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Title	Introducing pharmacogenetic testing with clinical decision support into primary care: a feasibility study
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Reviewer 1	Dr. David Comings
Institution	Carlsbad Science Foundation, Monrovia, CA
General comments (author response in bold)	Placing myself in the position of a reader of the CMAJ I had a few questions that I suspect readers would want clarified. 1. One question concerns drug-drug-gene interactions. Does this mean that some drug-drug interactions are important for some genotypes and not for others? This needs to be explained. Interestingly, [on page 8, l 51] it is stated that, "Medications are selected and dose-adjusted based on evidence-based drug-drug, drug-condition, or drug-gene interactions within the program." There was no mention here of drug-drug-gene interactions so I assume that category did not occur. ***Reference #7 from introduction gives the explanation: A drug-drug-gene interaction occurs when the patient's CYP450 genotype and another drug in the patient's regimen (e.g., a CYP2D6 inhibitor) affect that individual's ability to clear a drug. (7.Verbeurgt P, Mamiya T, Oesterheld J. How common are drug and gene interactions? Prevalence in a sample of 1143 patients with CYP2C9, CYP2C19 and CYP2D6 genotyping. Pharmacogenomics 2014;15(5):655–65.)*** ***Action: drug-drug-gene interactions added to text on page 8.*** 2. Need some explanation of the sentence [page 4, l 45], "non-interacting dynamically annotated visualization are more effective than [standard] alerts in reducing inappropriate imaging orders." There is a lot of jargon in this sentence that needs to be better explained. **Action: Re-written to say "Physicians and pharmacists describe alert fatigue and it has been demonstrated that information given to work within a physician's work-flow is more effective than alerts that result in changes to workflow, in reducing inappropriate orders for imaging."** 3. It would be helpful if Figure 2 was appended to include, after the 185 reports with complete data and 4 reports with partial data, in how many patients were the results relevant for improved patient care. The figure is distinct from how many patients had alleles affecting drug metabolism because some of those alleles would not be relevant for every patient. **We do not have this information as patients were not followed. We will be doing this in a future study. To gain ethics for this project we had to state in the consent form "You are also being invited to give permission for our research team to access your family physician's medical records to get further details about any medical or health conditions, medications prescribed, laboratory tests done for communication with our computer so that the recommendations for prescribing can be given to your Family Physician through your electronic health record. We will not store this information, when your prescription recommendations are completed all records of your identity will be erased from the processing system or rendered unreadable."** **Action: Added limitations section** 4. A final question of considerable importance for the reader who may chose to utilize such an approach, how much does it cost per patient to run this test panel? This is especially relevant since the authors state [p11, l 7] "Pharmacogenetic testing should be part of preventive medicine; if every person is tested prior to a need for medication, when the need for medication arises there would be no need to delay medication or give medication blindly whilst waiting for a test result." **Response: there are many companies on the market selling these tests and the costs vary widely depending on the jurisdiction. Ours was done in a research lab environment and included huge development costs and so is likely higher than the commercial rate. The estimated costs including personnel is in the range of $1,000 however this is based on estimates as many staff worked on overlapping areas of the project.**
Reviewer 2	Dr. Daniel Sitar
Institution	Dept. of Pharmacology and Therapeutics, University of Manitoba, Winnipeg, Man.
General comments (author response in bold)	1. You use MDSS throughout the manuscript without defining it. **In the introduction it says "Medication decision support systems (MDSS) need to be able to show not only other classes of drugs for that condition,..."** **Action: Added "A Medication Decision Support System (MDSS) is a health information technology system that is designed to provide health professionals with clinical decision support, that is, assistance with medication**

