



## The Pharmacogenomic Era in Asia: Potential Roles and Challenges for Asian Pharmacists

Yin-Fai Lee<sup>1</sup>, Ritchie Ching Chi Kwok<sup>2</sup>, Ian Chi Kei Wong<sup>2,3</sup> and Vivian Wai Yan Lui<sup>4\*</sup>

<sup>1</sup>School of Pharmacy, University of Bradford, Bradford BD7 1DP, UK

<sup>2</sup>Department of Pharmacology and Pharmacy, Li Ka Shing College, The University of Hong Kong, Hong Kong

<sup>3</sup>UCL School of Pharmacy, London WC1N 1AX, UK

<sup>4</sup>School of Biomedical Sciences, The Chinese University of Hong Kong, Hong Kong

### Abstract

Personalized medicine through Pharmacogenomics: choosing the right drug, and the right dose, for the right patients based on patient's genetic makeup-is gradually being realised in Western countries. Yet, the practice of pharmacogenomics in Asian countries lags behind that of the West, but the medical needs for pharmacogenomics are expected to surge as better patient care is demanded in Asia. As next-generation sequencing technology advances quickly, previous technical challenges for performing pharmacogenomic studies or practices in Asia have been mostly resolved. What is lacking in Asia is an effective model of community-wide pharmacogenomics. On the delivery front, pharmacists, the drug and dosing professionals, can potentially be the main healthcare providers for pharmacogenomic services in Asia. The first large "Genomics for Precision Drug Therapy in the Community Pharmacy" in Canada, which is close to its completion, has successfully identified community pharmacists as key contact professionals for smooth facilitation and implementation of pharmacogenomics for personalized medication. It is anticipated that Asian pharmacists, with appropriate training, can have the capacity to provide expert pharmacogenomic supports for both physicians and patients in Asia.

**Keywords:** Genetic biomarkers; Oncology; Pharmacogenetics; Genetic profiling

### Introduction

"Choosing the right drug, and the right dose, for the right patients" based on patient's genetic profile has become a key concept for patient care. Pharmacogenomics, the study of the effects of genetics on drug responses, is taking on a reality role in patient treatment in various part of the world. Accurate genetic profiling of patients to guide drug choice or drug dosing has benefited a sizeable number of patients in oncology, neurology and many other diseases. In the past decade, genetically-informed drug use has proven to result in significant improvements of clinical outcomes, as well as reduction of avoidable Adverse Drug Reactions (ADRs).

### Pharmacogenomic Drug Labelings for Over 150 Drugs

As of today, the US Food and Drug Administration (FDA) has identified more than 150 drugs with pharmacogenomics biomarkers for patient's drug response or safe drug use (<http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm>). These very informative pharmacogenomics biomarker labelings serve to remind health-care professionals on the use of these drugs in relation to particular genetic make-ups of patients. The genetic make-up of an individual can affect one's response to drug exposure and metabolism, risk for adverse side-effects, and most importantly, clinical responses. Often, these genetic-related outcomes are linked to the presence of genetic variants or genetic polymorphisms of drug targets, drug metabolizing enzymes, or other response-related disposition genes in the patients, thus making them distinct from the general population in terms of patient care and drug administration. Thus, special medical attentions are needed for these patients. A decade ago, due to the limited pharmacogenomics information and the scarcity of drugs requiring such a special genetic attention, the clinical use of pharmacogenomic tests in the community were also limited. However, the rapid expansion of gene-drug knowledge and increase in the number of drugs with "individualized" genetic indications have promoted and

generalized the use of pharmacogenomics in clinical management in Western countries. In the US, the FDA drug genetic biomarker drug list has detailed the pharmacogenomic-specific indications for various drugs used for cancers, diabetes, psychiatric conditions, cardiology, infection, etc. Besides, many common drugs for regular medical uses are also on the list, such as codeine, warfarin, celecoxib, etc. In fact, the Clinical Pharmacogenetics Implementation Consortium (CPIC) of the National Institutes of Health's Pharmacogenomics Research Network has developed gene-drug guidelines ([www.pharmgkb.org](http://www.pharmgkb.org)) on new developments relevant for clinicians and researchers. Recently, the European Medicines Agency (EMA) and Health Canada (Santé Canada) (HCSC) have issued similar pharmacogenomic guidelines and drug lists. It is important to note that, Japan, the first country in Asia, has also made these pharmacogenomics information available via the Pharmaceuticals and Medical Devices Agency (PMDA), Japan.

