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Proposed LCD DL38337
MolDX: Pharmacogenomics Testing

The American Psychiatric Association, the medical specialty society representing over 38,500 psychiatric physicians and their patients, is pleased to have the opportunity to comment on the proposed Local Coverage Determination (LCD) for Pharmacogenetics Testing. We appreciate the willingness of Noridian to cover pharmacogenetic testing when it has value for a patient's treatment. Although the LCD is relevant to medications of multiple classes for multiple disorders, we will focus our remarks on indications for pharmacogenetic testing in the treatment of psychiatric disorders.

In general, we view several indications as appropriate for pharmacogenetic testing. With some medications, pharmacogenetic testing prior to treatment initiation is important to identify whether a patient is at heightened risk of developing a serious complication. In this context, knowledge of the patient's genetic status can contribute to a decision to avoid use of a specific medication when several possibilities are under consideration. For example, as noted in the LCD, it is important to be able to test for HLA-B*15:02 and HLA-A*31:01 prior to initiating treatment with carbamazepine, oxcarbazepine and phenytoin to detect whether a patient may be at risk for Stevens-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN). Although these medications are most often used for their anticonvulsant properties, we would advocate for pharmacogenetic testing to be permitted when these medications are used to treat other diagnoses, including bipolar disorder.

With other medications, such as those metabolized through cytochrome P450 enzymes, pharmacogenetic testing may be less relevant to initial medication selection but may be important for optimizing medication doses to limit toxicity or enhance outcomes based on principles of pharmacokinetics and known metabolic pathways. In these contexts, pharmacogenetic testing may be indicated once a medication is selected for use or may be more relevant when doses are being adjusted after a patient is already taking a medication. For example, with pimozide, product labelling recommends CYP2D6 genotyping to identify poor metabolizer

status before exceeding a dose of 4 mg of pimozide daily in adults or 0.05 mg/kg/day in children. In a patient with partial medication response and no major side effects at the upper end of the typical dosing range, identifying an ultra-rapid metabolizer status via pharmacogenetics would suggest a reason to use higher doses in an effort to improve outcomes.

We believe that each of these circumstances is alluded to in the LCD but that they should be delineated more explicitly in the sections of the document on Coverage Indications, Limitations, and/or Medical Necessity and Specific Coverage Information. Although we recognize that most indications for pharmacogenetic testing will be related to treatment safety, we would advocate for coverage determinations to also consider enhanced efficacy as a legitimate reason for pharmacogenetic testing in the limited circumstances described above.

We concur with the text of the LCD in noting that:

> Pharmacogenomics testing is considered reasonable and necessary in limited circumstances as described in this Local Coverage Determination (LCD) as an adjunctive personalized medicine decision-making tool once a treating clinician has narrowed treatment possibilities to a small group of specific medications based on other considerations including the patient's diagnosis, the patient's other medical conditions, other medications, professional judgement, clinical science and basic science pertinent to the drug, and the patient's preferences and values. Pharmacogenomics testing is not considered reasonable and necessary merely on the basis of a patient having a particular diagnosis.

However, the LCD also comments that:

> … if the record does reflect that the treating clinician has already considered non-genetic factors to make a preliminary prescribing decision, pharmacogenomics testing is not considered reasonable and necessary.

We would suggest that non-genetic factors will be important in narrowing the choice of possible treatments and even in selecting a preferred treatment, but that this would not eliminate a subsequent indication for pharmacogenetic testing. For example, if carbamazepine were determined to be the optimal medication for a patient on non-genetic grounds, it would still be important to test for the patient's HLA-B*15:02 and HLA-A*31:01 status before initiating treatment. Similarly, if pimozide were preferred, treatment could be initiated based on non-genetic factors, but pharmacogenetic testing would still be indicated at higher medication doses as recommended in the product labelling. Consequently, throughout the LCD, text should be modified to make clear that pharmacogenetic testing may be indicated during treatment with a specific medication and not simply when a medication is being selected for use.

