The essentials for a powerful clinical decision support software with embedded PGx: Evidence driven platform integrated into an EHR

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Introduction

Across North America, Europe, and Japan, an educated, aging population has been leading the advocacy for personalized medicine and started raising their collective voices in their healthcare journey.[1] With increasing awareness, this group of people have raised expectations for tailor-made drug therapies. The best first step in addressing that unmet medical need is through accurate drug prescribing along with information on why that drug was prescribed. The good news is that personalized medical care combined with precise drug therapies will support not only seniors, but all patients irrespective of age, ethnicity, or condition.

Studies have documented that personalized medicine can lead to better outcomes as well as reduce adverse drug reactions, a major cost to patients, payers and health systems.[2,3]

Inappropriate prescribing has serious health consequences: In the United States over fifty percent of prescribed drugs are ineffective for the individual, 5% of hospitalizations are due to adverse drug reactions (ADR)[4,5], and 10% of direct health care costs are due to an ADR.[6] (**Figure 1**). Given the digitization of medical and patient information, physicians, pharmacists, and nurse practitioners have surprisingly only recently had efficient or automated ways to access all the information they need to prescribe the right drug at the right dose.

Of further note, studies indicate that a high percentage of patients have actionable genotypes that could result in changes to medication therapy.[7,8] As a consequence, drug labels must now include pharmacogenetic information for accurate medication choices for patients.

Clinical decision support software (CDSS) is a sophisticated tool to aid physicians in prescribing the right medication in the right dose at the right time for patients. Integrating modern 'non-alert' CDSS into the Electronic Health Record (EHR) is a logical next step; integrating these two systems ensures that a patient's genetic make-up is combined with other laboratory, biophysical, and drug-risk data to provide the most appropriate and safest medication options to the clinician.

A path forward requires the adoption of digital automation tools for data entry and management combined with the use of Pharmacogenetic (PGx) data for real-time evidence-based guidance on available drugs. A modern cloud based CDSS* can support clinicians by being always up to date and by being capable of offering real-time medication guidance even when there is no pharmacogenetic information available. In that instance, smart CDSS systems would even be powerful enough to flag pharmacogenetic testing for medication suitability or rationalization for eligible patients.

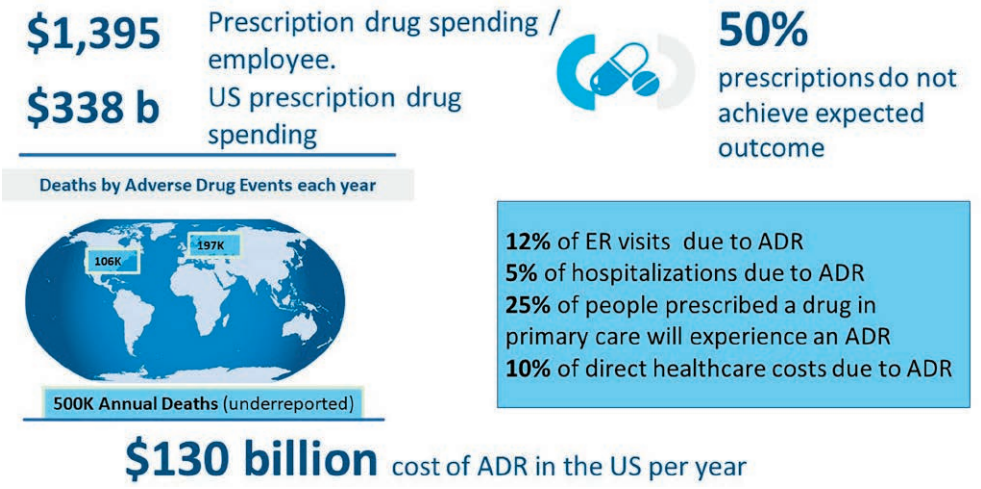

Figure 1: Prescriptions: pricey and full of pitfalls

Current Practices

Even with widespread reports and clinical studies on the influence of genetic variations on drug response, only a small percentage of clinicians order a PGx test and have the necessary tools to translate PGx data into clinical practice.[9,10] This hesitancy persists even though PGx guidelines for drug-gene recommendations are now available for a wide range of medications. Over 100 medications approved by the U.S. Food and Drug Administration (FDA) include information about PGx associations on the label.[11]

Practices could turn to commercially available PGx-based interpretation services and their reports, but many are static in nature, and few offer a real time decision support tool that factors in a patient's clinical profile. Other options include the PharmGKB database[12] that offers PGx-clinical guideline annotations established by the Clinical Pharmacogenetics Implementation Consortium (CPIC)[13,14] the Royal Dutch Pharmacogenetics Working Group (DPWG),[15] the Canadian Pharmacogenomics Network for Drug Safety (CPNDS)[16] and other societies. There are standardization efforts for genotype translations, phenotype terms, and reporting of PGx recommendations and these should be incorporated in the CDSS.

