SHORT COMMUNICATION

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Pharmacogenetic Risk for Adverse Reactions to Irinotecan in the Major Ethnic Populations of Singapore

Regulatory Evaluation by the Health Sciences Authority

Cynthia Sung, Pui Ling Lee, Liesbet L. Tan and *Dorothy S.L. Toh*

Health Products Regulation Group, Health Sciences Authority, Singapore

Abstract

Background: For genetic polymorphisms known to alter drug effect or safety, regulatory authorities can tap into population genomic databases and other sources of allele and genotype distribution data to make a more informed decision about the anticipated impact of such variants on the main ethnic groups in a country's population.

Objective: The aim of this short communication is to describe how the Singapore Health Sciences Authority (HSA) made use of allele and genotype distributions in the main ethnic groups in Singapore (Chinese, Malay, Indian) and population genetic tools to compare with North American Caucasians and Japanese.

Methods: Published papers and publicly accessible genomic databases were searched up to August 2009 to obtain allele and genotype frequencies for *UGT1A1*6 and *28,* two common variants of *UGT1A1*, a gene that encodes for a key enzyme in the pathway of irinotecan metabolism. These variants are associated with greater risk of serious toxicity.

Results: In Singapore, the combined prevalence of three high-risk genotypes, *UGT1A1*6/*6, *6/*28 and *28/*28*, is 9.7% in Chinese, 5.0% in Malays and 18.7% in Indians, compared with 11.5% in North American Caucasians and 8.1% in Japanese. Indians are at an elevated risk of irinotecan-induced neutropenia associated with *UGT1A1*28* compared with Chinese and Japanese, and at an even higher risk compared with North American Caucasians. On the other hand, Chinese and Japanese are at an elevated risk of irinotecan-induced neutropenia associated with *UGT1A1*6* relative to Indians in Singapore or North American Caucasians. Population genotype data were the basis for the HSA to request revision of the package insert from manufacturers of irinotecan products. Moreover, the data provided the impetus for the HSA to publicize the availability of *UGT1A1* genetic testing at the National Cancer Centre.

Conclusion: With the growing volume of genomic data and pharmacogenomic associations, a regulatory authority is now able to more readily utilize population genetic information and tools to supplement evaluations of drug products pertinent to the country's ethnic demography.

Background

With the rapidly increasing data on genetic variation among different populations, and identification and characterization of single nucleotide polymorphisms (SNPs), the opportunity exists to examine and compare variations in allele and genotype frequencies for the population at SNPs that alter the function or expression of the gene product. The information may be used to determine whether a particular population is or is not likely to have the same benefit-risk profile as another for which safety and effectiveness were established. The Health Sciences Authority (HSA) in Singapore has considered variations in its three major ethnic groups – Chinese, Malay and Indian, representing 74.7%, 13.4% and 9.2% of the resident population, respectively[1] – in evaluating the potential impact of functionally important pharmacogenetic variants.

Irinotecan is registered in Singapore for the treatment of patients with advanced colorectal cancer. Combination therapy of irinotecan with fluorouracil and folinic acid (leucovorin), in such regimens as FOLFIRI, is first-line treatment for this disease. Irinotecan is also used as a single agent in patients who have not responded to an established fluorouracil-containing treatment regimen. Common adverse events associated with irinotecan are diarrhoea, vomiting, nausea and neutropenia. Irinotecan-induced neutropenia can be severe, occasionally leading to hospitalization because of a significant risk of contracting life-threatening infections.

Irinotecan is converted in the body to a metabolite called SN-38, which is 200-fold more potent than irinotecan itself.[2] SN-38 is inactivated primarily by the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), which glucuronidates SN-38 to an inactive metabolite, SN-38G (figure 1). UGT1A1 is the same enzyme that mediates bilirubin conjugation. Glucuronidating activity is reduced when variants of the *UGT1A1* gene, *UGT1A1*28* or *UGT1A1*6,* are present. *UGT1A1*28* contains seven, rather than six, TA repeats in the *UGT1A1* promoter region and reduces enzyme expression; *UGT1A1*6* represents a nucleotide change from G to A that causes an amino acid change from glycine to arginine (211G>A) and lowers the enzyme's activity.[3] It is also the same mutation implicated in Gilbert's syndrome.[4] In general, patients with either of these two variants have higher blood levels of SN-38 after receiving the same dose of irinotecan.[5,6] Polymorphisms in other genes encoding drug metabolizing enzymes and transporters (e.g. *UGT1A9, ABCB1, ABCG2, ABCC2* and *SLCO1B1*) may also contribute to variation in irinotecan and SN-38 pharmacokinetics and the severity of neutropenia,[6-13] but the evidence for these other genes is considerably less well developed than for *UGT1A1*.[5,11,14-20]

