The Use of Pharmacogenomic Testing to Predict Therapeutic Efficacy and Adverse Reactions

Wing Chan
Pharm.D. (Univ. of MN, USA), R.Ph. (USA & HK)

Chief Pharmacist
Prenetics Limited

Adjunct Assistant Professor
School of Pharmacy
The Chinese University of Hong Kong

wing@prenetics.com
Conflict of Interests Declaration

I am under full time employment by Prenetics, Limited as the Chief Pharmacist for the development of pharmacogenomic testing products and to provide interpretation of pharmacogenomic test results for clinical decision making.
Learning Objectives

• Define pharmacogenomics, its clinical applications and its impact on the future of healthcare

• Discuss how pharmacogenomic-guided therapy reduces the incidence of adverse drug reactions and provides benefits to patients

• Review the clinical practice guidelines and evidence-based research available to support the use of pharmacogenomics

• Describe the global and local trend in the implementation of pharmacogenomics into clinical practice

• Demonstrate the contributions and the role of pharmacists in implementing personalized and precision medicine
Pharmacogenomics is the study of how an individual’s genetic variation affect a person’s response to drugs.

Variations in pharmacokinetic genes can affect drug blood levels.

Variations in pharmacodynamic genes can affect drug action at its target.

- National Institutes of Health
Clinical Guidance – 196 Total Drugs

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source: www.pharmgkb.org/view/drug-labels.do
### Dosing Guidelines - CPIC

These dosing guidelines take into consideration patient genotype and have been published by the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Royal Dutch Association for the Advancement of Pharmacy - Pharmacogenomics Working Group (PCGx) (manually curated by PharmGKB), or other professional societies (manually curated by PharmGKB).

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Review of Ongoing Pharmacogenomic Research in the Local Population

• A Personalized Approach to Pain Medicine Through Determination of Genetic Polymorphisms in Hong Kong Chinese

• Combined CYP2C9 and VKORC1 Frequencies and the Impact of Warfarin Dosing in Asians (Oral presentation PO-132, CardioRhythm 2017)

• CYP2D6 Alleles, CNV and Tandem Repeats in the Asian Population (Abstract #1144W, the 66th Annual Meeting of the American Society of Human Genetics)

• Development of personalized medicine using pharmacogenomic testing to predict individual responses to cardiovascular drugs

• Frequencies of genetic variants in SLCO1B1 and ABCG2 which may influence statin responses and susceptibility to statin-induced myopathy in the East and Southeast Asia region (Abstract #AB19, East meets West Symposium 2016)

• Genetic variations of CYP2C19 and Clinical Outcomes in Post-Angioplasty ACS Patients Treated with Clopidogrel

• Pharmacogenomics of Drug Response in Type 2 Diabetes Mellitus

• Retrospective Pharmacogenomic Analysis of Drug Response to Psychiatric Medications and ACHEI in Elderly Patients

• The Effect of CYP2C9 Genetic Variants and NSAID-Related Gastrointestinal Bleeding
Review of Ongoing Pharmacogenomic Research in the Local Population

_CYP2D6_ Alleles, CNV and Tandem Repeats in the Asian Population
Chan W, Cheung PY, Li MS, Sundaram SK, Tomlinson B, Tzang CH
Abstract #1144W, the 66th Annual Meeting of the American Society of Human Genetics

- _CYP2D6_ is a clinically important drug-metabolizing enzyme within Cytochrome P450 (CYP450) superfamily

- _CYP2D6_ metabolizes approximately 20% of commonly prescribed medications currently available on the market including beta blockers, antiarrhythmics, antidepressants, antipsychotics and opioids

- It has been shown that patients with _CYP2D6_ variants have more ADR and cost an extra USD $4000-$6000/year to treat

- Our group provided an comprehensive analysis on different _CYP2D6_ alleles, specifically the occurrences of CNV and tandem repeats, in the Asian population
Review of Ongoing Pharmacogenomic Research in the Local Population

**CYP2D6 Alleles, CNV and Tandem Repeats in the Asian Population**
Chan W, Cheung PY, Li MS, Sundaram SK, Tomlinson B, Tzang CH
Abstract #1144W, the 66th Annual Meeting of the American Society of Human Genetics

- The largest Asian study to date in terms of sample size (800 unrelated individuals) for CYP2D6 genotyping
- Comprehensive analysis on different CYP2D6 alleles in the Asian population
- Duplication of CYP2D6 alleles observed in 10.4% of individuals; Only 2.4% of the duplications were of functional alleles (i.e. CYP2D6*1 and CYP2D6*2)
- CYP2D6*10-*36 tandem repeats arrangement is very common in the study population (observed frequency of 31.2%)

Overall frequencies of CYP2D6 phenotypes in the Asian population.