Many CDSS platform report outputs are static, meaning they are out of date as soon as guidelines are updated and as new evidence becomes available (or new guidelines are established). Crucially, guidelines and reports on drug-gene interactions are better updated continuously to allow for timely decisions. For all stakeholders to be confident that the latest guidelines are being accessed, a real-time cloud based CDSS solution must be employed.

CDSS are often developed as stand-alone systems that function as part of a siloed web or mobile application. A better framework would build on embedding your CDSS into an EHR or pharmacy management system so that PGx utilization does not disrupt the workflow. Like any genetic test, PGx data is relevant throughout a patient's life, so long-term availability and usability of PGx results can only be possible with a CDSS that is seamlessly integrated into an EHR. The payoff for this sophisticated design is a CDSS that is integrated into an EHR that enables sharing of PGx results among health care professionals across conditions and along the healthcare journey.[17,18]

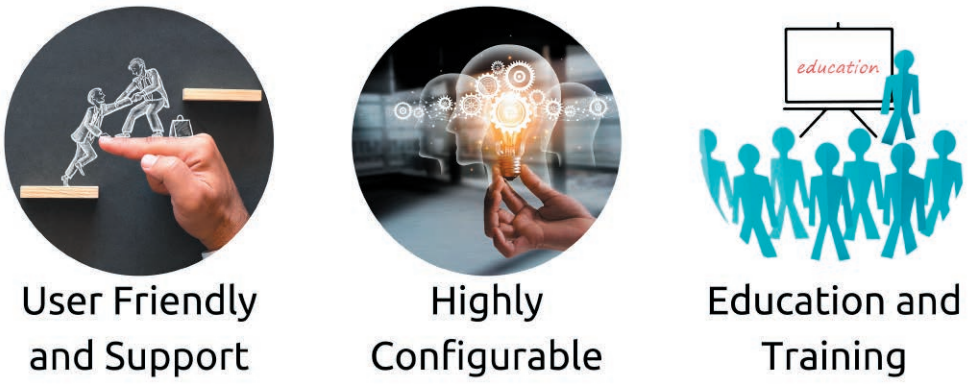

Figure 2: There are many aspects to a CDSS which include: a user-friendly application and user support, configurable software that can provide interoperability with EHRs and prescribing and dispensing software, and education and training

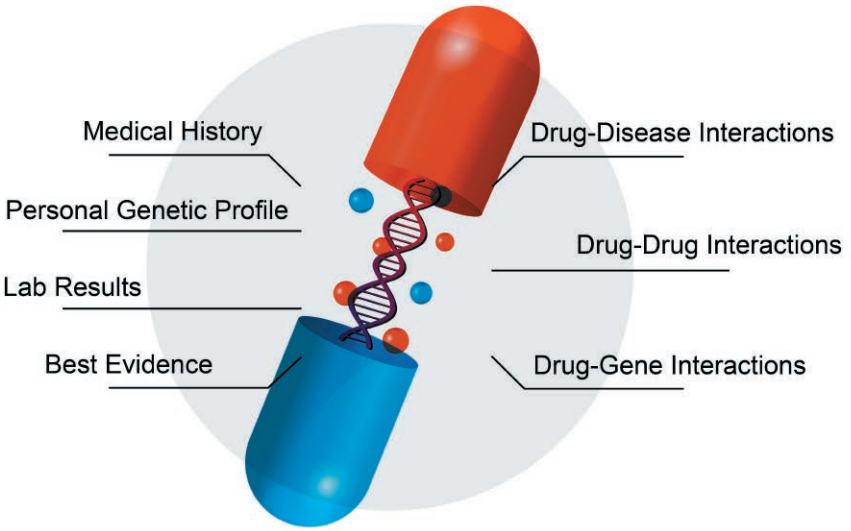

Figure 3: A holistic approach considers many factors to personalize treatment options

A Modern CDSS: Combining Functionality and a Quality System

A dynamic CDSS processes information in real-time and interacts with clinical data by following set rules in an evidence-based algorithm. Some practices resort to 'home grown' solutions or adopt what is available in the commercial market without performing a rigorous due diligence review. Homegrown tools are limited and so are quickly outgrown or reach a capability or performance ceiling. Further, our review of commercial digital automation tools found that few meet the comprehensive needs of clinicians nor provide the interoperability requirements of the Chief Medical Information Officers (CMIO) office.

