Olatokunbo Awodele, M.D, MPH
3333 Farnam
Omaha, NE 68131
policycomments@wpsic.com

IGNITE Response to Proposed LCD DL36398

The Implementing Genomics in Practice (IGNITTE) Consortium is a NHGRI research group that is implementing genome-informed personalized healthcare and translating in clinical settings to advance the practice, delivery and economics of health care. While personalized medicine is transforming the health system as we know it, we are bridging the gap between genomics research and patient care.

Knowledge related to pharmacogenetic testing is ripe for translation into practice. Drug therapy for many conditions is currently plagued by an unacceptable level of adverse drug reactions, inefficacy, and poor compliance. Adverse drug reactions are responsible for the death of approximately 100,000 patients per year, and are also the cause of over 2,216,000 hospitalizations per year. This is one of several reasons for poor compliance and adherence to many therapeutic drugs, which ultimately reduces drug efficacy and worsens the societal disease burden. Genomic science has the potential to change this. For many of the most commonly used drugs, the specific genetic variants that result in either toxic adverse reactions or sustained efficacy are now known. The use of genetic testing for improving drug efficacy and reducing adverse drug reactions is now endorsed by many expert organizations. The FDA has placed genetic testing recommendations and black box warnings in 121 labels. Guidelines are being written for gene-drug pairs for which there is overwhelming evidence for the benefit of using genetic testing during drug therapy. For example, the Clinical Pharmacogenetics Implementation Consortium, a working group of investigators from the NIH Pharmacogenomics Research Network, has published guidelines for using pharmacogenetic data in the prescribing of 16 commonly used drugs, and 6 more are in development. These guidelines are being endorsed by the American Society of Health-System Pharmacists and are accepted into the guidelines.gov website. In addition, the Dutch Pharmacogenomics Working Group has also written guidelines for 53 drugs. Preemptive pharmacogenetic testing may reduce health care system. Thus we support guideline-based Pharmacogenomic testing.

CPIC: Guidelines

Drug	Guidelines
abacavir	CPIC Dosing Guideline for abacavir and HLA-B
allopurinol	CPIC Dosing Guideline for allopurinol and HLA-B
amitriptyline	CPIC Dosing Guideline for amitriptyline and CYP2C19,CYP2D6
atazanavir	CPIC Dosing Guideline for atazanavir and UGT1A1
azathioprine	CPIC Dosing Guideline for azathioprine and TPMT
boceprevir	CPIC Dosing Guideline for boceprevir,peginterferon alfa-2a,peginterferon alfa-2b,ribavirin,telaprevir and IFNL3
capecitabine	CPIC Dosing Guideline for capecitabine and DPYD
carbamazepine	CPIC Dosing Guideline for carbamazepine and HLA-B
citalopram	CPIC Dosing Guideline for citalopram,escitalopram and CYP2C19
clomipramine	CPIC Dosing Guideline for clomipramine and CYP2C19,CYP2D6
clopidogrel	CPIC Dosing Guideline for clopidogrel and CYP2C19
codeine	CPIC Dosing Guideline for codeine and CYP2D6
desipramine	CPIC Dosing Guideline for desipramine and CYP2D6
doxepin	CPIC Dosing Guideline for doxepin and CYP2C19,CYP2D6
escitalopram	CPIC Dosing Guideline for citalopram,escitalopram and CYP2C19
fluorouracil	CPIC Dosing Guideline for fluorouracil and DPYD
fluvoxamine	CPIC Dosing Guideline for fluvoxamine and CYP2D6
imipramine	CPIC Dosing Guideline for imipramine and CYP2C19,CYP2D6
ivacaftor	CPIC Dosing Guideline for ivacaftor and CFTR
mercaptopurine	CPIC Dosing Guideline for mercaptopurine and TPMT
nortriptyline	CPIC Dosing Guideline for nortriptyline and CYP2D6
paroxetine	CPIC Dosing Guideline for paroxetine and CYP2D6
peginterferon alfa-2a	CPIC Dosing Guideline for boceprevir,peginterferon alfa-2a,peginterferon alfa-2b,ribavirin,telaprevir and IFNL3

CYP2C19

Amitriptyline (and other tricyclics [eg, clomipramine, doxepin, trimipramine, imipramine])

We disagree with the conclusions in the LCD as the evidence supports genotypic-based drugs selection for amitriptyline and other tricyclics. The CPIC Dosing Guideline for amitriptyline recommends an alternative drug for CYP2C19 ultrarapid metabolizers and a 50% dose reduction for CYP2C19 poor metabolizers (below, https://www.pharmgkb.org/drug/PA448385).

a) While the RCT may be the preferred source for evidence, other credible studies and sources can and are used regularly to define clinical practice. The recommendation to lower the dose in poor metabolizers was moderate in strength and has been made based in other clinical studies using pharmacokinetic and pharmacodynamic data (Kirchheiner et al. 2004) (Kitzmiller et al. 2011)

b) The genotyping is not used to determine dose. It is used to identify those patients for whom use of the drug at standard dosing is appropriate. More importantly from a clinical standpoint, it identifies those patients for whom standard dosing and use of the drug may not be medically appropriate. These patients would either require a lower dose and therapeutic monitoring to reduce their risk of side effects or an alternate analgesic based on their genotype. The MAC's suggestion that starting with a lower dose is the answer for all patients and genotyping is not needed to do so is not consistent with clinical experience in treating depression. The appropriate treatment for the 35-50% of patients who are Extensive Metabolizer and 18-45% who are Intermediate Metabolizer is to start them on the standard dose. This is not the appropriate treatment for the other 2 groups of patients.

   In the absence of *CYP2C19* genotyping, the physician would start all patients on the recommended dose. This would be appropriate for the majority of patients, the 35-50% of patients who are Extensive Metabolizer and 18-45% who are Intermediate Metabolizer.

c) The suggestion referred to in the DLCD (to lower the dose) is only appropriate for the 2-15% of patients who are poor metabolizers (PM). This is not just a small reduction in dose: the recommendation is to reduce the dose by 50%.

