

Behind the PGx Challenge: Biofx

In the trenches: our columnist describes the informatics work behind building a guidance engine that would help put PGx squarely in the clinic

Pharmacogenomics holds the promise that drugs might one day be tailor-made for groups of individuals and adapted to each person's own genetic makeup. One of the many challenges facing this field is how to deliver relevant knowledge from the laboratory bench to the patient's bedside, and then from the clinician back to the laboratory — this includes a great bioinformatics challenge.

One solution to this transfer of knowledge is the development of a PGx guidance engine. This will first require supporting infrastructure, such as a comprehensive Pharmacogenomics Health Information Management System (PHIMS), and an easy-to-use interface like a tablet or other handheld device for clinicians. The PHIMS will include many components, one of which is a data warehouse where data from different sources is stored and accessible. The guidance engine will deliver information from the data warehouse to the physician in a meaningful format and will continually receive physician feedback to and from the data warehouse. Examples of information delivered to the physician include the applicability of pharmacogenomic testing as well as the interpretation of PGx test results. The physician can report back outcomes and interventions to help improve safety through evidence-based clinical practice.

Pharmacogenomics studies may consist of two phases: a retrospective study that aims to identify a relevant biomarker, followed by a prospective study,

usually a randomized clinical trial, to test the validity of any putative biomarker. Integrated medical software packages need to be created for use in these prospective studies; they will help accelerate the integration of pharmacogenomic knowledge into the clinic.

The goal is to make this software accessible to physicians and improve patient care based on individualized genetic testing when medically applicable and relevant. For example, after prescribing a drug, the physician will be alerted by the software if a pharmacogenomic test is available. If the test is ordered, results will be accompanied by guidance on how to interpret them and what steps may be taken (e.g. increase or decrease dosage, prescribe an alternative medication). The final decision will rest with the physician.

WHAT WE'RE DOING

The G enome Qu ebec and Montreal Heart Institute Pharmacogenomics Centre is currently developing a prototype of this pharmacogenomic clinical informatics system. It will be designed to:

- Facilitate the incorporation of pharmacogenomics testing for specific therapies by alerting the doctor that a test is available and applicable
- Facilitate the transfer of relevant pharmacogenomics information from lab to the clinic and back to the lab by making the software available on handhelds, tablets, or PCs in the clinic so that it can be used at the point of care
- Integrate other relevant clinical infor-

mation from the hospital in order to help the physician determine an appropriate course of therapy

- Provide clinical guidance on drug prescriptions to the physician based on the lab results
- Provide access to additional knowledge resources, such as the pharmacogenomics data warehouse which, among other things, keeps track of the electronic health records including what was prescribed on the basis of the pharmacogenomic test, whether test results triggered a change in proposed treatment regimen, and how well the patient is doing on the drug regimen.

PHIMS is being designed to bridge the gaps between current PGx research and the clinic (see description on p.20). The promise of pharmacogenomics will only be realized when clinicians and patients find it useful in managing healthcare. The PHIMS tool will begin the translation of genomic information into the clinic. Through its design, we hope to solve at least the bioinformatic challenges to moving this field ahead and into practice. Just like the PHIMS, the translation of pharmacogenomic information from bench to bedside will be an iterative process and an ongoing learning experience.

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PHIMS in Progress *(continued from p.19)*

The Pharmacogenomics Health Information Management System (PHIMS) is envisioned as a complete bioinformatics pipeline and builds upon components already developed or currently being developed at our center. Here's a description of the elements:

A) An interface (computer, tablet, or handheld) connecting to the guidance engine through the trusted third party that serves as the access point for clinicians, nurses, and administrators. A common application interface is used to simplify the alerting of available tests, requesting of those tests, provision of guidance based on the test results, and the opportunity to generate feedback on whether guidance was followed, as well as detail outcomes to help refine future guidance rules.

B) A schema to protect patient privacy in a secure, denormalized, double-coded environment has been developed through the use of a trusted third party (TTP) as an intermediary combined with public key encryption. The public and private keys work so that only the public key can be used to encrypt messages, and only the corresponding private key can be used to decrypt them. The TTP creates the private/public key pair and hands the PGx center its public key. The only way to reverse the process of double encoding is through the use of the TTP with its private key. The TTP also holds the ethical oversight of each project.

C) The guidance engine will generate guidance to help clinicians interpret the genetic test results and provide feedback on whether guidance was followed and what the outcome was. This system will enable the study of the effects of applied PGx on disease treatment.

D) The data warehouse is the access point for data mining and analysis. This is possible because the data warehouse is a federated database and will contain both publicly available data and clinical data such as the patient's electronic health record. It provides the context to help manage the validation, confirmation, and updates to new and existing pharmacogenomics guidance used by the

engine. The data warehouse will also combine quality control, clinical data source integration, medical knowledge mining, data analysis, and drug-specific clinical analysis. It is the source of the data that is used to formulate the rules used by the guidance engine.

E) Analysis is performed by biostatisticians and other researchers using custom or commercial tools on data extracted from the data warehouse.

F) Publicly available databases will be linked within the data warehouse to provide additional context into the inner workings of observed pharmacogenomic patterns (e.g., NIH, HapMap).

G) Other sources include center-specific technologies such as genotyping tools.

H) The Laboratory Information Management System (LIMS) is 21 CFR part 11 compliant and ISO 9001 and tracks the data of a regulated laboratory in accordance with

the principles of Good Laboratory Practices (GLP).

I) Genotyping QC: The center currently develops PGx content on multiple genotyping technologies, using multiple instruments. The Sherpa tool is being designed to gather raw genotyping data from diverse sources and present them for analysis and quality control in a standardized interface. The creation of abstract generic genotyping data by Sherpa allows the center to use a single analytical pipeline to analyze data across multiple genomic platforms. Sherpa allows a number of unique data visualizations that are currently not available in commercial software packages and is designed to go beyond current limitations in genotyping QC, and will streamline the genotyping data feed into the data warehouse. Sherpa guides the lab user through the multiple phases of data analysis and multiple levels of quality control to be able to get the clinical accuracy required for pharmacogenomics tests. The last phase of Sherpa development will be the assignment of a proposed phenotype based on a molecular profile derived from pharmacogenomic research which includes literature (mining) in the data warehouse.