In the discussion of clinical Indications for testing of CYP2D6, CYP2C19, and CYP2C9, we would suggest modifying the general format of the text, with added text denoted by italics:

The patient has a diagnosis for which a provider is considering treatment with <<list of medication classes>>, and the patient is open to treatment with such a medication. *Alternatively, the patient may be receiving treatment with one of these medications.* The patient's record must reflect this. There must be a specific actionable use (where "actionable use" is defined above) for the result of a <<specified>> genotype in at least one medication that the provider and patient are considering *or that the patient is already receiving*.

In the discussion of Special Documentation Requirements, we suggest adding a statement to address testing that occurs during treatment with a specific medication rather than prior to treatment initiation. For example, "If pharmacogenetic testing is being ordered to address safety or efficacy of a medication that the patient is already receiving, the record must describe the relevant drug-gene interaction and how the results of testing will influence clinical decision-making." For medications that have readily available serum levels and an evidence base for therapeutic and toxic ranges of serum levels (e.g., imipramine, desipramine, amitriptyline, nortriptyline, clozapine), data on CYP450 enzyme metabolizer status will be less informative than measuring serum levels directly.

In terms of combinatorial pharmacogenomics testing, we concur with the expert consensus described in the LCD that independent evidence will be needed to establish the validity and utility of these approaches. Results from well-designed clinical trials with appropriate controls and adequate sample sizes will be particularly important when proprietary algorithms are used that cannot be subjected to independent review. A recent review of combinatorial pharmacogenomic approaches to antidepressant selection (Zeier Z, Carpenter LL, Kalin NH, Rodriguez CI, McDonald WM, Widge AS, Nemeroff CB. Clinical implementation of pharmacogenetic decision support tools for antidepressant drug prescribing. Am J Psychiatry. 2018 Sep 1;175(9):873-886) concluded that "there is insufficient evidence to support widespread use of combinatorial pharmacogenetic decision support tools at this point in time" and noted that "a high level of evidence has been achieved only for the cytochrome P450 genotype data." Even less information is known about possible benefits of combinatorial pharmacogenetics approaches for use of antidepressant medications in conditions other than depression or for use of other psychotropic medications.

In addition to these general comments on the indications and coverage of pharmacogenetic testing, we have a number of suggestions on specific aspects of the LCD text:

In the section on definitions, the definition of actionable use specifies that "selection, avoidance, or dose change must be based on the FDA-label for the drug, an FDA warning or safety concern, or a CPIC level A or B gene-drug interaction." However, the CPIC prioritization flowchart (https://cpicpgx.org/prioritization/#flowchart) shows that genes may have other rationales for testing (e.g., actionable in other professional societies guidelines; recommended by an external group such as FDA; PharmGKB annotation levels 1A, 1B, 2A or 2B) prior to a full determination by the CPIC. We would suggest that these other levels of supporting evidence should also be considered as potentially actionable, particularly with respect to pharmacogenetic aspects of drug metabolism.

In the section on general coverage information, the LCD notes that "A multi-gene panel is not considered reasonable and necessary if only a single gene on the panel is considered reasonable and necessary." This restriction does not seem to consider the possibility that, under some circumstances, a multi-gene panel may be less costly either to the payer or to the patient than single gene testing.

We have concerns about the restriction that "Genotyping a specific gene is reasonable and necessary only once per lifetime per patient, unless repeat testing is for variants with an actionable use that have not previously been tested in that gene." A clinician who is providing care for a patient may not be aware that a patient has undergone prior genetic testing and, even if aware, the clinician may not have timely access to such results. A clinician who is acting in good faith to assure the safe prescribing of medications to a patient should not be penalized for repeat testing nor should the patient be penalized by denial of coverage.

