Southeast Asian Pharmacogenomics Research Network (SEAPharm): Current Status and Perspectives

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Abstract
Pharmacogenomics (PGx) is increasingly being recognized as a potential tool for improving the efficacy and safety of drug therapy. Therefore, several efforts have been undertaken globally to facilitate the implementation process of PGx.
into routine clinical practice. Part of these efforts include the formation of PGx working groups working on PGx research, synthesis, and dissemination of PGx data and creation of PGx implementation strategies. In Asia, the Southeast Asian Pharmacogenomics Research Network (SEAPharm) is established to enable and strengthen PGx research among the various PGx communities within but not limited to countries in SEA; with the ultimate goal to support PGx implementation in the region. From the perspective of SEAPharm member countries, there are several key elements essential for PGx implementation at the national level. They include pharmacovigilance database, PGx research, health economics research, dedicated laboratory to support PGx testing for both research and clinical use, structured PGx education, and supportive national health policy. The status of these essential elements is presented here to provide a broad picture of the readiness for PGx implementation among the SEAPharm member countries, and to strengthen the PGx research network and practice in this region.

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Background

Pharmacogenomics (PGx) is increasingly being recognized as a tool with the potential to improve efficacy and safety of drug therapy; therefore, several efforts have been made globally to facilitate the process of implementing PGx into routine clinical practice. Although several implementation strategies or models have been described at the institutional level [1–3], at the national or international level, the situations are more complex and require strong collaboration among key stakeholders and collective efforts. One of the efforts that has been made to facilitate the implementation at the national and international levels is the formation of PGx working groups to gather researchers and practitioners with the same interest to conduct PGx research, synthesize, and disseminate PGx data and create PGx implementation strategies. Notable examples of these groups are the Pharmacogenomics Research Network (PGRN) [4] and the Implementing GeNomics In pracTicE (IGNITE) network [5]. In Southeast Asia (SEA), the regional PGx network, namely Southeast Asian Pharmacogenomics Research Network (SEAPharm), was established in 2012 with the support from the Thailand Center of Excellence for Life Sciences (TCELS) [6]. Partners meet annually to share their valuable knowledge for research improvement and to strengthen PGx and medical genomics in the region. The host of the annual meeting alternates among the partners.
Pharmacogenes. Greece and the United Arab Emirates will participate as controls in this re-sequencing project in addition to genomic sequences of different populations that we can obtain from the 1,000 Genomes Project [12]. In preparation for this multinational study, and to ensure a smooth translation of PGx from research to clinical practice, a cross-sectional survey on the current status and perspective on PGx implementation at the national level was developed and distributed to all representatives from the SEAPharm member countries. The data from this survey are intended to describe the landscape of the essential elements for PGx implementation among the SEAPharm member countries, along with the barriers and concerns in relation to PGx implementation.

**Essential Elements for PGx Implementation among the SEAPharm Member Countries**

Successful PGx implementation at the national level requires several stakeholders to be involved. From the perspective of SEAPharm member countries, there are 6 key elements that are essential for PGx implementation: maintaining a pharmacovigilance (PV) database, the existence of an active PGx research community, economic research capabilities, dedicated laboratories to support PGx testing for both research and clinical use, structured PGx education, and supportive national health policy (Fig. 1). The availability and alignment of these elements are crucial and require efforts and strong collaboration among stakeholders, such as related government agencies, biomedical scientists and researchers, healthcare professionals, information technologists, and pharmaceutical industries. To date, Singapore and Thailand are the only two Southeast Asian countries where PGx implementation has been successfully adopted at the national level (Fig. 2), while the efforts to facilitate PGx implementation are being carried out enthusiastically in other SEAPharm member countries.

**PV and ADRs Reporting Systems**

A well-established PV system at the national level is the first key element for PGx implementation. It allows researchers to have access to valuable data, especially those related to uncommon ADRs such as SJS, TEN, or DILIs, to conduct epidemiologic and genetic association studies between ADRs (phenotypes) and certain types of genetic variation (genotypes). Reliable data from PV systems do not only help enhance the quality of PGx research but also enable accurate health economic studies of which

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**Fig. 1.** Key elements for PGx implementation. ADR, adverse drug reaction; PGx, pharmacogenomics/pharmacogenetics.