### Ethnic differences in pharmacogenetic variants distinguishes Asian populations

Increasing evidences reveal that the prevalence of pharmacogenetics variants in different ethnic groups can be significant (Table 1). Obviously, these ethnic differences will ultimately affect the practice of safe medication and effective drug use among patients of different ethnicity for certain drugs. For example, the *CYP2D6* gene encodes an

**\*Corresponding author:** Lui VVY, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, Tel: (852)-3943-3588; Fax: (852) 2603-5123; E-mail: [vlui002@cuhk.edu.hk](mailto:vlui002@cuhk.edu.hk)

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enzyme that breaks down many commonly used drugs in our body. Some drugs, such as tricyclic antidepressants (e.g. amitriptyline, nortriptyline) are metabolized to inactive forms for elimination by our body. However, ethnic genetic differences are widely recognized for this gene. Individuals harboring defective *CYP2D6* gene alleles are poor metabolizers of tricyclic antidepressants, and are prone to develop concentration-dependent adverse effects or even therapy failure [1]. The prevalence of *CYP2D6* poor metabolizer genetics is ~6-10% among Caucasians, and ~2% among Asians. In fact, *CYP2D6* genetic testing is considered medically necessary to guide patient treatment with amitriptyline, nortriptyline, and tetrabenazine, etc. Similarly, pharmacogenomic testing of *CYP2C9* and *VKORC1* gene alleles are also medically needed to predict responsiveness to anticoagulation therapy in patients using warfarin according to the US FDA pharmacogenomic information. *VKORC1* gene encodes the pharmacologic target of warfarin, vitamin K epoxide reductase, and its genetic variants can contribute to differences in warfarin sensitivity. Single nucleotide polymorphisms in the *VKORC1* gene (e.g., -1639G>A) are associated with variable warfarin dose requirements (e.g. the AA genotype is found in warfarin-sensitive patients). The allele frequencies for AA genotype (which will require a lower warfarin dose) is 14.2% in Caucasians as compared to 82.1% in Chinese [2]. In fact, it is recommended in the FDA approved drug label that *VKORC1* and *CYP2C9* genotype information, when available, shall be used in selection of both the initial and maintenance dose of warfarin. Similarly, genetic testing for the *CYP2C19* for poor or intermediate metabolizer genetics is considered medically necessary for patients with acute coronary syndrome (ACS) and those undergoing percutaneous coronary intervention with clopidogrel (an antiplatelet drug to inhibit blood clots). As high as 15-20% Asians are known to be poor metabolizers with no functional *CYP2C19* versus only 3-5% in Caucasians. It is recognized that Asian population requires special attention when clopidogrel is prescribed [3].

Another example is carbamazepine, an anticonvulsant and specific analgesic for trigeminal neuralgia. Carbamazepine has been found to be associated with serious and sometimes fatal dermatologic reactions, including Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson syndrome (SJS). Retrospective case-control studies have found that an inherited variant of the *HLA-B* gene, *HLA-B\*1502*, which is common in Chinese, is a marker for carbamazepine-induced SJS and TEN in

Han Chinese. The prevalence of *HLA-B\*1502* is >15% in Hong Kong, ~10% in Taiwan, but largely absent (0-1%) in Caucasians (FDA NDA 016608, from [www.accessdata.fda.gov/scripts/cder/daf/index.cfm](http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm)). Other examples include the use of codeine, an analgesic and cough suppressant, individuals with the ultra-rapid metabolizer genetics (e.g. *CYP2D6* gene duplications (\*1/\*1 × N or \*1/\*2 × N)) can cause life-threatening conditions or even deaths as they metabolize codeine rapidly into morphine. Such fast-metabolizer genetics of codeine occurs in 1-10% of Caucasians versus 0.5-1% in Chinese and Japanese (FDA NDA 206323). These are just a handful of examples of some drugs to be used with special attention based on ethnic differences. With more new drugs and more pharmacogenomic research on Asian populations, more and more clinically relevant gene-drug information will emerge.

