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Feasibility of using pharmacogenetic testing with Clinical Decision Support in private GP clinics in Singapore

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Background

About 1,700 private general practitioner (GP) clinics are providing 80% of the primary care services in Singapore. These GPs prescribe medications based on standard therapy and dosing guidelines. Medication change or dose modification takes place if the medication fails to work or produces side effects. This conventional "trial-and-error" process of drug optimization is associated with increased cost and exposes patients to risk of adverse drug reactions (ADRs). Pharmacogenetics (PGx) offers personalized medicine based on genetic profile for optimal medication choice, reducing unnecessary healthcare utilization, ADRs and polypharmacy.

Study Aims

i. To evaluate the adequacy of DNA yield from buccal samples collected by GP in a normal consultation.
ii. To estimate the number of cases in which the possession of PGx data together with a Clinical Decision Support System (CDSS) would alter the prescribing decisions for patients with common chronic disorders.

Methods

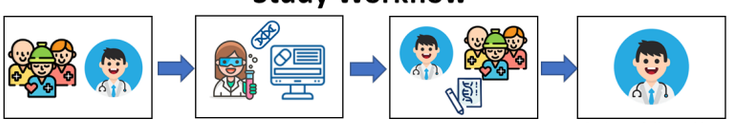
We used a prospective cohort study design, with seven GPs from six private practices in Singapore recruiting patients between October 2020 and March 2021. The patient eligibility criteria including the list of chronic conditions may be found in Table 1.

Prior to the start of patient recruitment, a pharmacogenetic panel was selected and actional pharmacogenetic variants were defined by Clinical Pharmacogenetics Implementation Consortium (CPIC), Dutch Pharmacogenetics Working Group (DPWG), or the U.S Food and Drug Administration (FDA). The definition of actionable variants and clinically actionable findings for this study can be found in Table 2.

Testing of the DNA was provided by the Genome Institute of Singapore using an Illumina array. Data on the selected PGx panel were incorporated into the Clinical Decision Support System (CDSS).

The feasibility and utilization of PGx testing, coupled with CDSS, in the management of patients with common chronic diseases was evaluated.

Study Workflow



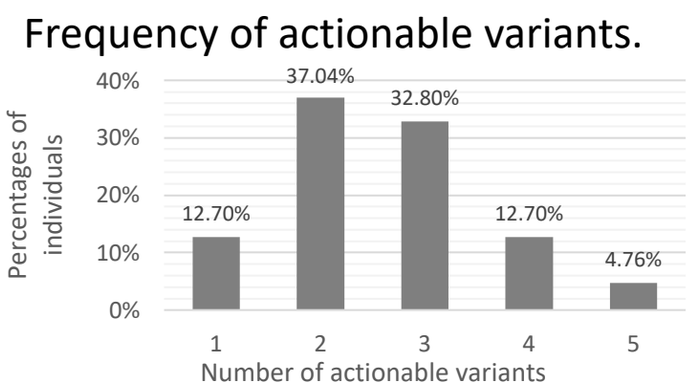
Results

Seven GPs from across different regions in Singapore (Northeast, East, Central and West) recruited 189 patients in this study. Buccal samples were collected by these GPs and the sampling success rate was 99.5% (188/189) from first attempt where samples were genotyped with sufficient DNA yield. For the sample yielding insufficient DNA, a second sample was successfully genotyped.

Baseline demographics showed that two thirds of our study patients had two or more chronic conditions listed in the inclusion criteria that required pharmacological treatment. The top 5 conditions were hypertension, hyperlipidemia, diabetes, gout and osteoarthritis.

We observed that 100% of our study population carry at least one actionable variant for medications included in the CDSS (Figure 1)

Genetic results were linked into the CDSS.



Twelve clinically actionable findings (6.3%) were identified by the GPs where eight of these resulted in either a change or partial change to patient's current medication while four had their medication unchanged due to patient preference in the absence of them experiencing any adverse effects.

Discussion & Conclusions

The frequency of genetic variants varies for each population. The frequency of alleles and diplotypes among primary care population in this study was different from the distribution seen in a Canadian population (Table 3).

Another study also demonstrated significant inter-population differences in drug response between Singaporeans (individuals of Chinese, Malay and Indian ancestry) and individuals of European ancestry†.

These data suggest that PGx testing within a routine consultation with a GP is feasible for chronic disease management in Singapore. The use of CDSS provides personalized medication options based on patient characteristics, drug-gene interactions (DGI) and PGx data. This is especially useful in cases of multimorbidity and polypharmacy which is common among patients with chronic conditions in an ageing population such as Singapore.

* Dawes, Martin et al., CMAJ Open, 2016.
† Brunham, LR et al., Pharmacogenomics J., 2014.

