Appendix 1 (as supplied by the authors): The Implementation of Pharmacogenomics into Primary Care Project.

Background

Each year in Canada, there are approximately 200,000 severe adverse drug events, claiming 10,000 to 22,000 lives, and costing $13.7 to $17.7 billion. In England, between 1999 and 2008, there were 557,978 adverse drug reaction-associated admissions, representing 0.9% of total hospital admissions. Over this period the annual number of ADRs increased by 76.8% (from 42,453 to 75,076), and in-hospital mortality rate increased by 10% (from 4.3% to 4.7%).{Wu TY, Jen MH, Bottle A, Molokhia M, Aylin P, Bell D, Majeed A. Ten-year trends in hospital admissions for adverse drug reactions in England 1999-2009. J R Soc Med. 2010 Jun;103(6):239-50. doi: 10.1258/jrsm.2010.100113. PubMed PMID:20513902; PubMed Central PMCID: PMC2878823}.

Physicians cannot predict whether a patient will gain the desired benefit from a prescribed medication or whether they will experience harmful side effects. This is particularly relevant in primary care, where Family Physicians (FPs) write the majority of prescriptions (≈20,000/year). Genetic tests may reduce this potential harm for many medications; however there is currently no way of incorporating genetic information into the routine FP prescribing processes. The need is for a decision support tool that uses genetic information to inform personalized drug prescribing.

The genomic approach to be used uses saliva to provide DNA for the identification of SNPs in the GenXys laboratory. These SNPs have been selected in reference to evidence of clinically actionable gene-drug associations. The SNP data will only be used to inform decisions about drug prescribing for diseases commonly seen and managed in primary care.

The overall project aim is to test a decision support tool, TreatGx, which creates a drug/dose recommendation, using SNP data and information in the family physician's or pharmacist's EMR, or entered directly by the physician, pharmacist or patient.

The objective of this study is to test TreatGx for feasibility with 200 patients in primary care

***Algorithm development*.** For each disease the algorithm development process begins with the identification of published epidemiological evidence for the management of the disease. The team uses a "level of evidence" approach starting with highest-level evidence such as high quality guidelines, and then moving onto systematic reviews, and if needed, information from randomised controlled trials. From this evidence, an algorithm framework is developed for the disease.

Most diseases have multiple drug options. The optimal drug(s), and drug dosage, for a person with the disease are determined by a set of factors including the clinical stage of the disease, the biophysical profile of the patient, concurrent medications, and the SNP status. Each algorithm may have separate stages reflecting the different decision stages over time for a disease, and the response of an individual to drugs. Dependent on the disease and the decision

stage a range of biophysical profile data (such as age, gender, kidney function etc), and the SNP test data are required for the algorithm to function optimally.

The algorithms result in a list of medication options based on the highest levels of evidence taking into account all the details of the individual person.

The group has already produced algorithms for gout (acute and chronic), chronic obstructive pulmonary disease (acute exacerbation and stable), depression, osteoarthritis, hypertension, hyperlipidemia, atrial fibrillation (rate control and anticoagulation), asthma, osteoporosis, migraine, diabetes, chronic heart failure, and epilepsy. These algorithms have proceeded through a peer review process with pharmacists and physicians.

SNP panel test selection. The TreatGx group has identified, from the Stanford-based PharmGKB and the Dutch Pharmaceutical Association, drugs that have evidence for undertaking a genetic test to inform dose as well as drug choice. Through this process, we produced a list of specific genetic tests with utility to enhance the rules for prescribing in primary care.
We are using a panel of genes involved in the absorption, distribution, metabolism and excretion (ADME) of drugs developed by the PharmaADME Consortium (http://www.pharmaadme.org/joomla/) and available from Life Technologies.

As the algorithms are developed, the genetic test information is incorporated into the decision tree. For example if a patient is diagnosed with moderate to severe depression and is not taking any other medication, the physician's choice would be between prescribing one of three drugs. The cheapest of these three drugs is Citalopram, making it the obvious choice for prescription. However, if the patient is a CYP2C19 ultrarapid metabolizer Citalopram would not be the best choice. The algorithm recommends another drug choice.

