoing percutaneous coronary intervention (PCI).8,9,10 CPIC recommends CYP2C19 genotyping for ACS/PCI patients while AHA/ACCF 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.3,4 However, testing should be limited to patients at high risk of poor outcomes, in which a single thrombotic event could be lethal.5,6 The FDA issued a Boxed Warning to the Plavix label saying that tests are available to identify genetic differences in CYP2C19 function and that healthcare professionals should consider use of anti-platelet medications or alternative dosing strategies for patients identified as poor metabolizers.7 However, no RCTs exist for CYP2C19 genotyping outcomes to prove that genotyping is always necessary when initiating clopidogrel. See Appendix Table B for literature search details.

Another transparency consideration is that cost-effectiveness studies are missing from both payers’ cited evidence. One large factor for coverage decisions is cost, and it is unclear whether the payers did not consider cost or considered it without citing the cost studies. Without the cost studies, we do not know how much effort and priority the payers placed on cost and furthermore, how much of their decision was based on cost. If the payers weighed cost more heavily than efficacy or clinical need, then the decision may not be as clinically relevant compared to if the payers weighed cost equal to efficacy and clinical need, especially since cost-effectiveness plays a role in genetic testing. The debate exists of whether testing for one uncommon adverse event is cost-effective when providers could switch to other agents such as ticagrelor or prasugrel (for patients that do not have prior stroke) that do not require genetic testing even though bleeding risk in non-coronary artery bypass graft is higher with those agents or that providers could simply increase the clopidogrel dose to avoid the complications and cost of testing.12 Some studies have found that CYP2C19 genotyping for clopidogrel is cost-effective when compared to initiating prasugrel or ticagrelor.8,9,10 Furthermore, according to a budget impact model, genotyping for CYP2C19 will increase market share for ticagrelor and prasugrel and decrease market share for clopidogrel, demonstrating genotyping guided therapy.11 Also, since PCI/ACS patients and patients at high risk of thrombosis such as high-risk PCI procedure patients are indicated for clopidogrel, it would be a more cost-effective option to save clopidogrel for these patients.

Another difference is that although payers 1 and 2 both cited clinical studies, their other sources were different types. Payer 1 analyzed clinical guidelines while payer 2 analyzed meta-analyses and systematic reviews. Although meta-analyses and systematic reviews encompass many studies and are valid, they do not include more evidence than clinical guidelines. Clinical guidelines include clinical studies as well as systematic reviews and meta-analyses, so they include a wider breadth of study types, and thus are more likely to have accurate clinical representations. Clinical guidelines represent the treatment algorithms and not only results, so although payers 1 and 2 came to the same coverage conclusions, payer 1’s usage of clinical guidelines is preferred for a more wholesome approach.

Looking at both literature search results as well as payer evidence, disconnect exists between coverage
decisions and the literature. The evidence for direct support of cardiovascular outcome improvement linked to clinical utility of genetic testing is not strong although the connection between polymorphisms and adverse effects is established. Notably, payers 1 and 2 still deemed CYP2C19 testing for clopidogrel to be medically necessary even though clinical utility and cardiovascular outcomes for this test have not been strongly proven, and no general consensus exists. The payers also state coverage more generally compared to the patient populations studied in the literature. The payers do not specify what population and clinical indication the coverage is for. Even though the payers cite their evidence, the decision does not seem to match what the literature concludes about clopidogrel CYP2C19 PGx testing.

**Limitations:**
This analysis also comes with several limitations. The registry only includes five of the top payers (112 Million lives), and many other payers exist. Without the other payers included, we may have missed other additional PGx policies. Also, for the literature search, we may have not identified some articles since the purpose of the search was not to make a comprehensive systematic search. This may have introduced some bias in our conclusions from the literature. In addition, we also had less detail on coverage decisions and extracted coverage decisions based on cited evidence when other reasons could have influenced those decisions.

**Policy Implications:**
As mentioned in discussion of results, payers are not always transparent in citing clear evidence that the general public and professionals can find and use. This makes it difficult for health professionals to deduce coverage decisions and could potentially decrease the degree of use of clinically useful testing and trust that patients’ place in payers to cover necessary testing. With the existing complications of a multi-payer system, such as non-standardization of testing coverage and evidence used for coverage decisions, the non-transparency adds an additional layer of complexity that is worthy of developing a systematic process to address.

Regarding evidence of PGx testing, a limited amount of studies on cost-effectiveness and clinical utility and benefit exist, making it difficult for policy makers to have a large amount of robust evidence for making coverage decisions. This is also why PGx testing is difficult to implement and why healthcare professionals have differing opinions regarding testing.

In addition, with the vague suggestions that the literature and guidelines provide for CYP2C19 testing and broad coverage without indications in the payer policies, single-gene PGx testing for CYP2C19 becomes difficult to decide. As more hospitals and academic institutions recognize the need for PGx testing, coverage and coverage rationale will become more important. Payers need to be better integrated into and involved with the PGx testing workflow and testing logistics as hospitals and institutions create these in a multidisciplinary team. Even with the smoothest single-gene PGx testing programs, if tests cannot be reimbursed or reimbursement is not standardized, the system hits a stopping point, and the use of CYP450 panels become near impossible to implement or be a covered benefit. Payers should update coverage policies more frequently and systematically to keep up with published clinical treatment and PGx testing guidelines as well as institutional level PGx developments and changes.

**Conclusions:**
In summary for single gene CYP2C19 PGx testing for clopidogrel, coverage and payer evidence cited are not consistent and coverage decisions are not always transparent. The clinical utility and benefit data on the test is lacking clear direction, testing reimbursement differs between payers and how tests are performed (e.g. single gene CYP2C19 vs. CYP450 panels, and while the use of the test is generally considered cost-effective for clopidegrel. These results demonstrate that a more standardized approach between payers and healthcare professionals is necessary to provide more transparent and robust evidence on both single gene PGx testing and CYP450 panel and link payer coverage decisions to available information in the literature.
References