



A precision medicine approach to personalized prescribing using genetic and nongenetic factors for clinical decision-making



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ARTICLE INFO

Keywords:

Precision medicine
Pharmacogenomics
Knowledge representation
Decision making
Personalized prescribing
Polypharmacy

ABSTRACT

Screening potential drug–drug interactions, drug–gene interactions, contraindications, and other factors is crucial in clinical practice. However, implementing these screening concepts in real-world settings poses challenges. This work proposes an approach towards precision medicine that combines genetic and nongenetic factors to facilitate clinical decision-making. The approach focuses on raising the performance of four potential interaction screenings in the prescribing process, including drug–drug interactions, drug–gene interactions, drug–herb interactions, drug–social lifestyle interactions, and two potential considerations for patients with liver or renal impairment. The work describes the design of a curated knowledge-based model called the knowledge model for potential interaction and consideration screening, the screening logic for both the detection module and inference module, and the personalized prescribing report. Three case studies have demonstrated the proof-of-concept and effectiveness of this approach. The proposed approach aims to reduce decision-making processes for healthcare professionals, reduce medication-related harm, and enhance treatment effectiveness. Additionally, the recommendation with a semantic network is suggested to assist in risk–benefit analysis when health professionals plan therapeutic interventions with new medicines that have insufficient evidence to establish explicit recommendations. This approach offers a promising solution to implementing precision medicine in clinical practice.

1. Introduction

Precision Medicine (PM) is an emerging paradigm in disease treatment and prevention that departs from the “one-size-fits-all” approach, aiming to tailor interventions based on individual differences in people’s genes, environments, and lifestyles [1,2]. The accessibility of analytical technology and innovation has significantly contributed to the growth of PM in the global market. In 2023, the PM market has experienced a notable increase of 14% [3]. PM is a potential digital innovation in healthcare providers that are expected to achieve mainstream adoption within the next five to ten years [4]. Furthermore, it stands as one of the prominent megatrends in the context of the fourth industrial revolution [5].

Since the Human Genome Project was completed in 2003 [6], genetic factor is one of biological factors that help in the diagnosis, prognosis, and treatment of individual characteristics of each patient. A number of studies on this matter has potentially increased after the success of Human Genome Project, intending to understand the relations between genetic variation and drug responses in terms of efficacy or harm under the research area of Pharmacogenomics (PGx) [7,8]. The PGx has been applied in several areas of medicine and plays an important role in PM [9–11]. Knowledge from PGx is compiled and summarized to clinical recommendations that can be used as decision support tools in routine clinical practice [12–14].

To achieve tailored treatment for individual patients based on PM, healthcare professionals who are related to prescribing process, like

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physicians or pharmacists, must integrate multidimensional factors, both non-genetic factors and genetic factors, to provide precise treatments for each patient. When PGx testing results affect that drug response in terms of pharmacokinetics or pharmacodynamics, this interaction is referred to as drug–gene interaction (DGI) [15,16]. PGx testing can help identify DGI, allowing for personalized prescribing and optimization of drug therapy based on an individual's genetic makeup. In addition, the potential interaction (PI) from non-genetic factors such as drug–drug interaction (DDI), drug–herb interaction (DHI), the interaction between drug and social lifestyles like alcohol drinking, smoking, or excessive caffeine consumption (DSI) together with potential consideration (PC) for patients based on liver function (LF), renal function (RF) are reviewed and screened along with DGI for personalized prescribing that toward PM [17–19].

The risk–benefit analysis for intervention planning in present times focuses on minimizing the medication's harm such as PI and PC, while keeping its efficacy. However, the incident rate of medication-related harm has highly increased [20]. These harms were possibly found in patients, especially in elderly patients who have comorbidities or comediations. This population group is gradually increasing and will become a major group of population in the world within ten years [21]. Thus, the intention to prevent medication-related harm is one of the global challenges on the topic of medication safety in polypharmacy [18].

