Genotyping *HLA* alleles to predict the development of Severe cutaneous adverse drug reactions (SCARs): state-of-the-art

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REVIEW

Genotyping *HLA* alleles to predict the development of Severe cutaneous adverse drug reactions (SCARs): state-of-the-art

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ABSTRACT

Introduction: Pharmacogenomics has great potential in reducing drug-induced severe cutaneous adverse drug reactions (SCARs). Pharmacogenomic studies have revealed an association between *HLA* genes and SCARS including acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN).

Areas covered: Pharmacogenomics-guided therapy could prevent severe drug hypersensitivity reactions. The US Food and Drug Administration (FDA), Clinical Pharmacogenetics Implementation Consortium (CPIC), and Dutch Pharmacogenetics Working Group (DPWG) provided guidelines in the translation of clinically relevant and evidence-based SCARs pharmacogenomics research into clinical practice. In this review, we intended to summarize the significant *HLA* alleles associated with SCARs induced by different drugs in different populations. We also summarize the SCARs associated with genetic and non-genetic factors and the cost-effectiveness of screening tests.

Expert opinion: The effectiveness of *HLA* screening on a wider scale in clinical practice requires significant resources, including state-of-the-art laboratory; multidisciplinary team approach and health care provider education and engagement; clinical decision support alert system via electronic medical record (EMR); laboratory standards and quality assurance; evidence of cost-effectiveness; and cost of pharmacogenomics tests and reimbursement.

1. Introduction

Severe cutaneous adverse drug reactions (SCARs) are one of the commonest medical challenges with high fatality and are considered to be a multifactorial drug side effect. The common SCARs seen in clinical practice include acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). The most common medications associated with SCARs are non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, antiepileptics, allopurinol, and antiretroviral drugs [1]. AGEP consists of numerous non-follicular sterile pustules in the epidermis, fever, and peripheral-blood leukocytosis of neutrophils (neutrophilia, neutrophil leukocytosis) [2,3]. SJS and TEN are characterized by widespread keratinocyte death resulting in extensive epidermal loss with mucous membrane erosions. SJS and TEN are considered as severity variants of the same drug-induced disease classified by the degree of detachment over the total body surface area; less than 10% is considered SJS, 10–30% is considered as SJS-TEN overlap, and over 30% is considered as TEN. DRESS is characterized by cutaneous exanthema, fever, hematologic abnormalities (eosinophilia or atypical lymphocytes), and internal organ involvement [2].

Studies have revealed the interaction between the highly polymorphic human leukocyte antigen (*HLA*) and drugs, and *HLA* genotypes have been implicated in explaining the variability and unpredictability of SCARs presentations among different individuals. A large number of studies have reported the association of the *HLA* alleles with AGEP, DRESS, and SJS/TEN across different populations [3–5]. This review aims to provide an association between SCARs and *HLA* alleles in different populations. This review also provides an overview of the pathogenesis of SCARs, pathomechanisms in *HLA* associated drug-induced SCARs, clinical pharmacogenetics implementation guidelines and recommendations, and pharmacoeconomic perspective of *HLA* genotyping before drug prescription.

2. Adverse drug reactions (ADRs) associated with immunological reactions

ADRs are classified into type A and type B reactions. Type A reactions are nonimmune-mediated and are due to the pharmacological activity of the drug. Type B reactions are immune-mediated and independent of pharmacologic activity [6]. The immune-mediated ADRs include urticaria, DRESS, AGEP, fixed drug eruption, SJS/TEN, drug-induced liver injury (DILI), thrombocytopenia, agranulocytosis, aplastic anemia, and drug-induced lupus [7].

The knowledge of SCARs epidemiology is essential to establish timely and appropriate genetic screening measures for selected patient groups and drug classes. The prevalence of AGEP is estimated to be between 0.35–5/million [8]. The incidence of AGEP is estimated between 1 and 5 cases per million inhabitants per year. For DRESS, population-based studies in Japan reported an incidence of 10 per million person-years [9]. Among the patients treated with aromatic anti-epileptic drugs, the risk of SJS/TEN is 1/10,000 to 1/1,000 and the risk of DRESS is 1 to 9 per 10,000. The risk of DRESS is higher among patients treated with lamotrigine (1 per 300 adults and 1 per 100 children exposed) [4]. The mortality rates have been reported up to 10% in DRESS [8]. On average, the mortality rate for SJS is between 1% and 5%, with global mortality rates up to 25–35% in patients with TEN.

Drugs may induce SCARs due to the CD8+ and CD4+ T-cells immune responses. SJS/TEN are caused by granulysin-producing cytotoxic CD8+ T cells, natural killer (NK) cells, and natural killer T (NKT) cells. Also, both CD4+ and CD8+ effector T-cells are activated in patients with DRESS [6]. The pathogenesis of AGEP involves activation, proliferation, and migration of drug-specific CD4+ and CD8+ T-cells to the skin [10].

The histology of AGEP shows typical subcorneal or intraepidermal spongiform or non-spongiform pustules with or without dermal edema, focal necrotic keratinocytes, neutrophil infiltrates sometimes with eosinophils, and mild vasculitis. SJS and TEN cases show histological features of massive epidermal necrosis (including all layers of the epidermis), focal adnexal necrosis, necrotic keratinocytes, mild mononuclear cell dermal infiltrate, and negative direct immunofluorescence test. In DRESS, the histological findings are described as non-specific lichenoid or eczematous lesions, focal necrotic keratinocytes, dense and diffuse dermal-epidermal infiltrates with lymphocytic exocytosis, dermal edema, and superficial perivascular infiltrate of mostly lymphocytes with or without eosinophils [11–13].

Drug hypersensitivity reactions (DHRs) were a strong association between *HLA*, drug or metabolite form, peptide and T-cell receptor (TCR). Drugs may induce an immune response as demonstrated by (1) Model 1: altered repertoire model proposes the altered self-peptides then leads to aTCR and induced the manifestations of immune system and caused by binding mechanism of non-covalent between drugs and HLA molecules (2) Model 2: hapten model is a small molecular of chemical or drug and presented as a stable hapten peptide complex and able to bind covalently to *HLA* which contribute to stimulate an immune response (3) Model 3: pro-hapten model is a covalent binding process of drugs metabolites and HLA molecule and stimulate the immune system and (4) Model 4: pharmacological interaction (p-i) model is an interact directly with immunologic receptors by non-covalent bonds, the mechanism of this theory include of drug bind to the *HLA* or TCR of T lymphocyte (CD8+) to elicit immune system [3]. Figure 1 shows the mechanisms of these reactions contributing to a greater understanding of T-cell-mediated drug hypersensitivity.