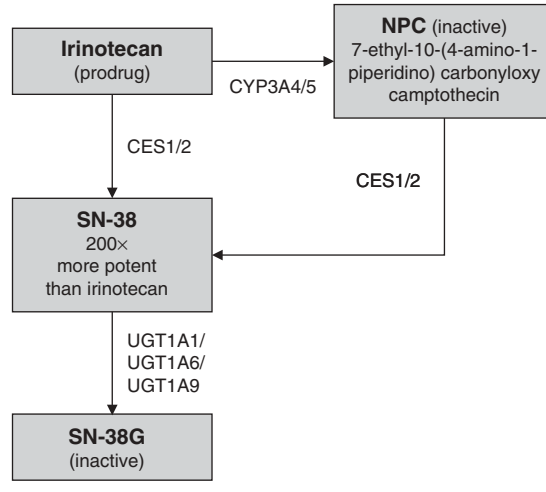

Fig. 1. Part of the complex metabolic pathway of irinotecan. CYP-3A4/5 refers to cytochrome P450 3A4 and 3A5. CES1/2 refers to carboxylesterases 1 and 2. UGT1A1 is the main enzyme that catalyzes the conversion of SN-38 to SN-38G (modified with permission from PharmGKB and Stanford University).[3]

In 2005, the US FDA amended the product label for Camptosar® (irinotecan hydrochloride) to warn of an increased risk of severe neutropenia among patients who are homozygous for *UGT1A1*28*. Dose reduction in such patients was also recommended.[21] The FDA, in consultation with the Advisory Committee for Pharmaceutical Science Clinical Pharmacology Subcommittee, reached this decision after reviewing data from several clinical trials that supported the conclusion of a greater risk of grade 3 or 4 neutropenia in patients homozygous for *UGT1A1*28*.[5,14,15] Their analysis also showed a correlation between plasma concentrations of SN-38 and the probability of experiencing severe neutropenia.[22] A small study of 45 patients conducted at the National Cancer Centre (NCC) of Singapore in which 15 were *UGT1A1*28* heterozygotes and none were homozygotes found no association with grade 4 neutropenia.[6] On the other hand, a meta-analysis of 9 studies and 821 subjects from North America and Europe, published in 2007, confirmed a significant association between the *UGT1A1*28/*28* genotype and severe neutropenia at doses >150 mg/m^2, but found no association at lower doses (100–125 mg/m^2).[23] A clinical study from Taiwan in 2008 (128 subjects) demonstrated that patients who were either heterozygous or homozygous for *UGT1A1*28* (15.6% and 4.7% of the study population, respectively) had a higher rate of neutropenic fever and grade 3 or 4 neutropenia[19] on a chemotherapy regimen containing irinotecan 180 mg/m^2. Other evidence is accruing, however, that rather than reduce the dose for *UGT1A1*28* homozygotes, it may be more appropriate to increase the dose in those who have only one or no copy of *UGT1A1*28* in order to achieve a better response rate.[24]

In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) also examined the evidence for an association between *UGT1A1* variants and neutropenia. The *UGT1A1*28* variant is much less common in Japanese compared with Caucasians (figure 2). On the other hand, *UGT1A1*6* is not uncommon in Japanese, yet appears to be absent in Caucasians (figure 3). Clinical data obtained in Japanese patients who were administered irinotecan doses ranging from 50 mg/m^2 to 180 mg/m^2 demonstrated that patients who were homozygous for