In real-world clinical practice, screening and identification of PI and PC in prescription process are retrieved from various screening tools or resources, which are heterogeneous in data formats, different reporting pattern and interpretation. For example, DDI checker tools, and LF/RF prescribing information [22,23], DHI recommendation [24], DSI management information from factsheet in clinical setting, and DGI prescribing guidelines [25,26]. One of the most important skills for health professionals as clinical pharmacists is clinical reasoning, which leads to clinical decision making in treating patients appropriately and just in time [27] but the results from clinical decision support tools are stratified. Thus, healthcare professionals use great efforts, spend a lot of time, and labor-intensive in order to gather all of PI and PC, assess the risk–benefit of each drug in prescription, and making the final prescription that is precise for the individual patient. In a real setting, it is difficult to decision making the best treatment, especially in urgent situations. Moreover, screening for PI and PC in patients can be complex and ambiguous in elderly patients because this population group have comorbidities and receive prescriptions from several physicians during the same visit [28]. This current approach is shown in Fig. 1. We can see that it involves acquiring the patient's personal health information, which includes PI and PC data. This information is used as input for the decision processes. In addition, these processes require access to relevant databases to support decision-making. The results of the judgments for each factor are then sent to the physician and pharmacist for consideration of the patient's risk and benefit. Based on this evaluation, a final prescription is obtained.

The concept of knowledge representation is critical in the field of healthcare, as it enables healthcare professionals to capture and store essential medical information in a way that is easily accessible and understandable. By providing access to a wealth of medical knowledge and expertise, knowledge representation facilitates better decision-making, ultimately leading to improved patient care [29–31]. A collection of well-known facts transformed into a data model based on the concept of knowledge representation is known as a knowledge-based [29]. When it comes to the field of information storing and organizing, the relational database stores data in tables composed of rows and columns. Each table represents a different type of data, and the tables are linked together using keys to establish relationships between them. This type of database is widely used in many applications due to its versatility and scalability [32]. Knowledge-based, on the other hand, is built on top of databases to provide a

way to store and organize information in a way that is easily accessible and searchable. Some examples of knowledge-based include semantic networks, ontologies, logic-based frameworks, or probabilistic models [30]. Knowledge-based is a structured repository of high-level information that can facilitate the development of intelligent systems capable of reasoning, learning, and making informed decisions based on data-driven insights.

According to the reviews [33–35], they report the studies presenting ideas towards personalized prescribing referring to the PGx factor as a major factor of PM principle. PGx applications, such as DGI screening tools, are being implemented widely in the USA and Europe and are integrated into Health Information Systems (HIS). The review of screening factors used in studies for personalized prescribing is shown in Table 1. There are studies of concept in screening with multidimensional factors and screening tools, which is a prototype that practically works [17,36–38]. These studies do not include DHI or DSI as part of personalized prescribing based on PM. Furthermore, most studies that have developed into applications are mainly not conducted with a knowledge-based. Therefore, an interpretation can only sometimes be up-to-date in case new knowledge is acquired [39–46].

Several works advised improving decision-making by managing heterogeneous knowledge from various sources and formats, making it actionable, curated, and convenient for health experts [47–49]. To address the limitations of the screening approach in prescription based on PM, expansion of DGI screening tools together with other PI and PC to screening tools that powerful approach and practice-oriented models have challenged for healthcare transformation to PM era [33,35,37,50, 51].

This work proposes an approach for precision medicine that can aid clinical decision-making through a Clinical Decision Support Tool (CDST). Unlike previous tools, this is the first CDST that combines both genetic and non-genetic factors, with a specific focus on PI. It encompasses DGI, DDI, particularly DHI, DSI, and incorporates PC based on LF, and RF. Three main contributions of this work can be given as follows:

1. We designed a curated knowledge-based practice that is actionable and ready for use in clinical decision support systems. This practice is called the Knowledge Model for PI and PC Screening (KM2PS).
2. We developed screening logic for PI and PC, which include detection and prediction modules.
3. We proposed the implementation of KM2PS as a screening tool for personalized prescribing to facilitate risk–benefit analysis in clinical decision-making for health professionals. Three case studies, a virtual case, a case report and a real case, are used to demonstrate the effectiveness and the proof-of-concept of this approach, respectively.

