November 21, 2019

Meredith Loveless, MD
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RE: MolDX: Pharmacogenomics Testing (DL38394)

Dear Dr. Loveless,

On behalf of the Association for Molecular Pathology (AMP) and the College of American Pathologists (CAP), we thank you for the opportunity to review and comment on CGS Administrators, LLC's proposed coverage policy for MolDX: Pharmacogenomics Testing (DL38394).

AMP is an international medical and professional association representing approximately 2,500 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 academic medicine, hospital-based and private clinical laboratories, the government and the in vitro diagnostics industry.

As the world's largest organization of board-certified pathologists and leading provider of laboratory accreditation and proficiency testing programs, the CAP serves patients, pathologists, and the public by fostering and advocating excellence in the practice of pathology and laboratory medicine worldwide.

We are submitting joint comments because both of our organizations share the same perspective regarding this draft local coverage determination (LCD). We appreciate the effort that has gone into the development of this proposed LCD, and we offer the following recommendations for CGS's consideration.

AMP and CAP commend CGS for recognizing the importance of providing coverage to Medicare beneficiaries for pharmacogenomic testing. Additionally, both groups greatly appreciate that CGS directly referred to both the Clinical Pharmacogenetic Implementation Consortium (CPIC) guidelines and the AMP minimum allele testing guidelines for pharmacogenomics as valid and informative resources on pharmacogenomic testing. AMP and CAP applaud CGS for covering a number of diverse genes in one policy and encourage CGS to continue utilizing pharmacogenomic-related clinical practice guidelines, such as those created by CPIC and AMP, in addition to the pharmacogenomic information included in FDA-labeling[1], to help craft future pharmacogenomic policies for additional genes.

[1] https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

Specific Coverage Information

This coverage policy is limited to CYP2D6, CYP2C19, CYP2C9, HLA-B*15:02, and HLA-A*31:01. We appreciate your inclusion of all of these genes in this draft LCD; however there are currently more pharmacogenes with high clinical validity supported by the CPIC guidelines[2], such as TPMT, NUDT15, DPYD, UGT1A1, CYP3A5, HLA-B*57:01, HLA-B*58:01, CACNA1S, CFTR, RYR1, SLCO1B1, G6PD, CYP2B6. CPIC has evaluated the evidence for other pharmacogenes that have not been incorporated into this draft policy and we recommend that these genes also be considered for inclusion. Beyond CPIC, three additional sources that should be used for determining pharmacogenes with clinical validity for future policies are the FDA-approved prescribing information[1], the Dutch Pharmacogenetics Working Group[3], and PharmGKB[4].

Additionally, we agree that the policy should remain unlimited by provider type.

Clinical Indications

CGS provides the clinical indications of single gene testing for CYP2D6, CYP2C19, CYP2C9, HLA-B*15:02, and HLA-A*31:01. AMP and CAP recommend the following revisions for the coverage of CYP2D6, CYP2C9, and CYP2C19.

CYP2D6

The draft LCD states that the following null alleles must be included for CYP2D6: *3, *4, *5, *6, *7, *10, *17, and *41. Additionally, the following duplications must be tested: *1xN and *2xN.

AMP and CAP recommend the following revisions:

- CYP2D6 *17 and *41 are decreased function alleles, not null alleles. These should be removed from the list as null alleles[5] and placed in a separate category of "decreased function" alleles.
- CYP2D6 *7 is an allele that is only found in 0.1 percent of Caucasians[6]. Therefore, this should be removed from the list.
- CYP2D6 *29, a decreased function allele found in 6.5 percent of African Americans[6], is missing and should be included.

Additionally, AMP will be publishing minimum testing requirements for CYP2D6. Upon release of those recommendations, we ask that CGS update the coverage requirements as needed based on those guidelines. AMP plans to provide this updated guidance to CGS as soon as it is available.

CYP2C9

We appreciate CGS's recognition of AMP and CAP's joint recommendation for variants *2, *3, *5, and *6 to be included as part of the CYP2C9 test. However, the proposed CYP2C9 requirement does not include CYP2C9 *8 and *11. These alleles are recommended by AMP together with CAP as part of a set of minimum alleles needed for clinical testing of CYP2C9[7]. CYP2C9 *8 and *11 are present in 6.7 percent and 1.4 percent of African-

[2] https://cpicpgx.org/guidelines/
[3] https://www.pharmgkb.org/page/dpwg
[4] https://www.pharmgkb.org/
[5] https://www.pharmvar.org/gene/CYP2D6
[6] https://api.pharmgkb.org/v1/download/file/attachment/CYP2D6_frequencies.xlsx, downloaded 10/2/2019

Americans, respectively[7]. Additionally, CYP2C9 *9, a decreased function allele found in 2 percent of Caucasians, should be included as well. For reference, please refer to "CYP2C9_frequency_table"[7].