3. Genetic susceptibility to SCARs

During pathological conditions of SCARs, HLAs present antigens to the TCR and then elicit specific T cell-dependent immune responses [3]. The occurrence of drug-induced SCARs is strongly associated with specific *HLA* alleles. These specific *HLA*-mediated SCARs are highly specific; hence, *HLA* alleles that are linked to SCARs represent biomarkers for the pharmacogenomics-guided therapy in a patient. The most important examples of this association include *HLA-B*57:01* (abacavir), *HLA-B*15:02/HLA-A*31:01* (carbamazepine), and *HLA-B*58:01* (allopurinol) in specific ethnicities [14]. The explanation of the genetic basis of SCARs may lead to an understanding of their pathogenesis and genetic screening for the risk genetic variants results in the prevention of SCARs. It has been shown that the genetic variant of the drug metabolism enzyme also plays a role in the pathogenesis of SCARs [15].

3.1. HLA alleles associated with SCARs

HLA is located on the chromosome 6, including of *HLA* class I, *HLA* class II and *HLA* class III. Variations at *HLA* class I (*HLA-A*, *HLA-B*, and *HLA-C*) and class II loci (*HLA-DR*, *HLA-DQ*, and *HLA-DP*) are associated with drug-induced SCARs.
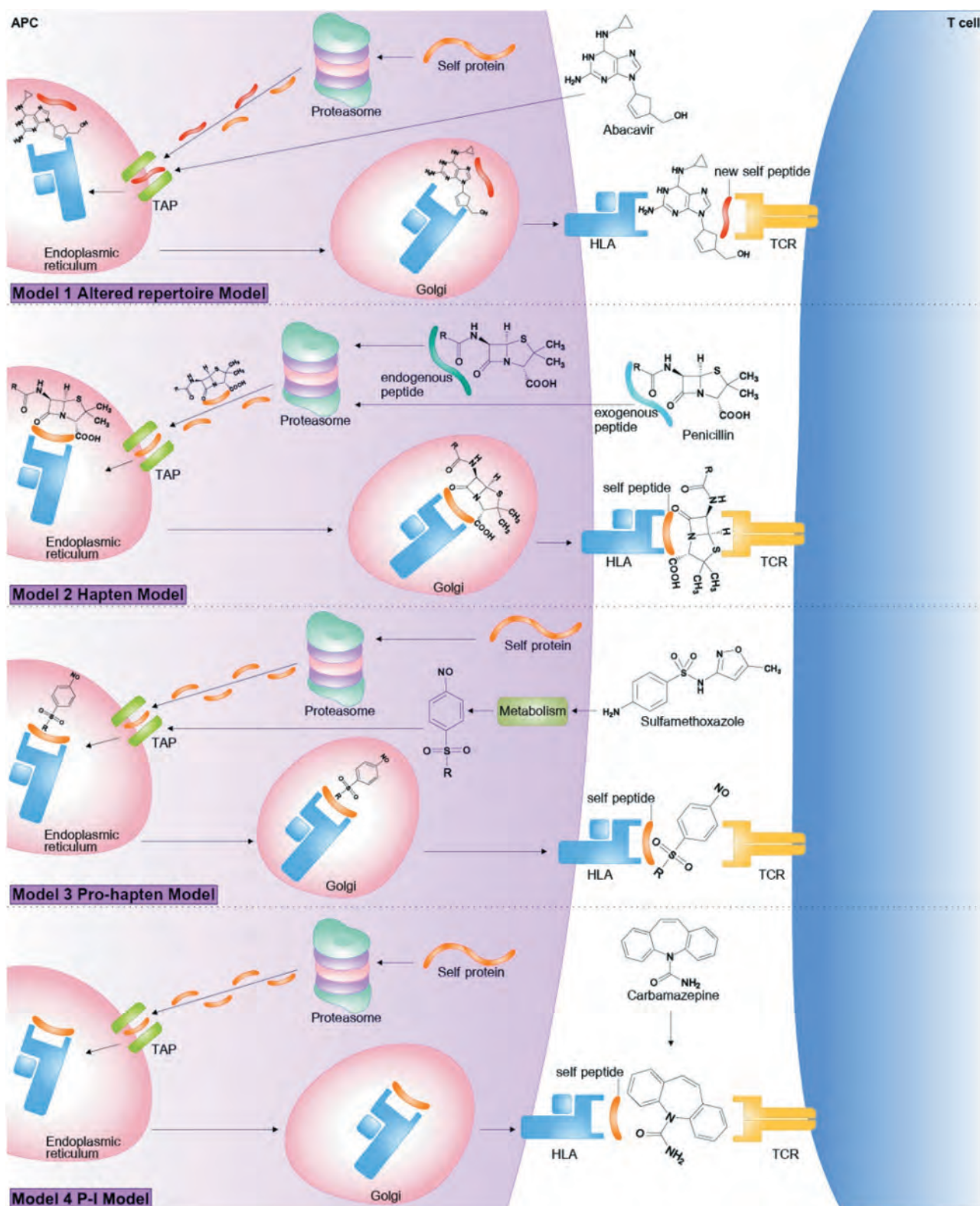
Figure 1. Mechanisms of drug hypersensitivity models with drug binding to HLA and TCR: **Model 1**; altered repertoire model proposes the altered self-peptides then leads to a TCR and induced the manifestations of immune system and caused by binding mechanism of non-covalent between drugs and HLA molecules, **Model 2**; hapten model is a small molecular of chemical or drug and presented as a stable hapten peptide complex and able to bind covalently to HLA which contribute to stimulate an immune response, **Model 3**; pro-hapten model is a covalent binding process of drugs metabolites and HLA molecule and stimulate the immune system and **Model 4**; pharmacological interaction (p-i) model is an interact directly with immunologic receptors by non-covalent bonds, the mechanism of this theory include of drug bind to the HLA or TCR of T lymphocyte (CD8+) to elicit immune system.

Table 1. The significant HLA alleles associated with SCARs induced by different drugs in different populations.