This paper is structured as follows: Section 2 describes an ideal approach for personalized prescribing. Section 3 explains the prescription screening process in detail. In Section 4, we present the design of KM2PS and validate the approach with three case studies. Section 5 discusses the findings, and Section 6 presents the conclusions.

2. The proposed personalized prescribing system

An approach to better screening, decrease screening time, and facilitate decision-making for personalized prescribing is shown in Fig. 2. The process starts with input, which includes prescription and patient health information such as medication profile, PGx testing data, liver and renal function, list of herbs being used, and social lifestyle. The input then goes through the screening logic, KM2PS, report generator, and risk analysis design making to generate a personalized prescription output. This process automates the screening process, decreasing the time it takes to get recommendations and facilitating decision-making for healthcare professionals. The details of each process are explained as follows.

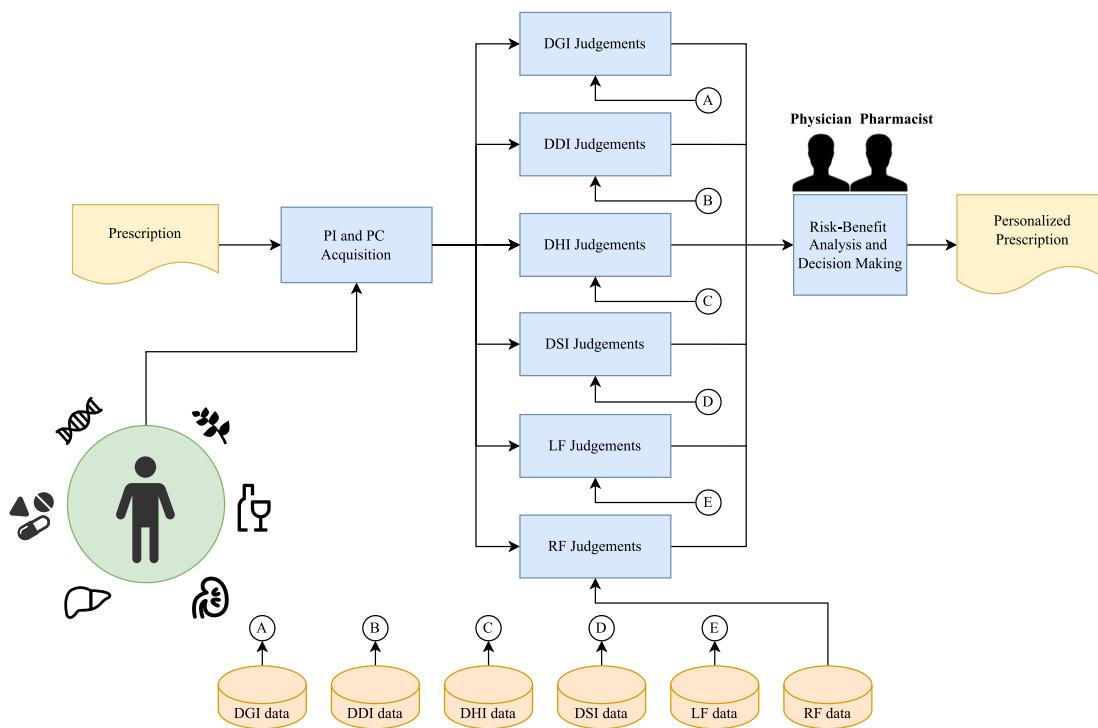


Fig. 1. The current approach of prescription screening.