CDSS is a sophisticated tool to aid physicians in prescribing the right medication in the right dose at the right time for patients. Its benefits also extend to the offices of the Chief Safety Officer and the Chief Financial Officer.

Four elements are worth evaluating prior to adopting a CDSS (see also **Figure 2**):

- User friendliness
- Interoperability with EHRs and prescribing and dispensing software
- Customizable outputs
- Education and training

Modern CDSS utilize algorithms to harvest data from the most currently available pharmacological information, epidemiological evidence, and guidelines for the management of disease. As noted above, a CDSS package should review and update the pharmacogenetic evidence on an ongoing basis using a "level-of-evidence" approach starting with drug-gene interactions and guidelines published by CPIC and DPWG. All information would then be cross-referenced with the drug monographs published by the FDA. It is also important that a modern CDSS has the capacity to accept genetic laboratory data that is annotated in various formats and sizes. Over the past several years we have seen a significant take up of genetic testing by consumers; millions of people have had genetic tests to date, roughly a third of which is from home-use genetic tests. To handle this kind of data, a CDSS needs to be PGx agnostic – essentially accepting clinically relevant data that meets an evidence threshold from all sources.

To bring this approach into practice, it is imperative that an interdisciplinary team of pharmacists, geneticists, and physicians convene to review the evidence and develop an automated algorithm framework for each condition. Each aspect integrated in the CDSS is weighted based on its severity and impact. A CDSS algorithm that can identify patient-specific medication safety issues due to comorbidities, kidney & liver function, drug-gene interactions, and drug-drug interactions helps simplify the prescribing process and increase accuracy (**Figure 3**). In practice it is important that the CDSS is still able to provide recommendations when factors such as kidney function or PGx are unknown, by taking all other clinical variables into account.

Next generation CDSS should also be able to identify deprescribing opportunities (taking patients off some or all prescribed drugs) through a global review of medications. For example, antihistamines are used for both insomnia and for allergic reactions. If used for sleep aids, then a CDSS can trigger a deprescribing note whereby alternative agents may have a better risk-benefit profile. Important in today's world, an opioid deprescribing note can also be triggered by a CDSS since opioids should be reviewed for risk-benefit, given the potential harm associated with chronic use. Finally, these algorithms need to be fully tested against a large data set across a vast number of simulated cases. One such CDSS, TreatGx™ from GenXys, routinely runs over 4,000 tests across 45 conditions covering approximately 40,000 prescribing options.