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the findings can then be fed into the decision-making process of PGx implementation.

According to the data from the SEAPharm members, all participants have implemented the PV system in their respective countries (Fig. 2). The ADR reporting systems adopted by all countries but Myanmar are both paper- and web-based. Presently, only a paper-based reporting system is available in Myanmar (online suppl. Table S1; for all online suppl. material, see www.karger.com/doi/10.1159/000502916). Although most of the member countries have developed their own national ADR reporting systems to record individual case safety reports, Brunei Darussalam and Nepal have respectively adopted the Vigiflow™ and Vigibase™ web-based system of the World Health Organization (WHO) Program for International Drug Monitoring (WHO-PIDM). However, regardless of the differences in the ADR reporting systems, it is worth noting that, other than Myanmar, all member countries of SEAPharm have also signed up to the WHO-PIDM, which requires the responsible organization in each country to eventually submit all ADR data to the program [13]. While this may facilitate the sharing and/or pooling of ADR data among member countries for potential PGx research, the reliability and quality of these data must be thoroughly evaluated, and data standardization will be necessary to minimize discrepancies in individual case safety reports from inconsistent conformation to the specific format setup by the WHO-PIDM.

Interestingly, despite the existence of PV systems in all SEAPharm member countries, ADR data including incidence, prevalence, and mortality data of SCARs and DILI are not available in several countries (online suppl. Table S2), while those with available data were not all extracted from the WHO-PIDM database but from local PV authorities and research studies. This raises a concern on the effectiveness of some of the systems in capturing the true ADR status within each country. Furthermore, economic burden data for SCARs are only available from Indonesia, Singapore, and Thailand while those for DILI are not available in any of the SEAPharm member countries.
PGx and Health Economic Research

Both PGx and health economic research are vital for demonstrating whether PGx testing for each drug-gene pair is clinically beneficial and financially viable [14]. However, it is important to note that efforts to promote and conduct PGx research should be placed as the top priority in all countries. The associated health economic studies cannot be undertaken when PGx data and findings are not available. In addition, given the differences in genetic epidemiology and diversity of at-risk alleles among the different countries, the importance of conducting individual PGx research in each of the countries is, therefore, obvious. Availability of such population- and national-specific PGx data can help key stakeholders, such as national policy makers or administrative staff in the hospital, to have a clearer picture on how PGx can have an impact on and improve the current health challenges faced by the individual country. At this point, although information on the types, scope, and quality of PGx research conducted in each member country were not addressed during this survey, majority of the SEAPharm member countries have either undertaken or started to conduct PGx research in one form or another (Fig. 2).

In contrast to PGx research, health economic research, such as cost-effectiveness analysis, has only been conducted in less than half of the SEAPharm member countries, namely Indonesia, Malaysia, Singapore, and Thailand. The health authority, such as the Ministry of Public Health, in each country will need these data to create policies such as conditions for reimbursement, health benefit packages, or patient groups to be covered if widespread PGx testing is to be made available in the country.

Dedicated Laboratory Facilities to Support PGx Testing

Along with the effort to conduct PGx research, laboratory facilities with capability or potential to perform PGx testing for the actionable drug-gene pair must also be available. According to the responses, half of the member countries have laboratories capable of performing PGx testing to support their research in PGx; and the majority of these countries also have laboratories with capability to support clinical PGx services. Those laboratories are able to perform genotyping for drug-metabolizing enzyme genes such as \textit{CYP}, \textit{TPMT}, or \textit{UGT1A1}; human leukocyte antigen (\textit{HLA}) genes; and/or other drug transporters or proteins such as \textit{SLCO1B1} or \textit{VKORC1}. However, the number and type of PGx testing among the SEAPharm member countries are different (online suppl. Tables S3, S4, S5). The available PGx testing is a mixture of commercial tests and local laboratory-developed tests. In addition, a total of less than 10 laboratories dedicated to PGx testing are available in the SEAPharm member countries. This alarmingly low number reflects a rather imbalanced presence of such facilities in the main healthcare centers of all countries.