   A physician would not intentionally start all patients with a 50% dose reduction and gradually increase the dose in order to reduce the risk of side effects when it is the appropriate treatment in 2-15% of patients. To do so would place the majority of the patients who are normal metabolizers at unnecessary risk of treatment failure from an inadequate therapeutic dose without a valid reason. It would delay the response to treatment even longer and contribute to patient frustration with treatment, which contributes to patient non-adherence and unwillingness to try medications. This is an issue with all medications; however, it is amplified with anti-depression treatment given the long time required before the patient notices a positive effect (4-8 weeks.)

   However, failing to recognize these patients are at higher risk for side effects and starting them at standard doses places them unnecessarily at risk for side effects which also contributes to stopping treatment. Therefore, identifying those patients who are poor metabolizers and starting them with the correct lower dose will reduce the probability of side effects and give the patient who is a poor metabolizer a better chance of successful treatment.

d) The DLCD does not address the importance of the genotyping for the 2-15% of patients who are ultrarapid metabolizers (UM) for whom the CPIC recommendation is to use an alternative drug or therapeutic monitoring. The physician would not know this is the appropriate management for the individual patient without *CYP2C19* results.

   In short, the genotyping would result a different therapeutic decision: reduced dose for the 2-15% who are poor metabolizers and selection of an alternate drug in 2-15% who are ultrarapid metabolizers.

e) The DLCD defers to therapeutic monitoring as a solution for the UM and PM, a solution that does not require genotype information, however, therapeutic monitoring is not routinely performed and would not be done unless circumstances suggested it was appropriate. Therefore, the physician would not know to request therapeutic monitoring unless the patient's metabolizer status is known. Without such information, all patients would be started on the standard dose and be at risk for side effects and/or treatment failure, both of which could be avoided with appropriate genotyping information.

Recent studies have demonstrated that use of pharmacogenomics testing to aid in the selection of antidepressants and antipsychotics can have a positive effect on patient care, reducing the number of drugs required for treatment response, reducing lost days at work and reducing healthcare utilization. (Winner, J. G. et al. 2013), (Winner, J. et al. 2013) A retrospective study has shown that a higher proportion of patients hospitalized for depression were ultrarapid and poor metabolizers. (Chou et al. 2000)

Given the level of evidence identified in the CPIC evaluation and the guideline recommendations for modification of treatment based on the CYP2C19 status, we believe the criteria that a test result have an impact on the patient's management has been met.

REQUEST:

- **Cover *CYP2C19* testing for use of amitriptyline, nortriptyline and the TCAs.**
- **Cover *CYP2C19* testing** for TCA for all its FDA labeled indications as well as off-label uses which have become part of medical practice, e.g. depression and neuropathic pain

Proton pump inhibitors (PPIs) (eg, esomeprazole, omeprazole, pantoprazole)

We disagree with the conclusions in the LCD as the evidence supports genotypic-based drugs selection for proton pump inhibitors. PPIs are widely available over the counter and are routinely prescribed. For CYP2C19 ultrarapid metabolizers (eg, *17/*17), physicians need to be extra alert to insufficient response and should consider increasing PPIs dose by 50-100% (https://www.pharmgkb.org/guideline/PA166104931). Therefore if a physician has genotypic information, there is evidence to support altering the prescription.

We reviewed the reference list to determine the evidence used to arrive at this non-coverage conclusion. We are unable to identify any references related to proton pump inhibitors. The medical literature has shown consistent *CYP2C19* phenotype-dependent differences in the mean 24- hour intragastric pH associated with omeprazole, esomeprazole and lansoprazole. There are higher rates of healing GERD in those identified as poor metabolizers for omeprazole and lansoprazole. (Furuta et al. 2002) (Furuta et al. 2012) (Kawamura et al. 2003)

A meta-analysis showed a 49% decrease in eradication of *H. pylori* in the EMs compared to the PMs (poor metabolizers). In addition to evidence supporting the link between genotype status, there are dosing strategies available. It is recommended that the physician proceed with normal dosing in those identified as poor and intermediate metabolizers. For those who are ultrarapid and extensive metabolizers, the recommendation is to increase the PPI dose or use rabeprazole. (Furuta et al. 2007) (Tamura et al. 2011) (Tang et al. 2013)

Clinically, one approach is to double the dose of the PPI, however, in clinical practice many drug formularies do not cover the increased dose or the use of alternate tiered drugs without a clinical rationale e.g. *CYP2C19* status.

REQUEST:

- **Cover *CYP2C19* testing for use of PPIs.**

<u>SSRIs (eg, fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram)</u>

We disagree with the conclusions in the LCD as the evidence supports genotypic-based drugs selection for SSRIs. SSRIs are typically used as antidepressants in the treatment of depression, anxiety disorders, and some personality disorders. For CYP2C19 ultrarapid metabolizers (eg, *17/*17), physicians should consider increasing the dose by 150% (https://www.pharmgkb.org/guideline/PA166104977) and monitor for adverse drug reactions or consider and alternate therapeutic. For sertraline, reduce the dose by 50% for patients with CYP2C19 poor metabolizer genotypes (PM), and monitor for adverse drug events in patients with CYP2C19 intermediate metabolizer genotypes (IM). Therefore if a physician has genotypic information, there is evidence to support altering the prescription.

We have 2 comments to consider.

a) Expand coverage to all TCAs. CPIC has addressed the issue of the other drugs within the TCA class. (CPIC Dosing guidelines: clomipramine, imipramine/doxepine, doxepine, trimipramine)

> "Tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply the CPIC Dosing Guideline for amitriptyline and *CYP2C19*, *CYP2D6* to other tricyclics including imipramine. In the guideline for amitriptyline, an alternative drug is recommended for *CYP2D6* or *CYP2C19* ultrarapid metabolizers and for *CYP2D6* poor metabolizers. Consider a 50% dose reduction for *CYP2C19* poor metabolizers and a 25% dose reduction for *CYP2D6* intermediate metabolizers."
>
> "Amitriptyline and nortriptyline are used as model drugs for this guideline because the majority of pharmacogenomic studies have focused on these two drugs. Because the tricyclics have comparable pharmacokinetic properties, it may be reasonable to apply this guideline to other tricyclics including imipramine (Supplementary Table S17), with the

acknowledgement that there are fewer data supporting dose adjustments for these drugs than for amitriptyline or nortriptyline."