	decision-making tasks." 2. Although you indicate the study is registered with ClinicalTrials.gov and approved by a Research Ethics Board, you never state that the study volunteers provided signed informed consent prior to obtaining the DNA samples. **Action: Added to study design and participants "Study volunteers provided signed informed consent prior to giving samples."** 3. Statistics - Although you claim you calculated 95% CI for proportions, none of these analyses are included in the manuscript. **These are presented in Table 1, and in text e.g. The mean DNA concentration for all attempted extractions (n = 190) was 59.6 ng/µL (95% CI: 54.0 to 65.2). The mean 260/280 absorbance ratio of extracted DNA was 1.87 (95% CI, 1.84 to 1.91).** 4. You have no control group with which to compare your study data generated. You need to compare outcomes for drug therapy in this cohort with and without genetic testing. How is release of genetic data protected from access by employers and/or insurance companies? Why is the absence of a control group acceptable when you cite authority that indicates that other intervention types (newer technologies - bottom of p9 and top of p10) expected to improve outcomes of drug therapy in fact could not demonstrate such an outcome, even though an improvement was expected? **Based on this study we will be performing a properly powered stepped wedge study to compare patient outcomes, e.g. adverse drug reactions. With the novelty of the process it was necessary to perform a proof of concept study to start with and as stated in the manuscript "We used a prospective cohort study design. Due to the known association between HLA-B*58:01 and life-threatening SCARs (severe cutaneous adverse reactions), induced by allopurinol, it is not ethical to perform a randomised placebo controlled study when including the care of people with gout in a pharmacogenetic study." There is not space within the manuscript to give fine detail The Consent form stated: There are possible non-physical risks associated with taking part in this study. For example, disclosure of genetic or tissue marker research data could result in discrimination by employers or insurance providers toward you or your biological (blood) relatives..... Your confidentiality will be respected. However, research records and health or other source records identifying you may be inspected in the presence of the Investigator or his or her designate by representatives of Genome BC, and UBC Clinical Research Ethics Board for the purposes of monitoring the research. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law..... You will be assigned three unique study numbers as a participant in this study. The study numbers will not include any personal information that could identify you (e.g., it will not include your Personal Health Number, SIN, or your initials, etc.)..... Your IDs will be stored on the TreatGx computer held in the Department of Family Practice, UBC, only the computer, the Principal Investigator and the Research Coordinator will have access to this information.** 5. What does this study add that is not already demonstrated in references 25 - 30? *Previous studies have not been done in primary care, have only incorporated decision support as alerts, have been completed as single drug or single disease states. We are providing an MDSS integrated into primary care.* **Stated in manuscript as:** **"Many of the drugs studied in pharmacogenetic trials are part of the primary care drug formulary and used for common conditions. Pharmacogenetic panels are now available at an affordable price, and patients are requesting the tests and asking physicians to use these results in their care. Prior to implementing a primary care pharmacogenetic panel, it is necessary to consider the ability of healthcare providers to incorporate this information into current medication selection processes.... ".** **"....However, as yet the number of studies involving pharmacogenetic testing in primary care is very limited.[25] There has been some exploration of clinical decision support including genomics and providing genomic interactions as alerts,[26] and the largest study to date shows very significant reductions in hospitalization in those tested (71%) compared with those untested (36%).[27] Preliminary results from two clinical studies, one recruiting from a hospital system and the other from a long-term care facility, produced actionable genotypes for dose changes or contraindication for the patients' current medications in 24% and 50% of patients respectively.[28,29] Given our finding that 97% of patients had at least one actionable pharmacogenetic variant, and a 5000 patient US study where 96% had actionable pharmacogenetic variants,[30] it is likely that future Canadian studies will demonstrate similar numbers."**
Reviewer 3	Daniel Streetman PharmD MS
Institution	Wolters Kluwer Health, Hudson, OH
General comments	1. The stated end-points of this study concern the ability for users to gather usable DNA

(author response in bold)

samples, the ability to use the MDSS, and perceptions about the MDSS; however, the paper's primary focus seems to be limited to the value of and need for such a decision support system, which is something not at all reported on herein.
Action: Changed wording in introduction to "The value of an MDSS can be assessed once feasibility of all processes has been demonstrated.
We conducted a study to assess the DNA collection process, investigate a panel of pharmacogenetic tests relevant to primary care patients, and assess the use of a condition-based genetic-informed medication decision support system."
2. Conversely, the outcomes studied here get essentially no specific attention in the Introduction, and the results of this investigation receive little specific discussion in the Interpretation. How often have other primary care clinicians been able to collect a usable DNA sample? How many of the first try vs. requiring a second collection? How do these purity results compare to others collected in a similar manner? How do opinions here compare to other previously reported?
This has not been done through family physicians previously; there is nothing to compare with.
Action: Added "There are no equivalent studies published with data from family physician offices. However, in a pharmacy-based study (n=54) by Swen et al nine saliva samples (16.7%) contained too little DNA, we had one sample that contained too little DNA. { Swen JJ, van der Straaten T, Wessels JAM, et al. Feasibility of pharmacy-initiated pharmacogenetic screening for CYP2D6 and CYP2C19. European Journal of Clinical Pharmacology. 2012;68(4):363-370. doi:10.1007/s00228-011-1130-4.} We achieved call rates of 99% overall, Swen et al report call rates for CYP2D6 and CYP2C19 of 93.3% and 100% respectively. The conclusion of the Swen study is that pharmacy-initiated pharmacogenetic screening in primary care with respect to quality of DNA collection with saliva kits and genotyping is feasible for a primary care setting; we have exceeded their criteria."
3. How did you define "drugs commonly prescribed by family physicians?" Is this based on actual data or opinion? How many of top 100/200/etc. drugs, based on prescription volume or sales, were represented? Which specific 22 drugs were ultimately included?
The actual numbers of drugs sold and the various rankings is difficult to find reliable data for and varies by province according to reimbursement schemes. Although protein pump inhibitors, SSRI's, Codeine, and statins account for a high number of prescriptions it is difficult to be at all accurate and so this data is not included.
Action: Ten diseases were selected for the study. This was done by the research team and was based on a mixture of relevance to primary care, difficulty in identifying medication options, and having the potential for pharmacogenetic test use: gout, chronic obstructive pulmonary disease, migraine, depression, osteoarthritis, hypertension, hyperlipidemia, atrial fibrillation, osteoporosis and epilepsy. The ten conditions account for 15.0% of all primary care consultations, both medical and administrative{Britt:2015uw}.
New Table with Drugs included

