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Commentary: A Novel Disease-Drug Database Demonstrating Applicability for Pharmacogenomic-Based Prescribing

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Introduction

Significant advances have been made in the clinical implementation of pharmacogenomics in recent years with tools for clinical decision support (CDS) being developed and integrated in the electronic health record (EHR). In this issue, the article by Hussain et al. describes the creation of a disease-drug association tool that enables providers to search by disease indications to receive a list of treatment options marked with pharmacogenomics annotations at the point of prescribing.

Pharmacogenomics (PGx), the use of genetic information to guide drug therapy, is an important component of precision medicine. After decades of research, genetic variations affecting efficacy and toxicity of more than 80 drugs have been identified and validated as clinically actionable¹. However, the translation of pharmacogenomics knowledge into clinical practice has been slow. Barriers that prevent the widespread use of PGx diagnostics include the lack of clear clinical guidelines, education/knowledge gap of the clinicians, turn-around-time and reimbursement issues. Additionally, computational tools for clinical decision support will need to be developed and integrated in the EHR to prompt and guide clinicians on how to use genetic information when prescribing drugs. Despite these complexities in implementation, we are gradually seeing more and more clinicians willing to take patient's genetic information into account to guide drug and dose selections. Preemptive multi-gene panel testing has also been deployed at a number of academic medical centers and clinical decision support tools integrated with EHR are being developed to assist the interpretation of results^{2–5}.

The article by Hussain et al. describes the creation of a disease-drug tool that integrates with the Genomic Prescribing System (GPS), an existing PGx CDS system⁶. The authors found that "PGx-based prescribing can inform the treatment of the great majority of medical

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conditions and would potentially affect nearly every patient with some of the most common U.S. medical diseases.” Their system enables the provider to search by disease indication mapped to standardized vocabulary (SNOMED) to receive a list of treatment options annotated with PGx information in a comparative mode to select the best fit for the patient. The clinician is able to select from the options based on comparing the patient genotype with the implications, if any, for each drug. The creation of the disease lexicon by compiling a list of all possible indications for the selected drugs was no small task and gives the tool an advantage over existing ones, as the comparison in the article shows.

Many CDS tools alerts clinicians of a patient’s possible response when they place a prescribing order^{3, 7–8}. One unique feature of the disease-drug search approach described by Hussain et al is that it alerts the clinician to possible PGx associations *before* selecting a treatment option, whereas many systems fire alerts *when* a treatment with a potential PGx association is selected. A clinician may ultimately make a different drug choice if shown PGx information before making a drug selection, rather than selecting a drug based on clinical factors and then checking for negative PGx or dosing adjustment after the prescription choice is entered. For example, it is possible that a clinician would avoid all drugs with PGx implications, regardless of if the implications were positive or negative, in favor of a drug with no PGx information available to avoid all possible PGx issues. However, having the genetic implications of drug selection displayed at the beginning of the prescription process could save the clinician valuable time, allowing for faster use of genetic information rather than a trial-and-error approach to selecting a drug without PGx ramifications.

The approach also differs from other strategies to implement PGx information into treatment decision in that it considers evidence beyond the examples with high level PGx knowledge that led to actionable dosing guidelines (e.g., CPIC level A evidence) and aims at a diverse selection of drugs to target common diseases. To enrich for PGx relevant drugs 3 different defined sources with a certain overlap and various level of evidence quality are used: 35 drugs for which CPIC level A evidence exists^{9,10} [<https://cpicpgx.org/genes-drugs/>], 46 drugs included in the genomic prescribing system (GPS)⁶ (which has a large component of cardiovascular related drugs), and 104 drugs listed on the FDA biomarker table (germline variations only) [<http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm>].

The inclusion of drugs from different resources (including such resources as PharmGKB; <http://pharmgkb.org>) gives a wider selection of drugs targeting common diseases. However, it should be noted that the PGx information from different resources uses different criteria to identify drugs as PGx relevant and carries different strength of evidence, with FDA biomarker annotation possibly being the most liberal gene-drug annotation while CPIC level A annotation is the most stringent among the three. When the information from different resources is aggregated, it will be valuable to clarify how the tool determines the composite level of evidence from various resources, the drug-gene selection criteria and include drug-drug interaction information. For example, a system could potentially score information from different resources according to level of evidence and then calculate an overall rating.