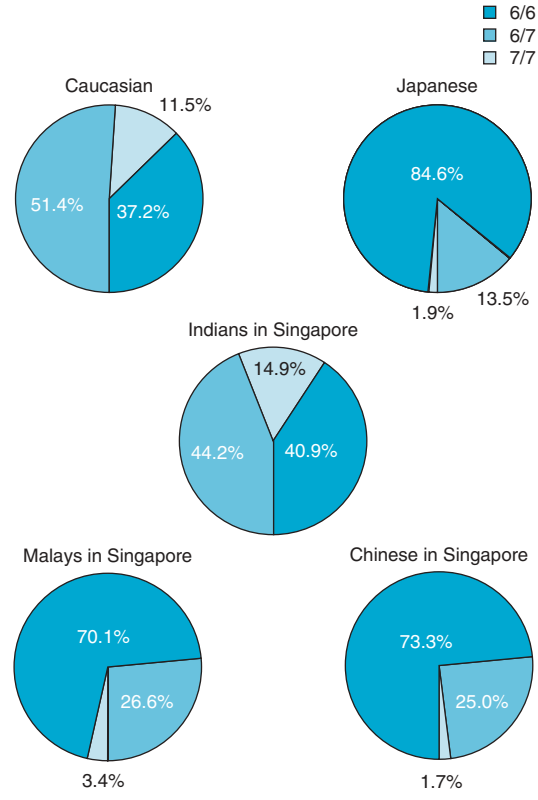

Fig. 2. Genotype distribution of *UGT1A1*28*.

*UGT1A1*6* or *UGT1A1*28*, or who were double heterozygotes (**6/*28*) had a lower ability to inactivate SN-38.[25,26] Furthermore, the rate of grade 3 or 4 neutropenia was 80% in **6/*6, *28/*28* or **6/*28*, 24% for *UGT1A1*6* or *UGT1A1*28* heterozygotes, and 14% without either *UGT1A1*6* or *UGT1A1*28*. In 2008, the PMDA updated its product label for irinotecan to alert prescribers of the association between an increased risk of serious adverse events and *UGT1A1*6*6, *6/*28* and **28/*28* variants.[27] The study conducted at the NCC of Singapore[6] reported an increased susceptibility for grade 4 neutropenia among carriers of at least one *UGT1A1*6* allele compared with those with the reference genotype, but the result did not reach statistical significance, possibly due to the small size of the study (n = 45).

Here we describe how the HSA made use of allele and genotype distributions in *UGT1A1* among

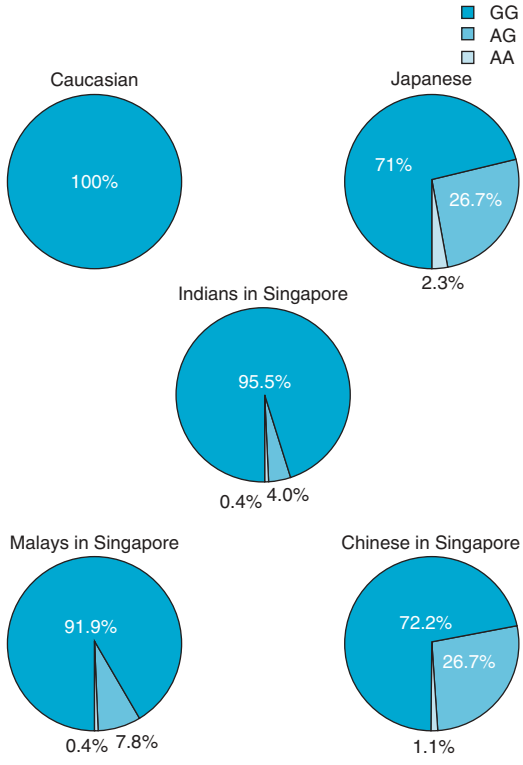

Fig. 3. Genotype distribution of *UGT1A1*6*.

ethnic groups in Singapore and applied population genetic tools to compare with North American Caucasians and Japanese as part of its deliberations on revising the irinotecan package with information on the risk of irinotecan-induced neutropenia associated with *UGT1A1* polymorphisms.

Methods

Sources of data on *UGT1A1*28* and **6* variants in the ethnic populations of Singapore were the NCC of Singapore,[6] the National University Hospital of Singapore[28] and the Singapore Genome Variation Project.[29] The distributions were compared with reference populations in the International HapMap Project[30] (phase 2, build 26) or literature sources.[16,28,31,32] Two population genetic tools used to assist in interpretation of the differences between populations were Wright's F_{ST} statistic calculated at individual SNPs, also known as the SNP-specific $F_{ST,}$ and the haplotype diversity map.[33] F_{ST} is a quantitative measure of differentiation between a subpopulation and the total population;[34] F_{ST} values between 0.05 and 0.15 are indicative of moderate differentiation, and values >0.15 are indicative of large differentiation. The haplotype diversity map provides a visual representation of haplotype structure among different populations.[35]