Gene	Drugs	Population affected
CYP2C19	Citalopram, Escitalopram, Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Sertraline	27%
CYP2C19	Clopidogrel	34%
SLCO1B1	Increased myopathy risk prescribing Simvastatin	28%
CYP2C9	Celecoxib , Flurbiprofen	3%

CYP2C9	**Warfarin dosing**	**15%**
VKORC1	**Warfarin dosing**	**69%**
G6PD	**Sulfamethoxazole**	**0%**
HLA-B *58:01	**Allopurinol adverse drug events**	**4%**
CYP2D6	**Metoprolol, Oxycodone, Propafenone, Tramadol, Venlafaxine**	**51%**
CYP2D6	**Codeine**	**10%**

4. How was it determined which variants were clinically actionable, and thus included? Of similar studies published, most seem to come up with similar but different lists, indicating some lack of consensus in such listings.
"Single nucleotide polymorphisms (SNPs) and copy number variants (CNVs) were ranked according to clinical annotations primarily from PharmGKB,[15] the Clinical Pharmacogenetic Implementation Consortium (CPIC)[16] and the Royal Dutch Pharmaceutical Association review (DPWG)[5]. Based on information from the PharmaADME Consortium (www.PharmaADME.org), as well as guidelines and drug labels, a pharmacogenetic panel was selected. This panel included 33 of the top ranking genetic variants in the following genes: CY2C9, CYP2C19, CYP2D6, G6PD, HLA-B, SLC01B1 and VKORC1. Modifications were made to this list in light of new evidence of clinically relevant SNP tests and resulted in a customized panel of 24 genetic variants for 20 drugs."
Action: Text changed to "Evidence for genotype guided dosing recommendations was compiled for drugs commonly prescribed by family physicians. Single nucleotide polymorphisms (SNPs) and copy number variants (CNVs) were ranked according to clinical annotations primarily from PharmGKB,[15] the Clinical Pharmacogenetic Implementation Consortium (CPIC)[16] and the Royal Dutch Pharmaceutical Association review (DPWG)[5]. Based on information from the PharmaADME Consortium (www.PharmaADME.org), as well as guidelines and drug labels, a pharmacogenetic panel was selected. This panel included 33 of the top ranking genetic variants in the following genes: CY2C9, CYP2C19, CYP2D6, G6PD, HLA-B, SLC01B1 and VKORC1. For clinical use HLAB tag/SNPs could not be used and assay performance was low for 2 SNPs, resulting in a customized panel of 24 genetic variants for 22 drugs."
5. Does the MDSS consider and/or somehow display information about the quality of the supporting evidence? Many of the recommendation in CPIC and DPWG guidelines are relatively lacking in specific supporting data, even if reasonable based on evidence with similar drugs, etc. Similarly, even with strong evidence for a drug-gene association, the evidence showing a value of using PGx test results to guide prescribing decisions is lacking for most actionable variants.
The quality of evidence was not in this prototype version of the MDSS. We used PharmGKB Level 1A or 1B annotations, where there are clear drug dosing guidelines. Level 1A and 1B clinical annotations meet the highest levels of criteria and are manually curated by PharmGKB. Level 1A annotations contain a variant-drug combination in a CPIC or medical society endorsed PGx guideline, or, implemented at a PGRN site, or, in another major health system. Level 1B annotations contain a variant-drug combination where the preponderance of evidence shows an association. The association must be replicated in more than one cohort with significant p-values, and, preferably

	with a strong effect size. **Action: Added into sentence "iii) drug-genetic information from PharmGKB (Level 1A or 1B annotations where there were clear drug dosing guidelines) and other resources to form logic trees."** 6. For which 4 of the 15 studied conditions was the software not used? Which drugs and genotypes were used most often and which were little or never used? **As we did not keep any data or follow patients we do not know what medications were prescribed, the data we do have was which condition was accessed by the pharmacist or family physician.** **Action: Added "The MDSS was most frequently accessed for hyperlipidemia (n = 53) and hypertension (n=52), and not accessed for acute gout, migraine, migraine prophylaxis, and atrial fibrillation rate control."** 7. How does reference 18 support the statement that PGx can help prevent ADRs? There are data for specific use-cases if the intent is just to show potential, but is there any evidence to really support such a statement in a broader, system-wide sense? **Action: Changed, this should be references 4-6.**