Title Page

Title: Introducing pharmacogenetic testing with clinical decision support into primary care: a cohort study.

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Abstract

Background: Inappropriate prescribing increases patient morbidity and death due to adverse drug events. The inclusion of genetic information into primary care medication practices is one solution. Our aim was to develop, and to determine the levels of use and usability of, a decision support tool which creates medication options adjusted for patient characteristics, drug-drug interactions, and pharmacogenetics.

Methods: We conducted a cohort study in six primary care settings, enrolling 191 adults with at least one of ten common diseases. Genotyping was undertaken, and genotypic data was linked to an evidence-based prescribing decision support system. The primary end point was ability to obtain and genotype samples. The secondary end points were yield and purity of DNA samples, ability to link results to decision support software, use of the decision support software, and feedback from users.

Results: Genotyping resulted in 189 (99%) patients with pharmacogenetic reports linked to the decision support program. We found 96.8% of samples had at least one actionable genotype for medications included in the decision support system. The medication support system was used by the physicians and pharmacists 236 times over a period of three months. These health professionals stated that the clinical decision support makes it easy to incorporate genetic information into decision-making and helps reduce inappropriate prescribing.

Interpretation: Physicians and pharmacists can collect saliva samples of sufficient quantity and quality for DNA extraction, purification and genotyping. Use of a clinical decision support system with integrated data from pharmacogenetic tests may result in safer prescribing practices.

Trial registration: The University of British Columbia Clinical Research Ethics Board approved the study (H14-02979), and it was registered at ClinicalTrials.gov (NCT02383290).

Introduction.

Drug-related adverse events in primary care are a significant and common cause of morbidity[1,2] with incidence rates as high as 25%.[3] There is high level evidence that pharmacogenetic testing is an effective method of reducing adverse drug events.[4-6] Results from a US cohort of 1143 patients experiencing adverse events indicate that a clinically significant 33% were due to drug-gene interactions or drug-drug-gene interactions.[7] Of the approximately four billion prescriptions filled in the United States in 2013, 18% had actionable pharmacogenetics.[8]

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.

Computerized order entry systems in electronic medical records, using drug database systems, enable the user to identify potential drug-drug and drug-condition reactions at the time of medication selection. Despite the introduction of these systems, and the increased use of electronic medical records, the prevalence of inappropriate prescriptions (35%) and high risk prescriptions (14%) remains very high.[10-12] Alert systems have proven ineffective at changing prescribing decisions.[13] Physicians and pharmacists describe alert fatigue, and it has been demonstrated that non-interrupting dynamically annotated visualization are more effective than alerts in reducing inappropriate imaging orders.[14] This may also be true for prescribing; avoiding alerts may lead to a reduction in inappropriate prescriptions. Medication decision support systems (MDSS) need to be able to show not only other classes of drugs for that condition, but assess whether the drug is safe and effective for the individual, taking into account other medications, diseases and the person's physical state.[9] We have developed a patient-centered MDSS that evaluates a list of potential drugs for a specific condition. The MDSS assesses the potential drug-

drug, drug-condition, drug-gene and drug-drug-gene interactions, and produces a list of drug options least likely to cause harm and most likely to be effective for that person.

We conducted a study to assess the DNA collection process, investigate a panel of pharmacogenetic tests relevant to primary care patients, and assess a condition-based genetic-informed medication decision support system.

Methods

Pharmacogenetic Panel Development

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*. 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 22 drugs.

TaqMan™ allelic discrimination qPCR assays were chosen based on the manufacturer guarantee of working assays on the Quant Studio™ 12K Flex Platform (Applied Biosystems). We developed a quality control and validation process to test the sensitivity and specificity of the assays. This included using Coriell Biorepository control samples, analyzing the results and comparing the experiment with known genotypes to determine feasibility and accuracy of the genetic test, and using sample replicates to assess concordance. In addition, a subset of experimentally determined genotypes was confirmed using Sanger sequencing. Once validated, these assays were incorporated onto our primary care pharmacogenetic panel.