Automated TreatGx Decision Process.

TreatGx will be used in Family Physicians offices and a pharmacy

Methods

Study Design: Non-randomised study, using historical incidence as a control. It is considered unethical to randomise patients due to the known tight association between some genetic markers and severe adverse drug events, for example HLA-B*58:01 and the life threatening SCARs induced by allopurinol { Ko TM, Tsai CY, Chen SY, Chen KS, Yu KH, Chu CS, Huang CM, Wang CR, Weng CT, Yu CL, Hsieh SC, Tsai JC, Lai WT, Tsai WC, Yin GD, Ou TT, Cheng KH, Yen JH, Liou TL, Lin TH, Chen DY, Hsiao PJ, Weng MY, Chen YM, Chen CH, Liu MF, Yen HW, Lee JJ, Kuo MC, Wu CC, Hung SY, Luo SF, Yang YH, Chuang HP, Chou YC, Liao HT, Wang CW, Huang CL, Chang CS, Lee MT, Chen P, Wong CS, Chen CH, Wu JY, Chen YT, Shen CY; Taiwan Allopurinol-SCAR Consortium. Use of HLA-B*58:01 genotyping to prevent allopurinol induced severe cutaneous adverse reactions in Taiwan: national prospective cohort study. BMJ. 2015 Sep 23;351:h4848. doi: 10.1136/bmj.h4848. PubMed PMID: 26399967; PubMed Central PMCID: PMC4579807.}

Study Population: Five British Columbian family physicians that use electronic health records will be recruited through TELUS Health or OSCAR practices. Each physician will be asked to produce a list of patients based on the following inclusion criteria. Twenty five patients will be

recruited from each of the five family practices. One pharmacy will also be recruited; they will recruit 50 patients.

Inclusion Criteria:

Family physicians using electronic health records

Pharmacy using electronic health record

Adults at least 18 years of age that have a diagnosis of gout, chronic obstructive pulmonary disease, depression, osteoarthritis, hypertension, hyperlipidemia, atrial fibrillation, asthma, osteoporosis or/and epilepsy.

Exclusion Criteria: Pregnant or breast feeding

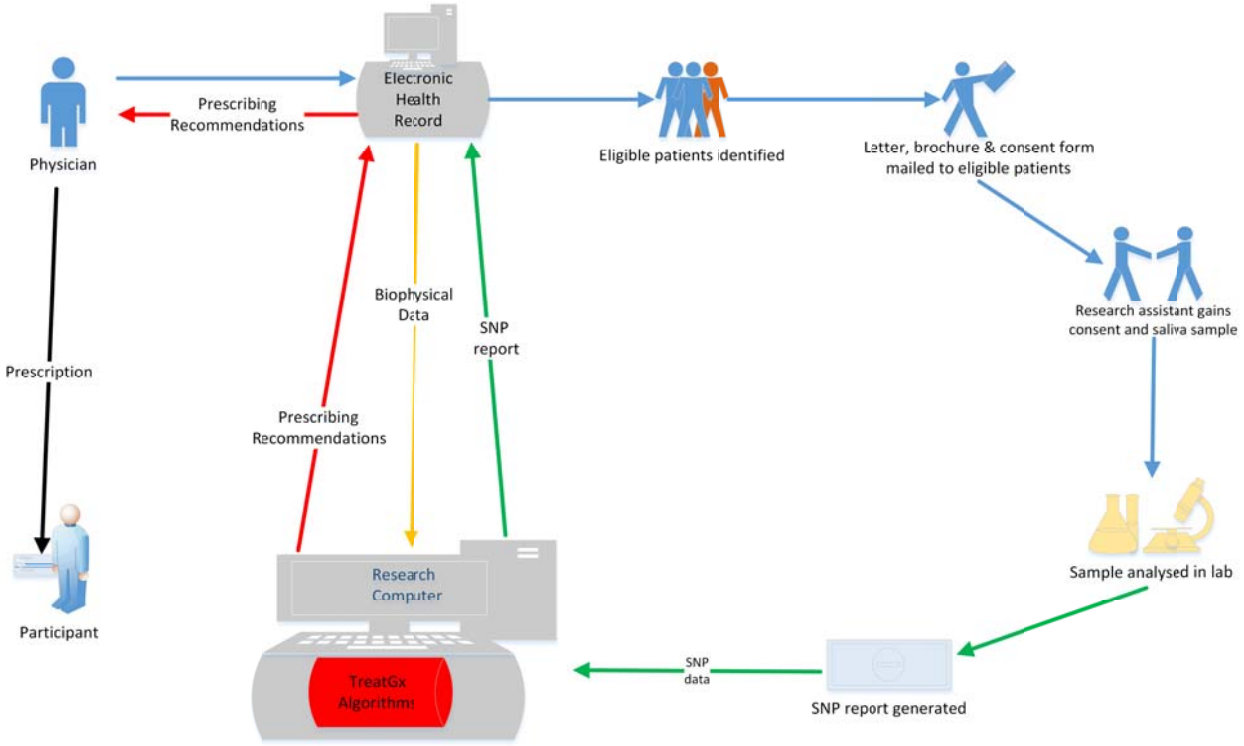
Outcomes: for this pilot study the outcomes are

