November 20, 2015

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RE: Draft Local Coverage Determination -- Genetic Testing for CYP2C19, CYP2D6, CYP2C9, and VKORC1 (DL36398)

Dear Dr. Awodele:

Thank you for the opportunity to comment on DL36398. The Association for Molecular Pathology (AMP) is an international medical and professional association representing approximately 2,300 physicians, doctoral scientists, and medical technologists who perform or are involved with laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Membership includes professionals from the government, academic medicine, private and hospital-based clinical laboratories, and the in vitro diagnostics industry.

The College of American Pathologists (CAP) is a national medical specialty society representing more than 17,000 physicians who practice anatomic and/or clinical pathology. College members practice their specialty in clinical laboratories, academic medical centers, research laboratories, community hospitals and federal and state health facilities.

Members of both AMP and CAP are experts in molecular pathology and the implementation of this coverage policy will directly impact their practices. We are submitting joint comments because at this time both of our organizations share the same concerns regarding this draft LCD, and we request that Wisconsin Physician Service Insurance Corporation ("WPSIC") consider implementing the consensus recommendations outlined in this letter.

1. CYP2C19

REQUEST:

- **We recommend coverage of *CYP2C19* testing for use in patients being treated with amitriptyline, nortriptyline, and the tricyclic anti-depressants.**
- **We recommend coverage for *CYP2C19* testing for tricyclic anti-depressants for all FDA labeled indications as well as off-label uses which have become part of medical practice.**

We disagree with the decision not to cover genotyping for *CYP2C19* for amitriptyline and the interpretation of recommendations from Clinical Pharmacogenomics Implementation Consortium (CPIC).

a) While the randomized controlled trial (RCT) may be the preferred source for evidence, it is not appropriate for all scientific questions and it is not the only credible source of studies available to define clinical practice. The recommendation to lower the dose in poor metabolizers (PM) was moderate in strength and has been made based in other clinical studies using pharmacokinetics 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. 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 Metabolizers (EM) and 18-45% who are Intermediate Metabolizers (IM) is to start them on the standard dose. This is not the appropriate treatment for the other two groups of patients.

c) The suggestion referred to in the draft LCD of using a lower dose is only appropriate for the 2-15% of patients who are poor metabolizers. This is not a small reduction in dose (the recommendation is to reduce the dose by 50%) and would not be considered standard of care for the 85-98% of patients who are not PM. We do not believe it is the place of the LCD to determine how the physician should prescribe and manage patient's risk for side effects. If there is a medically recognized test available, the physician should have the option to utilize it to manage patient care especially when the drug is indicated and is associated with risk that can be modified with adequate information, e.g. CYP status.

To start everyone at a 50% dose reduction 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 and contribute to patient frustration with treatment, non-adherence and unwillingness to try appropriate medications. This issue is amplified in patients with depression given the long time required after initiating therapy before the patient notices a positive effect (4-8 weeks) and side effects of drugs.

Failing to recognize that those who are PM are a sizable portion of patients 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. Identifying those patients who are poor metabolizers so that the correct lower dose is initiated will reduce the probability of side effects and give the patient who is a poor metabolizer a better chance of successful treatment.

The draft LCD 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 and not a 50% dose reduction. The physician would not know this is the appropriate management for the individual patient without *CYP2C19* results.

In short, the best available evidence currently confirms that genotyping will direct an actionable therapeutic decision: a reduced dose for the 2-15% who are poor metabolizers and selection of an alternate drug in the 2-15% who are ultrarapid metabolizers.

d) The draft LCD 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. 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:

- **We request that the LCD recognize individual medical review to allow coverage for *CYP2C19* testing in the patient on clopidogrel who would be considered high risk based on clinical characteristics.**

We are in agreement with *CYP2C19* coverage for clopidogrel testing in ACS patients. However, we note that both Scott and Holmes recognize a population on clopidogrel who might be at increased risk for adverse events for whom pharmacogenetic testing may be appropriate on an individual review basis. These patients may be considered for testing because of increased risk due to an adverse event while on clopidogrel (e.g. stent thrombosis) or other clinical characteristics such as diabetes mellitus, chronic renal failure, or angiographic variables (e.g., diffuse 3-vessel or left-main coronary artery disease or multifocal cervicocerebral atherosclerotic disease). (Scott et al. 2013), (Holmes, Jr. et al. 2010)

REQUEST:

- **We recommend coverage for *CYP2C19* testing in conjunction with initiating therapy with omeprazole, lansoprazole, pantoprazole, or esomeprazole at standard dosing as first line therapy unless other evidence is submitted.**

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 to support a non-coverage decision as required by Chapter 13.