A pharmacogenetic report was developed giving details on the method of testing, the genes tested, the drugs implicated, the alleles, and the predicted phenotype. Software was developed to transfer the genotype information into the MDSS.

Medication Decision Support Development

Ten common diseases were selected as being relevant to primary care and having the potential for pharmacogenetic test use: gout, chronic obstructive pulmonary disease, migraine, depression, osteoarthritis, hypertension, hyperlipidemia, atrial fibrillation, osteoporosis and epilepsy. As five of the diseases have two distinct therapeutic approaches, the ten diseases result in 15 “conditions”. For example, the therapeutic options are very different for a person with an acute flare-up of gout than a person in the chronic stages of gout. Having identified published epidemiological evidence for the management of the condition a team of pharmacists, physicians, and experts in evidence-informed healthcare used, i) the highest levels of evidence for treatment selection, ii) known drug-drug interactions from standard databases, published studies, and product monographs, and iii) drug-genetic information from PharmGKB and other resources to form logic trees. From the logic trees, we developed a set of rules based on factors that affect selection of optimal drug therapy for each condition, and these were programmed into the decision support tool.

The result of entering data into the MDSS is the generation of a list of drug options adjusted for the individual’s medical history, biophysical profile and genetic test results, as demonstrated in Figure 1.

Study Design and Participants

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 controlled study when including the care of people with gout in a pharmacogenetic study. We enrolled adults at least 18 years of age, who were not pregnant or breastfeeding and had a diagnosis of gout, chronic obstructive pulmonary

disease, migraine, depression, osteoarthritis, hypertension, hyperlipidemia, atrial fibrillation, osteoporosis and/or epilepsy. Family physicians and pharmacists recruited patients and obtained saliva samples.

Data Collection, DNA Isolation, Extraction and Genotyping

Patients gave saliva samples using the Oragene DNA collection kit (DNA Genotek) in the physician's office or pharmacy, and these were transported to the laboratory by research staff, mail or floatplane.

Genomic DNA was extracted using a magnetic-bead based extraction method (Ambion® MagMAX™, Applied Biosystems). Each sample was quantified with the Qubit 2.0 fluorometer (Thermofisher Scientific) and DNA quality was assessed using the 260nm and 280nm absorbance ratio (Pure DNA: 1.8-2.0, protein contamination: <1.8, RNA contamination: >2.0). SNP and CNV genotyping was carried out by qPCR on the QuantStudio™ 12K Flex System (Applied Biosystems). A genotype report was generated and sent to the MDSS, and a copy given to the physician/pharmacist.

Statistical Analysis

The primary end point was ability to obtain and genotype samples, determined by the number of samples received in the laboratory, and the number of genetic reports generated. Samples from all patients who entered the study were evaluated. The secondary end points were yield and purity of DNA samples, ability to link results to decision support software, and use of the MDSS. All samples were tracked for linkage to the MDSS, which recorded the number of times a physician/pharmacist entered the system and for how many patients they used decision support. DNA purity was determined by the 260/280 ratio with 1.8 to 2.0 taken as pure DNA. The physicians and pharmacists were asked for their opinions on usability and effect of the MDSS on their prescribing and advice to patients. For proportions the 95% confidence interval was calculated using the Wilson Score on Open-Epi v3.03.

Results

Two family practices on Vancouver Island, and three family practices and one pharmacy in Metro Vancouver, recruited and obtained saliva samples from a total of 191 patients. DNA was isolated from 190 samples and assessed for purity, prepared for analysis, and finally genotyped. The flow through the study is shown in Figure 2.

Of the initial saliva samples, 86.3% (164/190) were successfully genotyped after the first attempt, 7.4% (13/190) were genotyped after re-running the pharmacogenetic panel, and 1.1% (1/190) were genotyped after three or more attempts. 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).