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Inclusion criteria for patient selection	Exclusion criteria for patient selection
Patients aged 21 years and above seeking for consultation for one or more of the following chronic conditions that require medication and regular follow up: 1. Cardiovascular diseases - atrial fibrillation (anticoagulation, rate control), heart failure (chronic, fluid retention), hyperlipidemia, hypertension, peripheral arterial disease, post MI. 2. Musculoskeletal disorders – gout (acute, chronic), osteoarthritis, osteoporosis, rheumatoid arthritis. 3. Pain management – fibromyalgia, lower back pain, neuropathic pain, trigeminal neuralgia. 4. Mental health disorders – anxiety (generalized anxiety disorder, social anxiety disorder), bipolar 1 disorder, depression, schizophrenia. 5. Neurological disorders – epilepsy, migraine (treatment, prophylaxis). 6. Respiratory disorders – asthma, chronic obstructive pulmonary disease (acute exacerbation, stable). 7. Endocrine – diabetes mellitus type 2 8. Gastrointestinal disorders – dyspepsia, prevention of NSAID-induced ulcers.	1. Patients who are not returning to the same GP clinic for long term follow up. 2. Patient who is participating in another research study. 3. Patient who is pregnant or breastfeeding.

Table 1. Eligibility criteria for patient selection.

Terms	Definition
Actionable Variants	Phenotype_CYP2C19_CPIC:IM Phenotype_CYP2C19_CPIC:PM Phenotype_CYP2C19_CPIC:PM,PT_CYP2C9_:IM Phenotype_CYP2C19_CPIC:PM,PT_CYP2C9_:NM Phenotype_CYP2C19_CPIC:RM Phenotype_CYP2C19_CPIC:UM Phenotype_CYP3A5_:IM Phenotype_CYP3A5_:NM Phenotype_SLCO1B1_:DF Phenotype_SLCO1B1_:PF Phenotype_TPMT_:IM,rs116855232:C/C Phenotype_TPMT_:NM,rs116855232:C/T Phenotype_TPMT_:NM,rs116855232:T/T rs9923231:A/A rs9923231:G/A CYP2C9:*1/*3 Phenotype_CYP2C9_:IM
Clinical Actionable Findings	Genetic variants that are relevant to a patient's current condition and warrant an alteration to the existing medication regimen.

Table 2. Definition of actionable variants and clinically actionable findings in the study.

Actionable variants	Counts
Phenotype_CYP2C19_CPIC:IM	79
Phenotype_CYP2C19_CPIC:PM	20
Phenotype_CYP2C19_CPIC:PM,PT_CYP2C9_:IM	2
Phenotype_CYP2C19_CPIC:PM,PT_CYP2C9_:NM	18
Phenotype_CYP2C19_CPIC:RM	2
Phenotype_CYP2C19_CPIC:UM	1
Phenotype_CYP3A5_:IM	74
Phenotype_CYP3A5_:NM	14
Phenotype_SLCO1B1_:DF	27
Phenotype_SLCO1B1_:PF	5
Phenotype_TPMT_:IM,rs116855232:C/C	7
Phenotype_TPMT_:NM,rs116855232:C/T	30
Phenotype_TPMT_:NM,rs116855232:T/T	1
rs9923231:A/A	142
rs9923231:G/A	38
CYP2C9:*1/*3	13
Phenotype_CYP2C9_:IM	18

Figure 1a. Frequency of actionable variants among study patients.

Number of Actionable Variants	Number of Individuals, N (%)
1	24 (12.70)
2	70 (37.04)
3	62 (32.80)
4	24 (12.70)
5	9 (4.76)

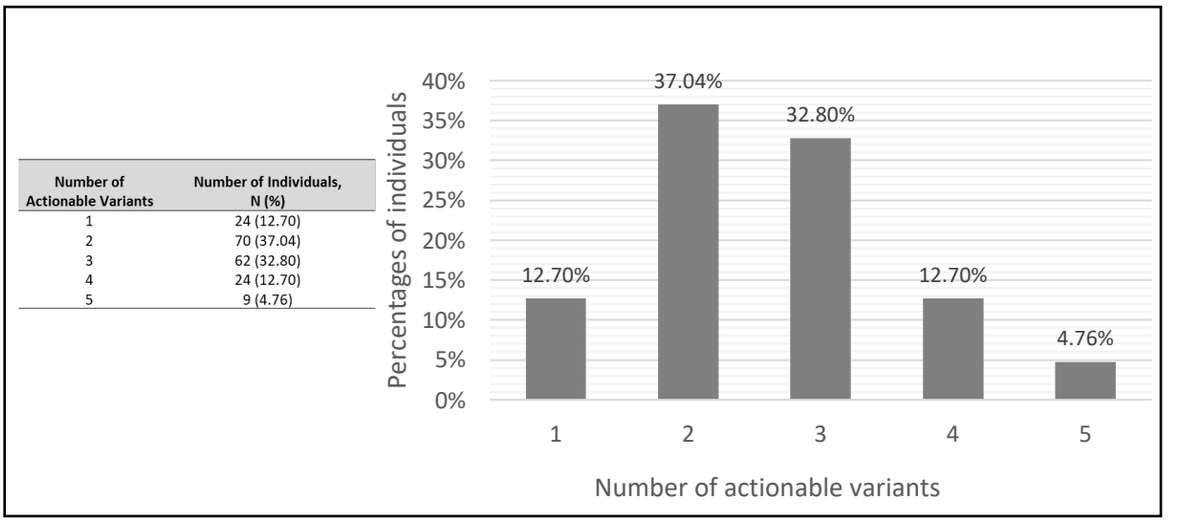

Figure 1b. The number of individuals with actionable variants.