HLA alleles	Drugs	Types of SCARs	Ethnic groups	Odds ratio	References
HLA-B*13:01	Dapsone	DRESS and SJS/TEN	Asian populations	19.6–122.1	**43–44**
		HSS	Chinese	20.53	**45**
		SJS/TEN, DRESS	Thai	54.0	**46**
HLA-B*13:01	Co-trimoxazole	SJS/TEN	Thai	3.88	**48**
		DRESS	Thai	15.20	**48**
		SJS/TEN and DRESS	Taiwanese, Thai Malaysian	2.46–40.11	**49**
HLA-B*15:02, HLA-C*06:02, HLA-C*08:01	Co-trimoxazole	SJS/TEN	Thai	6.11 / 2.07 / 11.19	**47–48**
HLA-B*15:02	Carbamazepine	SJS, TEN	Southern China mainland	114.83	**21**
			Southern Han Chinese	8.96	**22**
			Thai	54.76	**23**
			Han Chinese	2,504	**24**
			Malaysian	16.15	**25**
			Indians	71.40	**26**
			Vietnamese	33.78	**27**
HLA-B*15:02	Oxcarbazepine	SJS	Han Chinese	80.7	**33**
	Phenytoin	SJS, TEN	Han Chinese	3.5–5.1	**32**
	Phenytoin	SJS, TEN	Malays	5.71	**35**
	Phenytoin	SJS, TEN	Han Chinese	3.0–4.3	**33**
HLA-B*13:01, HLA-Cw*08:01, HLA -DRB1*16:02	Phenytoin	DRESS	Thai children	5.85	**34**
HLA-B*51:01, HLA-C*14:02	Phenytoin	SJS, TEN	Thai children	12.67	**34**
HLA-B*38:02	Phenytoin	SJS/TEN, DRESS	Malays	11.28–59.0	**35**
HLA-B*15:13	Carbamazepine	SJS, TEN	Asian population	17.43	**30**
HLA-B*15:11	Carbamazepine	SJS/TEN, AGEP	Caucasian, Japanese, Korean, Chinese, and patients of mixed origin	-	**28**
HLA-A*31:01	Carbamazepine	MPE/DRESS,	Europeans	49.4	**29**
HLA-B*57:01	Carbamazepine	SJS, TEN	Europeans	9.0	**29**
HLA-B*57:01	Abacavir	HSS	Brazilian, British, Hispanic, African, Iranian, and Indian	-	**16–17**
HLA-B*57:01, HLA-DR7, HLA-DQ3	Abacavir	HSS	Western Australian HIV-1-positive individuals	73–117	**18**
HLA-B*58:01	Allopurinol	SJS, TEN	Han Chinese	580.3	**36**
		SJS, TEN	Thai	348.3	**37**
		SJS, TEN	Japanese	40.83	**38**
		SJS, TEN, DRESS	Korean	97.8	**40**
HLA-A*33:03, HLA-C*03:02	Allopurinol	SJS, TEN	Asian populations	9.44 / 79.08	**41**
HLA-A*32:01	Vancomycin	AGEP, DRESS, SJS/TEN	Europeans	-	**51**
HLA-A*02:06, HLA-B*44:03	Cold medicine	SJS, TEN	Japanese	5.18 / 4.22	**52**
HLA-B*59:01	Methazolamide	SJS, TEN	Korean, Japanese / Han Chinese	249.8 / 305.0	**53, 54**
HLA-C*04:01	Nevirapine	SJS, TEN	Malawian	5.17	**55, 56**

**SJS = Stevens-Johnson syndrome, TEN = Toxic epidermal necrolysis, DRESS = Drug reaction with eosinophilia and systemic symptoms, HSS = Hypersensitivity syndrome, AGEP = Acute Generalized Exanthematous Pustulosis

Pharmacogenomic markers in the *HLA* coding genes in different ethnicities are summarized in Table 1.

The association of *HLA-B*57:01* and abacavir hypersensitivity has been reported in different ethnicities, including Australian, African American, Brazilian, British, Hispanic, African, Iranian, and Indian [16,17]. *HLA-B*57:01* was strongly associated with abacavir hypersensitivity in Western Australian HIV-1-positive individuals treated with abacavir [18]. Screening for *HLA-B*57:01* for patients before initiation of abacavir therapy has been recommended by the US Food and Drug Administration (FDA), Clinical Pharmacogenetics Implementation Consortium (CPIC), and Dutch Pharmacogenetics Working Group (DPWG) abacavir to reduce the risk of a hypersensitivity reaction [19,20].

The *HLA-B*15:02* allele is strongly associated with carbamazepine-induced SJS/TEN in Han Chinese, Thai, Malay, Indians, Vietnam populations [21–27]. The *HLA-A*31:01* allele is associated with carbamazepine-induced SJS/TEN, and AGEP in Caucasian, Japanese, Korean, Chinese, and patients of mixed origin [28]. A study conducted among the Europeans showed that *HLA-A*31:01* was associated with carbamazepine-induced MPE/DRESS, and *HLA-B*57:01* was associated with carbamazepine-induced SJS/TEN [29]. Furthermore, a meta-analysis investigating the association of *HLA-B* alleles and carbamazepine-induced SJS/TEN demonstrated *HLA-B*15:11* as a risk factor in the development of carbamazepine-induced SJS/TEN in the Asian population [30]. The US FDA recommends the genetic screening of *HLA-B*15:02* for all patients with ancestry in populations with increased frequency of *HLA-B*15:02*, before initiation of carbamazepine therapy [31]. The *HLA-B*15:02* allele is also strongly associated with phenytoin-induced SJS/TEN in Han Chinese [32]. Other associations include the alleles *HLA-B*13 :01*, *HLA-C*08:01*, and *HLA-DRB1*16:02* in phenytoin-induced SJS/TEN in Han Chinese [33]. The *HLA-B*51:01* and *HLA-C*14 :02* alleles have been linked with phenytoin-induced DRESS in Thai children [34]. The authors also showed that Thai children carrying *HLA-B*38:02* were at high risk for phenytoin-induced SJS/TEN. Phenytoin-induced DRESS and SJS/TEN have been associated with *HLA-B*15:13* in Malays [35]. The association between the *HLA-B*15:02* and oxcarbazepine-induced SJS has been reported in Han Chinese [33].

The variant *HLA-B*58:01* allele is strongly associated with allopurinol-induced SCARs. The *HLA-B*58:01* allele has been linked to allopurinol-induced SJS/TEN and/or DRESS in Han Chinese, Thai, Japanese, European, and Korean [36–40]. Li et al. reported a strong association between *HLA-A*33:03* and *HLA-C*03:02* alleles and allopurinol-induced SJS/TEN in Asian populations [41]. The CPIC recommends that allopurinol should not be used in patients who are positive for the *HLA-B*58:01* allele [42].