Recommendations for dose adjustment have been made by others for the TCAs based on pharmacokinetics, pharmacodynamics and the metabolizer status of the patient (Kirchheiner 2004) (Lotsch 2009). In response to the need for clinical guidance on the practical use of pharmacogenomics information, the Dutch Pharmacogenetics Working group published guidelines for gene-dosing for 54 drugs, including TCAs (Swen et al. 2011).

The FDA labels for the class of TCAs include language on *CYP2D6* metabolism and interactions in the TCAs. From a pharmacology perspective, the other TCAs should be included in the same coverage policy as amitriptyline and nortriptyline. There is no evidence to suggest otherwise. Because they have similar pharmacokinetics, it is unlikely that there will be new studies performed to address this specific issue. The patients should be provided the same medical care recommended for the TCAs amitriptyline and nortriptyline and supported by CPIC in the national, peer-reviewed pharmacogenomics guidelines.

b) Indications for amitriptyline.
Amitriptyline is used in treatment of neuropathic pain as well as treatment of depression. The CPIC guideline addresses the dosing issues associated with neuropathic pain. We would recommend coverage of testing for any use for which the TCA drugs will be covered by Medicare.

Dutch Pharmacogenetics Working Group Guideline for citalopram and CYP2C19

Phenotype (Genotype)	**Therapeutic Dose Recommendation**	**Level of Evidence**	**Clinical Relevance**
CYP2C19 PM (*2/*2, *2/*3, *3/*3)	None	Published controlled studies of good quality* relating to phenotyped and/or genotyped patients or healthy volunteers, and having relevant pharmacokinetic or clinical endpoints	Minor clinical effect (statistically significant difference): QTc prolongation (<450 ms female, <470 ms male); international normalized ratio (INR) increase < 4.5 Kinetic effect (statistically significant difference)
CYP2C19 IM (*1/*2, *1/*3, *17/*2, *17/*3)	None	Published controlled studies of good quality* relating to phenotyped and/or genotyped patients or healthy volunteers, and having relevant pharmacokinetic or clinical	Minor clinical effect (statistically significant difference): QTc prolongation (<450 ms female, <470 ms male); INR increase < 4.5 Kinetic effect (statistically significant

		endpoints	difference)
CYP2C19 UM (*17/*17)	Monitor plasma concentration and titrate dose to a maximum of 150% in response to efficacy and adverse drug event or select alternative drug (e.g. fluoxetine, paroxetine)	Published controlled studies of good quality* relating to phenotyped and/or genotyped patients or healthy volunteers, and having relevant pharmacokinetic or clinical endpoints	Minor clinical effect (statistically significant difference): QTc prolongation (<450 ms female, <470 ms male); INR increase < 4.5 Kinetic effect (statistically significant difference)

Dutch Pharmacogenetics Working Group Guideline for sertraline and CYP2C19

Phenotype (Genotype)	**Therapeutic Dose Recommendation**	**Level of Evidence**	**Clinical Relevance**
CYP2C19 PM (*2/*2, *2/*3, *3/*3)	Reduce dose by 50%.	Published controlled studies of moderate quality relating to phenotyped and/or genotyped patients or healthy volunteers, and having relevant pharmacokinetic or clinical endpoints	Clinical effect (statistically significant difference): long-standing discomfort (48-168 hr) without permanent injury e.g. failure of therapy with tricyclic antidepressants, atypical antipsychotic drugs; extrapyramidal side effects; parkinsonism; adverse drug events resulting from increased bioavailability of tricyclic antidepressants, metoprolol, propafenone (central effects e.g. dizziness); international normalized ratio 4.5-6.0; neutropenia 1.0-1.5x109/l; leucopenia 2.0-3.0x109/l; thrombocytopenia 50-75x109/l
CYP2C19 IM (*1/*2, *1/*3, *17/*2, *17/*3)	Insufficient data to allow calculation of dose adjustment. Be extra alert to adverse drug events (e.g., nausea, vomiting,	Published controlled studies of moderate quality relating to phenotyped and/or genotyped patients or healthy volunteers, and	Minor clinical effect (statistically significant difference): QTc prolongation (<450 ms female, <470 ms male); international normalized ratio increase < 4.5 Kinetic effect (statistically significant

	diarrhea).	having relevant pharmacokinetic or clinical endpoints	difference)
CYP2C19 UM (*17/*17)	None	no data was retrieved with the literature search	no data was retrieved with the literature search

REQUEST:

- **Cover *CYP2C19* testing for use of SSRIs.**

Warfarin

We agree with the conclusions in the LCD as the evidence does not support CYP2C19 genotypic-based drug selection for warfarin.

CYP2D6

Tamoxifen

We agree that that tamoxifen metabolism is complex.

Tricyclics (eg, clomipramine, doxepin, trimipramine, imipramine)

We disagree with the conclusions in the LCD as the evidence supports genotypic-based drugs selection for other tricyclics. Tricyclic antidepressants have comparable pharmacokinetic properties. There is CPIC Dosing Guideline for amitriptyline and CYP2C19, CYP2D6 to other tricyclics. In the guideline for amitriptyline, an alternative drug is recommended for CYP2D6 or CYP2C19 ultrarapid metabolizers and for CYP2D6 poor metabolizers. Consider a 50% dose reduction for CYP2C19 poor metabolizers and a 25% dose reduction for CYP2D6 intermediate metabolizers.