Results

Among the Singapore Indian population, the allele and genotype distributions of the *UGT1A1*28* variant are comparable with North American Caucasians (figure 2 and figure 4a), while among the Malay and Chinese populations in Singapore, they are much lower. On the other hand, the *UGT1A1*6* variant is absent in Caucasians and rare in the Singapore Indian population, whereas *6 heterozygotes and homozygotes are more commonly found in Japanese and in Singaporean and Beijing Chinese (figure 3 and figure 5a). Moreover, the prevalence of double heterozygotes (**6/*28*) in Singapore is 6.9%, 1.2% and 2.9% in Chinese, Malay and Indian populations, respectively,[28] while in Japanese the prevalence is 3.9%.[25] The combined prevalence in Singapore of three high-risk genotypes, *UGT1A1*6/*6, *6/*28* and **28/*28*, is 9.7% in Chinese, 5.0% in Malays and 18.7% in Indians.

As shown in figure 4a, each pairwise comparison of the three ethnic populations of Singapore, North American Caucasians and Japanese, was made using the SNP-specific F_{ST} statistic. For *UGT1A1*28,* Japanese, as well as Chinese and Malays in Singapore, exhibit moderate differentiation relative to Caucasians, with F_{ST} values of 0.113, 0.069 and 0.053, respectively (figure 4b). On the other hand, the Singapore Indian population is very similar to the North American Caucasian population (F_{ST} 0.000). At the SNP that defines the *UGT1A1*6* variant (dbSNP id rs4148323), F_{ST} is 0.000 between Chinese in Singapore and Japanese in Tokyo (figure 5b); hence, these two populations are expected to have a similar risk of neutropenia associated with the *UGT1A1*6* polymorphism. Interestingly, Chinese in Beijing show greater differentiation with the population of Caucasians of northern

a

Ethnic group	Allele frequencies							Source
	allele	frequency	count	allele	frequency	count	total	
Caucasian	6	0.628	186	7	0.372	110	296	[16, 31]
Japanese	6	0.911	184	7	0.089	18	202	[16, 31]
Chinese	6	0.858	302	7	0.142	50	352	[6, 28]
Malays	6	0.833	295	7	0.167	59	354	[6, 28]
Indians	6	0.630	194	7	0.370	114	308	[6, 28]

b

Ethnic group	Wright's F_{ST}				
	Caucasian	Japanese	Chinese	Malays	Indians
Caucasian					
Japanese	0.113				
Chinese	0.069	0.007			
Malays	0.053	0.013	0.001		
Indians	0.000	0.112	0.068	0.053	

Fig. 4. (**a**) Allele frequency of *UGT1A1*28* in five populations: North American Caucasian, Japanese (from several locations on Honshu island), Chinese in Singapore, Malays in Singapore and Indians in Singapore; (**b**) Wright's F_{ST} for pairwise comparison of populations for *UGT1A1*28*. F_{ST} values between 0.05 and 0.15 are indicative of moderate differentiation, and values >0.15 are indicative of large differentiation.

European descent (CEU F_{ST} 0.124) than do Japanese in Tokyo (F_{ST} 0.069) or Chinese in Singapore (F_{ST} 0.072) [figure 5b].

A haplotype diversity map of the *UGT1A1* gene for the Chinese, Malays and Indians in Singapore and four of the populations in the HapMap shows that Indians in Singapore have a similar haplotype structure as Caucasians, while Chinese and Malays in Singapore have a pattern similar to that of Japanese (figure 6).

a

Ethnic group	Allele frequencies							Source
	allele	frequency	count	allele	frequency	count	total	
CEU	G	1.000	120	A	0.000	0	120	HapMap
CHB	G	0.780	131	A	0.220	37	168	HapMap
JPT	G	0.871	148	A	0.129	22	170	HapMap
YRI	G	1.000	120	A	0.000	0	224	HapMap
CHS	G	0.865	166	A	0.135	26	192	SGVP
MAS	G	0.944	168	A	0.056	10	178	SGVP
INS	G	0.988	164	A	0.012	2	166	SGVP

b

Ethnic group	Wright's F_{ST}						
	CEU	CHB	JPT	YRI	CHS	MAS	INS
CEU							
CHB	0.124						
JPT	0.069	0.014					
YRI	0.000	0.124	0.069				
CHS	0.072	0.012	0.000	0.072			
MAS	0.029	0.057	0.016	0.029	0.018		
INS	0.006	0.105	0.052	0.006	0.056	0.015	

Fig. 5. (**a**) Allele frequency of *UGT1A1*6* in seven populations: HapMap populations: Utah residents of northern and western European ancestry (CEU), Japanese from Tokyo (JPT), Han Chinese from Beijing (CHB) and Yoruba people from Ibadan, Nigeria, Africa (YRI); Singapore Genome Variation Project (SGVP) populations:[29,30] Chinese in Singapore (CHS), Malays in Singapore (MAS) and Indians in Singapore (INS); (**b**) Wright's F_{ST} for pairwise comparison of populations for *UGT1A1*6*. F_{ST} values between 0.05 and 0.15 are indicative of moderate differentiation, and values >0.15 are indicative of large differentiation.