The FDA biomarker table is listed above as possibly being the most liberal source of PGx because it contains labels with a wide range of genetic information. It is important to understand the different levels of genetic information for drug labels in the FDA biomarker table, and to not make the assumption that this list represents all drugs which have support for PGx associations while those not listed do not. The list varies from drugs that require testing a patient for a particular genetic variation before use (e.g. abacavir), to those with recommendations but not strict requirements to test before use (e.g. warfarin label contains a genotype-based dosing table), to labels only with information about genes involved in drug metabolism or drug-drug interactions based on metabolizing enzymes (e.g. celecoxib), to drug labels reporting that genes were studied but not found to have any affect at all (e.g. indacaterol). It is unclear what, if any, prescribing recommendations could be given for some of the drugs on the FDA biomarker table.

For example, the label for drospirenone states, “Clinical studies did not indicate an inhibitory potential of DRSP towards human CYP enzymes at clinically relevant concentrations.” [http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021676s014lbl.pdf] So while this drug is on the FDA biomarker list with CYP2C19, there is actually no clear association and no action to be taken for CYP2C19 variants. Another example is succimer and G6PD deficiency, where the label states it “has been used for the treatment of lead poisoning in one patient with sickle cell anemia and five patients with glucose-6-phosphodehydrogenase (G6PD) deficiency without adverse reactions.” [http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/019998s013lbl.pdf] There are no actions to take based on G6PD variants.

Some labels on the FDA biomarker list refer to drug-drug interactions based on information showing multiple drugs metabolized by the same enzymes. While this is important to be aware of, there are often no genotype specific recommendations to follow. For example, the modafinil label discusses *in vitro* studies showing the drug inhibits CYP2C19, and suggests dosage reduction for *other* drugs also metabolized by CYP2C19 may be required. [http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020717s037s038lbl.pdf] The label also goes further to say that poor metabolizers for CYP2D6 may need dose modifications for medications that have ancillary metabolism via CYP2C19, such as tricyclic antidepressants (TCAs). However, CYP2D6 and CYP2C19 genotype would not impact the dosage of *this* medication, but rather *other* medications given simultaneously. Therefore, a system should not necessarily trigger PGx warnings for modafinil based on the fact that it is on the FDA biomarker list alone. However, this type of information would be valuable for pharmacists who have access to patient medication lists.

An active discussion about the amount and quality of evidence needed for a drug-variant pair to be considered clinically actionable is ongoing in the PGx community. It would have been interesting to see the authors perspective on how to efficiently include and weigh the PGx information from the 66 drugs tagged with only FDA label PGx information in decision support since the PGx relevant information on the drug label varies widely from specific dosing recommendation to cautions regarding drug-drug interactions.

These issues aside, developing CDS tools integrated in the EHR represents a critical step towards implementation of precision medicine. The Clinical Pharmacogenetics Implementation Consortium (CPIC; <http://cpicpgx.org>) evaluates evidence from existing literature and creates guidelines to guide clinicians on how genetic test results should be translated into specific prescribing actions. CPIC have also established an informatics subgroup to support the adoption of the CPIC guidelines by developing tools to combine clinical information from the EHR with the information from the CPIC guidelines and use them for clinical decision support. From the experience of creating guidelines and implementing at practice sites, CPIC emphasized five principles for the development of knowledge resources for precision medicine⁶. These include support traceability between variants, primary results, and clinical interpretations; rate level of evidence for variant as well as for the overall recommendation; use standards to facilitate information exchange; support long term reinterpretation of results as new evidence emerges and ready to be integrated with other knowledge at the point of care.

In addition to the development of intuitive clinical decision support tools, clinical guidelines and knowledge resource, emphasis should also be placed on integrating CDS into EHR systems nationally, continued and much-needed efforts toward healthcare practitioner education in pharmacogenomics, and assessment of the clinical utility to expand the evidence base supporting pharmacogenomic testing.

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