A second saliva sample was collected from 10 of the 12 patients that could not be genotyped. This increased the overall success rate to 99% (189/190 patients), however four of the recollected samples only generated partial reports.

Of the 185 patients with complete reports, 96.8% had at least one actionable genotype for medications included in the MDSS. Single variants were seen in 24.3% of patients, 35.1% had two variants, and 37.3% had three or more of the variants tested. The complete list of variants is shown in Table 1.

The genetic results were linked directly into the MDSS software platform and presented to healthcare professionals in a report that included the method of testing, the drugs implicated and the predicted phenotype. The healthcare professional was able to log in to the system, select their patient and then select the relevant condition. Figure 1 shows how, after completing patient biophysical information, the software displays a list of medication options. The medications are selected and dose-adjusted based on evidence-based drug-drug, drug-condition, or drug-gene interactions within the program.

The physicians, pharmacists and support staff used the software to review the patients' therapy for one or more condition and then provided feedback about the process. The software was

used 236 times over a period of three months, for 11 of the 15 conditions, by the physicians and pharmacists. The frequency with which specific conditions were accessed was, as expected, in proportion to the most commonly seen primary care conditions. Comments from the health professionals fell into three distinct themes: i) The need for instructions on entering variables; ii) The belief that the system will help them to reduce inappropriate prescriptions; iii) The belief that the system successfully integrates the genetic information in a way that makes it easy to assimilate this information into their decision making.

Interpretation

The challenge of identifying the right medication for the right patient at the right time remains as hard today as it has ever been. The current situation is described as a cascade of failure[17] due in part to the problem of multimorbidity and polypharmacy. Pharmacogenetic testing for variants that are associated with alterations in drug response can help prevent adverse reactions,[18] but adds to the problem of increasing complexity in prescribing. The challenge for healthcare professionals is how we actually undertake the process of incorporating this information in the limited time available within a consultation given to deciding on, and writing a prescription.[19] Pre-emptive pharmacogenetic testing, ordered prior to the need for pharmacological prescription, may be one approach, but the need for some sort of system to help professionals use the genetic information is also necessary.[20] It has been suggested that to impact the level of utilization of pharmacogenetic test results, pharmacogenetic testing could be ordered by the pharmacist and incorporated into a medication therapy management session or comprehensive medication review[21]. We demonstrated that it is possible for both family physicians and pharmacists to obtain saliva samples from patients, send the samples to the laboratory, complete the biophysical and laboratory data needed for a MDSS, and take decisions based on individualized medication options.

The use of electronic medical records has increased over the last 10 years but has not been associated with a drop in adverse drug events.[2] The use of alerts within the EMR systems when

selecting a drug is not a successful strategy since they are ignored in 49% to 96% of cases,[22] and the alert system is unlikely to be the most effective intervention within the time constraints of normal family practice.[23] An alternative to alerts is to build a condition-based clinical decision support system, derived from the clinical guidelines for all conditions, that provides options which are safe and effective for that patient.[9] We built a system that starts with all the possible option pathways for treatment and results in a list of optimal, individualized drug therapy options. These drug options are already adjusted for renal and hepatic function, comorbidities, concomitant medications, and genetics. This is the first time a multi-drug, multi-condition approach has been used in primary care including both family physician offices and a pharmacy. We have demonstrated the achievability of recruitment of patients, obtaining of saliva samples, DNA extraction, genotyping, and the use of a MDSS to translate patient genotypes into condition-based medication options for the health professional and patient.

The list of drugs that have associated pharmacogenetic tests includes drugs used in many conditions seen and managed in primary care such as cardiovascular conditions, hyperlipidemia and depression.[24] 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. The high proportion of patients with actionable genotypes, coupled with the fact that 11% of Canadians aged 45 to 64, and 30% of seniors aged 65 to 79, take at least five

prescriptions drugs concurrently[31] indicates that pre-emptive administration of a pharmacogenetic test has enormous potential. 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.