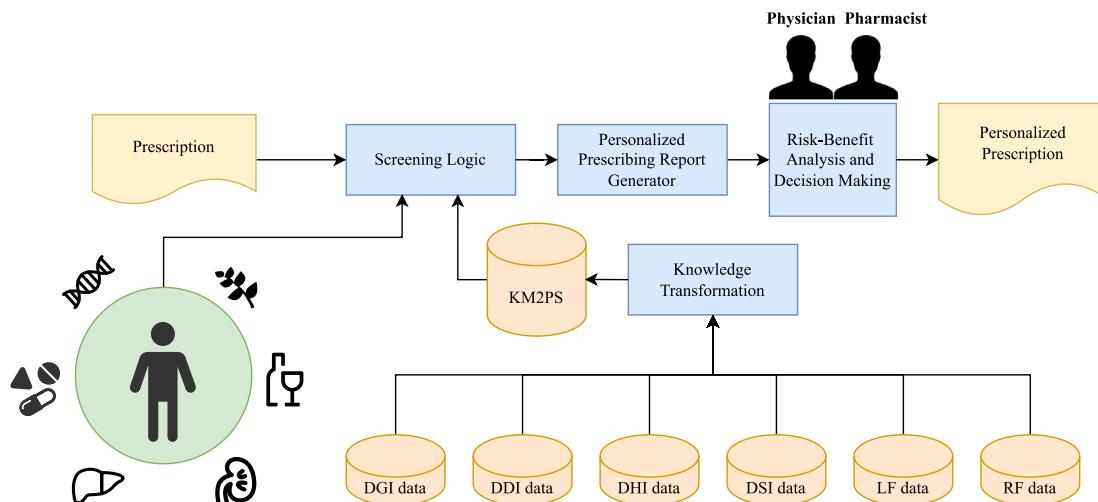


Fig. 2. The proposed personalized prescribing system.

Table 1
The comparison of studies for personalized prescribing and screening factors.

Reference No.	Type of work		Screening factors					
	Conceptual	Implementation	DGI	DDI	DHI	DSI	LF	RF
[17]	✓	–	✓	✓	–	–	✓	✓
[38]	✓	–	✓	✓	–	–	✓	✓
[36]	✓	–	✓	✓	–	–	–	–
[37]	✓	–	✓	✓	–	–	–	–
[39]	–	✓	✓	✓	–	–	–	–
[40]	–	✓	✓	✓	–	–	–	–
[41]	–	✓	✓	✓	–	–	–	–
[42]	–	✓	✓	✓	–	–	–	–
[43]	–	✓	✓	–	–	–	–	–
[44]	–	✓	✓	–	–	–	–	–
[45]	–	✓	✓	–	–	–	–	–
[46]	–	✓	✓	–	–	–	–	–

2.1. Knowledge transformation and KM2PS

Knowledge transformation refers to the process of extracting knowledge from various sources, including DGI, DDI, DHI, DS, LF, and RF data. This extracted knowledge is then transformed and integrated into a knowledge model, KM2PS, which serves as a screening tool for personalized prescribing. The process of transforming knowledge, based on the concept of knowledge representation, involves the extraction and integration of diverse information related to prescription screening, including the identification of entities and relationships between them. These entities and relationships are then defined as classes and super-classes encompassing domain knowledge, which determines an entity's generalization [52].

KM2PS is designed to facilitate the clinical decision-making process by providing healthcare professionals with a personalized prescription report highlighting potential drug-drug interactions, drug-herb interactions, liver and renal function concerns, and other patient-specific factors that may affect medication safety and efficacy. The system utilizes a screening logic component that merges the screening criteria with the clinical judgment and expertise of precision medicine specialists to generate personalized recommendations for each drug.

2.2. Screening logic

The criteria for identifying PI and PC involves reviewing each pair of medications in a prescription and evaluating specific factors, including the drugs being used, PGx testing data, herbal supplements, social lifestyle factors, and the patient's liver and renal function. Screening logic is an automated process that utilizes patient-specific information, as described above, to identify such occurrences. The screening logic is designed to decrease the human workforce and screening time, thus improving the efficiency of the process. From the process of knowledge transformation, all pairs of PI and PC are contained in KM2PS as explicit criteria, I_{km} . These criteria are then encompassed within the screening logic component, which screens the prescription and sends the results to the report generator.