An association between *HLA-B*13:01* and dapsone-induced DRESS and SJS/TEN has been reported in Asian populations [43,44]. It was reported that *HLA-B*13:01* was a predictor of the dapsone-induced HSS in Chinese [45], as well as to DRESS and SJS/TEN in Thais [46]. Co-trimoxazole-induced induced SJS/TEN has been strongly associated with *HLA-B*15:02, HLA-C*06 :02*, and *HLA-C*08:01* alleles in the Thai population [47,48]. Also, the *HLA-B*13:01* allele has been associated with DRESS induced by co-trimoxazole in Thais [48]. In a multicountry case-control association study involving Taiwan, Thailand, and Malaysia, the *HLA-B*13:01* allele showed a strong association with co-trimoxazole-induced SJS/TEN and DRESS [49]. Vancomycin is associated with a risk of AGEP, DRESS, and SJS/TEN [50]. Konvinse et al. reported a strong association between *HLA-A*32:01* and vancomycin-induced DRESS in Europeans [51]. Cold medicines-related SJS/TEN has been strongly associated with *HLA-A*02:06* and *HLA-B*44:03* alleles in the Japanese population [52]. *HLA-B*59:01* was strongly linked with methazolamide-induced SJS/TEN in Japanese, Korean and Han Chinese [53,54]. *HLA-C*04:01* was reported as a risk of SJS/TEN from Nevirapine in Malawian [55,56].

3.2. Other gene variants for SCARs

CYP2C9 variants have been associated with phenytoin-induced SCARs, and CPIC recommends consideration of at least a 25% reduction in the starting maintenance dose for patients who are *CYP2C9* intermediate metabolizers and a 50% reduction for *CYP2C9* poor metabolizers [57,58]. *CYP2C9*3* allele has been reported as a marker for phenytoin-induced DRESS in Thais [59–62]. A study by Chung et al. showed that *CYP2C9*3* was strongly associated with phenytoin-induced SCARs in Taiwan, Japan, and Malaysia [15]. The association between *CYP2B6* polymorphisms and nevirapine-induced SJS/TEN was first reported in HIV-1 patients from Mozambique. In the study, the *CYP2B6 T983C* polymorphism was found to be significantly associated with a higher risk to develop SJS/TEN with an OR of 4.2 [63].

4. Non-genetic factors for SCARs

A study by Yampayon et al. reported that omeprazole co-medication was strongly associated with phenytoin-induced DRESS in Thai patients [59]. A study by Zhao et al. showed that patients taking multiple-drug combinations and with a complex medication history, which greatly contributed to the development of SCARs [64]. The use of multiple drugs results in the accumulation of drugs, reactive metabolites, and drug interaction because of excessive demands on enzyme systems for oxidation or acetylation of multiple drugs [65]. Reactivation of human herpesvirus (HHV)-6 has been reported to be associated with DRESS and SJS/TEN [66,67]. Also, Epstein–Barr virus (EBV) is associated with SJS [68]. *Mycoplasma pneumoniae* have been implicated in the development of atypical SJS [69]. Among the host factors, the presence of systemic lupus erythematosus, tuberculosis, and HIV have been found to increase the risk of SCARs. Drugs that are associated with a higher risk of SCARs include aromatic anti-epileptic agents, allopurinol, antimicrobial agents (co-trimoxazole, vancomycin, aminopenicillin, minocycline, sulfasalazine, and dapsone), and NSAIDs (celecoxib and ibuprofen) [8]. Incidences of SCARs including SJS, TEN, and DRESS have been reported

after immunotherapy owing to the reactivation of T-cells [70,71].

5. Current understanding of pathomechanisms in *HLA* associated drug-induced SCARs

The HLA molecule contributes to the pathogenesis of the drug-induced SCARs. The HLA molecules bind to specific drug antigens and contribute to drug-induced SCARs by presenting the drug antigens to specific TCR which activate T-cell-mediated immune responses [72]. In carbamazepine-induced SJS/TEN, carbamazepine can directly interact with *HLA-B*15:02* protein and the endogenous peptide-loaded *HLA-B*15:02* molecules present carbamazepine to cytotoxic lymphocytes (CTLs) that leads to the apoptosis of keratinocytes resulting from the degranulation of perforin and granzyme B and Fas/FasL interaction [73]. In allopurinol-induced SCARs, Yun et al. explained that allopurinol and its metabolite, oxypurinol, bind to the *HLA-B*58:01* molecule in the F pocket of the peptide-binding groove and activate drug-specific T cells [74].

6. Databases with *HLA* alleles frequency

The Allele Frequency Net Database (AFND, www.allelefrequencies.net) provides frequency data on the polymorphisms of *HLA*, killer-cell immunoglobulin-like receptors (KIR), major histocompatibility complex class I chain-related genes (MIC), and several cytokine gene polymorphisms in worldwide populations [75]. The allele frequencies data on *HLA* in one or many populations can be explored using the query tool *HLA* Allele Freq Search (http://allelefrequencies.net/hla6006a.asp) in AFND. An additional tool for exploring the *HLA* haplotype frequencies and *HLA* rare allele in a set of populations at two or more loci is available in AFND (http://allelefrequencies.net/hla6003a.asp). Also, a database for HLA adverse drug reactions (HLA-ADR, http://allelefrequencies.net/hla-adr/) has been added to the AFND. HLA-ADR is a database for the analysis of HLA and adverse drug reactions and covers 46 drugs/drug classes.

7. DHRs in Southeast Asia: regional issues and challenges

DHRs represent a significant public health problem with a prevalence of 10-20% in hospitalized patients and up to 7% in the general population exposed to drugs [76]. Tang et al. surveyed the diagnostic modalities used in the evaluation and management of DHRs among member countries of the Asia Pacific Association of Allergy, Asthma and Clinical Immunology (APAAACI) which included respondents from five Southeast Asian countries [77]. The authors reported that *HLA* genotype testing before prescribing carbamazepine, allopurinol, and abacavir was not mandatory or recommended by local pharmacy regulatory agencies in the majority of countries despite strong associations for SCARs with Asian ethnicity. In Southeast Asia, a wide knowledge gap, accurate diagnosis, and management of DHRs are the major challenge

of healthcare practitioners (HCPs). There is a lack of guidelines and/or consensus documents to support the clinical management of DHRs in Southeast Asian countries. There are not collaborative research networks regarding DHRs in the Southeast Asian region. Multi-country clinical networks need to be established to include more patients with the same reaction to the same drug in the same clinical context to conclude the pathophysiology of drug allergy. There is also a gap in establishing a multidisciplinary group to facilitate the investigators, integrate basic and clinical studies, and establish guidelines for the diagnosis and management of drug allergy within South East Asia.

8. Clinical pharmacogenetics implementation guidelines and recommendations

Several pharmacogenomics guidelines and recommendations are available from international committees with expertise in the field of pharmacogenomics. However, the recommendations from these guidelines vary due to the differences in the drafting standards for these guidelines [78].

