July 7, 2016

Novitas Solutions Medical Policy Department
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Re: Draft Local Coverage Determination for Biomarkers Overview (DL35062)

Dear Dr. Patterson,

Thank you for the opportunity to comment on the draft Local Coverage Determination (LCD), entitled Biomarkers Overview (DL35062). 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. AMP members are experts in molecular pathology, and the implementation of this coverage policy will directly impact their practice.

The College of American Pathologists (CAP) is a national medical specialty society representing 18,000 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.

We thank you for your decision to cover biomarker testing for the management of Medicare beneficiaries. The inclusion of the genes outlined in this draft policy is well supported by the evidence and published guidelines, as well as by recent peer reviewed literature. We applaud Novitas' efforts to develop this LCD in accordance with the LCD development process as outlined in the Medicare Program Integrity Manual.

However, we do believe that the medical literature and common medical practice standards supports the coverage of additional testing. We address our primary concerns in this summary coverage letter and expand upon them in more detail in the Coverage Guidance section that follows.

You will notice that many of the recommendations that we are making are identical to recommendations that we made in response to the prior version of this dLCD (DL33638) in March 2015. We would welcome a dialogue as to why virtually all of our prior recommendations, each based on well-established medical literature, were not incorporated into this revised version.

1. Coverage Guidance – Germline Mutations

Use of Testing in Diagnosis and Management

Molecular diagnostic testing should be held to the same standard and not a more rigorous or limited one, than other diagnostic tests covered by Medicare. The results of this testing directly impact the care provided to a patient. We discuss the critical role this testing plays in confirming a patient's diagnosis, identifying options for

treatment, providing options to manage symptoms, and the identification and management of comorbidities. Besides impacting the delivery of care, molecular diagnostic testing may confirm a suspected diagnosis or provide additional information about the condition in its cause. These implications of molecular diagnostic testing meet Medicare's definition of "reasonable and necessary."

With regard to molecular diagnostic testing for inherited diseases, this draft LCD inexplicably proposes to deny coverage for a large sub-group of "common" molecular diagnostic target genes that have proven diagnostic utility (CFTR, fragile X, DMD, etc), while proposing to cover certain other "rare" inherited disorder target genes (GJB2, Gba, G6pc, etc.). We would very much like to know the specific medical utility criteria that Novitas has applied to separately classify these two seemingly inseparable groups of inherited disease testing targets.

2. Pharmacogenomics

This draft LCD addresses a broad spectrum of pharmacogenomics testing. While we agree with many of Novitas' recommendations, we provide evidence that supports the expansion of these coverage recommendations.

We respectfully ask that you consider these comments which were prepared by a consortium of providers in the Novitas jurisdiction as well as other members of AMP and the CAP, laboratory directors, staff and consultants who provide service to Medicare beneficiaries covered by Novitas. We are happy to be of assistance in providing additional clinical information, references, contacts, or whatever is needed to assist you with this DLCD. If we can be of assistance with clinical information or other resources to assist Novitas with future draft Local Coverage Determinations please contact Tara Burke, AMP Policy Analyst, at tburke@amp.org or Nonda Wilson, CAP Manager, Economic and Regulatory Affairs, at nwilson@cap.org.

Sincerely,

Association for Molecular Pathology
College of American Pathologists

I. COVERAGE GUIDANCE – GERMLINE MUTATIONS

Use of testing in diagnosis and management

The Draft Policy Language states: "…there must be a recognized decision impact of such biomarkers by the clinical community. In other words, there must be acceptance/uptake of specific testing into patient management. It should be taken into account that to reach the medical necessity threshold, such acceptance should be based on the strongest evidence available, ideally from along the spectrum of high-quality, masked randomized controlled clinical trials, and much less preferably from lower levels of evidence, which are predicted upon expert opinion only without primary study data."

Medicare considers genetic testing medically necessary to establish a molecular diagnosis of an inheritable disease when all of the following criteria are met:

- The beneficiary must display clinical features of an associated disease, but noting that coverage of molecular testing for carrier status or family status is considered screening and statutorily excluded from coverage; and
- The result of the test will directly impact the treatment being delivered to the beneficiary; and
- After history, physical examination, pedigree analysis, genetic counseling, and completion of conventional diagnostic studies, if a diagnosis remains uncertain such testing can be covered.