2.3. Personalized prescribing report generator

A personalized prescribing report (PPR) generator is a component that generates a personalized report based on the screening results. It takes input from the screening logic module and generates a specific report for the patient. The report includes recommendations for each drug based on the identified PI and PC and other patient-related factors such as age, gender, and comorbidities. The report also includes information on the severity of the identified PI and PC and the level of evidence supporting the recommendation. The report is designed to be clear, concise, and easily understood by healthcare professionals to aid in decision-making for appropriate drug interventions for their patients.

2.4. Risk–benefit analysis and decision making

Risk–benefit analysis and decision making is the final step in the process of personalized prescribing. It involves evaluating the personalized prescribing report generated by the PPR generator and conducting a comprehensive risk–benefit analysis to determine the best course of action for the patient by health professionals such as physicians or pharmacists. The risk–benefit analysis weighs the possible harm of the prescription, such as adverse medication responses or drug–drug interactions, against the potential benefits, such as improved health outcomes.

After weighing the risks and benefits, the final decision on the precise prescription option for the patient can be made. This decision is based on the output of the personalized prescription report, the results of the risk–benefit analysis, and the healthcare professional's clinical knowledge and judgment experience. The goal of risk–benefit analysis and decision-making is to ensure that the patient receives the best possible treatment while minimizing the potential for harm.

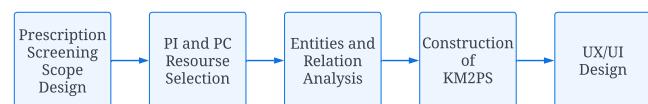


Fig. 3. Simple diagram of the development process.

3. System development process

In this section, the development process for the proposed system is presented as shown in Fig. 3. Five key steps involve identifying the scope of the prescription screening process, selecting the appropriate PI and PC resources for the screening process, analyzing the entities and relations between the data in these resources, constructing the KM2PS, and developing the UX/UI. Each of these steps is detailed in the paper, providing a comprehensive guide to implementing KM2PS in a clinical setting.

3.1. Prescription screening scope design

To define the scope of prescription screening that is actionable practice and ready to be used, we consult with PGx-trained specialists such as pharmacists or medical scientists at Pharmacogenomics and Personalized Medicine (PPM) in Ramathibodi Hospital, Mahidol University, Thailand. This specific setting utilizes PGx for therapeutic intervention planning specifically for Thai patients covered under the Universal Coverage Scheme. Next, we analyze the method of prescription screening by using existing PI and PC resources. Then, the critical points in prescription screening are extracted into the 11 requirements. Finally, the following requirements will be the scope of personalized screening in prescription screening for this study.

1. The approach could detect PI and PC.
2. If any PI or PC occurs, the approach could provide the interaction type of that PI or PC.
3. If any PI or PC occurs, the approach could provide the drug information and interaction factors of that PI or PC.
4. If any DGI occurs, the approach could provide the alleles information, predicted genotype, predicted phenotype of that DGI.
5. If any DDI occurs, the approach could provide the drug ability of that DDI.
6. If any DHI occurs, the approach could provide the herb ability of that DHI.
7. If any DS occurs, the approach could provide the social lifestyles ability of that DS.
8. If any PI or PC occurs, the approach could provide the recommendation of that PI or PC.
9. If any PI or PC occurs, the approach could provide the recommendation level of that PI or PC.
10. If any PI or PC occurs, the approach could provide the recommendation summary of that PI or PC.
11. If any PI or PC occurs, the approach could provide the reference of that PI or PC.

By adhering to these requirements, we aim to improve the accuracy and efficiency of prescription screening and promote informed decision-making for personalized prescribing.