CPIC guidelines suggest testing for *HLA-B*15:02* and *HLA-A*31:01* alleles, which are associated with SCARs among patients taking certain aromatic anticonvulsants, in populations with increased frequency of *HLA-B*15:02* and *HLA-A*31:01* alleles. The CPIC recommendations include avoiding the use of carbamazepine and oxcarbazepine and selecting an alternative drug if a patient is carbamazepine-naïve or oxcarbazepine-naïve and *HLA-B*15:02* positive. For carbamazepine-naïve individuals testing positive for *HLA-A*31:01* allele, carbamazepine should be avoided and an alternative therapy must be chosen [79]. As recommended by the DPWG guidelines, carbamazepine should not be used for individuals positive for *HLA-B*15:02, HLA-A*31:01*, and *HLA-B*15:11* alleles and, if possible, choose an alternative drug. The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) strongly recommends genetic testing for *HLA-B*15:02* for carbamazepine-naïve patients originating from populations where *HLA-B*15:02* is common, its frequency unknown, or whose origin is unknown before initiation of carbamazepine therapy. Genetic testing for *HLA-B*15:02* is optional in patients originating from populations where *HLA-B*15:02* is rare. The CPNDS has also recommends genetic testing for the *HLA-A*31:01* allele for all carbamazepine-naïve patients with moderate-risk ethnic backgrounds before initiation of carbamazepine therapy [31]. CPIC, DPWG, and CPNDS provide similar therapeutic guidelines regarding genetic testing for *HLA-B*15:02* before initiating carbamazepine therapy in the risk population.

The CPIC recommends that allopurinol should not be prescribed to allopurinol-naïve individuals who are *HLA-B*58:01*-positive, and an alternative drug should be considered for these patients to avoid the risk of developing SCARs [42]. The American College of Rheumatology (ACR) also recommends *HLA-B*58:01* screening in sub-populations where both the *HLA-B*58:01* allele frequency is elevated and the *HLA-B*58:01*-positive subjects are at high risk for severe allopurinol

hypersensitivity reaction [80]. Both CPIC and ACR recommend testing all allopurinol-naïve patients for *HLA-B*58:01* in the population with a high frequency of this allele.

The CPIC guidelines provide information for the interpretation of *HLA-B* and/or *CYP2C9* genotype tests so that the results can guide the dosing and/or use of phenytoin. The CPIC recommends avoiding phenytoin (or its prodrug fosphenytoin) for *HLA-B*15:02*-positive patients regardless of *CYP2C9* genotype, patient ancestry, or age. Also, the US FDA label recommends that consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for *HLA-B*1502* (https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/010151s036lbl.pdf).

9. The pharmacoeconomic perspective of *HLA* genotyping before drug prescription

HLA genotyping has been recommended before drug prescription so that those positive for the risk allele are not given the drug associated with the SCARs. The successful translation of *HLA*-guided treatment strategies depends on the cost-effectiveness of routinely assessing *HLA* markers before initiating drug therapy [81]. An economic evaluation assesses the costs and outcomes of health care interventions that may improve health care and health outcomes

[82]. Several studies have conducted pharmacoeconomic analyses of *HLA*-based approaches.

Choi et al. reported the *HLA-B*15:02* screening strategy to be more cost-effective than a no screening strategy before carbamazepine therapy in epilepsy patients of Asian ancestry in the United States [83]. In Thailand, *HLA-B*15:02* screening was found to be a cost-effective intervention for preventing carbamazepine-induced SJS/TEN on patients with neuropathic pain, but not on patients with epilepsy [84]. This finding was further supported by Tiamkao et al. by studies in Thai patients and recommended specific *HLA-B*15:02* screening for carbamazepine (Figure 2) for implementation in the national policy [85]. Among the Singaporean Chinese and Malays, Dong et al. found the screening of *HLA-B*15:02* allele and providing alternate antiepileptic drugs to be more cost-effective compared with no screening of *HLA-B*15:02* allele and providing carbamazepine to all [86]. On the contrary, *HLA-B*15:02* screening is unlikely to be cost-effective in an ethnically diverse Malaysian population and Singaporean Indians [86,87]. Plumpton et al. examined the total costs and quality-adjusted life-years (QALYs) by genotype-guided dosing (with lamotrigine prescribed for patients who test positive for *HLA-A*31:01* allele) versus standard care of carbamazepine prescription without testing in UK populations [88]. The study found that routine screening for the *HLA-A*31:01* allele before initiation of

HLA-B result	Genotype	Interpretation
Positive	HLA-B*15:02/xx:xx HLA-B*15:02/15:02	This patient has specific HLA-B*15:02 allele that positively correlated with Carbamazepine- and Oxcarbazepine-induced SJS,TEN. If patient is Carbamazepine- Oxcarbazepine-naive, these drugs should be avoid.
Negative	HLA-B*xx:xx/xx:xx	Normal risk for Carbamazepine- and Oxcarbazepine-induced SJS,TEN.

Figure 2. Pharmacogenomic card of pharmacogenetics testing for specific drug-biomarker (positive/negative result).

Possibility Genotype	Interpretation
*HLA-B*15:02/58:01*	This patient has two specific HLA-B*15:02 and HLA-B*58:01 allele which associated with Carbamazepine and Oxcarbazepine-induced SJS,TEN and Allopurinol-induced SJS, TEN, DRESS, MPE respectively. If patient is Carbamazepine, Oxcarbazepine and Allopurinol-naive, these drugs should be avoid.

Figure 3. Pharmacogenomic card of pharmacogenetics testing for *HLA-B* genotyping.

carbamazepine for epilepsy likely to represent a cost-effective intervention in the UK population.

Jutkowitz et al. evaluated the cost-effectiveness of *HLA-B*58:01* testing before the initiation of allopurinol in gout patients according to race/ethnicity in the US [89]. The analysis found that *HLA-B*58:01* testing is cost-effective for Asians, African Americans, but not for Caucasians or Hispanics. Saokaew et al. conducted the cost-effectiveness of *HLA-B*58:01* testing before initiating allopurinol therapy compared with usual care (no genetic testing) in Thailand [90]. The results revealed the genetic testing of *HLA-B*58:01* before allopurinol therapy as a highly potential cost-effective intervention in Thailand. Contrary to the findings of Jutkowitz et al. and Saokaew et al., Chong et al. suggested that *HLA-B*58:01* screening before allopurinol pharmacotherapy is unlikely to be a cost-effective intervention in Malaysia [91]. With the advancement in genomic technologies and a reduction in the price of genomic testing, the pharmacogenomics-guided treatment strategy will be more cost-effective and *HLA* screening will be a core clinical service. *HLA* typing by next generation sequencing (NGS) can sequence entire *HLA* gene to identify novel risk loci for drug toxicities [92].