Medicare recognizes that diagnosis and treatment are covered medical services, specifically including diagnostic testing. In the MLN ABN brochure it states:

> *Medicare defines medical necessity as services that are:*
>
> - ***Reasonable and necessary,***
> - ***For the diagnosis or treatment of an illness or injury to improve the functioning of a malformed body member, and***
> - ***Not excluded under another provision of the Medicare program.***

Also, the PIM instructions, Chapter 13, Local Coverage Determinations §13.5.1-Reasonable and Necessary Provisions in LCDS provide additional elements the contractor is to consider in deciding if a service or treatment meets these criteria. Some of the additional points to be considered are whether it

- **Is safe and effective;**
- **Meets but does not exceed the patient's medical need; and**
- **Is at least as beneficial as an existing and available medically appropriate alternative**

We understand that the use of testing must be medically necessary and appropriate for the patient and condition. **However, we would like to emphasize that molecular pathology testing should be held to the same standard, and not a more rigorous or limited one, than other diagnostic tests covered like chest x-rays, CT, MRIs, Pet scans, EKG or other blood tests when used to confirm suspected medical diagnosis.**

1) The result of the test will directly impact the treatment being delivered to the beneficiary.
We want to be sure we are defining this in the same way so that it is consistent and reflects the full practice of medicine. We specifically want to ensure that the definition is not so narrow that it only includes those very few molecular pathology tests that are directly linked to the selection of a specific drug for treating, curing, or reducing the symptoms of a disease.

Alternatively, it is critical that "medical necessity" be considered more broadly in terms of the total "care of the patient", the "plan of care" or the "treatment plan. "As in other areas where they are used by Medicare, (e.g. SNF, Home Care, Hospice), the treatment plan includes everything related to the care of the patient. It is more than just how a physician uses the information to direct immediate short-term care. It should specifically include how the test information is used by the patient and the entire care team with respect to their condition, life, and future. That is an important part of a "treatment plan".

We will expand on some of the following examples of the direct impact of a test:

- **Confirming the diagnosis**

- **Directing other tests to obtain a diagnosis-ruling out some causes, redirecting to others**
- **Options for curative intervention: drug choices/response; Surgical or invasive interventions**
- **Options for symptomatic management-physical and mental/emotional**
- **Identification of associated comorbidities to be assessed and or/ monitored.**
- **Decision-making about life issues, including management of comorbid conditions**

Diagnostic testing

This has a major impact on the "plan of care." It confirms the clinical diagnosis. If the conditions have known treatment, the importance of testing is obvious. However, even if there is no known treatment for a condition at the time it's diagnosed (such as the case with the majority of molecular diagnostic tests for inherited diseases); obtaining a diagnosis for a patient's symptoms/illness is still important and directly impacts the care of the patient in a number of ways. Obtaining a definitive diagnosis is the reason a person seeks medical attention – to get a diagnosis so they know what is causing symptoms, whether or not it can be cured, what will help the symptoms, what the prognosis is, and how the disease/symptoms will progress. Making sure one is not missing curable conditions is obviously of major importance for the patient and physician. Having a confirmed diagnosis can provide reassurance that there is an underlying medical reason for symptoms and that it is not "all in their head".

Identifying options for treatment

There are conditions for which the treatment options and timing of treatment is affected by the molecular diagnostic test results, especially the subtype. An example is Long QT syndrome. There are others for which there is no treatment or cure. The diagnosis still impacts the treatment. By confirming a different diagnosis, it can explain why a current treatment course which was appropriate for the presumed diagnosis is not as effective as expected. This would influence the physician recommendations and the patient's decision about whether to continue said therapy. It can also prevent the patient pursuing treatment for presumed (incorrect) diagnosis, treatment that carries its own risks and may be less effective or not effective at all for the accurate diagnosis. It helps the patient evaluate other approaches they have been pursuing to cure or help their illness, (e.g. vitamins or supplements, massage, acupuncture, etc.). If there is no known treatment to cure the condition, it can shift attention to the symptomatic care and discussion of long-term implications and decision making.