Numerous studies have been published addressing antidepressants and *CYP2D6* status. Higher non-response rates have been reported in those who are PMs or IMs. (Muller et al. 2012), (Kawanishi et al. 2004) Mulder et al reported higher normalized plasma concentration ratios of antidepressants compared for those who were PMs/IM compared to EMs. They found that there was also an increased risk of a plasma concentration above the therapeutic range for PMs and IMs. (Mulder et al. 2006) Dose adjustment of *CYP2D6*-dependent drugs has been recommended for PMs, IM, and Ums. (Kirchheiner &

Rodriguez-Antona 2009) Rau found an increase frequency of adverse effect in those found to be PM and higher frequency of non-responds in UMs. (Rau et al. 2004)

Laika et al examined the side effects for PMs and IMs. In general, they found that patients treated with *CYP2D6* drugs had a longer hospitalization and delay in the onset of response. They noted a 'pronounced, significant increase in side effects with PMs compared to non-PMs for those on CYPD26 drugs. They noted an increase rate. They recommend that "Identification of IM status might help to avoid adverse effects by starting treatment with lower doses for *CYP2D6* drugs and keeping doses low throughout the treatment. In the case of nonresponse, switching to another drug might be better than increasing the dose for IMs. Increasing the dose, however, would be an option for EMs and UMs." (Laika et al. 2009)

Chou et al reported that "the cost of treating patients with extremes in *CYP2D6* activity (UM and PM) was on average $4,000 to $6,000 per year greater than the cost of treating patients in the efficient metabolizer (EM) and intermediate metabolizer (IM) groups". They also noted that the total duration of hospital stay longer for those in *CYP2D6* PM group (Chou et al. 2000). Ruano et al reported a longer length of stay associated with PM. (Ruano et al. 2013)

***CYP2D6* - Antipsychotics**

Genotyping information can be used to inform 2 different decisions.

a) To predict efficacy and guide selection (or avoidance) of a drug metabolized by *CYP2D6* and/or *CYP2C19*. The studies with antipsychotics have not consistently defined use of genotyping to predict efficacy of different drugs and would not support this as an indication for testing.
b) To identify those patients at higher risk for a side effect. This use would apply for the antipsychotics at this time. Extrapyramidal symptoms and tardive dyskinesia are frequent, permanent adverse events associated with antipsychotic use. Avoidance of EPS and TD are important treatment goals. Studies have found a significant association between EPS and PMs. (Crescenti et al. 2008), (Kobylecki et al. 2009), (de Leon et al. 2005a) For patients facing lifetime treatment with antipsychotics and lifetime risk of EPS, having a mechanism that would allow the clinician to make therapeutic choices that could decrease the chance of developing EPS is important.

REQUEST:

- **Cover *CYP2D6* testing for use of TCAs.**

Codeine

We disagree with the conclusions in the LCD as the evidence supports genotypic-based drugs selection for CPIC Guidelines for Codeine.

Chronic pain and its management have a major impact on the healthcare system, physicians and patients. Chronic pain is estimated to affect about 100 million adults in the US. This includes post-operative pain, cancer pain, neuropathic pain as well as osteoarthritis and other chronic conditions. Gaskin and Richard estimated the direct healthcare cost of pain and healthcare costs attributed to pain ranged from $560 to $635 billion in 2010 dollars; additional costs due to pain ranged from $261-300 billion. The annual costs of pain are greater than the costs associated with heart disease ($309 billion), cancer ($243 billion), and diabetes ($188 billion). Indirect costs include workplace absenteeism, disability, and early retirement (Gaskin & Richard 2012). It is estimated that chronic opioid use in the US ranges from 1.3-4.6% of the population. In 2011, 238 million prescriptions were filled in the US, the 3rd most frequently prescribed class of medications in the US. (Xu & Johnson 2013)

a) The DLCD states that codeine is "widely used without genotyping". We would note that the CPIC recommendations on the use of *CYP2D6* testing and dose adjustment are relatively new (2012), with an update in 2014. It takes time for guideline recommendations to be disseminated and adopted in practice. This does not negate the strength of the evidence that supports the clinical use of *CYP2D6* genotyping, drug selection and dosing for codeine (and opioids also metabolized at least in part by *CYP2D6*- tramadol, hydrocodone, and oxycodone).

b) The DLCD states that the decision for non-coverage is based on 'insufficient evidence to support the clinical utility of genotyping for management of codeine therapy". We disagree with this assessment. The draft LCD is in conflict with the CPIC guidelines classified as strong recommendations based on sufficient evidence. The CPIC guidelines provide a detailed analysis of the literature and provide recommendations for gene- dose treatment.

   The strength of evidence profile for CYP2D6 for codeine is the same profile that the DLCD has accepted to support its decision to cover CYP2C19 testing for clopidogrel and CYP2 for amitriptyline/nortriptyline.

   The FDA requires a black-box warning for codeine and CYPD6 status: "Warning: Death related to ultra-rapid metabolism of codeine to morphine" highlights respiratory depression and death in children after tonsillectomy and/or adenoidectomy and evidence of being ultra-rapid metabolizers.

   The label does not imply that all patients should be tested, however, it points out the serious consequences for children and the elderly. It focuses on one common use of codeine in children, however, it would apply to use for any condition, e.g. cancer, trauma, post-surgery. While some physicians may choose to prescribe other drugs, codeine is still a valuable and appropriate, low-cost drug for pain management. The limitations associated with both the ultra- and poor-metabolizers can be identified by testing. The results of the testing can then be used for pain management treatment decisions in the future.

c) We believe the references cited in the DLCD do not provide sufficient evidence of high quality to refute the findings presented by CPIC. The DLCD cites 3 references that are potentially related to *CYP2D6* and codeine:

Crews 2012: This is the CPIC recommendation on *CYP2D6* and codeine with recommendations on dose adjustment which was updated in 2014. They have reviewed 66 articles and rated the level of evidence high in 50, moderate in 12 and weak in 4. They concluded that the level of evidence supporting their recommendations is substantial and strong. Their recommendations for adjustments in dosing for those who are ultrafast, extensive and poor metabolizers is strong. The recommendation for intermediate metabolizers is moderate.

Capon 1996: This is a study of 10 patients: 6 extensive metabolizers who were studied on 4 occasions after administration of dextromethorphan, dextromethorphan and quinidine, placebo and quinidine alone and 4 poor metabolizers studied on 2 occasions (after dextromethorphan and after placebo.)

Schadel 1995: This is a study of 9 patients, 5 extensive metabolizers and 4 poor metabolizers. Both were given a single dose of dextromethorphan after an initial dose of quinidine. The concentrations of destromethorphan were measured. They established that the elimination of dextromethorphan primarily depends on *CYP2D6* activity and not renal elimination.

