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CYP450 genotyping and cumulative drug–gene interactions: an update for precision medicine

“...YouScript clinical decision support system, demonstrated a 39% reduction in hospitalizations and a 71% reduction in emergency department visits among a cohort of elderly, polypharmacy-treated patients subjected to CYP genetic testing and comprehensive interaction management...”

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Approximately US\$3.5 billion is spent annually as a result of adverse drug events (ADEs) [1], responsible for approximately a third of rehospitalizations and resulting in more than 700,000 annual emergency department visits by Medicare patients [2]. A substantial opportunity exists to reduce these iatrogenic events by taking a comprehensive and, when warranted, pharmacogenetics-guided approach to medication management based on the use of sophisticated clinical decision support (CDS) tools.

Missing major interactions

Genetic-based variation in therapeutic drug levels presents a major problem for healthcare providers [3] when choosing which drug and dose to prescribe. The problem is compounded by polypharmacy treatments as the drug interaction checkers common to most electronic health records (EHR) and e-prescribing systems (eRx), alert as to how two medications could interact but do not take into account the cumulative effects of multiple interacting genes and medications. These complex cumulative interactions seen in polypharmacy patients are often additive and may be more problematic than binary drug–drug interactions because they can

result in drug level changes exceeding those resulting from binary drug–drug interactions. These cumulative drug–drug interactions (cDDIs), drug–drug–gene interactions (DDGIs) and drug–gene interactions (DGIs) are entirely missed by most commonly used drug interaction systems used by healthcare providers.

A growing number of publications describe strategies for the management of DGIs but provide little or no guidance as to how to interpret and manage DDGIs and cDDIs. However, two recent studies help define this problem by putting these higher order interactions into context using the YouScript CDS tool, which is an evidence-based, algorithm-driven software service that identifies all four classes of medication interactions and calculates their cumulative effects [4]. Patients in these studies had CYP450 testing ordered from treating physicians who also provided their medication lists which were put into the CDS along with genotypes. The first study looked at 1100 patients tested for CYP2D6, CYP2C9 and CYP2C19. It found that DGIs and DDGIs accounted for 34% of the total potential clinically significant interactions, and DDIs accounted for



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the remaining 66% [4]. Genelex internal data suggest that of the total DDIs 13% are cDDIs. More recently, a retrospective analysis of more than 20,000 patients who had been referred for pharmacogenetic testing of *CYP2D6*, *CYP2C9*, *CYP2C19*, *CYP3A4* and *CYP3A5* were analyzed for interaction type. This study examined the frequency of CYP metabolic phenotypes, listed the most common interacting medications, tabulated severity by interaction type and looked at differences in interaction severity between younger and older (65+ years) populations. The study's major finding was that DGIs and DDGIs represented 25 and 22% of the total interactions observed, respectively [5]. The older, Medicare, cohort was at increased risk for these cumulative interactions due to increased polypharmacy. These studies highlight the prevalence of genetic risk for out of range drug levels in polypharmacy-treated patients as a consequence of the low incidence of normal metabolizers. Many previous studies have shown that more than 75% of patients have variations in at least one CYP enzyme, and may not respond to medications the way a prescriber expects.

CYP450 pharmacogenetics

The purpose of pharmacogenetics is to understand the role of genetics in determining how patients respond to drug treatments. Individual patient genetics has been shown to account for 20–95% of the variability in individual patient drug response [6] and results in as much as a 1000-fold difference in drug levels. The fact that current methods to detect ADEs miss more than a third of potential drug interactions, masked due to unknown patient genetic status [4], has prompted the US FDA to recommend that DGIs be considered as important as DDIs [7]. To facilitate the use of PGX they maintain the table of pharmacogenomic biomarkers which has now grown to more than 137 entries [8]. Variation seen in several polymorphic genes has been shown to cause dramatic differences in drug metabolism and response. Among the most common are the CYP genes, encoding enzymes that metabolize more than 70% of commonly prescribed drugs used to treat many disease states. For more than a decade, genetic testing of CYPs has been available from accredited clinical laboratories. Evidence-based dosing guidelines are available from widely endorsed organizations, such as the Clinical Pharmacogenetic Implementation Consortium [9] which describes 44 drug–gene pairs with 'A' level evidence for genotype-guided dosing. As a result, the use of pharmacogenetic test results to help guide treatment decisions is increasingly becoming the standard of care.