3.2. PI and PC resource selection

KM2PS construction requires knowledge related to potential drug interactions, which can be acquired from various tertiary drug information databases commonly used by health experts at PPM. These databases include Clinical Pharmacogenetics Implementation Consortium (CPHARM) [25], Pharmacogenomic Knowledge Base (PharmGKB)

[53], and Table of Pharmacogenomic Biomarkers in Drug Labeling by the US Food and Drug Administration (USFDA) [26], which provide information on pharmacogenomics and clinical recommendations when DGI occurs. Additionally, Lexicomp [54], DailyMed [55], and Drugbank [56] are major resources for clinical recommendations related to DDI, LF, and RF. For DDI caused by cytochrome P450, the Drug Interactions Flockhart Table [57] is a useful resource that categorizes interactions as “Inhibitor”, “Inducer”, or “Substrate”. The “Medplant” database from Mahidol University, Thailand [58] is a valuable resource for DHI information on commonly used Thai herbs, along with clinical suggestions. To manage the interactions between social lifestyles and drugs, literature reviews are gathered and recorded in personal documentation such as fact sheets (PPMSheet) or PDF files. For KM2PS prototype development, CPHARM was chosen as the DGI resource due to its popularity [54]. Flockhart, Medplant, and PPMSheet were chosen as the resources for DDI, DHI, and DSI, respectively, due to their simple categorizations that aid in risk–benefit analysis. DailyMed was chosen as the resource for LF and RF due to the clear organization of drug monographs [55].

3.3. Entities and relations analysis

We consider data from already-existing PI and PC resources as previously described to understand the knowledge concept, vocabulary, lexical, specific terms, and knowledge structure. A semantic network such as a knowledge graph has been chosen as the knowledge representation method to represent the criteria for identifying PI and PC in KM2PS [59]. Next, the vocabulary, lexical, and specific terms are defined as entities and relations between entities that cover the prescription screening scope. These entities and relations will represent the well-known facts of PI and PC screening. Moreover, we generalize concepts of prescription screening based on PM to sets of classes and superclasses that encompass domain knowledge. These classes are attributes that determine the metadata of an entity.

Fig. 4 shows an example of entities, relations, and classes enumeration of DGI prescription screening from Guideline for Proton Pump Inhibitors and CYP2C19 (GPC) [60]. The information presented in the blue box is generalized to the class “Gene”, while the variant forms of a gene that occur at the exact location, referred to as alleles such as *1, *17, or *9 in the grey box, are generalized to the class “Allele”. The combination of two alleles that specify an organism’s genetic material, referred to as pairs of alleles such as *17/*17, *1/*17, or *1/*9 in the red box, are generalized to the class “Predicted_genotype”. The observable characteristics of an organism resulting from its genotype in the green box are generalized to the class “Predicted_phenotype”. The relation between the instants of Gene class and Predicted_phenotype class is defined as “has_phenotype” relation. In contrast, the relation between the instants of Gene class and Predicted_genotype class is defined as the “has_genotype” relation. To provide an example of entity definition, we define the *1, *17, and *9 instances as entities. These entities are assigned to the “Allele” class. Similar to the method for entity definition of metabolizer, namely “ultrarapid metabolizer”, “rapid metabolizer”, and “normal metabolizer” instances are defined as entities, which these entities can be specified as the class “Predicted_phenotype”.

3.4. Construction of KM2PS

Although most knowledge models from various applications are suitably designed and managed for structured data, around 80% of all data in daily life are unstructured and inevitable, even data structures in the medical knowledge domain [61]. It seems that the representation of knowledge as knowledge graph has more advantages than relational databases [32,62,63]. In this study, KM2PS is divided into two layers: the concept layer and the instant layer. The concept layer presents components like classes or superclasses that describe the prescription screening scope, while the instant layer is constructed to store entities and relations. More details and an example of KM2PS are described in Section 4.1.2.

3.5. UX/UI design

UX/UI design is critical to integrating KM2PS into CDST as a screening tool for the prescribing-assessment process. The required inputs for KM2PS must be presented user-friendly and intuitively to ensure a seamless experience for healthcare professionals. To achieve this, the data must be prepared as suitable sets for retrieval on KM2PS with clear labels and categories that align with the healthcare professional’s workflow. The sets’ members depend on the PI and PC types declared in the concept layer, which should be presented clearly and organized. The detection module and inference module of CDST’s screening logic must be designed to provide clear and concise feedback to the user about the detected PI and PC and any potential drug interactions.