- feasibility of recruitment,
- feasibility of obtaining SNP data,
- feasibility of integrating SNP data into EHR,
- use of decision support by family physicians and pharmacists,
- reported usability of tool, and
- estimated level of inappropriate prescribing.

We will track how many times the system is used, ask the family physicians, and pharmacists to give feedback on usability, record timing between receiving samples, time to the laboratory, time to analysis, and time to electronic record.

Procedures:

Family Physicians offices:



Appendix to: Dawes M, Aloise MN, Ang JS, et al. Introducing pharmacogenetic testing with clinical decision support into primary care: a feasibility study. *CMAJ Open* 2016. DOI:10.9778/cmajo.20160070.

Once TreatGx can communicate with the EHR, it will use the patient biophysical profile and SNP panel results, as recorded in the EHR, to produce prescribing recommendations either in real time, or at any time convenient to the clinician. Both of these 'timing' approaches have been suggested by clinically active Family Physicians. TreatGx decision support is designed for use by community-based Family Physicians working in office settings, as this is where most prescribing takes place.

TELUS Health will contact users of their electronic health records and Dr Dawes will contact OSCAR EMR users, sending an information leaflet to family physicians asking if they would like to participate in the project. The first five physicians to agree to participate will be selected and requested to complete the consent process.

Anonymized patient data from the EHR server will provide the information to the TreatGx algorithm program. TreatGx is run on a separate server to the EHR. The TreatGx program will send back to the EHR the personalized drug recommendation as well as providing the prescriber with the reasons for that recommendation and possible alternatives.

The five family physicians will be asked to run an algorithm in their records to generate a list of patients that are eligible to participate in the study. The family physician will check this list of patients against the inclusion criteria to confirm eligibility. The office administrator will generate labels for these patients that can be put on envelopes to be mailed to the eligible patients. These prepaid envelopes will contain a letter from the family physician, a brochure describing the study, and a consent form. The letter will state that unless the patient contacts the clinic saying that they do not want to be contacted they will be telephoned by a researcher in approximately two weeks' time. After two weeks, the medical office assistant will generate a list of patients with their telephone numbers for the research coordinator or assistant to make contact with the patients.

The research coordinator or assistant will call participants, discuss the study and, make an appointment for a research assistant to visit the participant at a time and place convenient to the participant. Participants will be requested not to eat, drink, smoke, chew gum, brush their teeth or use mouthwash for at least 30 minutes before attending the appointment as this would interfere with the saliva sample.

At the appointment the research assistant will check that the participant has read the consent form and will answer any questions. Once the consent form has been signed, the research assistant will ask the participant for a saliva sample. To give the sample participants will be asked to spit into a tube, it needs approximately two teaspoons of saliva to perform the test. The research assistant will attach a prefilled identification label to the sample and transport it to the laboratory. This identification label is a unique identifier for the laboratory. Giving the sample will take no more than five minutes. Thirty minutes has been suggested for the visit so the participant has time to read the consent form through with the research assistant and ask any additional questions.