We question the use of the articles by Capon and Schadel to support the non-coverage of testing for codeine: they involve very small patient group, test only 2 of the 4 metabolizer types with limited study objectives and the focus is primarily on evaluating the effect of concurrent drugs, inhibition with quinidine. This is in contrast with the many more recent articles identified by CPIC that relate directly to the subject and clinical use of genotyping.

d) The DLCD does not address the impact of genotyping information on all 4 groups. It focuses its comments on only one of the 4 metabolizer types, the ultrafast metabolizer (UM). It cites the low frequency of patients and implies that the adverse effects experienced by that small a number are not sufficient to warrant attention, especially since most adverse effects are 'not classified as serious'.

We would disagree with this rationale. Given the number of patients with chronic pain who are prescribed opioids, the percentage who are UM may be small but the actual number of patients impacted is significant. Second, the impact of genotyping is not limited to the UM population as cited in the DLCD. Genotyping affects all patients but especially those who are ultrafast and poor metabolizers.

For the physician prescribing the analgesic, knowledge of the genotyping affects the decision about the choice of drug and dosing for all patients. While knowledge of the role of the CYP450 system on drugs and drug interactions has been known for many years, without the diagnostic tools readily available to classify the individual patient's status, physicians have had to increase monitoring and attention to all patients, putting some at risk for adverse events and others at

risk for treatment failure due to under-dosing. Having access to the diagnostic data on genotyping allows the physician to identify the 77-92% of patient who are Extensive Metabolizers for whom the selection of codeine dosed according to the label recommendations is appropriate and should be sufficient to achieve pain relief without excess side effects. This allows the physician to focus attention on those known to be at risk.

Knowing the genotype and metabolizer status, the physician can not only identify the specific patients most at risk but also has guidance on what they are at risk for and how medication should be adjusted to be consistent with the patient's genotype. The physician no longer has to 'fly blind' – starting all patients on the same dose and monitoring for side effects or lack of effectiveness or conversely starting everyone at a low dose with gradual increases which would only be appropriate for the 1-2% mentioned in the DLCD.. It would provide inadequate pain relief for the majority of patients.

e) The group highlighted in the DLCD is the ultrarapid metabolizers (UM). The CPIC data has indicated that it affects 1-2% of patients; however, in the supplemental data (2014), it cites a higher number, 0-10% which is closer to what others have reported.

Knowledge that a patient is an ultrarapid metabolizer alerts the physician to the fact that these patients are at increased risk for toxicity even at low doses. For this group, selection of an alternate drug is recommended. However, unless a person's genotype is known, the physician has no clinical reason to not start them on standard dosing. By doing so, the physician would unintentionally put this group of patients at unnecessary risk for adverse events, a risk that could be avoided with genotyping information and use of alternate analgesics. Some would consider this an iatrogenic adverse event that could be avoided with appropriate lab testing.

Although most patients will not have severe life-threatening adverse events as the DLCD states, from the physician and patient's perspective, the events that do occur should not be dismissed as 'not clinically relevant'. For those patients who do not have as severe a response, the common adverse reactions of nausea, vomiting, constipation, drowsiness, lightheadedness, dizziness, sedation, SOB, and itching. Papaleontiou et al reported the following rate of common adverse events: 30% for constipation, 28% for nausea and 22% for dizziness. (Papaleontiou et al. 2010) In their analysis, this prompted discontinuation of opioids in 25% of cases. While these are not life-threatening usually, they are associated with morbidity and hospitalization (e.g. obstipation). Use of the genotype would help the physician identify 50% of the patient who are UM and most likely to experience these side effects. (Lotsch 2009) These patients could be started on an alternate drug.

In addition to increased office visits and hospitalizations, adverse events are associated with increased use of other medications to manage the adverse events, eg. antiemetics and medication for constipation. (Xu & Johnson 2013)

Opioid use has been linked to numerous complications in the elderly, e.g. fractures due to falls and pneumonia. It is not known whether these occurred more often in those who are ultrarapid metabolizers; however, the adverse event profile of those who are UM, for whom

adverse events occur at low doses would lend itself to these events, e.g. dizziness, lightheadedness and falls especially in those with gait disturbance due to other comorbid conditions. (Xu & Johnson 2013) The studies indicate the risk for falls and fractures is highest during the first 2 weeks of initiating therapy which would be the evaluation and dose adjustment period if the genotype is not known. (Miller et al. 2011) For the elderly, the DLCDs recommended approach would put them at most risk for complications.

The severe and life-threatening events should not be dismissed. Case reports detail severe and life-threatening events with the use of standard doses in people who are ultrarapid metabolizers. Gasche et al reported life threatening opioid intoxication in a 62 yo man given low doses of codeine for a cough given in the hospital for bilateral pneumonia. He was given 25 mg of codeine 3 times a day for cough; on day 4, he became unresponsive. Twelve hours after the last dose of codeine, his blood level of morphine was 20-80 times as high as the blood level that would be expected with normal metabolism. By genotype, he was an ultrarapid metabolizer. (Gasche et al. 2004)

f) The CPIC report noted that 'there is a large amount of variability within the patient genotyped as extensive metabolizers (14) and it is possible that some of these subjects may develop symptoms similar to patients genotyped as ultrarapid metabolizers (15)." The physician always has to continue to monitor patients and make appropriate adjustments but having a way to identify those at most risk and take alternate action. The presence of variability among EM does not diminish the fact that is it possible to identify those who are highest risk (ultrarapid metabolizers (UM)] and take alternate action from the start by selecting an alternate drug and avoiding known increased sensitivity to the drug and adverse events. .

g) The DLCD does not acknowledge the importance of *CYP2D6* status on those identified as poor metabolizers. It is estimated that 5-10% of the population will be poor metabolizers (PM). If the genotyping has identified the patient as a poor metabolizer, the CPIC states the current evidence is strong and supports avoidance of codeine and use of an alternate analgesic because of the possibility of lack of effect.