Options for symptomatic management

Knowing the conditions and its natural history can help guide recommendations for symptoms management and prevention (or delay of) secondary complications. Referrals and treatment planning by PT, OT, and SLP may be involved. Emotional support and treatment may be appropriate as the patient adjusts to the diagnosis with its implication for the present and future. They may need to learn new coping skills and create a network of support, which has been found to improve morbidity and mortality. Having a specific diagnosis can open the door to resources about the condition and support from others with the condition, from a patient's perspective, these are all the direct result of having a definitive diagnosis, even when there is no current cure or treatment. A correct diagnosis can lead to clinical trials for new drugs that are effective for treating patients.

Impact on decision making

Having a diagnosis helps the patient with the decision-making about life issues affected by the condition, its prognosis, its natural history.

Identification of associated comorbidities to be assessed and/or monitored.

Many conditions with definitive molecular diagnostic tests are complicated medically, not only because of the primary presenting condition, but also because of other conditions that are associated with the primary condition and/or because of how the condition presents and affects the patients.
Examples:

- **Fragile X-premutations of the FMR1 may not present as Fragile X (developmental delay, autism, etc.) Rather, they may present later in life displaying a neurodegenerative effect: ataxia, tremor, memory loss, peripheral neuropathy, etc.**
- **Prader-Willi syndrome- patients may not demonstrate the full phenotypic features and may not properly be diagnosed in their youth. Having an accurate diagnosis is relevant to the primary care physician. Features of PWS that are relevant to the physician providing daily care or evaluating the patient in the ED: very high threshold for pain and inability to localize pain, thermal dysregulation and failure to develop fevers, lack of vomit response in light of**

ingestion of toxic substances or pathogens, hyperphagia for food and water to the point of rupture/water intoxication and sensitivity to anesthesia.

If the test is performed for pharmacogenomic reasons, the medical necessity impact should be considered from that perspective. The key questions are whether the test will be able to guide choices of the drug, dosing, side effects, or testing, or duration of the treatment. The criteria provided by CMS become more relevant in this case: specifically providing care that does not exceed the patient's need and is "at least as beneficial as an existing and available medically appropriate alternative".

We provide the example of warfarin testing because it is relevant to the decision about whether a test will meet "reasonable and necessary" criteria and be covered. In 2009, Medicare initiated a National Coverage Analysis (NCA). They reviewed literature, developed a draft position, reviewed public comments and issued their recommendations (NCD 90.1). In their analysis and final decision they considered whether pharmacogenomic testing improved the outcome. Improving the outcome would be in comparison with the current standard of care: does it do as well as the current standard; does it do better; can it replace the current approach or is done in addition to the current approach?

For warfarin, the question was whether the test results affected the decision to use warfarin, the initial dose, the dose amount or interval, the need for testing, and/or the number of adverse events because of increased bleeding risk from high PT/INR.

From Medicare's perspective,

- **If the test did "as well as" the standard, it could potentially be covered depending on how it relates to the current standard approach.**
- **Does the evidence indicate that the test in question is sufficient and could be an alternative to or substitute for the standard approach or would modify the standard approach significantly if both were used (e.g. frequency of PT/INR testing)?**
- **If it cannot replace the current recommended testing, then would it be provided 'in addition' to the standard? If this is done 'in addition', the critical question is whether it results in any real changes in the management of the patient.**
- **If it would be done in addition to the standard approach and it didn't improve results, then it would 'exceed the patient's need' and not be medically needed. It would not be considered to be an important part of their care and the decisions for care.**

There are a number of conditions and drugs for which the evidence and the guidelines demonstrate the importance of gene testing in the choice and/or dose of drugs for treatment with respect to directing or limiting treatment options. All should follow the same criteria as listed above.