The development of condition-based prescribing using an evidence-based approach has been discussed[32] but this is the first time it has been used for multiple-drugs and multiple-conditions in primary care. To our knowledge, our study is the first that successfully explores the use of condition-based medication decision support that also incorporates pharmacogenetic information in community primary care.

Conclusion

Within primary care, it is possible to collect saliva samples of sufficient quantity and quality for DNA extraction, purification and genotyping. These pharmacogenetic tests can be incorporated into a condition-based medication decision support tool that provides a list of dose-adjusted medication options which have been filtered for potential adverse drug reactions. The system was used extensively, indicating that use of a clinical decision support system with integrated data from pharmacogenetic tests may result in safer prescribing practices.

Table 1. Frequency of alleles and diplotypes for fully genotyped patients tested in primary care (n=185).

Gene	Alleles/ Diplotypes	Frequency of Alleles/ Diplotypes No. of patients	% (95%CI)	Phenotype
SLCO1B1 rs4149056	T/T	132	71 (64-77)	Normal function
	T/C	49	27 (21-33)	Intermediate function
	C/C	4	2 (0-4)	Low activity
G6PD rs5030868	C/C	185	100 (98-100)	Normal variant
	C/T	0	0 (0-2)	Variable activity
	T/T	0	0 (0-2)	Low activity
VKORC1 rs9923231	G/G	38	21(15-27)	Normal activity
	G/A	89	48 (41-55)	Intermediate activity
	A/A	58	31 (25-38)	Low activity
HLAB *58:01	*58:01 Negative	176	95 (91-97)	Normal
	*58:01 Positive	7	4 (2-8)	Increased hypersensitivity
	Undetermined	2	1 (0-4)	Unknown
CYP2C19	*1/*1	80	43 (36-50)	Extensive metabolizer
	*1/*2,*2/*17,*1/*4,*1/*8	55	30 (24-37)	Intermediate metabolizer
	*2/*2,*2/*3,*3/*3	8	4 (2-8)	Poor metabolizer
	*1/*17,*17/*17	42	23 (17-29)	Ultra-rapid metabolizer
CYP2C9	*1/*1,	118	64 (57-70)	Extensive metabolizer
	*1/*2,*1/*3,*2/*2,*2/*3	62	33 (27-41)	Intermediate metabolizer
	*3/*3	5	3 (1-6)	Poor metabolizer
CYP2D6 Codeine CPIC guidelines	*1/*1,*1,*2,*2/*2,*1/*10,(*10/*10)3N,(*2/*4)3N,*1/*17,*1/*3,*1/*4, *1/*5,*1/*41,*2/*10,*2/*4,*2/*5,*2/*9,*2/*41,*10/*10,*41/*41	148	80 (74-85)	Extensive metabolizer
	*3/*41,*3/*9,*4/*10,*4/*9,*4/*41,*5/*10,*5/*9	19	10 (7-15)	Intermediate metabolizer
	*3/*4,*4/*14A,*4/*4,*4/*5,*4/*6	13	7 (4-12)	Poor metabolizer
	(*1/*1)xN,(*1/*10)3N,(*1/*2)3N,(*2/*2)3N	5	3 (1-6)	Ultra-rapid metabolizer
CYP2D6 DPWG guidelines[¶]	*1/*1,*1,*2,*1/*10,*1/*17,*1/*41,*2/*2,*2/*10,*2/*41,*2/*9,(*1/*10)3N	94	51 (44-58)	Extensive metabolizer
	(*2/*4)3N,*1/*3,*1/*4,*1/*5,*2/*4,*2/*3,*10/*10,(*10/*10)3N, *2/*5,*41/*41,*3/*41,*3/*9,*4/*9,*4/*10,*4/*41,*5/*10,*5/*9	74	40 (33-47)	Intermediate metabolizer
	*3/*4,*4/*14A,*4/*4,*4/*5,*4/*6	13	7 (4-12)	Poor metabolizer
	(*1/*1)xN,(*1/*2)3N,(*2/*2)3N	4	2 (1-5)	Ultra-rapid metabolizer

[¶]Ambiguous genotypes DPWG guidelines CYP2D6 (*2/*4)3N and CPIC CYPD26 (*1/*10)3N were assigned the “worst-case” phenotype.