Because the poor metabolizer does not have a functional *CYP2D6*, they have no activity and no capacity to metabolize codeine to its active form, morphine. PMs form only trace amounts of morphine and experience no analgesic effect, however, there is no difference in adverse effects between the PM and the EM. Thus prescribing codeine to a patient who is a poor metabolizer will provide no beneficial analgesic effects but will expose them to the same adverse side effects experienced by the extensive metabolizer. (Eckhardt et al. 1998) Lotsch et al reported that 87.5% of patients were correctly identified by *CYPD26* genotyping as being likely to have low morphine formation from codeine and not experience analgesic effect. (Lotsch et al. 2009)

Because pain management and overuse of pain medication is a major national concern, this information is extremely valuable for both the physician and the patient. The patient who is a poor metabolizer is not likely to achieve pain relief with standard doses; they will most likely tell the doctor that the codeine doesn't work and ask for higher doses. This could be mis-interpreted as 'drug-seeking' behavior. [Xu] Use of the genotyping information would allow the

clinician to identify the patient as a poor metabolizer and initiate pain management with an alternate, more appropriate analgesic.

h) For the person who is an Intermediate Metabolizer (2-11% of patients), a standard dose can be given initially but it is recommended the clinician monitor the patient for effectiveness.

i) As noted in the CPIC reports knowledge of *CYP2D6* status is important for children, neonates whether they are administered codeine directly or receive it indirectly because the mother is an UM and breastfeeding. CPIC guidelines note that the serum concentrations of morphine may be high for breastfeeding women on standard codeine therapy who have the ultrarapid phenotype. This can lead to high levels of morphine in the breast milk and dangerously high morphine exposure for the breastfed infant. Fatal opioid poisoning has been reported in breastfed neonates with mothers who are UM metabolizers receiving codeine.

While the FDA label Black Box warning addresses respiratory depression and death in children who had evidence of being ultra-rapid metabolizers due to CYP2D6 polymorphism and received codeine for post-operative pain management after tonsillectomy in children, the risk still remains for all children requiring opioid pain management for other indications, e.g. cancer, trauma, post-surgery for other reasons. The label also warns of risk of death in those who are ultra-rapid metabolizers due to increased conversion to the active morphine resulting in higher than expected morphine levels.

In its response to this issue (A52908, #15), Palmetto noted: "The CYP2D6-codeine interaction is relevant to pediatrics and the Medicare benefit does not apply to children." We disagree: the Medicare benefit applies to ALL Medicare beneficiaries regardless of age. Coverage decision must be appropriate for all Medicare patients – including the 20% who are beneficiaries based on disability status, which includes children. It is also relevant when the mother is a Medicare beneficiary and is breastfeeding, e.g. post-Caesarian section. Use of codeine in the mother who is an ultra-rapid metabolizer will affect the neonate; therefore, the information is part of the physician's assessment and decision of pain management for the mother.

To recognize that testing could have an impact on the patient's treatment but deny coverage because they are not over 65 creates a 2-tiered system of coverage and discriminates against those who are Medicare based on disability status.

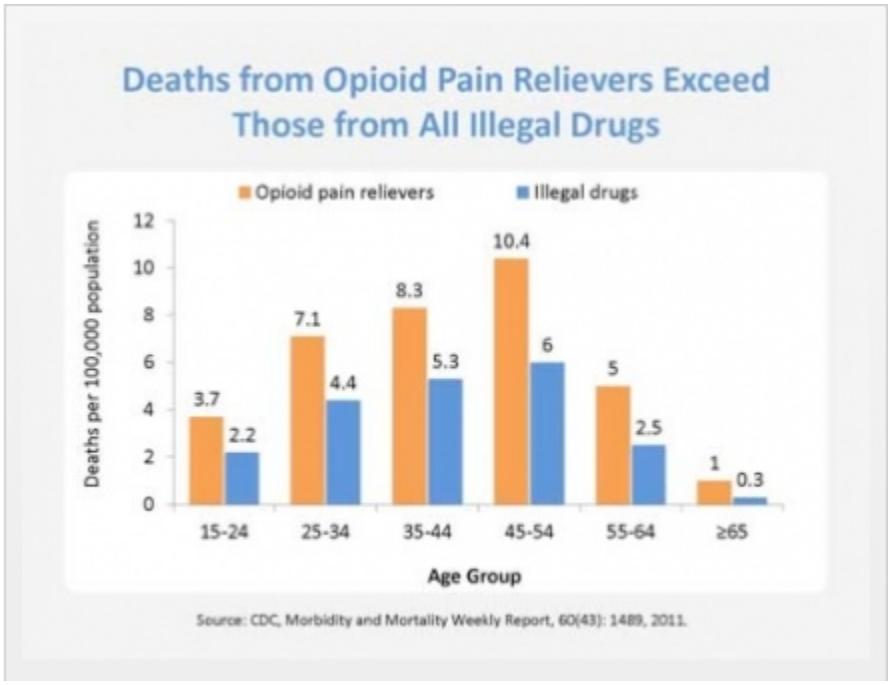
j) When considering codeine or other narcotics for management of chronic pain, knowledge of the *CYP2D6* status has clinical use from another perspective. Given the fact that many elderly patients are on over 14 drugs, knowledge of the *CYP2D6* status is important when considering the addition of codeine to the existing drug regimen. Pergolizzi et al reported a prevalence of drug-drug exposure (DDE) of 23% in the Medicare population with chronic low back pain and 26% in those with osteoarthritis. (DDE is defined as taking more than one drug metabolized through CYP450 enzyme system.) (Pergolizzi, Jr. et al. 2011)

Each DDE has the potential for drug-drug interaction. Pergolizzi has reported that the healthcare utilization by patients co-prescribed with an additional CYP450-metablized drug had significantly greater medical costs as measured by ambulatory visits, medications and inpatient length of stay compared to those not co-prescribed medications in patients with osteoarthritis and chronic back pain. (Pergolizzi, Jr. et al. 2012a), (Pergolizzi, Jr. et al. 2012b) In considering the patient's list of medications and knowledge of the *CYP2D6* status, the FDA information and CPIC recommendations would tell the physician they should select an alternate narcotic drug that is not metabolized by *CYP2D6*, e.g. morphine or fentanyl.

Palmetto has stated in other LCDs that one of the criteria for coverage is the link between the test results and modification of the clinical management of the patient. There are national guidelines that link the *CYP2D6* genotype with recommendations for different management of codeine for 3 of the 4 types of metabolizers, based on strong evidence. In these patients, the CPIC guidelines recommend use of an alternate drug for those who are UM to avoid unnecessary risk of toxicity and adverse events and for those who are PM to avoid unnecessary exposure to adverse events from use of a drug that is not likely to provide any analgesic effect. This should be sufficient to support coverage of *CYP2D6* testing a reasonable and necessary. (The strength of evidence profile for CYP2D6 for codeine is the same profile that the DLCD has accepted to support its decision to cover CYP2C19 testing for clopidogrel and CYP2D6 for amitriptyline/nortriptyline.

