Editorial

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Pharmacogenomics

The importance of phenoconversion when using the *CYP2D6* genotype in clinical practice

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"*CYP2D6* genetic test results should be continually evaluated in the light of concomitant medications throughout a patient's lifetime."

Tweetable abstract: Clinical phenoconversion needs to be incorporated when interpreting and applying *CYP2D6* results in clinical care. This article describes how this can be performed either manually or by utilizing online tools and resources. #Phenoconversion #Pharmacogenomics

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Pharmacogenetic testing for *CYP2D6* is increasingly being used in practice to guide prescribing of commonly used medications (e.g., opioids and antidepressants) [1]. The *CYP2D6* gene is highly polymorphic, and genetic variation leads to altered CYP2D6 enzyme activity that may result in medication toxicity or ineffectiveness [2]. Enzyme activity is categorized into four phenotypes: poor, intermediate, normal and ultrarapid metabolizers [3]. Phenotypes are determined by the individual's genotype and the associated activity score [4,5]. This genotype-based phenotype can be further interpreted by taking into account the use of CYP2D6 enzyme inhibitors resulting in a clinical phenotype. Often the clinical phenotype differs from the genotype-based phenotype, a scenario known as phenoconversion [6–9]. Phenoconversion is prevalent in clinical settings; it has been observed that 20–30% of individuals taking an enzyme inhibitor experienced phenoconversion [10–12]. It is estimated that 33% of the population are CYP2D6 intermediate or poor metabolizers based on genotype, and that portion increases to 50% being categorized as intermediate or poor metabolizers when the clinical phenotype is considered. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published six *CYP2D6* pharmacogenetic guidelines for several medications, including antidepressants and opioids [13–19]. These guidelines include clinical recommendations based on phenotype; clinicians should use the individual's clinical phenotype when applying recommendations in practice. Integrating CYP2D6 phenoconversion into clinical practice is underutilized, as many clinicians have limited knowledge on inhibitors and little experience incorporating them with genotype, or are unaware of the tools available to facilitate integration [6,20]. The purpose of this article is to educate clinicians on the importance of utilizing phenoconversion in clinical practice.

Clinical considerations for incorporating CYP2D6 phenoconversion

A detailed tutorial on integrating CYP2D6 phenoconversion into clinical pharmacogenetics has been previously published, but the key steps for clinicians are described briefly herein [6]. First, a *CYP2D6* genotype test must be ordered (or obtained from the patient if they were already tested). Pharmacogenetic test results are lifelong results, so retesting is not necessary as long as key clinical variants have been assessed [21]. When evaluating *CYP2D6* results, the genotype-based CYP2D6 phenotype and medication list should first be reviewed. The clinical CYP2D6 phenotype is subject to change depending on concomitant medications. When reviewing a patient's laboratory report, the *CYP2D6* genotype (e.g., *CYP2D6* *1/*9) may be presented in conjunction with an 'activity score',

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sometimes abbreviated as AS (e.g., AS = 1.5, 'normal metabolizer'). The AS represents the patient's genotype-based CYP2D6 phenotype, or the enzyme activity predicted based on genotype alone. If an AS is not reported, it should be calculated by summing the assigned 'activity value' for each star allele (e.g., *1 = 1 and *9 = 0.5; AS = 1.5, normal metabolizer) [4,5]. The Pharmacogenomics Knowledge Base maintains resources listing the AS assignment for each allele and resultant CYP2D6 phenotype based on AS (www.pharmgkb.org/page/cyp2d6RefMaterials). Alternatively, online CYP2D6 AS and phenoconversion calculators, such as the one developed by the authors at the University of Florida (https://precisionmedicine.ufhealth.org/phenoconversion-calculator/), can be used as a quick point-of-care resource [6].

Once the genotype-based AS is calculated, the effect of concomitant CYP2D6 inhibitors should be calculated. A list of CYP2D6 inhibitors can be found at the US FDA table of inhibitors (www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers), along with their associated classification as strong, moderate or weak [22]. If the patient is taking a strong (e.g., bupropion, fluoxetine and paroxetine) or moderate (e.g., duloxetine and mirabegron) CYP2D6 inhibitor, the AS should be multiplied by 0 or 0.5, respectively. There is consensus among experts that weak inhibitors do not require adjustment of the AS, because they minimally impact the area under the curve [6]. When a strong inhibitor is present, the clinical phenotype will always be a poor metabolizer because the AS is multiplied by zero. For a moderate inhibitor, it depends on the genotype-based AS. It is possible that phenoconversion will not occur in the presence of a moderate inhibitor, and in this scenario the genotype-based phenotype and clinical phenotype would be the same. For example, if the patient's genotype-based AS was 0.5, a moderate inhibitor would adjust it to 0.25 (0.5 × 0.5), and in both cases the patient would be classified as an intermediate metabolizer.