10. Clinical implementation of genetic screening to prevent SCARs

Several studies have established the association of genetic variants encoding drug-metabolizing enzymes and *HLA* with drug-induced SCARs. Pharmacogenomics testing before the prescription of drugs responsible for SCARs has the potential to prevents SCARs and save money by improving the cost-effectiveness of health care delivery. The *HLA* pharmacogenomics tests have high predictive values for drug associated SCARs in several populations [93]. A preemptive and multiplexed approach is suggested over-reactive and one-gene-per-test approach for addressing the disadvantages of reactive genotyping for drug-specific variants when a pharmacogenomics drug is prescribed because the genetic data can be available at the time of prescribing the culprit drugs for SCARs, genotypes for multiple pharmacogenes per test are available before prescribing related drug pharmaco-
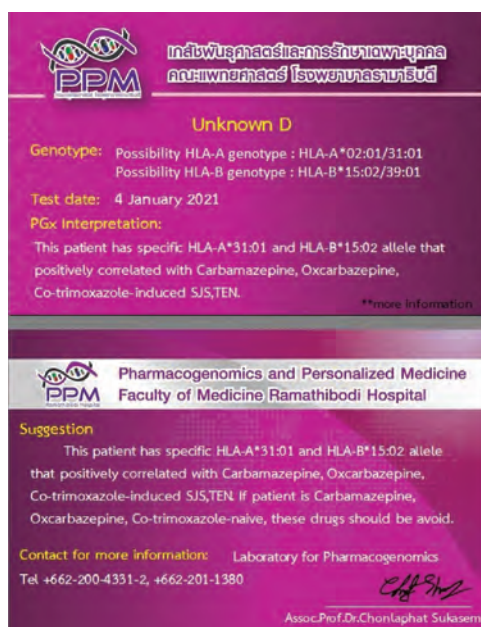
Possibility Genotype	Interpretation
HLA-A*02.01/31.01 HLA-B*15.02/39.01	This patient has two specific HLA-A*31:01 and HLA-B*15:02 allele which associated with Carbamazepine and Oxcarbazepine-induced SJS,TEN. If patient is Carbamazepine and Oxcarbazepine-naive, these drugs should be avoid.

Figure 4. Pharmacogenomic card of pharmacogenetics testing for *HLA-A* and *HLA-B* genotyping.

genomics, data can be used over long periods, and the incremental cost to obtain multiple genetic variant genotypes is small [94]. The Vanderbilt University Medical Center (VUMC) has implemented a program of preemptive genotyping, the Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment (PREDICT), which uses clinical data available in the electronic medical record to calculate the risk of being prescribed a risk medication for ADRs. In PREDICT, the prescriber receives an alert that the patient may benefit from (multiplexed) genetic testing. The panel of variants is then genotyped and the selected genotypes are then released into the medical record of patients to guide clinicians who are prescribing medications [95]. The clinical implementation of screening for the *HLA* risk alleles that represent the strongest predictor of drug-induced SCARs is successfully applied in clinical practice among the populations with a higher frequency of the risk alleles before initiation of the risk drugs. For instance, *HLA-B*57:01* for abacavir, *HLA-B*15:02* for carbamazepine, oxcarbazepine, and phenytoin, *HLA-B*58:01* for allopurinol, *HLA-B*13:01* for dapsone [3,96].

11. National policy for *HLA* screening to prevent SCARs: Thailand model

The incidence of drug-induced SJS/TEN is reported to be 10.35 per 1,000 persons while the mortality rate is reported to be 7–50% in the Thai population [97]. Screening for *HLA-*

*B*15:02* is mandated in Thai patients before initiation of carbamazepine therapy to prevent carbamazepine-induced SJS/TEN (Figure 2). The Thai universal health coverage scheme reimburses 28 USD per person for the *HLA-B*15:02* testing [98]. Currently, in Thailand, several pharmacogenomics tests are performed for the prevention of drug-induced SCARs (Figures 2-4). These include *HLA-A*31:01* for carbamazepine-induced hypersensitivity, *HLA-B*57:01* for abacavir-induced drug hypersensitivity, *HLA-B*13:01* for dapsone-induced SCARs, and *HLA-B*58:01* for allopurinol-induced SCARs (Figure 5) [99]. Unlike *HLA-B*15:02*, pharmacogenomics screening is not currently mandated for *HLA-A*31:01* before initiation of carbamazepine therapy in Thailand.

12. Future direction for research and implementation in SCARs

Multiple genetic variations are responsible for the development of drug-induced SCARs. The development of a diagnostic marker for drug-induced SCARs is important for the early detection, prevention, and treatment of drug-induced SCARs patients. With the advent of next-generation sequencing, genome sequencing must be established in both clinical and research settings to prevent drug-induced SCARs [100]. The genomic database containing both the genotype and the specific phenotype data for a population or ethnic group should be developed to support a clinical

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PHARMACOGENOMICS AND PERSONALIZED MEDICINE REPORT

Name-Surname :	Unknown D	Age :	62	years	Gender :	Male
Hospital Number :	-	Hospital/Source :			Ramathibodi Hospital	
Specimen :	EDTA Blood	Phone/Fax :			+6622003000	
Ethnicity :	-	Requested date :			3 January 2021	
Physician :	-	Reported date :			4 January 2021	

HLA-A and HLA-B genotyping; PCR-SSO (TEST CODE 410074)

HLA allele :		
Possibility genotype† :	HLA-A*02:01/31:01	
	HLA-B*15:02/39:01	
Drug/Disease-Gene	**Genotype**	**Therapeutic recommendation (CPIC guideline)**
Abacavir (HLA-B*57:01)	Negative HLA-B*57:01	Abacavir can be used per standard dosing guideline with a normal/low risk of Abacavir hypersensitivity.
Allopurinol (HLA-B*58:01)	Negative HLA-B*58:01	Allopurinol can be used per standard dosing guideline with a normal/low risk of Allopurinol-induced MPE, SJS, TEN, DRESS.
Carbamazepine/Oxcarbazepine (HLA-A*31:01, HLA-B*15:02)	Positive HLA-A*31:01 Positive HLA-B*15:02	This patient has a positive HLA-A*31:01 and HLA-B*15:02 allele marker which associated with Carbamazepine/Oxcarbazepine induced SJS, TEN. If patient is Carbamazepine/Oxcarbazepine-naïve, Carbamazepine/Oxcarbazepine should be avoided.
Co-trimoxazole (HLA-B*13:01, HLA-B*15:02)	Positive HLA-B*15:02	This patient has a positive HLA-B*15:02 allele marker which associated with Co-trimoxazole-induced SJS/TEN. If patient is Co-trimoxazole-naïve, Co-trimoxazole should be avoided.
	Negative HLA-B*13:01	Co-trimoxazole can be used per standard dosing guideline with a normal/low risk of Co-trimoxazole-induced DRESS.
Dapsone (HLA-B*13:01)	Negative HLA-B*13:01	Dapsone can be used per standard dosing guideline with a normal/low risk of Dapsone-induced SJS, TEN, DRESS.
Nevirapine (HLA-B*35:05)	Negative HLA-B*35:05	Nevirapine can be used per standard dosing guideline with a normal/low risk of Nevirapine-induced skin rash.