As for oncology treatment, there are specific pharmacogenomic markers to be highlighted for Asians. According to the latest cancer statistics in China, lung cancer is the most common cancer, followed by cancers of the stomach, esophagus, liver, and colorectal [4]. For lung cancers, activating mutation of the *epidermal growth factor receptor* (*EGFR*) gene is a responder genotype for EGFR tyrosine kinase inhibitors (TKIs) which is enriched in Asian non-small cell lung cancer (NSCLC). NSCLC patients with *EGFR* activating mutations are highly responsive to EGFR TKIs (Table 1). As *EGFR* activating mutations can be as common as 50-60% of lung adenocarcinoma patients in Asia-Pacific versus only 12-13% in UK and the US [5,6], genetic testing for *EGFR* mutation in Asian lung cancer patients is almost essential prior to treatment selection. Such a current clinical practice in Asia was initiated by a Pan-Asia study showing marked improvements in progression-free survival (PFS) in advanced NSCLC patients with *EGFR* activating mutations [7]. Interestingly, for colon cancer, *BRAF*(V600E) activating mutation is a biomarker for poor prognosis, and the presence of *KRAS* mutations predict resistance to EGFR TKI in advanced cases. A recent study showed that Asian colorectal cancers are more likely to be *BRAF* wildtype and without *KRAS* mutations, implicating a significantly lower frequency of occurrence of a resistance genotype to EGFR TKI in Asian colorectal cancer patients [8]. As for other Asian-prevalent cancers, such as liver cancer [9], esophageal cancer [10], and nasopharyngeal cancer [11], the genomic findings have recently been revealed and it is anticipated that more pharmacogenomic biomarkers will be developed in the near future.

Drug <sup>A</sup>	Therapeutic Area <sup>A</sup>	Referenced Subgroup <sup>A</sup>	Prevalence
Codeine	Anesthesiology	<i>CYP2D6</i> Ultra-rapid metabolizers	more common in Caucasians (1-10%) and less in Chinese and Japanese (0.5-1%) <sup>B</sup> .
Warfarin	Cardiology or Hematology	<i>VKORC1</i> A allele carriers (e.g., -1639G>A)	Allele frequencies for AA genotype (lower warfarin dose requirement): 14.2% in Caucasians versus 82.1% in Chinese [2].
Amitriptyline	Psychiatry	<i>CYP2D6</i> poor metabolizers	~6-10% in Caucasians vs ~2% in Asians[1]
Clopidogrel	Cardiology	<i>CYP2C19</i> poor metabolizers	poor metabolizers: 3-5% in Caucasian vs 15-20% in Asians[3]
Carbamazepine	Neurology	<i>HLA-B*1502</i> allele carriers	>15% in Hong Kong, about 10% in Taiwan, but largely absent (0-1%) in Caucasians <sup>C</sup> .
Erlotinib	Oncology	<i>EGFR</i> exon 19 deletion or exon 21 substitution (L858R) positive	<i>EGFR</i> activating mutation frequencies: ~ 50-60% of NSCLC in Asia-Pacific versus only 12-13% in UK [5].
Irinotecan	Oncology	<i>UGT1A1*28</i> allele carriers	Allele frequencies for <i>UGT1A1</i> 7/7 genotype (high incidence of neutropenia) is 12-13% in Caucasians, 23% in Blacks and lower (2-8%) in Asians [2,12].

<sup>A</sup>AS in FDA; Table of pharmacogenomic biomarkers in drug labeling (<http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm>);

<sup>B</sup>FDA NDA 206323 from [www.accessdata.fda.gov/scripts/cder/daf/index.cfm](http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm);

<sup>C</sup>FDA NDA 016608 from [www.accessdata.fda.gov/scripts/cder/daf/index.cfm](http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm).

**Table 1:** Examples of drugs exhibiting ethnic differences in pharmacogenomic variants.

Immunotherapy is a very promising effective anticancer therapy, which sought to awaken the host's immune response to elicit specific anti-tumor activity against one's tumor. Many new humanized monoclonal antibodies or inhibitors against the Programmed cell death protein 1 (PD-1) or its ligand (PD-L1) have been developed recently. As far as pharmacogenomics is concerned, the use of the FDA approved anti-PD-1 antibody pembrolizumab for NSCLC, (as well as for head and neck cancer, and melanoma) is recommended as a first-line therapy for NSCLC tumors with wildtype *EGFR* or *ALK* genes. It should be noted that since *EGFR* mutations are more common in Asian NSCLC, the mutational status of *EGFR* (as well as *ALK*) should be determined before the use of pembrolizumab. Note that many additional inhibitors against other immune checkpoints or immune escape mechanisms are currently under development, and whether there are genetic components associated with responses or resistance to these new therapies remain to be determined.