![Phenotype Frequencies Chart]
Review of Ongoing Pharmacogenomic Research in the Local Population

Frequencies of genetic variants in SLCO1B1 and ABCG2 which may influence statin responses and susceptibility to statin-induced myopathy in the East and Southeast Asia region
Chan W, Cheung PY, Li MS, Sundaram SK, Tomlinson B, Tzang CH
Abstract #AB19, East meets West Symposium 2016

- Genetic variations of SLCO1B1 resulted in a decreased function of the liver uptake transporter and has been used to predict an individual's risk for myopathy

- ABCG2 polymorphism produced efflux transporter with decreased activity leading to an increased plasma concentration and greater LDL cholesterol lowering effects

- This study provides important insights on the individual and combined frequency of SLCO1B1 and ABCG2 variations which are known to affect statin response and myopathy risk, in the Asian population
Review of Ongoing Pharmacogenomic Research in the Local Population

Frequencies of genetic variants in SLCO1B1 and ABCG2 which may influence statin responses and susceptibility to statin-induced myopathy in the East and Southeast Asia region

Chan W, Cheung PY, Li MS, Sundaram SK, Tomlinson B, Tzang CH

Abstract #AB19, East meets West Symposium 2016

- **SLCO1B1** and **ABCG2 421 C>A** polymorphisms have been shown to affect statin responses

- Close to one-fifth (20.9%) of Asian subjects with SLCO1B1 phenotypes for intermediate to high statin-induced myopathy risk

- 10.5% of subjects with reduced function alleles of both SLCO1B1 and ABCG2 genes

Distribution of individuals having zero, one, two and three or more SLCO1B1/ABCG2 risk alleles in 670 Asian subjects among the study population.
Review of Ongoing Pharmacogenomic Research in the Local Population

Combined *CYP2C9* and *VKORC1* Frequencies and the Impact of Warfarin Dosing in Asians
Chan W, Cheung PY, Li MS, Sundaram SK, Tomlinson B, Tzang CH
Oral presentation PO-132, CardioRhythm 2017

- Genetic variations of *CYP2C9/VKORC1* is one of the most studied area in Warfarin pharmacogenomics

- Adequate knowledge of the proportion of population that is impacted by the variants alleles of *CYP2C9* and *VKORC1* will also help to highlight the critical importance of personalization of warfarin treatment

- The present study is aimed to provide an overview on individual and combined frequencies of *CYP2C9* and *VKORC1* variants which are relevant for warfarin dosing in Asian individuals
Overview of combined frequencies of \textit{CYP2C9} and \textit{VKORC1} variants which are relevant for warfarin dosing

Over two-thirds of the subjects carry 2 or more risk alleles (i.e. \textit{CYP2C9*2}, \textit{CYP2C9*3} and \textit{VKORC1 -1639 A})

This information can be used to predict the dose of warfarin required or to identify subjects who may be more suitable for NOACs

Predicted warfarin daily dose (based on FDA dosing table) in mg/day, stratified by \textit{CYP2C9} and \textit{VKORC1-1639 G>A} polymorphisms in the 856 Asian subjects recruited in the present study.
A Personalized Approach to Pain Medicine Through Determination of Genetic Polymorphisms in Hong Kong Chinese
Choi SW, Cheung PY, Li MS, Sundaram SK, Tzang CH, Chan W

- As a proof of concept study, a cohort of patients with chronic, moderate to severe, non cancer pain were recruited

- Retrospective chart data review for medication history and clinical outcomes including adverse drug reactions and Numerical Rating Scale (NRS) for treatment effectiveness

- Ongoing study with preliminary analysis completed on the recruited subjects who are taking tramadol

- Based on PharmGKB database, SNPs with established clinical annotations relevant for tramadol responses such as CYP2D6, CYP2C9, CYP2C19, ABCB1 and UGT1A were considered for genotyping
A Personalized Approach to Pain Medicine Through Determination of Genetic Polymorphisms in Hong Kong Chinese
Choi SW, Cheung PY, Li MS, Sundaram SK, Tzang CH, Chan W

- To develop a combinatory pharmacogenomic model in predicting responses to chronic pain medications in the clinical significant population (n=200)
- The model is developed and tested based on the correlations between genotypes and clinical outcomes
- Significant improvement in prediction accuracy with combinatory model as compared to single gene (CYP2D6) model (85% vs 54%)

Predication Accuracy = 85%
\[ p\text{-value} < 0.0005 \]
Review of Ongoing Pharmacogenomic Research in the Local Population

Development of personalized medicine using pharmacogenomic testing to predict individual responses to cardiovascular drugs

Yan BP, Lee VWY, Cheung PY, Li MS, Sundaram SK, Tzang CH, Chan W
Project Reference: ITS/210/16FX, Innovation and Technology Fund, $2.8 million)

• Investigate the genetic profile of 500 ACS patients, with a target on the specific genes that are known to affect commonly prescribed cardiovascular drugs

• Prospectively observe the clinical outcomes of 500 ACS patient including adverse drug reactions and major adverse cardiovascular outcomes