We disagree with the conclusion that CYP2C19 genotyping does not relate to health outcomes. 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)

The meta-analysis by McNicholl et al. showed that non-CYP2C19 metabolized PPIs (such as rabeoprazole or esomeprazole) could achieve a higher cure rate of H. pylori in patients with the EM or UM phenotype than CYP2C19 metabolized PPIs (such as omeprazole or lansoprazole). In addition to evidence supporting the link between genotype status, there are guidelines with recommended dosing strategies based on genotype status. It is recommended that the physician proceed with normal dosing in those identified as poor or intermediate metabolizers. For those what are ultrarapid and extensive metabolizers, their 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.

2. CYP2D6

REQUEST:

- **We recommend coverage of *CYP2D6* testing for all TCAs.**
- **We recommend coverage of *CYP2D6* testing for all FDA-labeled indications and off-label indications accepted as medical practice and covered by Medicare, e.g. use of amitriptyline for treatment of neuropathic pain.**

We are in agreement with the recommendation to cover *CYP2D6* genotyping for amitriptyline and nortriptyline and offer the following comments for consideration:

a) We request that you 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, pharmacodynamic 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.

***3. CY2D6* and *CYP2C19* with antidepressants and antipsychotics**

REQUEST:

- **We recommend covering testing of CYP2C19 and CYP2D6 for use with SSRIs**
- **We recommend covering testing of CYP2D6 for patients on antipsychotics.**

We disagree with the decision not to cover testing based on insufficient evidence. There are increasing numbers of studies looking at both *CYP2D6* and *CYP2C19* status in the selection of antidepressants and antipsychotics which should be considered. (de Leon et al. 2006) (de Leon et al. 2005b) (Kirchheiner et al. 2001) (Kirchheiner et al. 2004) (Kirchheiner & Rodriguez-Antona 2009) (Kirchheiner et al. 2010)(Muller 2013)(Rundell 2011) Pharmacogenetic testing is being used in more settings to guide treatment decisions. (Jurgens et al. 2012), (Hall-Flavin et al. 2012), (Hall-Flavin et al. 2013) Studies demonstrate that CYP2D6 and *CYP2C19* poor metabolizer were treated for a longer time in hospital (median 57.5 vs. 40.0 days). (Kropp et al 2006)

a) CYP2D6 – Antidepressants

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 increased frequency of adverse effect in those found to be PM and higher frequency of no response in UMs. (Rau et al. 2004)

Laika et al examined the side effects for PMs and IMs and 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 CYP2D6 drugs. 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 was longer for those the in *CYP2D6* PM group. (Chou et al. 2000) Ruano et al reported a longer length of stay associated with PM. (Ruano et al. 2013)

b) CYP2D6 - Antipsychotics

Pharmacogenomic testing associated with antipsychotics has focused on efficacy of testing in drug selection and drug dosing and genotype and extrapyramidal (EPS) adverse effects. We support CYP2D6 testing for antipsychotics because it has an impact on treatment decisions to reduce the development of adverse drug reactions in those at high risk based on their metabolizer status.

We believe the evidence outlined below supports this coverage.

- Herbild et al addressed the impact of the use of *CYP2D6* and *CYP2C19* testing on cost in patients hospitalized with schizophrenic spectrum. (Herbild, Andersen, Werge, Rasmussen, & Jurgens, 2013) They found that there were statistically significant differences in cost: pharmacogenetic testing significantly reduces costs among the PM and UM to 28%. It also affected the use of primary care services and pharmaceuticals.

- Ravyn et al do not support routine use of testing for all antipsychotics, but they do state that the evidence is sufficient to support its use for some antipyschotics. They recommend dose reduction or selection of alternative drug to avoid adverse drug reactions for patients who have the PM phenotype for haloperidol, Iloperidone, risperidone, and zuclopenthixol.

In the conclusion, they state the following:
"No randomized clinical trials have yet evaluated whether use of CYP450 genotyping in antipsychotic treatment decision making is associated with better treatment response or reduced likelihood of adverse events in adult psychiatric patients. Randomized trials are not only cost prohibitive, they may not be practical because some polymorphisms are too infrequent (Mrazek and Lerman, 2011). Additionally, given the current high predictive value of pharmacogenetic tests, it would not be ethical to randomize patients to treatments that are potentially toxic for known phenotypes. "

"Collectively, the literature provides a consistent body of evidence supporting the use of genotypic testing to prevent adverse events in adults receiving some antipsychotics."