Additionally, the PPR generated by the system must be presented in a way that is easy to read and interpret. The report should include relevant information such as the detected PI and PC, potential drug interactions, and recommendations for alternative drug interventions. The report’s UX/UI design should consider the healthcare professional’s preferences for displaying information and ensuring that the report is provided in a clear and orderly manner to aid decision-making. The UX/UI design of the report should consider the healthcare professional’s preferences for displaying information and ensure that the report is presented clearly and organized to facilitate decision-making.

4. Design and validation results

This section presents the results of the development and evaluation of the proposed system. It is divided into two sub-sections, with the first part discussing the design results and the second part presenting the validation results. The design results sub-section outlines the key components of the proposed system, including the KM2PS, the screening logic, the input interface design, and the personalized prescribing report. The validation results sub-section presents the outcomes of both virtual and real case studies that were conducted to evaluate the effectiveness of the proposed system.

4.1. Design results

4.1.1. Activity diagram of the proposed system

The proposed system is performed as the object-oriented conceptual model by the standard Unified Modeling Language (UML) diagram. The UML activity diagram in **Fig. 5** illustrates the activities performed by the proposed prescription screening tool during the prescribing process. The physician assesses the patient’s problems based on the existing information obtained from the patient and the medication history retrieved from the HIS. Subsequently, the prescription is created and stored in the HIS. The pharmacist receives the prescription and screens it for PI and PC by retrieving patient parameters from the consultation with the patient and from the HIS. Once the gathering of patient parameters is completed, the pharmacist submits these parameters into the Prescription Screening Tool to identify any PI and PC in the prescription. The personalized prescribing report is established after successfully screening the prescription. This report is utilized to analyze the risk–benefit of each drug in the prescription, and the final decision is assessed by the physician. After the final decision is made, the prescription is modified and updated in the HIS. The modified prescription is then prepared and dispensed to the patient by the pharmacist.

4.1.2. KM2PS model

To develop the prototype of KM2PS, six knowledge resources are reference delegates that are actionable practices for prescription screening. The superclasses and classes in **Table 2** such as Allele, Drug, Gene, or Herb, are generalized for describing the concept of PI and PC. After transforming these resources into a ready knowledge-based format, we could find entities with the same classes. These entities are not held in

Gene		
Predicted phenotype	Genotype	Examples of CYP2C19 diplotypes ^a
CYP2C19 ultrarapid metabolizer	An individual carrying two increased function alleles	*17/*17
CYP2C19 rapid metabolizer	An individual carrying one normal function allele and one increased function allele	*1/*17
CYP2C19 normal metabolizer	An individual carrying two normal function alleles	*1/*1
CYP2C19 likely intermediate metabolizer ^b	An individual carrying one normal function allele and one decreased function allele or one increased function allele and one decreased function allele or two decreased function alleles	*1/*9, *9/*17, *9/*9
CYP2C19 intermediate metabolizer	An individual carrying one normal function allele and one no function allele or one increased function allele and one no function allele	*1/*2, *1/*3, *2/*17, *3/*17
CYP2C19 likely poor metabolizer ^b	An individual carrying one decreased function allele and one no function allele	*2/*9, *3/*9
CYP2C19 poor metabolizer	An individual carrying two no function alleles	*2/*2, *3/*3, *2/*3
Indeterminate	An individual carrying one or two uncertain function alleles	*1/*12, *2/*12, *12/*14

Allele

Predicted_phenotype Predicted_genotype

Fig. 4. An example of DGI entities and relations assignment from Guideline for Proton Pump Inhibitors and CYP2C19.

only one resource such as Table 2, Drug class in KM2PS is founded in all knowledge resources. Therefore, the entities specified as Drug class should be revised into the same pattern to reduce the heterogeneous data and make data interoperability.