• Analyze and reports on association between genetic profile, patient characteristics and clinical outcomes

• Develop a personalized therapeutic algorithms derived from correlations between genetic profile, patient characteristics and clinical outcomes to guide treatment decisions

• Evaluate the cost effectiveness of pharmacogenomic guided vs non-guided treatment in the study population
Clinical Practice Today in USA

Mayo Clinic
Rochester, Minnesota

Mount Sinai
New York City, New York

Cincinnati Children’s Hospital Medical Center
Cincinnati, Ohio

Brigham and Women’s Hospital
Boston, Massachusetts

Stanford University Medical Center

Center for Personalized Therapeutics—The University of Chicago
Chicago, Illinois

St. Jude Children’s Research Hospital
Memphis, Tennessee

Cleveland Clinic
Cleveland, Ohio

University of Maryland Medical Center and Baltimore Veterans Administration Medical Center
Baltimore, Maryland
Implementation of well-established pharmacogenomic genotypes into EHR

High Risk Gene/Drug

- CYP2C9/warfarin
- VKORC1/warfarin
- CYP2D6/codeine
- HLAB1502/carbamazepine
- CYP2D6/tricyclic antidepressants
- CYP2C19/tricyclic antidepressants
- CYP2D6/SSRIs
- CYP2C19/clopidogrel
- SLCO1B1/simvastatin
- CYP2D6/tramadol

source: https://emerge.mc.vanderbilt.edu/projects/emerge-pgx/
Example of the gene/drug alert on EHR

PROBLEM
This patient's CYP2C19 genotype is associated with very impaired metabolic activation of the prodrug clopidogrel (Plavix) and elevated risk for stent thrombosis or other cardiovascular events following PCI.

REASONS
Reduced clopidogrel activation in this genotype results in significantly reduced platelet inhibition, increased residual platelet aggregation, and decreased clopidogrel efficacy.

RECOMMENDATIONS – MODIFY TREATMENT BY CHOOSING ONE OF THE FOLLOWING:

(A) Prescribe prasugrel (EFFIENT) 10 mg daily
   - Contraindications: History of stroke or transient ischemic attack, active bleeding
   - Caution: Increased bleeding risk: Age > 75 years, Body weight < 60 kg

OR

(B) Prescribe ticagrelor (BRILINTA) 90mg twice daily
   - Contraindications: History of intracranial haemorrhage, active bleeding, severe hepatic impairment
   - Caution: Aspirin doses > 100 mg/day reduce ticagrelor effectiveness and should be avoided.

More information on clopidogrel and CYP2C19

For questions about this alert or the personalized medicine program, please contact: PMP.HELP@ctsi.ufl.edu or (352) 380-1441.

Last CYP2C19=*2/*2 on 6/1/2013

Pharmacists’ Role in the Implementation of Personalized Medicine Program

• Pharmacists are well positioned to implement clinical pharmacogenomics programs, with expertise in pharmacokinetics, pharmacodynamics, and patient care

• Transform pharmacists’ role from transitional dispensing behind the counter to a more clinically oriented practice

Crews et al., Am J Health Syst Pharm. 2011;68(2):143-150
ASHP Statement on Pharmacist’s Responsibilities in Clinical Pharmacogenomics

• Advocate for the rational and routine use of pharmacogenomic testing
• Provide test result interpretation and clinical guidance
• Optimize medication therapy based on pharmacogenomic test results
• Educate and provide information on the clinical application of pharmacogenomic to health professionals, patients, and members of the public
• Support and participate in research and networks that guide and accelerate the application of pharmacogenomics to clinical practice
Useful Resources for Pharmacogenomics

PharmGKB – Pharmacogenomics Knowledge Database
https://www.pharmgkb.org/index.jsp

CPIC Guidelines - Professional PGx Dosing Guideline Body
https://cpicpgx.org

dbSNP - Database for Single Nucleotide Polymorphisms

FDA Biomarker Table – PGx Information on Package Inserts
http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

CYP Nomenclature Database
http://www.cypalleles.ki.se
Summary

• Pharmacogenomics is the science that underpins the role of an individual’s genetic makeup to predict how well a drug works, as well as what side-effects are likely

• Potential benefits of Precision Medicine is to maximize therapeutic efficacy while avoiding adverse drug reactions

• Limitations:
  • Many genes likely involved in how someone reacts to a drug, making targeting different drugs very complex
  • Drug interactions with other drugs and environmental factors need to be determined before any conclusions made on genetic influence

• Pharmacists are well positioned to implement clinical pharmacogenomics programs, with the expertise in pharmacokinetics, pharmacodynamics and patient care
“Most medical treatments have been designed for the ‘average patient’. As a result of this ‘one-size-fits-all-approach,’ treatments can be very successful for some patients but not for others.”

THE WHITE HOUSE ON THE PRECISION MEDICINE INITIATIVE