Notes: †The HLA-B*XX:XX allele was determined by PCR-SSOP method which is intermediate resolution HLA typing. This report is based on The Common and Well-Documented (CWD) database.

** SJS – Steven-Johnson's syndrome, TEN – toxic epidermal necrolysis, MPE – maculopapular exanthema, DRESS – drug reaction with eosinophilia and systemic symptoms.

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Figure 5. Pharmacogenomic panel for *HLA-A* and *HLA-B* genotyping report.

interpretation of genomic test results [101]. Also, a big-data approach must be implemented to consolidate several current resources into larger, more dynamic, and collaborative knowledge bases in the pharmacogenomics of SCARs. Future research should aim to advance our understanding of the genetic basis of drug-induced SCARs and use that knowledge to reduce SCARs cases. A preemptive pharmacogenomics panel testing approach must be implemented to personalize therapy with high-risk drugs [102].

Further research is required to evaluate the cost-effectiveness of pharmacogenomics-guided therapy. More research is required to identify genetic determinants of drug-induced SCARs to help reveal pathogenic mechanisms of drug-induced SCARs.

13. Clinical implementation of *HLA* genotyping for prevention of SCARs in Thailand

Several genetic variants of genes encoding drug-metabolizing enzymes (DMEs) and HLAs have been identified as the risk factors for SCARs, including SJS, TEN, maculopapular exanthema (MPE), and DRESS. Thailand has taken significant footsteps in the field of pharmacogenomics, interpreting genetic test results, and applying genetic information to drug therapy decisions in larger hospitals Several public and private hospitals offer pharmacogenetic screening for the *HLA* genotyping before prescription such as Ramathibodi Hospital (University Hospital) and Bumrungrad International Hospital (Private Hospital). The health insurance system in Thailand has three major schemes for the entire population, which are the Civil Servant Medical Benefit Scheme (CSMBS), the Social Security Scheme (SSS), and the Universal Coverage (UC) scheme [103]. The private health insurance schemes exist in Thailand, providing coverage to the pharmacogenomics services depending on the health benefits package.

The UC scheme, operated by the National Health Security Office (NHSO), has the coverage for *HLA-B*15:02* screening with a reimbursement of 28 USD per person in Thailand [98]. *HLA-B*15:02* testing is mandatory in Taiwan and Hong Kong and is highly recommended as standard of care in Singapore before initiation of carbamazepine therapy [104,105]. The reimbursement for the *HLA-B*58:01* screening test is likely to include within the UC by 2021 in Thailand. Saokaew et al. reported that routine testing for *HLA-B*58:01* in patients being prescribed allopurinol for gout is highly cost-effective in Thailand [90]. *HLA-B*58:01* testing is recommended for Southeast Asian and African-American descent individuals to reduce the occurrence of allopurinol-induced SCARs and related deaths [106]. Moreover, *HLA-B*13:01* for co-trimoxazole and dapsone [46,48,107,108] should be considered include in the UC and strongly recommended before starting prescription.

To effectively implement pharmacogenomics services across the country, some steps need to be followed to ensure that the appropriate evidence and resources are in place to facilitate the successful implementation of pharmacogenomics services. A genetic variant predictive of drug response must be identified for the first time during clinical studies. The clinical validity of the genetic variant must be replicated in an independent cohort of the observed genotype-dependent outcome. Cost-effectiveness analysis, another important characteristic influencing clinical translation, must be assessed to compare the costs of pharmacogenomics screening and health gains. After the genetic screening is proven to be cost-effective, a peer-reviewed guideline for the translation of pharmacogenomics test results is formulated to make clinical decisions. Finally, policymakers capture the potential of pharmacogenomics to meet public health goals through the integration of pharmacogenomics into public health policy [109].

14. Conclusions and future perspectives

In this review, we intended to summarize the significant *HLA* alleles associated with SCARs induced by different drugs in different populations. Both genetic and non-genetic factors
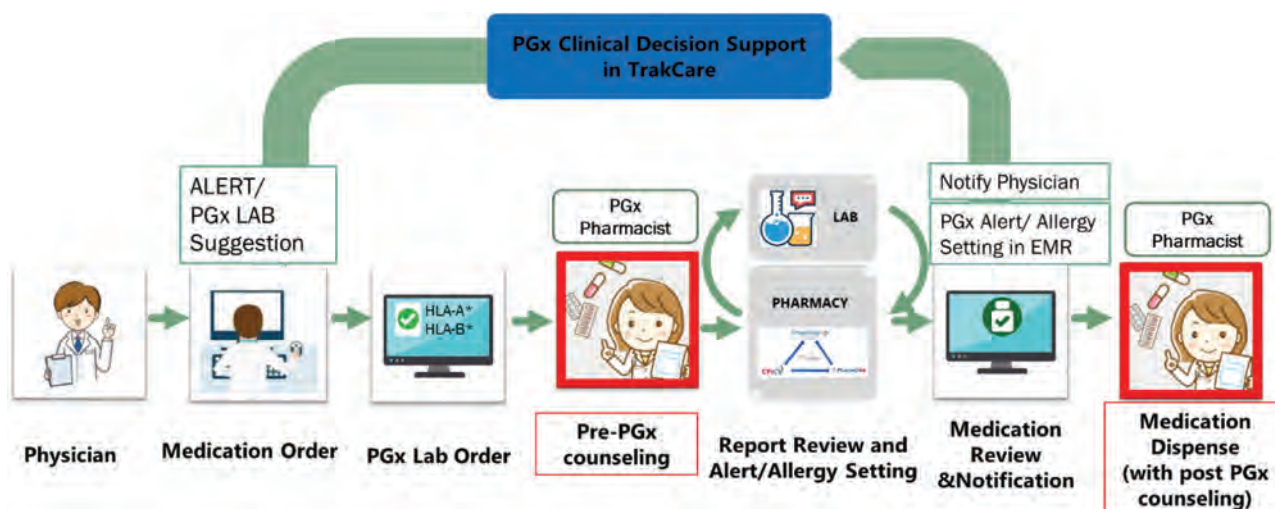