Supportive National Health Policy for PGx Implementation

Globally, majority of the PGx implementation exists at an institutional level as clinical PGx services in hospitals. However, one of the limitations for these services is the running costs to sustain them in the long run. Supportive regulation or national health policy for PGx testing is essential for facilitating PGx implementation across a country and also for promoting sustainability of clinical PGx services that have already been established in hospitals [15]. To date, only Singapore and Thailand have health policy for PGx testing. However, the coverage is limited to the testing for \textit{HLA-B*1502} in the patients newly started on carbamazepine with the aim to prevent SJS/TEN.

Health technology assessment, widely used as a method to determine national reimbursement policies for new therapeutics, is needed in evaluating the values of PGx testing from the point of clinical and health economic perspectives. Organizations with the capability to provide such data to the national health authority are needed in each country to facilitate the decision making process for PGx implementation.

Structured PGx Education

Several PGx education approaches have been proposed and adopted, including intracurricular coursework; postgraduate training program in PGx; provisioning of PGx online resources, such as massive open online courses; traditional continuing education program; and internal PGx training within institution [15]. Among SEAPharm member countries, most countries have didactic lectures or coursework related to genetics and/or pharmacogenetics as part of the curricula for students at the undergraduate level. However, PGx education for students at the graduate level, including Doctor of Pharmaco-
cy, residency training, Master and Doctor of Philosophy programs, is mainly available as learning modules (online suppl. Table S6). Specific training or education programs dedicated to PGx have not been established at this time. Conference and hands-on workshops for PGx have been held in almost half of the member countries. Online resources for PGx education are available as articles or recorded presentation from PGx conferences posted on websites. Based on the current data, PGx education in most of the SEAPharm member countries seems to be either lacking or fragmentary. Hence, attention should also be paid on the creation of structured PGx education and training to strengthen involved personnel and to ensure the sustainability and effectiveness of PGx implementation. The development of regional PGx educational resources may help speed up the capacity-building process in SEA.

### Barriers and Concerns Related to PGx Implementation

As mentioned before, many factors can affect the PGx implementation process. In addition to the key elements identified thus far, several other issues should also be looked at to ensure the success and sustainability of the implementation plan. From the opinions and perspectives of the SEAPharm member countries, common barriers or concerns towards PGx implementation are listed in Table 1.

Research funding is the top concern highlighted by all member countries; even in Singapore and Thailand where PGx implementation have already been rolled out. Awareness for PGx, acceptance by clinicians, and availability of personnel with experience or expertise in PGx and the lack of structured education and training in PGx are the other important barriers and concerns that can greatly delay the PGx implementation process. Efforts to resolve these issues also require time and initiation from key stakeholders at the national level.

Electronic medical record (EMR), as a tool to maximize the utilization of PGx data in practice, is another important element that is essential for the success of PGx implementation. More importantly, EMR with integrated clinical decision support (CDS) tools capable of facilitating and informing clinicians on the most appropriate patient care decision when PGx data are available should be made available. Even though EMR is available in most SEAPharm member countries, except Myanmar (online suppl. Table S7), the proportion of hospitals with EMR system ranges widely from approximately 15 to 100% in the different member countries. The EMR systems used in each country are varied and different in terms of system providers and the numbers of system used. Such varia-