The laboratory will analyze each sample using Quantum technology and transmit the SNP results to the research coordinator electronically. The research coordinator will upload the results into the TreatGx computer and send to the family physician. The transmission to the family physician will be in the same format as blood results.

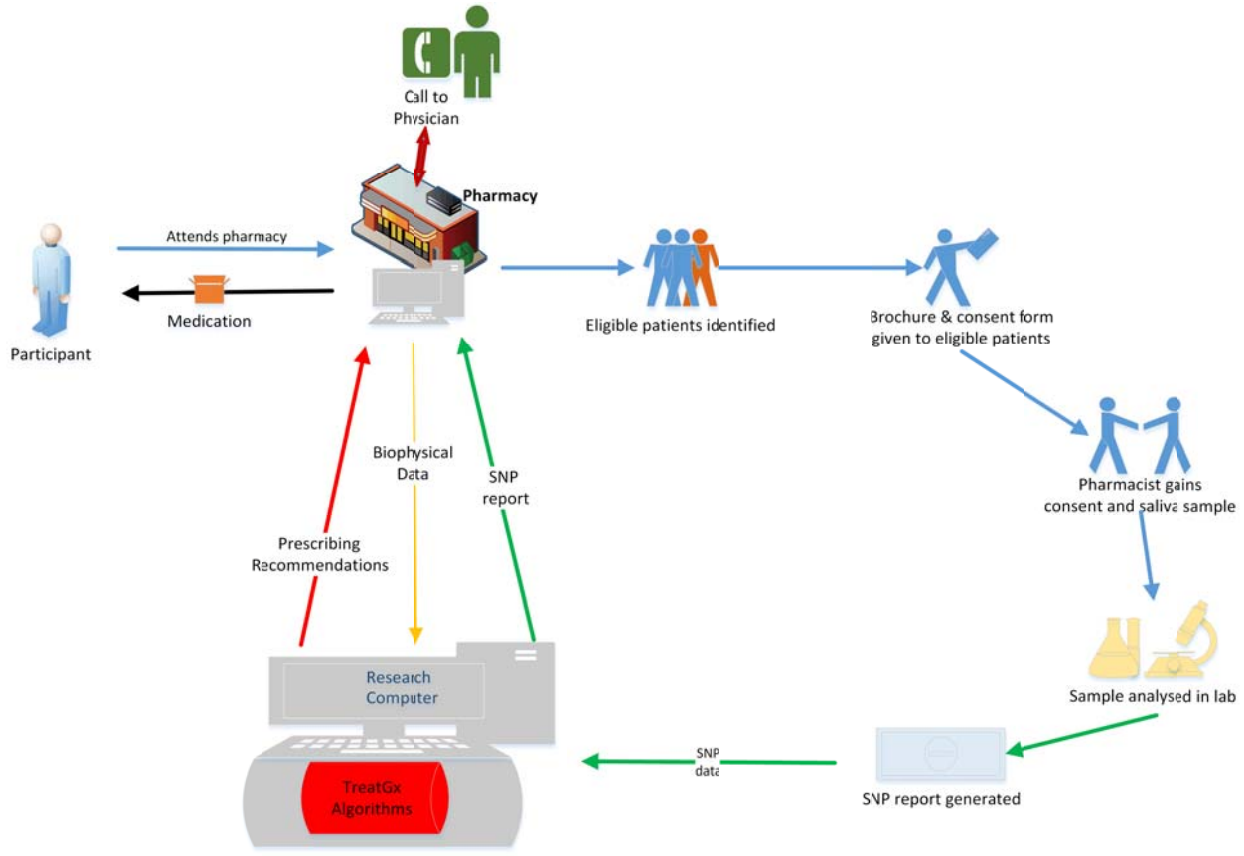
At the patient's next appointment with the Family Physician, TreatGx will be available for use through the electronic health record (EHR). When the physician enters TreatGx, information will be exchanged between the two servers enabling prescribing recommendations to appear on the physicians screen. Data from the EHR will not be stored on the TreatGx server. The physician will decide to use the recommendations or not and fill a prescription for the patient.