Figure 6. The pharmacogenomics workflow must be arrangement and efficient through the process of handing over of the genotyping results to the patients.
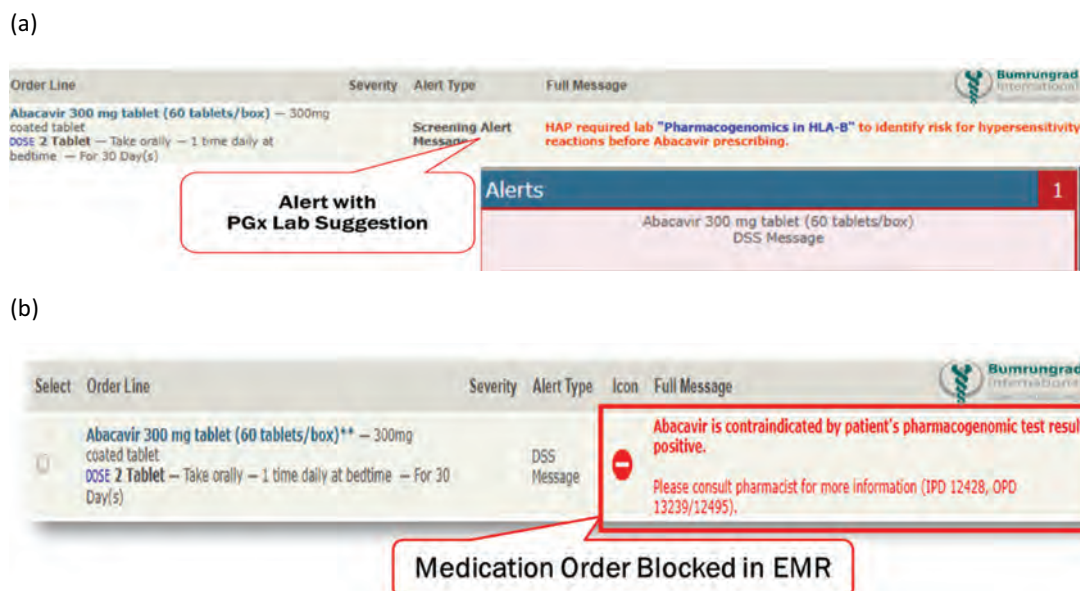
(a)

(b)

Figure 7. The pharmacogenomics clinical decision support (CDS) should be integrated with EMR to deliver synchronous interventions as an example in Bumrungrad International Hospital, Bangkok, Thailand. The pop -up alert in the order entry system advising the clinician to order a pharmacogenomics screening test based on a drug order or pop -up alert prompted by a specific drug -gene interaction (7a). The *HLA* screening results must be incorporated into electronic medical record (EMR) and CDS to support clinicians in the prescribing process (7b).

are involved in drug-induced SCARs. Considering all the evidence favoring *HLA* screening, it is recommended to implement routine screening for the *HLA* risk alleles to prevent drug-induced SCARs in the populations with a high frequency of risk *HLA* alleles such as Thai and South East Asian [99,110]. The frequencies of each *HLA* allele in different populations be found in the public database. We also reviewed the economic evaluations and clinical implementation of pharmacogenomics-based therapy in preventing drug-induced SCARs. In the future, the cost-effectiveness evaluation needs to be conducted for the *HLA* pharmacogenomics-guided treatment, allowing a wider clinical application and supporting the decision-makers and other stakeholders to make implementation decisions.

15. Expert opinion

Establishing the *HLA* risk alleles screening in clinical pharmacogenomics setting requires state – of-the -art laboratory and the multidisciplinary team with highly qualified personnel to perform and delivery high-quality genetic testing. The pharmacogenomics workflow must be arrangement and efficient through the process of handing over of the genotyping results to the patients. The collaboration between physicians and pharmacist is also a key to the successful implementation of pharmacogenomics in clinical settings. Pharmacists should inform and assist physicians and patients in the use and interpretation of pharmacogenomics information. Counselors should provide support and education to the patients that explain what genotyping is and why it was done to facilitate informed decision-making (Figure 6).

Clinical decision support (CDS) alert system is essential to overcome the barriers associated with the generation and utilization of pharmacogenomics guidelines into clinical practice. The pharmacogenomics CDS should be integrated with electronic medical record (EMR) to deliver synchronous interventions

(i.e. pop-up alert in the order entry system advising the clinician to order a pharmacogenomics screening test based on a drug order or a pop-up alert prompted by a specific drug–gene interaction) and asynchronous interventions (i.e. inbox message or e-mail when new pharmacogenomics test results are available). *HLA* screening results must be incorporated into EMR and CDS to aid clinicians in the prescribing process (Figure 7(a,b)).

Insurance companies are reluctant to reimburse pharmacogenomics tests due to a lack of evidence. Evidence-based guidelines can be compiled from the FDA labeling and CPIC guidelines for pharmacogenomics informed therapeutic recommendations. When the routine screening for genetic variants in pharmacogenes associated with prescription drugs is found to be cost-effective, health insurance companies are likely to reimburse routine pharmacogenomics testing.

The successful implementation of pharmacogenomics-based medicine in routine clinical practice will maximize drug efficacy and minimize adverse drug reactions, and decrease the overall cost of health care with the reduction in adverse drug reactions. An increasingly more affordable pharmacogenomics testing, combined with the high risk predicted by *HLA* alleles, allows us to hope that in the near future, the SCARs might be prevented and eradiated by *HLA* screening approach. A standardized

guideline does not exist, and the approach must likely to be varied for different setting, however *HLA-B* genotyping e.g. *HLA-B*1502* (carbamazepine), *HLA-B*5701*(abacavir), *HLA-B*5801* (allopurinol) and *HLA-B*13:01* (co-trimoxazole and dapsone) is strongly recommended before starting prescription. The effective of *HLA* screening on a wider scale in clinical practice requires significant resources, including state-of-the-art laboratory; multidisciplinary team approach and health care provider education and engagement; clinical decision support alert system via EMR; laboratory standards and quality assurance; evidence of cost-effectiveness; and cost of pharmacogenomics tests and reimbursement.

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   To strengthen the utilization of pharmacogenetic testing in hospital, Dr Chonlaphat Sukasem has first invented and launched a pharmacogenetic card approach to prevent SCARs in Thailand. This article also summarised the primary requirements to succeed the clinical implementation of pharmacogenomics as fllowing; (1) pharmacogenetics tools (pharmacogenetic card, precision medicine report and interpretation systems); (2) pharmacogenetics infrastructure and facilities (pharmacogenomics laboratory, (3) pharmacogenomics clinic and pharmacogenetic testing); (4) pre- and post-pharmacogenetics counseling; (5) pharmacogenetic knowledge and education for health professionals; (6) pharmacovigilance system; (7) EMR and training program for the pharmacist to be a pharmacogenetician.

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