REQUEST:

- **Recognize the CPIC review of the evidence and dosing recommendations for codeine.**
- **Cover *CYP2D6* genotyping for codeine.**



Tetrabenazine

We agree with the conclusions in the LCD as the FDA Label requires CYP2D6 genotyping and is on the FDA Pharmacogenomic Biomarker Drug Labeling (http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm). Patients requiring doses above 50 mg per day should be genotyped for the drug metabolizing enzyme CYP2D6 to determine if the patient is a poor metabolizer (PM) or an extensive metabolizer (EM). People with CYP2D6 poor metabolizer genotypes should be treated with lower doses.

Excerpts from the tetrabenazine drug label:
DOSAGE AND ADMINISTRATION.
Patients requiring doses above 50 mg per day should be genotyped for the drug metabolizing enzyme CYP2D6 to determine if the patient is a poor metabolizer (PM) or an extensive metabolizer (EM).
The maximum daily dose in PMs is 50 mg with a maximum single dose of 25 mg.
The maximum daily dose in EMs and intermediate metabolizers (IMs) 100 mg with a maximum single dose of 37.5 mg.
Medications that are strong CYP2D6 inhibitors such as quinidine or antidepressants (e.g., fluoxetine, paroxetine) significantly increase the exposure to alpha-HTBZ and beta-HTBZ, therefore, the total dose of XENAZINE should not exceed a maximum of 50 mg and the maximum single dose should not exceed 25 mg.
In vitro studies indicate that alpha-HTBZ and beta-HTBZ are substrates for CYP2D6. Strong CYPD6 inhibitors (e.g., paroxtine, fluoxetine, quinidine) markedly increase exposure to these metabolites. A

reduction in XENAZINE dose may be necessary when adding a strong CYP2D6 inhibitor (e.g., fluoxetine, paroxetine, quinidine) in patients maintained on a stable dose of XENAZINE. The daily dose of XENAZINE should not exceed 50 mg per day and the maximum single dose of XENAZINE should not exceed 25 mg in patient staking strong CYP2D6 inhibitors.
After oral administration in humans, at least 19 metabolites of tetrabenazine have been identified. alpha-HTBZ, beta-HTBZ and 9-desmethyl-beta-DHTBZ, are the major circulating metabolites, and they are, subsequently, metabolized to sulfate or glucuronide conjugates. alpha-HTBZ and beta-HTBZ are formed by carbonyl reductase that occurs mainly in the liver. alpha-HTBZ is O-dealkylated by CYP450 enzymes, principally CYP2D6, with some contribution of CYP1A2 to form 9-desmethyl-alpha-DHTBZ, a minor metabolite. beta-HTBZ is O-dealkylated principally by CYP2D6 to form 9-desmethyl-beta-DHTBZ.
The results of in vitro studies do not suggest that tetrabenazine, alpha-HTBZ, or beta-HTBZ are likely to result in clinically significant inhibition of CYP2D6, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A. In vitro studies suggest that neither tetrabenazine nor its alpha- or beta-HTBZ metabolites are likely to result in clinically significant induction of CYP1A2, CYP3A4, CYP2B6, CYP2C8, CYP2C9, or CYP2C19.
Poor Metabolizers: Although the pharmacokinetics of XENAZINE and its metabolites in subjects who do not express the drug metabolizing enzyme, CYP2D6, poor metabolizers, (PMs), have not been systematically evaluated, it is likely that the exposure to alpha-HTBZ and beta-HTBZ would be increased similar to that observed in patients taking strong CYP2D6 inhibitors (3- and 9-fold, respectively). Patients who are PMs should not be given doses greater than 50 mg per day and the maximum recommended single dose is 25 mg.
Extensive or Intermediate CYP2D6 Metabolizers: In patients who express the enzyme, CYP2D6, (extensive (EMs) or intermediate (IMs) metabolizers), the maximum recommended daily dose is 100 mg per day, with a maximum recommended single dose of 37.5 mg.
Before patients are given a daily dose of greater than 50 mg, they should be tested for the CYP2D6 gene to determine whether they are poor metabolizers (PMs) or extensive or intermediate metabolizers (EMs or IMs). When a dose of tetrabenazine is given to PMs, exposure will be substantially higher (about 3-fold for a-HTBZ and 9-fold for b-HTBZ) than it would be in EMs. The dosage should therefore be adjusted according to a patient's CYP2D6 metabolizer status by limiting the dose to 50 mg in patients who are CYP2D6 poor metabolizers.

Galantamine

We agree with the conclusions in the LCD as dosage adjustment is not necessary in patients identified as poor metabolizers as the dose of drug is individually titrated to tolerability.

Excerpts from the galantamine label: Galantamine is metabolized by hepatic cytochrome P450 enzymes, glucuronidated, and excreted unchanged in the urine. In vitro studies indicate that cytochrome CYP2D6 and CYP3A4 were the major cytochrome P450 isoenzymes involved in the metabolism of galantamine, and inhibitors of both pathways increase oral bioavailability of galantamine modestly (see Drug Interactions). O-demethylation, mediated by CYP2D6 was greater in extensive metabolizers of CYP2D6 than in poor metabolizers. In plasma from both poor and extensive

metabolizers, however, unchanged galantamine and its glucuronide accounted for most of the sample radioactivity.

Population pharmacokinetic analysis indicated that there was a 25% decrease in median clearance in poor metabolizers compared to extensive metabolizers. Dosage adjustment is not necessary in patients identified as poor metabolizers as the dose of drug is individually titrated to tolerability.

Galantamine is indicated for treatment of Alzheimer's disease. Excerpts from the galantamine product monograph:

CYP2D6 Poor Metabolizers: Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of the CYP2D6 isozyme. Such individuals have been referred to as poor metabolizers. After a single oral dose of 4 mg or 8 mg galantamine, CYP2D6 poor metabolizers demonstrated a similar Cmax and about 35% AUCinf increased of unchanged galantamine compared to extensive metabolizers.