<table>
<thead>
<tr>
<th>Barriers</th>
<th>Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Research related</em></td>
<td><em>1. Sustainability of research funding</em></td>
</tr>
<tr>
<td>1. Lack of PGx research funding</td>
<td><em>2. Uncertainty of economic situation</em></td>
</tr>
<tr>
<td>2. Lack of PGx research collaboration</td>
<td><em>3. Lack of awareness for PGx</em></td>
</tr>
<tr>
<td>3. Lack of research management</td>
<td><em>4. Limited access to PGx data or medical records</em></td>
</tr>
<tr>
<td>4. Lack of structured education and training in PGx research</td>
<td><em>5. Lack of pharmacovigilance data</em></td>
</tr>
<tr>
<td><em>Personnel/infrastructure/facility related</em></td>
<td><em>6. Ethical concerns</em></td>
</tr>
<tr>
<td>1. Lack of experts or clinicians with experience in PGx research/practice</td>
<td><em>7. Acceptance from clinicians</em></td>
</tr>
<tr>
<td>2. Insufficient facility or infrastructure to support PGx research/service</td>
<td><em>8. Being technology recipient</em></td>
</tr>
<tr>
<td>3. Variety of EMR systems</td>
<td><em>9. Understanding about PGx testing among clinicians and the public</em></td>
</tr>
<tr>
<td><em>Health policy or system related</em></td>
<td><em>10. Religious concerns</em></td>
</tr>
<tr>
<td>1. Lack of national policy or guideline for PGx testing</td>
<td></td>
</tr>
<tr>
<td>2. Lack of health technology assessment</td>
<td></td>
</tr>
<tr>
<td>3. Lack of good pharmacovigilance system</td>
<td></td>
</tr>
<tr>
<td>4. Lack of reimbursement for PGx testing</td>
<td></td>
</tr>
<tr>
<td><em>Others</em></td>
<td></td>
</tr>
<tr>
<td>1. Lack of awareness for PGx</td>
<td></td>
</tr>
<tr>
<td>2. Lack of support from clinicians</td>
<td></td>
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<tr>
<td>3. Small population size</td>
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PGx, pharmacogenomics/pharmacogenetics; SEAPharm, Southeast Asian Pharmacogenomics. *Indicated for the answers/responses selected by more than half of the member countries.*

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Chumnumwat et al.
Pharmacogenomics Implementation Status in Southeast Asia

education is particularly pronounced in Malaysia, Philippines, and Singapore. Therefore, integration of CDS tools to support clinical application of PGx data can be challenging among these countries, especially when the capability to integrate PGx data into the systems is not known.

Conclusions

The status of the essential elements required to support PGx implementation are different in each SEAPharm member country (Fig. 2). Therefore, the needs for each country are also different. Top priorities in each country might be placed for elements that are unavailable; while, the available elements may require a more thorough evaluation to ensure the optimal quality.

PGx research has either just started or is in progress in the majority of member countries; however, insufficient facilities to support and sustain PGx research is common among them. Member countries have agreed that sharing of PGx knowledge and technology can be a potential step in easing this issue. Financial support from national authorities is seen as an important solution to bring down the barriers arising from a shortage in personnel with PGx expertise/experience and insufficient infrastructure and facilities for PGx research.

In member countries where PGx has already been adopted at the national level, there are still other issues, especially those playing out at the institutional or hospital level, which need to be overcome. They include knowledge and attitude towards implementation of clinical PGx services among clinicians and administrative staff, a proper model or workflow for clinical PGx service, PGx education for clinicians, and integration of PGx data into EMR with CDS tools [2, 16]. In addition, expanding the list of drug-gene pairs covered by national health policy is seen as a future goal achievable when sufficient PGx and health economic data are generated to aid in the decision-making process.

Efforts to implement PGx into clinical practice are proceeding at different rates in the member countries, with some only starting the discussion while others are either underway or have already been adopted at the national level; e.g., the screening for HLA-B*1502 for carbamazepine prescription in Singapore and Thailand. Nevertheless, all SEAPharm member countries realize the importance and potential benefits of PGx implementation on the healthcare system in their respective countries. All share the same vision of aiming to reduce unnecessary healthcare costs from inefficient or inappropriate drug therapies by maximizing the effectiveness of drugs and minimizing adverse drug events.

Statement of Ethics

Ethical approval is not applicable for this paper.

Disclosure Statement

The authors have no conflicts of interest to disclose.

Author Contributions

All authors were involved in the creation of the concept and the writing of the manuscript.

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