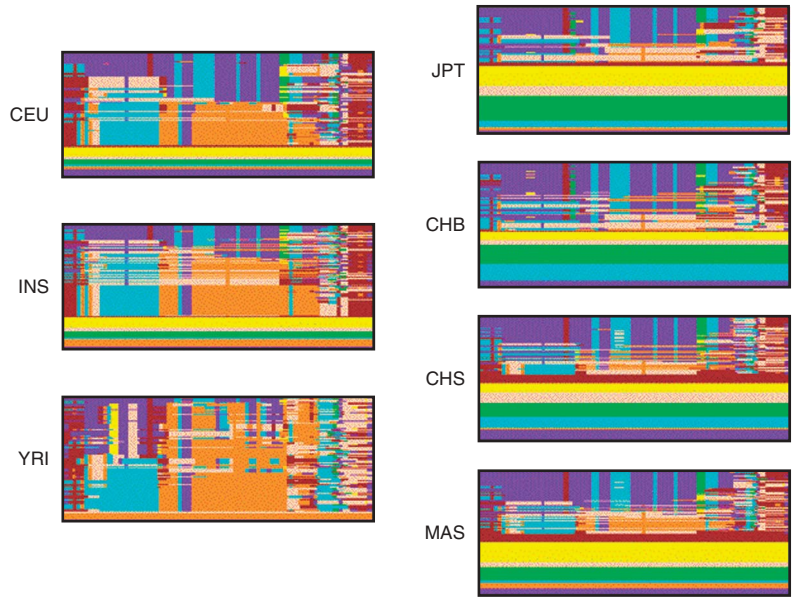

Fig. 6. Haplotype diversity map of the *UGT1A1* gene based on seven populations (reproduced from Pharmacogenomics, Aug 2010, Vol. 11, No. 8, Pages 1077-1094, with permission of Future Medicine Ltd). **CEU** = Utah residents of northern and western European ancestry; **CHB** = Han Chinese from Beijing; **CHS** = Chinese in Singapore; **INS** = Indians in Singapore; **JPT** = Japanese from Tokyo; **MAS** = Malays in Singapore; **YRI** = Yoruba people from Ibadan, Nigeria, Africa.

In view of the available evidence of greater risk of irinotecan toxicity associated with *UGT1A1*6* and *UGT1A1*28* variants, and the high prevalence of high-risk *UGT1A1* genotypes in the local population, especially among Indians, in 2009 the HSA Pharmacogenetics Advisory Committee recommended updating the package insert for irinotecan products with information regarding the increased risk of neutropenia associated with both *UGT1A1*6* and *UGT1A1*28*. Consequently, the HSA requested that all manufacturers of irinotecan products marketed in Singapore update the 'Warnings and Precautions' section of the package insert to include the following cautionary statement: "The active metabolite of irinotecan, SN-38, is metabolized predominantly by UDP-glucuronosyltransferase (UGT). It has been reported that patients who are homozygous (UGT1A1*6/*6 or UGT1A1*28/*28) or heterozygous (UGT1A1*6/*28) in allele UGT1A1*6, UGT1A1*28 of UGT may be at increased risk for serious adverse reactions (especially neutropenia) caused by reduced glucuronidation of SN-38. Added caution should be exercised when administering in such patients."[36]

Essential to pharmacogenetic-based decision making is the availability of a genetic test for *UGT1A1* variants. The HSA notified the clinical pharmacology laboratory at the NCC of the upcoming label change, and the laboratory made arrangements to process samples from oncologists from any institution in the country, to provide the test *gratis* and to return results within 48 hours. The NCC test performs *UGT1A1* genotyping for both *UGT1A1**6 and **28* variants, employing a direct sequencing method. The HSA also informed healthcare professionals of the population distribution of higher-risk *UGT1A1* variants in Singapore's ethnic groups through the April 2010 *HSA Adverse Drug Reaction News*, a newsletter distributed every 4 months to all healthcare professionals and also made available online,[37] and provided information regarding the NCC laboratory where *UGT1A1* genotyping could be performed.