Other studies have found a significant association between EPS and PMs. (Crescenti et al. 2008), (Kobylecki et al. 2009), (de Leon et al. 2005a) (Fleeman 2011) 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.

FDA-approved package insert. The FDA label describes what is considered safe use for drugs. It establishes a standard of care for those prescribing a drug. For drug interactions, the FDA label for dose of FANAPT should be reduced by half in patients co-administered a strong CYP2D6 or CYP3A4 inhibitor and increased with the other drug is discontinued. The dose of FANAPT should be reduced by 50% in patients who are poor metabolizers of CYP2D6.

4. CYP2D6

REQUEST:

- **We request that WPSIC uniformly apply the required level of evidence. For example, the strength of evidence for CYP2D6 for codeine is the same in the CPIC guidelines as that for CYP2C19 for clopidogrel and CYP2D6 for amitriptyline/nortriptyline. However, WPSIC determined there was a sufficient level of evidence for the latter, but not the former.**
- **We request that Medicare provide coverage for medically necessary testing for ALL beneficiaries, regardless of age or reason for eligibility for Medicare, e.g. disability.**
- **We request coverage for *CYP2D6* genotyping for codeine (and related drugs) based on presence of national guidelines, the strength of evidence cited in the guidelines and the presence of an FDA black box warning.**

We disagree with the position of non-coverage. We believe the criteria for coverage have been met. There is sufficient evidence to support coverage for CYP2D6 testing for codeine use (and opioids also metabolized at least in part by *CYP2D6*- tramadol, hydrocodone, and oxycodone). Information provided by testing influences the physician's decision about use of codeine for 3 of the 4 types of metabolism. It is relevant to a broad range of Medicare beneficiaries, including children, in mothers who are breast-feeding, adults with acute and chronic disease, and especially the elderly who are vulnerable to drug-drug interactions associated with drugs affected by CYP2D6.

a) The draft LCD states that codeine is "widely used without genotyping". Clinical practice guidelines and FDA-labeling provide the standard of care which physicians strive to meet. They are also what CMS instructs MACs to use as the foundation for LCDs. The LCD is not supposed to interfere with physicians following the guidelines, which occurs when it is a policy that does not cover care consistent with the guidelines. It takes time for physicians to adopt practices recommended in guidelines. We note that the CPIC guidelines on CPY2D6 genotyping and codeine use are relatively new, first published in 2012. It will take time for guidelines to gain adoption but those who do follow them should not be penalized by having the recommended care not covered.

b) The draft LCD 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. In fact, the draft LCD is in conflict with the CPIC guidelines which classified the evidence for its recommendations as 'strong'. The CPIC guidelines and supplemental material provide a detailed analysis of the literature to support its recommendations for gene- dose treatment.

There appears to be an inconsistency in the acceptance of the CPIC strength of evidence profile for testing and drugs addressed in this DLCD. 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. The DLCD does not contain references which refute the strength of evidence cited in the CPIC guidelines for codeine, which would support its contrary position.

In addition CYP2D6 and codeine have a Black Box warning by the FDA: "The FDA Black Box 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 Warnings and Precautions section cites the risk of death in ultrarapid metabolizers associated with respiratory depression or death as well as the risk of respiratory depression in elderly, debilitated patients.

Because the label must have FDA approval, it creates a standard of care for the safe use of codeine. Based on the warnings in the label, if a physician chooses to prescribe codeine, knowledge of the metabolizer status is part of the safe use of the drug. While some physicians may choose to prescribe other drugs, codeine is a valuable and appropriate drug for pain management; it is a stable, oral, low-cost drug. It is still the drug of choice for pain control for most patients. The limitations associated with both the ultra- and poor-metabolizers can be identified by testing and managed appropriately. The results of the testing can then be used for future pain management treatment decisions. An LCD coverage policy should support the physician's decision to ensure the safe use of drugs based on warnings from the FDA; it should not create an obstacle by not covering testing identified in the FDA-approved label.

c) Impact on decision-making:

For the physician prescribing the analgesic, knowledge of the genotype affects the decision about the choice of drug and dosing for all patients with 2 major goals: to avoid adverse drug reactions/side effects and to achieve adequate pain control. 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, the physician no longer has to 'fly blind' – starting all patients on the same dose putting some at risk for adverse drug reactions or events and some at risk for treatment failure and no pain relief. Conversely, to ensure everyone's safety, the physician could start everyone at a low dose with gradual increases, an approach which would only be appropriate for the 1-2% who are UM. This approach would provide inadequate pain relief for 98-99% of patients.