DGIs & DDGIs

The cumulative effects of DDIs and DGIs are the source of DDGIs [10]. An example of a DDGI is a patient with a loss of function allele (DGI) affecting the metabolism of one of the drugs they are taking, then adding a second concomitant inhibiting drug affecting the same enzyme. These cumulative interactions can phenoconvert patients from intermediate to poor metabolizers of substrate drugs and are especially important because a third of patients are intermediate metabolizers of at least one of the three most important CYPs [4]. DDGIs can also occur when an individual is taking a drug metabolized by two CYPs and a medication is added that inhibits one of the CYPs, while their genetics alter the activity of the other enzyme(s). For example, the binary interaction between omeprazole and clopidogrel may be magnified by an individual's *CYP2C19* genotype. Omeprazole is a strong inhibitor of *CYP2C19*, which is required for activation of the prodrug clopidogrel thereby further reducing clopidogrel effectiveness [11]. In *CYP2C19* intermediate metabolizers, the DGI (clopidogrel–*CYP2C19*) is confounded by the DDI (clopidogrel–omeprazole), further decreasing the activation of clopidogrel. Such DDGIs result in the phenomena of phenoconversion in which a CYP intermediate metabolizer now has the phenotype of a poor metabolizer. Thus, when patients are taking multiple medications, the potential for DGIs should always be taken into account as they may result in DDGIs. When a drug with a narrow therapeutic range is used, such DDGIs may be of substantial clinical significance and deserve careful consideration when selecting related drug therapy [12].

Integrating cumulative DGI alerts

To date, most EHR, eRx and other healthcare software systems lack the ability to store and mine individual pharmacogenetic data in a meaningful way. According to Cara *et al.*, an ideal drug interaction alert software should interface with the patient's electronic medical or pharmacy chart to promptly and efficiently link drug interaction data with the patients' full medication and pharmacogenetic profiles; alert clinicians when interactions are detected; be capable of assessing cDDI, DGI and DDGI including relevant transporter and pharmacodynamics markers; provide clinicians with a frequently updated summary of the quality of the evidence supporting the mechanism and clinical significance of reported interactions; specify the severity and rate of onset of interactions; and include clear management recommendations [13]. Like Confucius said, "To know what you know and what you do not know, that is true knowledge." Current tools already

miss what we do know, and improved altering needs to be a priority.

Potential for reductions in hospitalizations & emergency department visits by taking cDDIs, DGIs & DDGIs into account

A recent study by the University of Utah (UT, USA) on the comprehensive approach to medication management, based on the YouScript CDS system, demonstrated a 39% reduction in hospitalizations and a 71% reduction in emergency department visits among a cohort of elderly, polypharmacy-treated patients subjected to CYP genetic testing and comprehensive interaction management in the 4 months following testing. In total, more than 95% of prescribing physicians found the CDS-generated reports helpful and approximately a half implemented recommended changes in patient medication regimens [14].

Conclusion

There is little doubt that the information provided by a pharmacogenetic test can be critical to finding the right medication or dose for an individual patient, but how that information is presented to a healthcare provider, and subsequently used, can have a major impact on treatment outcomes. Evidence-based guidelines for genotype-guided therapy are being developed for DGIs without reference to the polypharmic background into which they will frequently be introduced. Therefore, increased understanding of the cumulative effects of DDGIs and cDDIs is a significant opportunity to work toward minimizing ADEs and an important

step toward accomplishing the goals of the Triple Aim (improved care of the individual, improved health of the patient population and decreased per capita costs) [15].

CDS software should take into account patient genetic-based metabolic capacity and their total medication list to help prescribers determine the best medications and dosages for each patient. Such CDS tools can be used to identify appropriate use of genetic testing which needs to be more widely reimbursed. In addition, the resulting clinical information needs to be available to prescribers and pharmacists in a comprehensive manner throughout the healthcare software ecosystem. A greater sense of urgency is needed to integrate this kind of information (DGI, DDGI and cDDI) and technology into EHR, eRx and interaction checkers in a user-friendly, patient-centered way. This will vastly improve the alerts healthcare providers consider when prescribing; improving their ability to identify and treat ADE risk patients. Transitioning to comprehensive, genotype-guided medication management presents one of our greatest opportunities to improve patient care while reducing costs.

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