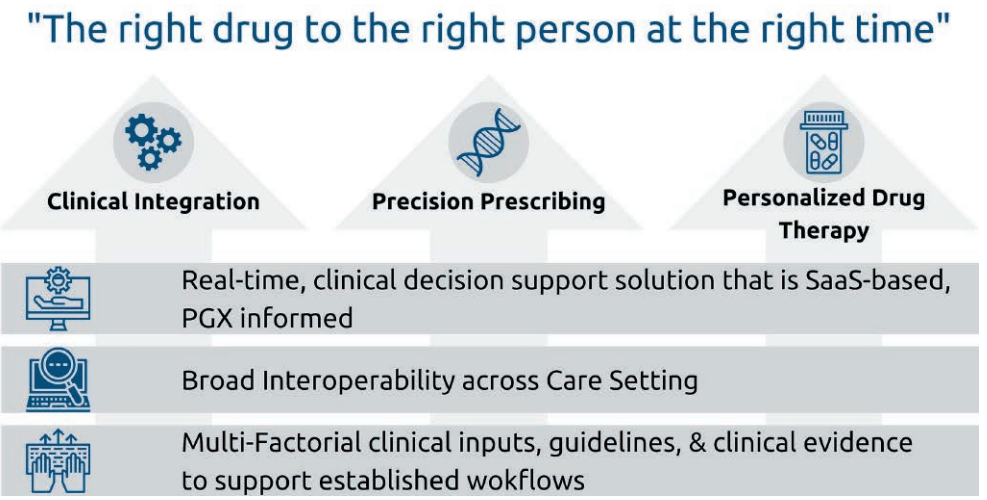

Figure 4: Removing trial and error prescribing using a CDSS

Summary and Future Developments: Real-world CDSS Application

A 43-year-old woman with a history of chronic pain and fibromyalgia is seen for pain management. She reports being extremely sensitive to medications and often experiences side effects and intolerances. Her mental health has declined due to her ongoing pain, and she has been on long term disability and unable to work. Her pain started several years ago after a car accident, but there seems to be no ongoing musculoskeletal injuries or issues, but she describes shooting pain in her back and neck while doing certain activities and often at rest. She is tired and fatigued all the time and often does not have the energy to get out of bed in the morning. Her physicians are frustrated and do not know what to try next. She is reluctant to try more medications due to her previous side effects.

Without pharmacogenetic testing, she is likely to continue living in pain and being unable to work, which is causing a financial strain for her and her family.

With pharmacogenetic testing, it is discovered that she has several genetic variants that will affect her response to chronic pain and fibromyalgia medications (including tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and opioids). By using a CDSS from the EHR, her physician can avoid certain medications and adjust the dosage of other medications to ensure her risk of side effects is minimal. The CDSS considers pharmacogenetics in addition to other clinical information about the patient (kidney function, current medications, comorbid conditions, etc.), Eventually she starts and tolerates a low dose of a medication that improves her pain and allows her to increase her activity. After a while, she can attend occupational therapy and eventually a gradual return-to-work program.

As noted above, the value of CDSS is measured by its ability to improve decision-making in prescribing drugs by providing real-time support to clinicians. Using a CDSS that integrates current evidence and algorithms that identify medication safety issues (e.g., inappropriate drugs) will optimize medication selection specifically tailored to each patient's profile and improve health outcomes (**Figure 4**).

Education and training of health care professionals on the benefit of PGx-guided CDSS should be made more readily available. To this end, transparency is necessary when an option is provided by the CDSS on why the specific recommendation was made. With smart CDSS designs, clinicians will not need to turn to geneticists to utilize pharmacogenetics effectively. What clinicians clearly need is a system that incorporates PGx data into the optimized medication list.

A dynamic real-time CDSS is projected to become an integral tool of any Chief Medical Information Officer, Clinical Safety Officer, or any clinical leader. Knowledge of pharmacogenetics is becoming more prevalent with the onus on health systems and genetic lab companies to make it usable at the point of care. Pharmaceutical companies are also now expected to properly and fully disclose when pharmacogenetics plays an important role in patient response. Had health systems in Hawaii utilized advanced PGx informed CDSS we suggest that Bristol Myers Squibb and Sanofi-Aventis U.S. may have avoided the litigation suit with regards to Plavix being ineffective in as many as 30% of patients as reported by Bloomberg.[19]

The integration of CDSS into the care journey can lead to a significant improvement in the quality of care and quality of life of patients. Clinicians can include PGx data into their workflow and their prescribing decisions with real confidence. Clinical adoption of pharmacogenetics will provide the healthcare provider with an ability to foresee implications of prescribing a drug and make a clinical decision based on real-time information. Incorporating real-time PGx data through an EHR-interoperable CDSS allows a health care system to efficiently adopt pharmacogenetics and enhance practitioners' actionable power, a capability every modern clinician needs and indeed can now have.

Summary Points for a Powerful CDSS with PGx

- Recommendations based on up-to-date guidelines: Updateable
- Integrated into an EHR: Interoperable
- PGx and biophysical information: Multifactorial
- Any data format or size: Lab agnostic JoPM

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Hagit has an extensive background in the field of personalized medicine and genomics. She received her PhD at the Karolinska Institute in Stockholm in molecular genetics focusing on the overlapping genetic pathways in Alzheimer's and cardiovascular disease. She did her postdoctoral training in pharmacogenetics at the University of British Columbia followed by research in cancer genomics at Mount Sinai hospital in Toronto. In her role at GenXys Health Care Systems, Hagit is leading projects with physicians and pharmacists to integrate and report pharmacogenetic information for clinical decision support.

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* It is worth noting that the term CDSS is interchangeable with Medication Decision Support Software (MDSS) and Precision Prescribing Software.

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