At the level of treating the individual patient, having the diagnostic data on genotyping allows the physician to know whether this patient is one of the 77-92% who are Extensive Metabolizers. If they are, the selection of codeine dosed according to the label recommendations is appropriate and should be sufficient to achieve pain relief without excess side effects. If they are an UM or PM, the physician knows how to adjust management. If they are UM, they are more vulnerable to side effects and at risk for toxicity even at lower doses. They should be started on a lower dose and monitored closed or they should be started on an alternate drug. If they are PM, they are not expected to achieve pain relief from codeine based on their metabolism profile and should be started on an alternate drug.

The results of the testing have lifetime value, for other drugs identified with CYP2D6.

UM – Those at higher risk for adverse drug reactions and events at low doses. 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 are clinically relevant and relatively common. 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. They are associated with morbidity and hospitalization (e.g. obstipation). In addition to increased

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

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)

EM 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 presence of variability among EM does not diminish the fact that it is possible to identify those who are highest risk (ultrarapid metabolizers (UM)] for adverse events and not expose them unnecessarily to adverse reactions.

PM: The DLCD does not acknowledge the importance of *CYP2D6* status on those identified as poor metabolizers, which is estimated to be 5-10% of the population. 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)

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 & Johnson 2013) 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.

IM 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.

d) Patient populations affected: Children and mothers who are breastfeeding

Children are affected by this DLCD in 2 ways: direct and indirect exposure. As noted in the CPIC recommendations, knowledge of *CYP2D6* status is important for children. Neonates may be at risk directly if they are administered codeine or they may receive it indirectly because the mother is an UM and they are receiving breast milk. 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. In this case, knowledge of the mother's status is relevant to the risk to the neonate.

While the FDA label Black Box warning addresses respiratory depression and death in children for post-operative pain management after tonsillectomy in children, the risk is present for all children requiring

opioid pain management for other indications, e.g. cancer, trauma, post-surgery for other reasons. The label includes a warning of risk of death in any patient who is an ultra-rapid metabolizer due to increased conversion to the active morphine resulting in higher than expected morphine levels.

Palmetto noted the following in its response to this comment (A52908, #15): "The CYP2D6-codeine interaction is relevant to pediatrics and the Medicare benefit does not apply to children." We agree the interaction is relevant to pediatrics but we disagree with the conclusion: 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 the beneficiary is not over 65 creates a 2-tiered system of coverage and discriminates against those who are Medicare based on disability status.

Patients with chronic pain and the elderly:
Knowledge of the CYP2D6 status has implications for a large portion of the population, especially with chronic pain management and drug-drug interactions.

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. 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)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). (Gaskin & Richard 2012)

Given the fact that many elderly patients are on multiple 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.

Opioid use has been linked to numerous complications in the elderly, e.g. fractures due to falls and pneumonia. 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 recommended by the DLCD when the genotype is not known. (Miller et al. 2011) The approach recommended in the DLCD would put them at most risk for complications.

5. VKORC1

REQUEST:

- **Both *CYP2C9* and *VKOCR1* should be covered within the context of a clinical study/coverage with evidence development according to NCD 90.1.**

Based on our review of the CMS NCD 90.1, we believe that it applies to both *CYP2C9* and *VKORC1* for use with warfarin dosing. As such, WPSIC is required to implement the NCD and does not have the discretion to create a local coverage decision that is in conflict with the NCD. It is our opinion that a decision not to cover *VKORC1* testing for any use would be in conflict with the NCD requirements. We believe the statement on coverage for *VKORC1* should be the same as the statement for *CYP2C9* based on NCD 90.1.

We recognize that it is within the purview of the contractor to decide if there are other indications for *VKORC1* testing for which there is sufficient medical evidence to support a separate coverage decision. This decision should be clearly stated – that WPSIC will cover *VKORC1* under NCD 90.1 and that all other uses will be considered investigational and not covered.

We respectfully ask that you consider these comments which were prepared by a consortium of providers in the WPSIC jurisdiction as well as other members of the Association for Molecular Pathology, laboratory directors, staff and consultants who provide service to Medicare beneficiaries covered by WPSIC. We are happy to be of assistance in providing additional clinical information, references, contacts, or whatever is needed to assist you with this draft LCD. Please direct your correspondence to Mary Steele Williams, AMP Executive Director, at mwilliams@amp.org or Nonda Wilson, CAP Manager, Economic and Regulatory Affairs, at nwilson@cap.org.

Sincerely,

Association for Molecular Pathology
College of American Pathologists

References

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