Notably, phenoconversion is reversible, and therefore continuing to evaluate for the presence of CYP2D6 inhibitors is key to ensure the correct phenotype is being used in practice. Typically, 5–7 days after discontinuing the inhibitor, the patient will revert to their genotype-based phenotype. Medication interventions in the case of phenoconversion may include discontinuing the CYP2D6 inhibitor so that the genotype-based phenotype is the same as the clinical phenotype, and as such this time frame must be considered. For example, if a patient who is prescribed tramadol is a genotype-based normal metabolizer but has a 'poor metabolizer' clinical phenotype due to fluoxetine, they would be expected to get pain relief from the tramadol about 1 week after discontinuing fluoxetine.

Patient case

Judy is a 62-year-old female with a past medical history of chronic pain, depression, generalized anxiety and high blood pressure. She presents to her primary care doctor with reports of returned symptoms of depression secondary to family conflicts, and her doctor prescribes fluoxetine (20 mg daily). Her current other medications include: tramadol (50 mg every 6 h as needed; Judy reports taking two doses per day), hydroxyzine (50 mg four-times daily as needed; Judy reports taking one per day a few times per week), lisinopril (20 mg daily) and hydrochlorothiazide (25 mg daily). Judy returns to her doctor 1 month later and reports uncontrolled severe pain, for which she has taken tramadol four times per day without relief. As tramadol worked well for Judy before, the doctor reassesses for pharmacogenetic implications. He first reviews her medical record for her *CYP2D6* genetic results and finds her genotype is *1/*2; that is, she is a CYP2D6 normal metabolizer. He refers to CPIC guidelines to enter Judy's *CYP2D6* genotype and confirm she is a normal metabolizer (AS = 2.0), so tramadol would be expected to work well. To assess phenoconversion, her doctor reviews her other medications. Fluoxetine is a strong CYP2D6 inhibitor according to the FDA. Judy's AS of 2.0 should be multiplied by 0, for an adjusted AS of 0, which translates to a clinical phenotype of 'poor metabolizer'. Phenoconversion has occurred, and clinically Judy should be treated as a CYP2D6 poor metabolizer.

According to CPIC guidelines, tramadol should be avoided in CYP2D6 poor metabolizers and alternative agents considered. Given that Judy's chronic pain was well controlled prior to initiating fluoxetine, one option would be to change her antidepressant. Antidepressants make up a large portion of the CYP2D6 inhibitors that can have a clinical impact; specifically, bupropion, fluoxetine and paroxetine are strong CYP2D6 inhibitors, while duloxetine is a moderate inhibitor. Bupropion and paroxetine are therefore not good alternatives. To determine the effect of duloxetine, the genotype-based AS (2.0) would be multiplied by 0.5, which translates to an AS of 1.0 – an 'intermediate metabolizer' phenotype [4]. In both intermediate and normal metabolizers, CPIC guidelines recommend using tramadol. However, if there is no response in the intermediate metabolizer patient, an alternative should be considered.

Challenges incorporating phenoconversion into practice

Incorporating phenoconversion at the point of care remains challenging for busy providers who may be unaware of its implications. One solution that has been proposed is the use of clinical decision support tools to help integrate pharmacogenetics into clinical decision-making. However, incorporating phenoconversion into those tools is difficult, primarily because phenoconversion depends on having an accurate medication list and accounting for medication changes happening in real time. Medication lists in the medical record are inaccurate or outdated in many real-world scenarios, which limits the capabilities of clinical decision support to determine effects of clinical phenoconversion [23]. A manual alternative would be for the healthcare provider to utilize tools that are available outside of the medical records to help determine the correct clinical phenotype to use in practice, such as those provided in this article [6,20]. Medical practices are increasingly incorporating a pharmacist's guidance for interpreting and applying genotype results in practice. Additionally, while pharmacogenetic test results do not change (i.e., they are applicable for life), medications do. The laboratory report that provides a *CYP2D6* result is a static document and does not consider dynamic changes that may be caused by other medications, such as phenoconversion. As a result, *CYP2D6* genetic test results should be continually evaluated in the light of concomitant medications throughout a patient's lifetime.

Conclusion

As pharmacogenetic information is becoming increasingly available in the clinic to inform drug therapy decisions, complex factors such as clinical phenoconversion need to be incorporated into the interpretation and application of test results into patient care. While performing manual CYP2D6 phenoconversion calculations is challenging in a real-world clinical practice environment, online tools and resources are emerging to streamline this process and integrate it into point-of-care clinical decision-making.

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