Discussion

Singapore is located at the tip of the Malay Peninsula where the Straits of Malacca meets the

South China Sea. Beginning from the late 19th century, it developed as a vibrant trading port that attracted people from China, India, Indonesia, Arab and European nations. Historically, the Chinese came mostly from the southern provinces of China, e.g. Guangdong, Fujian and Hainan. The majority of the Singapore Indian population trace their ancestry to South India, especially the Tamil Nadu region. The total population of Singapore in 2009 was nearly 5 million. Chinese, Malays and Indians account for 97.3% of the resident population of 3.7 million. In 2009, the Singapore Genome Variation Project (SGVP) completed the first phase of a haplotype map of Chinese, Malay and Indian individuals whose four grandparents were of the same ethnicity.[38] Over 1.6 million SNPs were catalogued for 96 Chinese, 89 Malays and 83 Indians in Singapore.

The growing number of sources of genomic data on various ethnic populations offers regulatory authorities a new avenue to decide whether a genetic association to an adverse drug reaction is likely to be a risk factor for the ethnic groups in their countries. In Singapore, the genotypes *UGT1A1*28/*28, *6/*6* and **6/*28* that are associated with elevated risk of irinotecan-induced neutropenia are found in 9.7% of the Chinese population, 5.0% of the Malay population and 18.7% of the Indian population. This compares with 11.5% in North American Caucasians and 8.1% in Japanese. With the Singapore Indian population having nearly a one in five chance of carrying one of these high-risk genotypes and Singapore Chinese having a one in ten chance, in 2009 the HSA requested that irinotecan manufacturers revise the package insert to include the pharmacogenetic association with severe neutropenia, and publicized the association and availability of a genotyping test at the NCC.

Several additional studies have been published on *UGT1A1* pharmacogenetics and irinotecan usage since the request for a change to irinotecan's package insert in Singapore in 2009. A small clinical study of 42 subjects in Japan reported that efficacy and toxicity to FOLFIRI (irinotecan dose 180 mg/m^2) were not affected by the presence of single variant alleles, i.e. *UGT1A1 *1/*28* or **1/*6*.[39] A meta-analysis of 1760 patients found that carriers of at least one *UGT1A1*28* allele have an elevated risk of severe diarrhoea, but only at doses >125 mg/m^2.[40] From the same research group, a meta-analysis of 1998 patients demonstrated that *UGT1A1*28* homozygotes are at risk for severe neutropenia at all doses, including at low doses (80–145 mg/m^2) compared with **1/*1* and **1/*28* genotypes.[41] A question remains, however, whether tumour response rates are lowered when reducing the irinotecan dose. Possibly, pharmacogenetic information could be used to increase the dose in wild-type genotypes in an effort to achieve higher tumour response rates.[42] A group in Japan is investigating an alternate strategy of selecting a chemotherapy regimen, FOLFIRI or FOLFOX (a chemotherapy regimen consisting of folinic acid, fluorouracil, and oxaliplatin), depending on *UGT1A1* genotypes.[43] The number of patients with high-risk *UGT1A1* genotypes in this study was small (6 of 61 treated patients); hence, a larger prospective trial is needed to adequately address whether the similar response rates but lower rates of neutropenia seen in this study can be substantiated. Another important consideration is the cost effectiveness of genotyping. One study has modelled a US population with an 11% prevalence of *UGT1A1*28/*28* and found that genotyping appears to be cost effective, but the conclusion was quite sensitive to any reduction in efficacy from lowering the irinotecan dose.[44] Inputting Singapore's statistics, healthcare costs and alternate chemotherapy options into the model would provide additional guidance to oncologists regarding the clinical utility of genotyping in the Singapore context.

Conclusions

The era of genomics is producing an abundance of information about genetic variation within and across populations. Regulatory authorities, which are interested in the benefit-risk profile of a drug on a population-wide basis, can use allele and genotype frequencies and population genetic tools to supplement evaluation of drug products by tapping into burgeoning genomic databases. Revision of the irinotecan drug label in

Singapore provides one such example. Regulatory authorities can also facilitate the use of pharmacogenetic information by providing information regarding genotyping facilities and communicating their findings with healthcare professionals.

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Correspondence: Dr *Cynthia Sung*, Health Products Regulation Group, Health Sciences Authority, 11 Biopolis Way #11-03, Singapore 138667.
E-mail: cynthia_sung@hsa.gov.sg