Figure 1. Example of Medication Decision Support System drug options for a 62-year-old patient with depression who is a CYP2C19 poor metabolizer

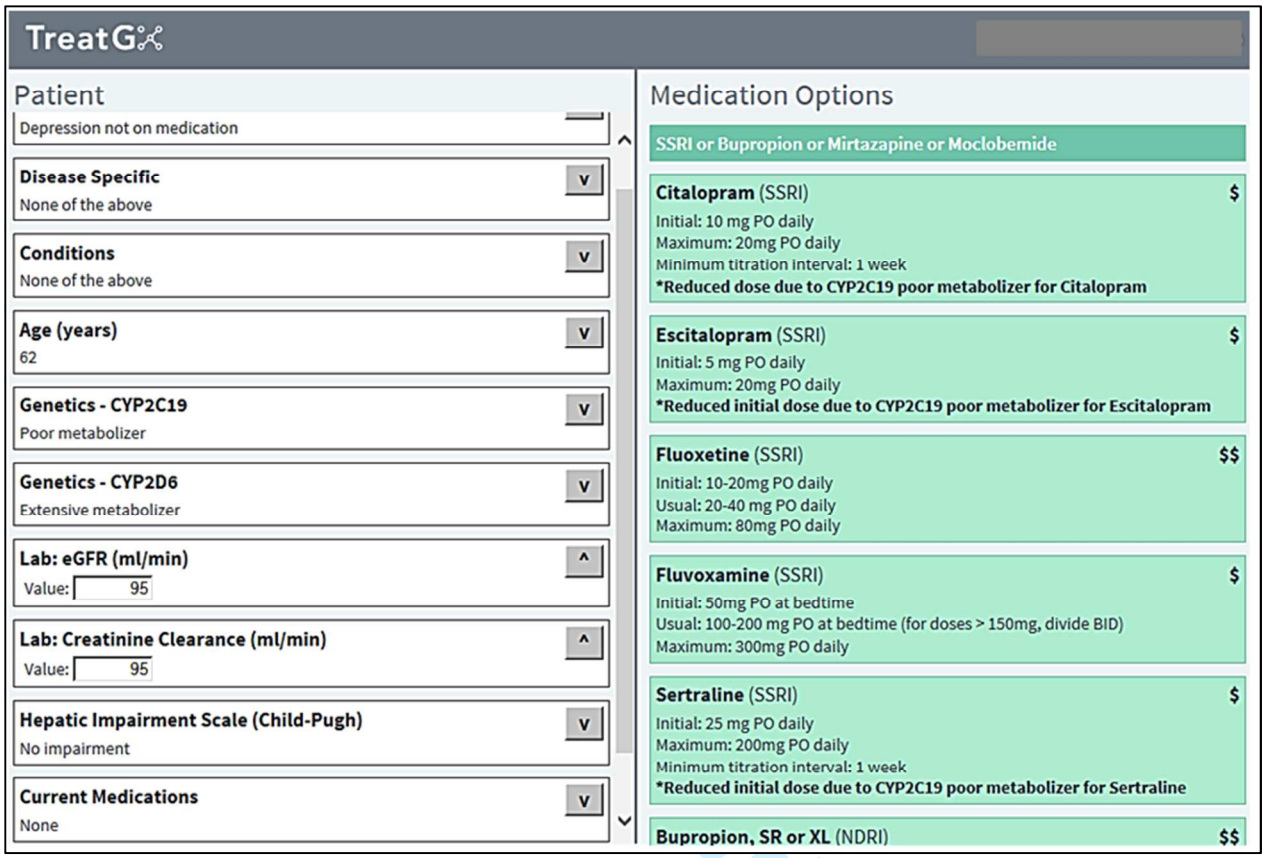
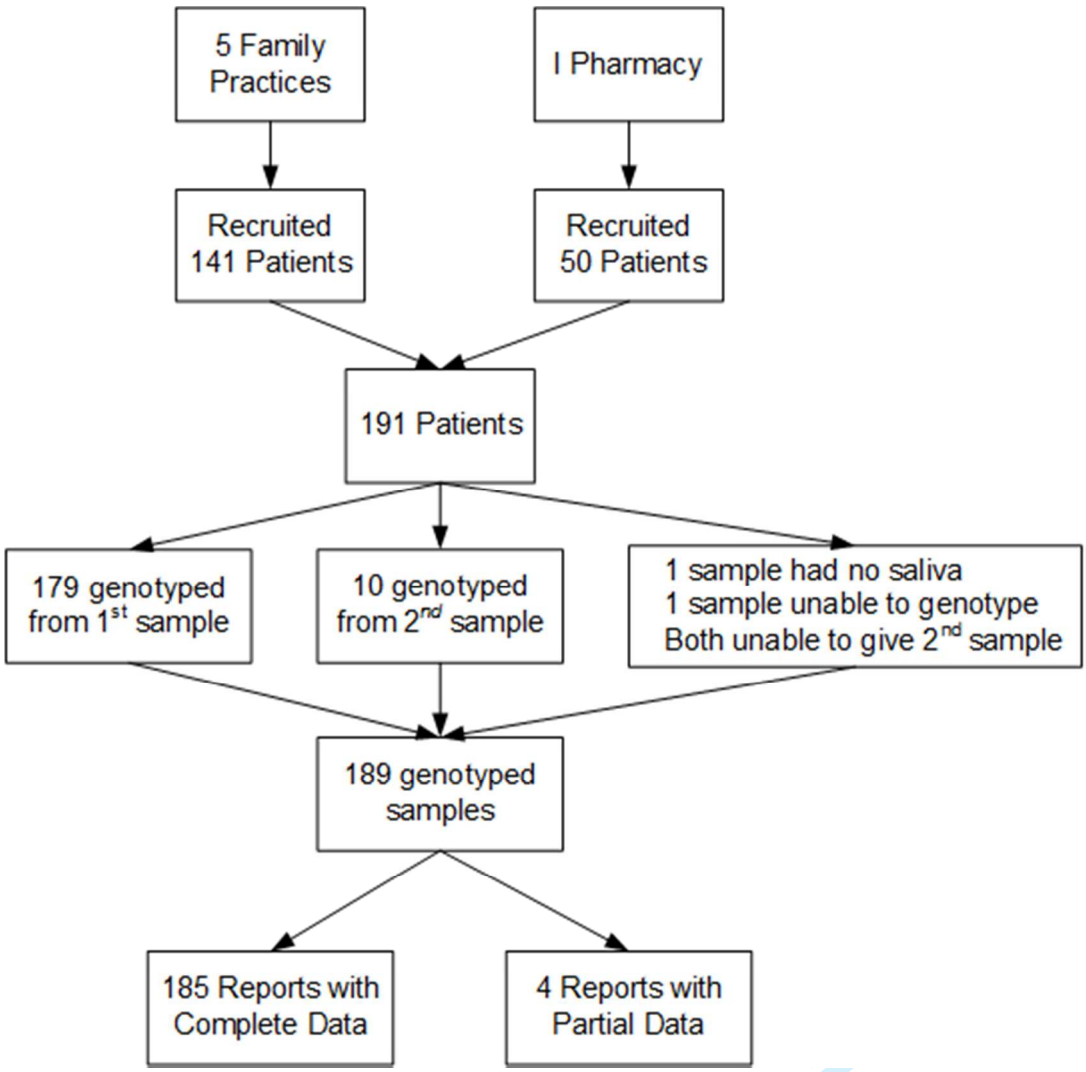


Figure 2. Study Flow



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