Additionally, the draft LCD considers single gene testing for CYP2C9 reasonable and necessary when "the patient has a diagnosis for which a provider is considering treatment with an antidepressant, anxiolytic, mood stabilizer, or Mayzent, and the patient is open to treatment with such a medication." We appreciate the broader coverage of medication classes when multiple medications are impacted by variation in a specific pharmacogene (i.e., CYP2D6 and antidepressant therapy). We propose that "antidepressant, anxiolytic, mood stabilizer" be changed to "nonsteroidal anti-inflammatory drug or phenytoin" to more accurately reflect the data supporting the use for testing of CYP2C9 in the CPIC guidelines[2].

CYP2C19

We suggest that the description for CYP2C19 be changed to "provider is considering treatment with an antidepressant, anxiolytic, mood stabilizer, clopidogrel, or antifungal" to more accurately reflect the data supporting the use for testing of CYP2C19 in the CPIC guidelines[8].

Technical Requirements

Pharmacogenomic testing provides the greatest benefit to patients when the healthcare provider is able to easily determine when an actionable prescribing change and/or treatment is indicated by the patient's genotype. We agree with the requirements included in the draft LCD and support requiring the completion of an interpretation in order for the test to be considered reasonable and necessary.

Noncovered Indications

Pharmacogenomic testing is not covered if a treating clinician is not considering treatment with a medication that has an actionable drug-gene interaction. Indications for pharmacogenetic testing continue to evolve as evidence is generated. We recommend that currently noncovered indications for pharmacogenetic testing be re-considered on an annual basis.

Special Documentation Requirements

AMP and CAP are concerned that it would be difficult for many laboratories, including commercial reference laboratories, to complete the proposed documentation requirements for pharmacogenomic testing. In most instances, commercial reference laboratories do not have access to the patient's medical record, which would make obtaining the proper documentation for coverage exceedingly difficult, if not impossible. Additionally, it is unclear how a laboratory would document that the ordering physician has "the necessary experience/training to both diagnose the condition being treated and also to prescribe medication."

In regards to the ordering physician, the draft LCD states that the patient's medical record "must reflect the specific drug-gene interaction(s) of concern. General classes of medications or drug-gene interactions do not meet this requirement." This may be difficult because some doctors may not be knowledgeable of the exact gene that must be documented. This means that if a physician, other than a pharmacogenomic specialist, orders a test it might not be covered.

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[7] Pratt et al., 2019, J Mol Diag, 21(5): 746. https://jmd.amjpathol.org/article/S1525-1578(18)30594-4/fulltext

[8] https://cpicpgx.org/content/guideline/publication/voriconazole/2016/27981572.pdf

We agree that physicians should document medical necessity for any testing in the patient's medical record, as part of good medical care, however, tying the documentation to coverage is difficult for the commercial reference laboratory. **We recommend that CGS remove this requirement as it is unworkable with how pharmacogenomic tests are ordered.** Additionally, we fear that physicians would be unlikely to order pharmacogenomic tests based on this level of justification required, thereby potentially restricting patients' access to appropriate testing.

Subject Matter Panel and Contractor Advisory Committee (CAC) Meeting on June 26, 2019

We agree with the panel that combinatorial pharmacogenomics tests with a proprietary algorithm that are not available for public review should require independent evidence to establish validity and utility. We believe that proprietary algorithms with gene content that do not have associated CPIC or other society guidelines may make it more difficult to assess their clinical validity and potential utility. Additionally, we appreciate that you view CPIC as a valuable source of pharmacogenomic evidence.

Pharmacogenomic Testing in Psychiatric Disease

Gene-drug interactions

AMP and CAP encourage the use of CPIC's gene-drug practice guidelines, specifically on gene-drug interactions[9] and recommends the use of drug-gene pairs that have high level of evidence (e.g., CPIC's Level A or B). We would note that the CYP2D6 and methylphenidate pairing is currently assigned a CPIC level of "B/C".

CPT Coding

We suggest that the following CPT Codes be included:

Gene	CPT code
TPMT	81335
SLCO1B1	81328
VKORC1	81355
CYP3A5	81231
CYP2B6	81479 (Not otherwise specified)
IFNL3	81283
DPYD	81232
G6PD	81247
UGT1A1	81350

[9] https://cpicpgx.org/genes-drugs/

HLA Class II Typing	81382
NUDT15	81306
HLA Class I Typing	81381

In the case that CGS agrees with us to expand coverage to the additional pharmacogene RYR1 (for more information, please refer to our comments on "Specific Coverage Information" above), we recommend that additional CPT codes added to this policy include, but not be limited to, the following list:

Gene	**CPT Code**
RYR1, targeted sequence of exons	81406
RYR1, full sequence	81408

ICD-10 Coding

We request that any ICD-10 code relevant to psychiatric or neurologic disease (such as depression, anxiety, mood disorders, neurologic, etc) or pain be added to this list. Specifically, we request that additional ICD-10 codes added to this policy include, but not be limited to the following list:

B02.22 Postherpetic trigeminal neuralgia

B20 Human immunodeficiency virus [HIV] disease

D57 Sickle-cell disorders

F31.0 Bipolar disorder, current episode hypomanic

F31.10 Bipolar disorder, current episode manic without psychotic features, unspecified

F31.11 Bipolar disorder, current episode manic without psychotic features, mild

F31.12 Bipolar disorder, current episode manic without psychotic features, moderate

F31.30 Bipolar disorder, current episode depressed, mild or moderate severity, unspecified

F31.31 Bipolar disorder, current episode depressed, mild

F31.32 Bipolar disorder, current episode depressed, moderate

F31.60 Bipolar disorder, current episode mixed, unspecified

F31.61 Bipolar disorder, current episode mixed, mild

F31.62 Bipolar disorder, current episode mixed, moderate

F31.70 Bipolar disorder, currently in remission, most recent episode unspecified

F31.72 Bipolar disorder, in full remission, most recent episode hypomanic

F31.74 Bipolar disorder, in full remission, most recent episode manic

F31.76 Bipolar disorder, in full remission, most recent episode depressed

F31.78 Bipolar disorder, in full remission, most recent episode mixed

F31.89 Other bipolar disorder

F45.41 Pain disorders exclusively related to psychological factors

G43-G43.D1 Migraines

G44-G44.89 Headache syndromes

G50.0 Trigeminal neuralgia

G50.1 Atypical face pain

G52.1 Disorders of glossopharyngeal nerve

G54.6 Phantom limb syndrome with pain

G56.4-G56.42 Causalgia, upper limb

G57.7-G57.72 Causalgia, lower limb

G89 Pain, not elsewhere classified

G89.0 Central pain syndrome

G89.2 Chronic pain, not elsewhere classified

G89.21 Chronic pain due to trauma

G89.22 Chronis post-thoracotomy pain

G89.29 Other chronic pain

G89.3 Neoplasm related pain (acute) (chronic)

G89.4 Chronic pain syndrome

G90.5-G90.59 Reflex sympathetic dystrophy

H57.1-H57.13 Localized pain, eye pain

H92.0-H92.09 Localized pain, ear pain

K08.8 Localized pain, tooth pain

K14.6 Localized pain, tongue pain

M25.51-M25.519 Localized pain, shoulder pain

M25.5-M25.579 Localized pain, joint pain

M54-M54.9 Localized pain, spine pain

M54.5 Localized pain, lumbar region pain

M54.9 Localized pain, back pain

M79.10-M79.18 Myalgia

N23 Localized pain, renal colic

N64.4 Localized pain, breast pain

M79.6-M79.676 Localized pain, limb pain

N94.810 Vulvar vestibulitis

N94.81-N94.819 Vulvodynia

R07.0 Localized pain, throat pain

R07.1-R07.9 Localized pain, chest pain

R10-R10.9 Localized pain, abdomen pain

R10.2 Localized pain, pelvic and perineal pain

R30.9 Localized pain, painful urination

R51 Localized pain, headache

R52 Generalized pain NOS

T82.84-T82.848S, T83.84-T83.84XS, T84.84-T84.84XS, T85.84-T85.84XS Pain from prosthetic devices, implants, and grafts

T88.7 Unspecified adverse effect of drug or medicament

Z17.0 Estrogen receptor positive status [ER+]

Z21 Asymptomatic human immunodeficiency virus [HIV] infection status

Z94.0 Kidney transplant status

Z94.1 Heart transplant status

Z94.2 Lung transplant status

Z94.3 Heart and lungs transplant status

Z94.4 Liver transplant status

Z94.81 Bone marrow transplant status

Z94.82 Intestine transplant status

Z94.83 Pancreas transplant status

Z94.84 Stem cells transplant status

In the case that CGS agrees with us to expand coverage to the additional pharmacogenes RYR1 and CACNA1S (for more information, please refer to our comments on "Specific Coverage Information" above), we suggest that ICD-10 codes for any procedure that would involve volatile anesthetic agents (surgeries) be added. Additionally, we request that specific ICD-10 codes for malignant hyperthermia be added to this policy that include, but are not limited to the following:

T88.3 Malignant hyperthermia due to anesthesia

T88.3XXA Malignant hyperthermia due to anesthesia, initial encounter

T88.3XXD Malignant hyperthermia due to anesthesia, subsequent encounter

T88.3XXS Malignant hyperthermia due to anesthesia, sequela

Thank you again for the opportunity to review and comment on this proposed policy. We are happy to be of assistance in providing additional clinical or other information to assist you with this draft LCD. Please direct your correspondence to Sarah Thibault-Sennett, AMP Policy Analyst, at sthibaultsennett@amp.org or Nonda Wilson, CAP's Manager, Economic and Regulatory Affairs, at nwilson@cap.org.

Sincerely,

Association for Molecular Pathology

College of American Pathologists