In the discussion of the CYP 2D6 testing, we would suggest changing the older term "neuroleptic" to the more common term "antipsychotic." In terms of specific drugs for which CYP2D6 pharmacogenetic testing may be indicated, we recommend including iloperidone for which the package insert states **"**The dose of iloperidone should be reduced in patients who are poor metabolizers of CYP2D6." Similarly, a potential need for dose reduction in CYP2D6 poor metabolizers is noted in the product labelling for clozapine. For both clozapine and iloperidone, the CPIC site notes an actionable pharmacogenetic interaction. Additionally, based on our review of the literature and package inserts as part of the new APA Practice Guideline for the Treatment of Schizophrenia (anticipated December 2019 publication), there are also other antipsychotic medications that are metabolized through CYP2D6 and might also have levels affected. These include chlorpromazine, fluphenazine, haloperidol, perphenazine, and thioridazine. This guideline also reviews the use of tetrabenazine, deutetrabenazine and valbenazine in the treatment of tardive dyskinesia, each of which is primarily metabolized through CYP2D6. Product labeling notes that, in CYP2D6 poor metabolizers, doses of tetrabenazine should not exceed 50 mg per day and doses of deutetrabenazine should not exceed 36 mg per day. CYP2D6 poor metabolizers may also be at an increased risk for concentration-dependent adverse reactions, such as QT prolongation, with valbenazine treatment. Thus, addition of these medications to the LCD would be consistent with our guideline as well as with the evidence that these medications are major substrates for CYP2D6.

Among the antidepressant medications, duloxetine is listed on the CPIC website as having actionable information provided by CYP2D6 pharmacogenetic testing and fluoxetine is listed as having informative information. In the CPIC guideline on selective serotonin reuptake inhibitors (Hicks JK, Bishop JR, Sangkuhl K, Müller DJ, Ji Y, Leckband SG, Leeder JS, Graham RL, Chiulli DL, LLerena A, Skaar TC, Scott SA, Stingl JC, Klein TE, Caudle KE, Gaedigk A; Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. Clin Pharmacol Ther. 2015 Aug;98(2):127-34), fluoxetine is described as having

complex metabolism involving CYP2C9 as well as CYP2D6 and no clear data on whether CYP2D6 phenotypes influence the relative levels and effects of fluoxetine and its active metabolite, norfluoxetine. Nevertheless, we would advocate for inclusion of fluoxetine in the LCD for CYP2D6 pharmacogenetic testing because of instructions in the product labelling that CYP2D6 poor metabolizer status may predispose to increased fluoxetine exposure and contribute to QT prolongation. Knowledge of CYP2D6 poor metabolizer status would also be valuable given the prolonged half-lives of fluoxetine and norfluoxetine and relevance of CYP2D6-related drug-drug interactions with many other psychotropic medications.

In contrast, citalopram and sertraline are listed in the LCD as having a gene-drug interaction for CYP2D6 as well as for CYP2C19, however, the CPIC website does not identify either drug as actionable at CYP2D6 (https://cpicpgx.org/genes-drugs/). In addition, other drug information databases (e.g., Lexicomp®, IBM Micromedex®) do not describe major effects of CYP2D6 in citalopram or sertraline metabolism, although both may function as weak CYP2D6 inhibitors and use CYP2D6 as a minor metabolic pathway.

For CYP2C19, diazepam is listed on the CPIC website as having actionable pharmacogenetic information. Knowledge of metabolizer status may be particularly useful with diazepam given its long half-life and multiple active metabolites.

In conclusion, with current evidence, the APA does not view diagnosis, per se, as providing a rationale for pharmacogenetic testing but neither do we think that diagnosis should be used as a reason for excluding coverage of pharmacogenetic testing if it would otherwise be appropriate for a specific medication. For example, making a diagnosis of a depressive disorder should not be a sufficient rationale for ordering pharmacogenetic testing. Instead, pharmacogenetic testing may be useful if a specific medication is considered or used, but only if pharmacogenetic information would aid in making clinical decisions about the use or dosing of that medication. Testing would also be relevant if that same medication were used for a different disorder (e.g. an anxiety disorder). By the same token, testing should be covered for individuals with any diagnosis (including, but not limited to, schizophrenia, bipolar disorder, depressive disorders, anxiety disorders or neurological disorders), if the specific medication is justifiably being used to treat a given condition and if pharmacogenetic testing provides clinically important information about the use of that medication.

Again, we appreciate the willingness of Noridian to cover pharmacogenetic testing when it has value for a patient's treatment. As noted in the LCD, we expect that evidence on pharmacogenetics will continue to evolve and we would value opportunities to provide input on future versions of the LCD.

Sincerely,

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