A total of 356 patients with Alzheimer's disease enrolled in two Phase III studies were genotyped with respect to CYP2D6 (n=210 hetero-extensive metabolizers, 126 homo-extensive metabolizers, and 20 poor metabolizers). Population pharmacokinetic analysis indicated that there was a 25% decrease in median clearance in poor metabolizers compared to extensive metabolizers. Dosage adjustment is not necessary in patients identified as poor metabolizers as the dose of drug is individually titrated to tolerability due to observed inter-patient variability.

Donepezil (Aricept)

We agree with the conclusions in the LCD as the evidence does not support CYP2D6 genotypic-based drug selection for donepezil.

CYP2C9

Warfarin

Based on our review of the NCD, we believe that it applies to both *CYP2C9* and *VKORC1* for use with warfarin dosing. As such, MACs are required to implement the NCD and does not have the discretion to create a local coverage decision that is in conflict with the NCD, e.g. non-coverage for VKORC1 testing when it is consistent with the NCD requirements. The statement on coverage for *VKORC1* should be the same as the statement for *CYP2C9* based on NCD 90.1.

It is within the purview of the contractor to decide if there are other indications for *VKORC1* for which there is sufficient medical evidence to support a separate coverage decision. It should be

clearly stated that the MAC will cover VKORC1 under NCD 90.1 and that all other uses will be considered investigational and not be covered.

REQUEST:

- **Revise the statement on *VKORC1* to be consistent with NCD 90.1 and the statement on coverage for *CYP2C9* both of which are addressed in NCD 90.1 and should be covered within the context of a clinical study/coverage with evidence development.**

Celecoxib and flurbiprofen

We disagree with the conclusions in the LCD as the FDA Label indicates that CYP2C9 genotyping provides actionable information and is on the FDA Pharmacogenomic Biomarker Drug Labeling (http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm).

Celecoxib is metabolized primarily by CYP2C9. Patients who are known or suspected to be poor CYP2C9 metabolizers should be administered celecoxib with caution. Consider a dose reduction by 50% (or alternative management for juvenile rheumatoid arthritis (JRA)) in patients who are known or suspected to be CYP2C9 poor metabolizers.

Excerpt from the CELEBREX drug label:

Poor Metabolizers of CYP2C9 Substrates: Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin) should be administered celecoxib with caution. Consider starting treatment at half the lowest recommended dose in poor metabolizers. Consider using alternative management in JRA patients who are poor metabolizers.

Celecoxib metabolism is primarily mediated via CYP2C9.

CYP2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as those homozygous for the CYP2C9*2 and CYP2C9*3 polymorphisms. Limited data from 4 published reports that included a total of 8 subjects with the homozygous CYP2C9*3/*3 genotype showed celecoxib systemic levels that were 3- to 7-fold higher in these subjects compared to subjects with CYP2C9*1/*1 or *I/*3 genotypes. The pharmacokinetics of celecoxib have not been evaluated in subjects with other CYP2C9 polymorphisms, such as *2, *5, *6, *9 and *11. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3% to 1.0% in various ethnic groups.

Consider a dose reduction by 50% (or alternative management for JRA) in patients who are known or suspected to be CYP2C9 poor metabolizers.

In vitro studies have demonstrated that cytochrome P450 2C9 plays an important role in the metabolism of flurbiprofen. CYP2C9 poor metabolizers should be administered flurbiprofen with caution due to the possibility of high plasma levels resulting from decreased clearance.

Excerpts from the Flurbiprofen label:

Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates (such as warfarin and phenytoin) should be administered flurbiprofen with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

REQUEST:

- **Recognize the FDA label of the evidence and dosing recommendations for celecoxib, and flurbiprofen.**
- **Cover *CYP2C9* genotyping for celecoxib and flurbiprofen.**

REQUEST:

- **For the indications that we have above, we request that the ICD10 codes be expanded**
- **Include ICD10, T78.40, T80-T88, T88.7 for drug allergy not-otherwise specified**
- T36 Poisoning by, adverse effect of and underdosing of systemic antibiotics
- T37 Poisoning by, adverse effect of and underdosing of other systemic anti- infectives and antiparasitics
- T38 Poisoning by, adverse effect of and underdosing of hormones and their synthetic substitutes and antagonists, not elsewhere classified
- T39 Poisoning by, adverse effect of and underdosing of nonopioid analgesics, antipyretics and antirheumatics
- T40 Poisoning by, adverse effect of and underdosing of narcotics and psychodysleptics [hallucinogens]
- T41 Poisoning by, adverse effect of and underdosing of anesthetics and therapeutic gases
- T42 Poisoning by, adverse effect of and underdosing of antiepileptic, sedative- hypnotic and antiparkinsonism drugs
- T43 Poisoning by, adverse effect of and underdosing of psychotropic drugs, not elsewhere classified
- T44 Poisoning by, adverse effect of and underdosing of drugs primarily affecting the autonomic nervous system
- T45 Poisoning by, adverse effect of and underdosing of primarily systemic and hematological agents, not elsewhere classified
- T46 Poisoning by, adverse effect of and underdosing of agents primarily affecting the cardiovascular system

- T47 Poisoning by, adverse effect of and underdosing of agents primarily affecting the gastrointestinal system
- T48 Poisoning by, adverse effect of and underdosing of agents primarily acting on smooth and skeletal muscles and the respiratory system
- T49 Poisoning by, adverse effect of and underdosing of topical agents primarily affecting skin and mucous membrane and by ophthalmological, otorhinorlaryngological and dental drugs
- T50 Poisoning by, adverse effect of and underdosing of diuretics and other and unspecified drugs, medicaments and biological substances

We respectfully ask that you consider our comments which were prepared by providers in the IGNITE consortium as well as other members of the Association for Molecular Pathology, laboratory directors, staff and consultants who provide service to Medicare beneficiaries covered by WPS. We are happy to be of assistance in providing additional clinical information, references, contacts, or whatever is needed to assist you with this DLCD. Please direct your correspondence to Dr. V.M. Pratt. Ph.D, FACMG.

Sincerely,

V.M. Pratt, Ph.D, FACMG

On behalf of the IGNITE Consortium

Clinical Validity, Clinical Utility and Economics Workgroup

Indianapolis, IN 46202
Ph: (317)-274-8322