Besides drug efficacy, some chemotherapy, such as Irinotecan, are also known to display a pharmacogenomic difference for its associated adverse drug reaction. For instance, the incidence of grade 4 neutropenia in patients who are homozygous for the *UGT1A1*\*28 allele (*UGT1A1* 7/7 genotype) has a 50% incidence of grade 4 neutropenia, versus 12.5% and 0% incidences in patients with heterozygous *UGT1A1* 6/7 genotype and homozygous wild-type allele (*UGT1A1* 6/6), respectively. This Irinotecan risk homozygous genotype (*UGT1A1* 7/7) varies among different ethnic groups. It occurs in 12-13% Caucasians, higher (23%) in Blacks and lower (2-8%) in Asians [2,12]. Thus, the preferred use or cautious use of cancer therapies can be guided by the pharmacogenomic profiles of patients.

### Current Status of Pharmacogenomic Practices in Asia

For over a decade, the distinct higher prevalence of *EGFR*-activating mutations in Asian NSCLC patients has unexpectedly catalysed the initial use of genetics to guide effective drug treatment of NSCLC in Asia. Now, *EGFR* genetic test has become a standard test upon the diagnosis of lung adenocarcinoma to guide drug choice in many parts in Asia. Some of these tests are funded by public hospitals in Asia. However, a decade has passed and challenges are emerging when pharmacogenomics demands on multiple diseases are rising in Asia. The current status in more medically advanced regions in Asia is that molecular tests which are critical for guiding treatments with well-proven clinical benefits are usually adopted (either in public or private settings). However, pharmacogenomic tests that will not directly guide treatments are less commonly used. For instance, pharmacogenomic tests, like *UGT1A1* test that are used for assessing the risk of drug toxicity are seldom used in Asia as it is generally accepted by clinicians that these tests can be easily replaced by intensive monitoring of side effects. The successful implementation of pharmacogenomic testing will require the availability and affordability of technologies for rapid and reliable genetic analysis, the availability of solid Gene-Drug knowledge, and most importantly, an effective model on how to run and implement pharmacogenomics in clinical and community settings. Recent advances in Western countries have resolved some of these technological challenges so that rapid and reliable pharmacogenomics testing, including the use of Next-Generation Sequencing (NGS) can be achieved in a relatively robust manner, even in Asia. Pharmacogenomic tests are becoming more affordable than ever as the actual cost of sequencing has dropped exponentially in the last 15 years from about 8000 US dollars per raw megabase of DNA sequence to about 0.01 US dollar in 2015. On the knowledge front, the world's Gene-Drug knowledge are growing exponentially as basic

and translational pharmacogenomic research data are accumulating. As mentioned above, over 150-200 drugs are already available with pharmacogenetic information for drug use as approved by main regulatory bodies in various parts of the world. Today, most of these technical challenges are being resolved in Western countries. Yet in Asia, it is clear that a large number of well-trained experts in NGS, and gene-drug knowledge, especially on those genetic information that are particularly relevant for Asian populations, are much needed in order to support a large population of Asian patients demanding pharmacogenomic care.

### Pharmacists in Pharmacogenomics

Both the Western world and Asia are facing the same challenge of "how to run pharmacogenomics with high practicality in the hospital or community settings?" Several survey studies were carried out in Western countries to investigate what models were the best for the implementation of pharmacogenomics for the community, and different models have been proposed [13,14]. In some of these early models, pharmacists, the recognized pharmacotherapy professional, have been proposed to provide and support the pharmacogenetics care with physicians. It is obvious that with the growing pharmacogenomic details on drug use and the growing number of drugs with pharmacogenomic and dosing indications, physicians alone cannot effectively bear the load for the community. On the other hand, pharmacists are well-trained drug experts and medical professionals who have long been involved in identifying potential adverse reactions, drug interactions and conduct direct patient counselling on drug use. In both the US and the UK, evolutions of healthcare and pharmacy practice have created opportunities for pharmacists to take on new roles and expand their services [15]. Contemporary pharmacy practice has evolved from one where the pharmacist primarily supervises medication distribution and counsels patients, to a more expanded clinical role in providing patient-centred medication therapy management, health improvement, and disease prevention services in a team-care setting [15-17]. It would only seem natural that pharmacy practice be further expanded to include pharmacogenomics service to meet the increasing patient demands on a more thorough understanding of gene-drug or dosing details. In fact, the National Genetics Education and Development Centre in the UK had held a meeting in collaboration with Royal Pharmaceutical Society to identify the role played by pharmacists as the provider of the pharmacogenetics service [18]. They have recognised the role of pharmacists in providing the pharmacogenetics care to the public. In addition, they also identified some additional educational needs in genetics/pharmacogenetics to allow pharmacists to fulfil this expert role adequately in the coming future. This can potentially be achieved through a pharmacogenetics inclusive curriculum during their professional training and continuing education of practising pharmacists.