2) Coverage based on the level of clinician's uncertainty in making the diagnosis

Diagnostic testing is used for a number of recognized purposes in the practice of medicine:

- **To confirm a suspected diagnosis**
- **To provide additional information about the physiologic/ structural condition associated with the signs/symptoms and provide additional guidance on the cause**

Standards of practice have been developed for diagnosing many conditions that include molecular diagnostic testing requirements and recommendations.

i. **Cases in which the diagnosis is made on the basis of phenotype, presentation, and other lab tests (molecular diagnostic testing is not needed).**
ii. **In most cases, even if the clinical presentation is consistent with the diagnosis of a genetically-based condition, the definitive diagnosis cannot be made until the molecular testing confirms it. This is similar to the use of diagnostics to confirm presumptive diagnosis made on the basis of history, symptoms, examination, such as glucose testing to confirm the suspected diagnosis to diabetes or an x-ray to confirm the suspected diagnosis of a fracture of a bone.**

It would be medically inappropriate to give the diagnosis of a genetically-based condition without performing the testing that would confirm the genetic evidence, especially if they are part of the clinical guidelines for that condition.

Coverage for all Medicare beneficiaries regardless of eligibility by age or disability

We would also like to address the beneficiaries to whom the draft LCD applies. While the majority of beneficiaries covered by Medicare are over 65, Medicare also covers people who are disabled and have chronic kidney disease. In 2012 there were a total of 50.829 million beneficiaries of which 8.624 million were disabled or 17%. In the fee for service program, the disabled make up 23% of the Medicare beneficiaries (6.87 million out of the 37.214 million beneficiaries in the FFS). The LCDs need to be appropriate for all Medicare beneficiaries, regardless of age. Medicare beneficiaries under age 65 should have the same coverage for care that is medically necessary and appropriate as those over 65.

Many of the conditions diagnosed by molecular testing may present in early childhood or infancy; testing would be conducted at the time of diagnosis. Young, disabled Medicare beneficiaries should have access to this testing.

However, appropriate diagnosis may not occur in childhood, before a person becomes a Medicare beneficiary. There are a number of reasons testing in adults may be appropriate: 1) The patient was never tested and appropriately diagnosed while the diagnosis is relevant; 2) testing has evolved to be more sensitive/specific; the patient tested negative at the time of the initial presentation or tested positive but it was a false positive and prognosis/treatment decision require accurate diagnosis; 3) the phenotypic presentation can vary significantly and the diagnosis was not apparent or considered.

REQUEST:

- **We request that decisions about coverage and determinations of medical necessity be appropriate for all Medicare beneficiaries, both for those eligible by age (>65) and disability status. Tests which are used to diagnose a condition should be covered in those who are eligible by the disability status, assuming other criteria for medical necessity are met. The beneficiary and their providers should not have to appeal an inappropriate denial.**

II. PHARMACOGENOMICS

***CYP2C19* - Clopidogrel**

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 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.**

***CYP2C19*-Amitriptyline**

REQUEST:

- **We recommend coverage of *CYP2C19* and CYP2D6 testing for use in patients being treated with amitriptyline, nortriptyline, and the tricyclic anti-depressants.**

  EXCERPT
  However, the Clinical Pharmaco-genetics Implementation Consortium did not have enough evidence to make a strong recommendation for dose modification based on genotype, and a moderate recommendation was given based on data outside of randomized trials. Additionally, even with genotype information, a suggestion is given to start patients on low dose, gradually increasing to avoid adverse side effects. Consequently, genotyping is not needed with this approach.

We disagree with Novitas' decision not to cover genotyping for *CYP2C19* for amitriptyline and the interpretation of the recommendations from 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 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, rather 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 that 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 (normal) Metabolizers and 18-45% who are Intermediate Metabolizers 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 (PM). 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 appropriate for a LCD to determine how the physician should prescribe and manage a 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 treating 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% of patients who are poor metabolizers and selection of an alternate drug in the 2-15% who are ultrarapid metabolizers.

   The CPIC guidelines also address the combination of testing results for CYP2D6 and CYP2C19. In considering the two results, only 2 groups of patients would be started on the standard dose of TCA: those who are extensive metabolizers for both or a normal/extensive metabolizer (NM/EM) for CYP2D6 and Intermediate (IM) for CYP2C19. Tricyclic use is to be avoided for 11 of the 16 possible combinations or used with drug monitoring. A dose reduction of 50 % is recommended for CYP2D6 – NM/EM and CYP2C19 PM and a 25% reduction with drug monitoring for those who are CYPD6 IM and CYP2C19 NM/EM or IM.