Pharmacies

The Peoples Pharmacy will participate in the study. A study representative will visit the pharmacy to discuss the consent form and study procedures with the pharmacists.

Once TreatGx can communicate with the pharmacy server, it will use the patient biophysical profile and SNP panel results, as recorded by the pharmacist, to produce prescribing recommendations in real time.

Anonymized patient data from the pharmacy server will provide the information to the TreatGx algorithm program. TreatGx is run on a separate server to the pharmacists. The program will send the pharmacist personalized drug recommendations as well as providing the pharmacy with the reasons for that recommendation and possible alternatives. If the suggestions are for a modification to the prescription the pharmacist will call the physician to consult.



The Peoples Pharmacy will recruit 50 participants. Eligible people filling a prescription in the pharmacy will be informed of the study by the pharmacist and given a brochure and consent

form. They will be advised to read all the information in their own time and ask any questions they have. If they want to join the study they will be asked to return to the pharmacy.

Once the consent form has been signed, the pharmacist will ask the participant for a saliva sample. To give the sample participants will be asked to spit into a tube, it needs approximately two teaspoons of saliva to perform the test. The pharmacist will attach a prefilled identification label to the sample and send it to the laboratory. This identification label is a unique identifier for the laboratory. Giving the sample will take no more than five minutes. Thirty minutes has been suggested for the visit so the participant has time to read the consent form through with the pharmacist and ask any additional questions.

The laboratory will analyze each sample using Life Technology Studios Quant technology and transmit the SNP results to the research coordinator electronically. The research coordinator will upload the results into the TreatGx computer and send to the pharmacy. The transmission to the pharmacy will be in the same format as blood results.

The pharmacist will link to the TreatGx server, information will be exchanged between the two servers enabling prescribing recommendations to appear on the pharmacists screen. Data from the pharmacist's server will not be stored on the TreatGx server. If the recommendation differs from the patients prescribed medication the pharmacist will contact the prescribing physician who will decide to use the recommendations or not.

Outcome Evaluation

Outcome	Measured by
1. Feasibility of recruitment	a) Number of family physicians and participants recruited b) Demographic details of family physicians
2. Feasibility of obtaining SNP data	a) Number of saliva samples analysed and reports generated. b) Time from giving sample to laboratory receiving. c) Time from laboratory receiving sample to generation of report.
3. Feasibility of integrating SNP data into EMR	a) Report from TELUS/OSCAR and pharmacy on entering SNP data into records. b) Time from generation of report to entry in EMR.
4. Use of decision support by FPs, patients and pharmacists	a) Number of times TreatGx accessed
5. Reported usability of tool	a) Family physician/pharmacists interviews
6. Estimated level of inappropriate prescribing	a) Family physician/pharmacists interviews

For timing measurement the research assistant and pharmacists will be asked to record and report to the study coordinator the time each sample was given. The laboratory will record and report the time when samples arrive at the laboratory, the sample starts analysis, a report is generated and the report is sent.

Family physicians and pharmacists will be asked to give feedback approximately three months after they have recruited their last patient. Family physicians and pharmacists will be asked how they would like to give their feedback. The options will be to send a written report, or an

interview by telephone or face-to-face with the study coordinator. Family physicians will be asked for simple demographic information; size of practice, geographical site (e.g. rural), number of family physicians in practice, age, number of years working as a family physician, and number of years working with an EMR. Demographic information is required to assess whether feasibility is generalizable.

Analysis

No complex analysis is planned as this is a feasibility study. Simple demographics, number counts, times, DNA quality, and statements from interviews will be reported. Data will be used to refine the processes and inform a bigger study.

The Steering Committee meets quarterly to oversee all project activities. The Scientific Committee meets monthly to oversee the technical development of the project and the trials. The scientific committee reports to the steering committee. Day-to-day management of the pilot trial is overseen by the Research Coordinator who reports to Dr. Dawes on a weekly basis.

Appendix to: Dawes M, Aloise MN, Ang JS, et al. Introducing pharmacogenetic testing with clinical decision support into primary care: a feasibility study. *CMAJ Open* 2016. DOI:10.9778/cmajo.20160070.