In fact, in Canada (British Columbia), the first large "Genomics for Precision Drug Therapy in the Community Pharmacy" study, which primarily involves the community pharmacists as the patient-contact professionals to conduct pharmacogenomic tests in the community, is close to its completion soon. This large study involves thirty-three community pharmacies with practising pharmacists who are pharmacogenomically trained to educate, counsel and collect samples from community volunteered patients for direct pharmacogenomics testings. Post-sample collection, pharmacogenomic testing of 158 gene positions is performed at the University of British Columbia. This is the first, and the largest community pharmacogenomic implementation and feasibility study, which is focused on investigating the model

of provision of pharmacogenomics service through community pharmacies, where pharmacists are the main healthcare providers for this service. Upon determination of the genetic information of the patients, those patients with “flagged” genetic variants are recommended for therapy suggestions or modifications by the trained pharmacists. In the preliminary results, pharmacists indicated that patients were doing this pharmacogenomic testing mainly because of three reasons: ineffective current drug therapy, wanting to address an adverse drug reaction, and to guide the initiation of a therapy. Upon the pharmacogenomic testings, pharmacists had recommended change in drug therapy, modification of drug dosing, discontinuation of the current drug, as well as increased levels of monitoring of patients. Importantly, physicians showed positive feedbacks though detailed findings are anticipated to be reported likely this year ([www.bcpharmacy.ca/genome](http://www.bcpharmacy.ca/genome)).

In Asia, the Asian physician-based care model makes it a real challenge for efficient implementation of a wide range of pharmacogenomic services as compared to the Western team-care model for patient care. In order to run pharmacogenomics effectively in Asia under the physician-based care model, physicians will need to be trained extensively to make them familiarized with every pharmacogenomic detail of all old and new drugs. In theory, physicians alone may potentially fulfil this role. However, in Asia, with the large patient population and the extreme low physician to patient ratio (~only 1-1.9 physicians per thousand population vs. 3.3-3.7 physicians per thousand population in the US and the UK), the relatively short time of consultation in public hospital settings, and the often unilateral physician-patient communication among Asian physicians [19], detailed pharmacogenomics counselling delivered by physicians to patients is not ideal. This is further complicated by the ever-increasing number of drugs with pharmacogenomics guidelines, indications and ethnic-specific details. Although genetic counsellors have been proposed in a study to be co-provider of this pharmacogenomic service alongside pharmacists in the US [13], the very low number of genetic counsellors in Asia makes this an unlikely option. As suggested by the emerging models in Canada and the UK, pharmacists, with some pharmacogenomic training, can effectively take up a healthcare professional role and provide a large workforce to provide pharmacogenetics care with professional counselling to the patients and public in Asia.

## Conclusion

Currently, pharmacists' role in Asia is mainly drug distribution, and clinical pharmacy is in its early stage of development, particularly in the community setting. Asian pharmacists, with appropriate pharmacogenomic training, can have the capacity to provide pharmacogenomic supports to physicians and patients provide counselling, as well as professional drug use or dosing advices. Therefore, it is strategically important to expand pharmacy education to ensure appropriate undergraduate and post-graduate training in pharmacogenomics in Asian countries to meet the upcoming pharmacogenomic demands in Asia. Furthermore, with the currently noted ethnic differences in many pharmacogenetic variants for various medications, Asian pharmacists and pharmacy researchers are uniquely posed to lead or be involved in Asian population-based pharmacogenomic studies to discover new Asian-prevalent pharmacogenetics variants to improve patient care in this part of the world. Lastly, an Asian network, similar to that of the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) efforts may identify new predictive genomic biomarkers for severe ADRs among Asians [20].

## Conflict of Interest

VWY served as a scientific consultant for Novartis Pharmaceuticals (HK) Limited. RCK serves as the Chief Pharmacist of the Hong Kong Integrated Oncology Center.

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