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* and CYP2D6 status, we believe the criteria that a test result have an impact on the patient's management has been met.

***CYP2C19* – Proton Pump Inhibitors**

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.**

EXCERPT
Proton pump inhibitors are used to treat several gastric acid-related conditions including duodenal ulcer, gastric ulcer and gastroesophageal reflux disease. Proton pump inhibitors can also be used to treat Helicobactor pylori. Several proton pump inhibitors are metabolized by CYP2C19. However, there is insufficient data to warrant CYP2C19 genotyping to determine health outcomes or adverse drug reactions in treatment with proton pump inhibitors.

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 Novitas' 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. (Futura et al 2002)(Kawamura et al. 2003)

The meta-analysis by McNicholl et al. showed that non-CYP2C19 metabolized PPIs (such as rabeprazole 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) (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.

***CYP2C19* – Selective Serotonin Reuptake Inhibitors**

We disagree with the conclusions in the LCD as the evidence supports genotypic-based drug 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.

REQUEST:

- **We recommend coverage of CYP2C19 testing for genotypic-based drug selection for SSRIs.**

CYP2C19 – Warfarin

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

CYP2D6-Antidepressants

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.**

EXCERPT: ***Coverage Indications:***

- *Amitriptyline or nortriptyline for treatment of depressive disorders*

We are in agreement with the recommendation to cover *CYP2D6* genotyping for amitriptyline and nortriptyline. We have 2 comments to consider.

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.

CYP2D6-Tetrabenazine

We agree with the conclusions in the draft 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 a normal/extensive metabolizer (NM/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 a normal/extensive metabolizer (NM/EM).

The maximum daily dose in PMs is 50 mg with a maximum single dose of 25 mg.
The maximum daily dose in NMs/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 patients taking 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.

Normal/Extensive or Intermediate CYP2D6 Metabolizers: In patients who express the enzyme, CYP2D6, (extensive (EMs)/normal (NMs) 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

(NM/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 NMs/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.

REQUEST:

- **Recognize the genotyping requirements and dosing recommendations on the FDA label for tetrabenazine.**

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)

REQUEST:

- **We recommend coverage of CY2D6 for antidepressants.**

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 antipsychotics. 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 - "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.

<u>*CYP2D6*-Codeine</u>

REQUEST:

- **We request that the required level of evidence be applied uniformly, e.g. 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, which Novitas has determined have a sufficient level of evidence to cover.**
- **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.**

EXCERPT:
The efficacy and toxicity, including severe or life- threatening toxicity after normal doses of codeine has been linked to an individual's CYP2D6 genotype. However, genotyping would indicate avoidance of codeine due to risk of adverse events in only 1-2% of the populations, and there is considerable variation in the degree of severity of adverse events, with most not classified as serious. Furthermore, codeine is widely used without genotyping. At this time, there is insufficient evidence to support clinical utility of genotyping for management of codeine therapy.

We disagree with the draft policy's 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 draft LCD. The strength of evidence profile for CYP2D6 for codeine is the same profile that the draft LCD has accepted to support its decision to cover CYP2C19 testing for clopidogrel and CYP2D6 for amitriptyline/nortriptyline. The draft LCD 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 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 genotyping 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 draft LCD states, from the physician and patient's perspective, the events that do occur are 'clinically relevant' and relatively common. For patients who do not have as severe a response, the common adverse reactions of nausea, vomiting,

constipation, drowsiness, lightheadedness, dizziness, sedation, shortness of breath, 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. 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, eg. 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 year old 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/NM: 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 at highest risk (ultrarapid metabolizers (UM)] for adverse events and not expose them unnecessarily to adverse reactions.

PM: The draft LCD 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 misinterpreted 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.

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 draft LCD 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.

It is our belief that 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 draft LCD when the genotype is not known. (Miller et al. 2011) The approach recommended in the draft LCD would put them at most risk for complications.

***CY2D6* - Donepezil**

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

***CYP2D6* - Galantamine**

We agree with the conclusions in the LCD as the evidence does not support CYP2D6 genotypic-based drug selection for galantamine as the drug is titrated to tolerability.

***CYP2D6* - Tamoxifen**

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

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