The concept layer and instant layer of KM2PS are depicted in Fig. 6. The upper part of this figure represents the concept layer by six white rectangle nodes or superclasses representing four PIs and two PCs. The arrows between the nodes indicate the “superclass_of” relation that connects the superclasses to each other, with the “Thing” node at the top of the hierarchy. For instance, the “DGI” is a superclass. The DGI superclass is described by classes such as Allele, Drug, Gene, Recommendation, Predicted_genotype, Predicted_phenotype, Interaction_code, Reference, Recommendation_level, and Recommendation_summary. The classes are represented as nodes labeled with smaller rectangles, and the arrows between nodes indicate the “part_of” relation connecting them to their respective superclasses.

The lower part of the figure represents the instant layer, which is composed of nodes labeled with different colors. The nodes represent entities, such as Pastel yellow nodes representing drug names, Seafoam blue nodes representing gene names, and Pastel orange nodes representing interaction codes. The arrows between nodes indicate the relation connecting them, and the example of a Pastel orange node, “dg1258”, is shown to have ten relations, including has_drug, has_drug_class, has_allele, has_gene, has_genotype, has_phenotype, has_recommendation, has_recommendation_level, has_recommendation_summary, and has_interaction, which connect it to respective nodes. To indicate the relationship between the entities in the instant layer and the respective classes in the concept layer, the nodes in the instant layer are connected to their respective classes in the concept layer by the “is_a” relation.

4.1.3. Input interface

The user interface in Fig. 7 has been designed to collect the necessary input data for screening, which includes seven patient parameters. These parameters consist of (i) the gene list, (ii) PGx testing, (iii) predicted genotype as alleles in diplotype format, (iv) the drug list, which includes both current medications and any additional drugs that the doctor is considering at the time of the visit, (v) the herbs list, (vi) social lifestyle information such as alcohol, smoking, and caffeine consumption, (vii) liver function as Child-Pugh class, and (viii) renal function as the class of estimated Glomerular Filtration Rate (eGFR).

The input form in the user interface has been designed to be user-friendly and easily customizable, allowing for the insertion or deletion

Table 2

Classes and superclasses for representation of the knowledge model in concept layer.

Superclasses	Classes for describing the concept of superclasses
DGI	Allele, Drug, Gene, Reference, Recommendation, Predicted_genotype, Predicted_phenotype, Drug_class, Recommendation_level, Recommendation_summary, Interaction_code
DDI	Drug, Gene, Interaction_type, Interaction_level, Reference, Recommendation, Recommendation_level, Recommendation_summary, Interaction_code
DHI	Herb, Active_compound, Scientific_name, Pharmacologic_effect, Drug, Gene, Interaction_type, Interaction_level, Reference, Recommendation, Recommendation_level, Recommendation_summary, Interaction_code
DSI	Lifestyle, Drug, Gene, Interaction_type, Interaction_level, Reference, Recommendation, Recommendation_level, Recommendation_summary, Interaction_code
LF	Drug, Child_pugh_class, Reference, Recommendation, Recommendation_level, Recommendation_summary, Interaction_code
RF	Drug, eGFR_class, Reference, Recommendation, Recommendation_level, Recommendation_summary, Interaction_code

of the requested information, as shown in Fig. 7. Parameters (i)–(v) are presented as a drop-down list with pre-fill search and checkbox options. Parameter (vi) is presented as a Yes/No question, while parameters (vii) and (viii) are multiple-choice options. For parameters (ii) and (iii), the user is prompted to select either “HLA/Drug related SCAR screening test” or “Drug/Gene related toxicity test”. The information on parameters (ii) and (iii) used in the study is obtained from two sources, including the Pharmacogenomics Test Request Form [64], and CPHARM [25].

4.1.4. Operation of screening logic

The prescription screening tool is a facilitating tool for clinical decision-making by detecting explicit PI and PC and extracting dynamic inference. The additional outputs of this tool are results that are hidden knowledge because of its semantic properties. It can be a preliminary suggestion for health professionals to be aware of other aspects than only of outputs from the general query process, especially the situation of prescription screening the newest drugs because there is not enough

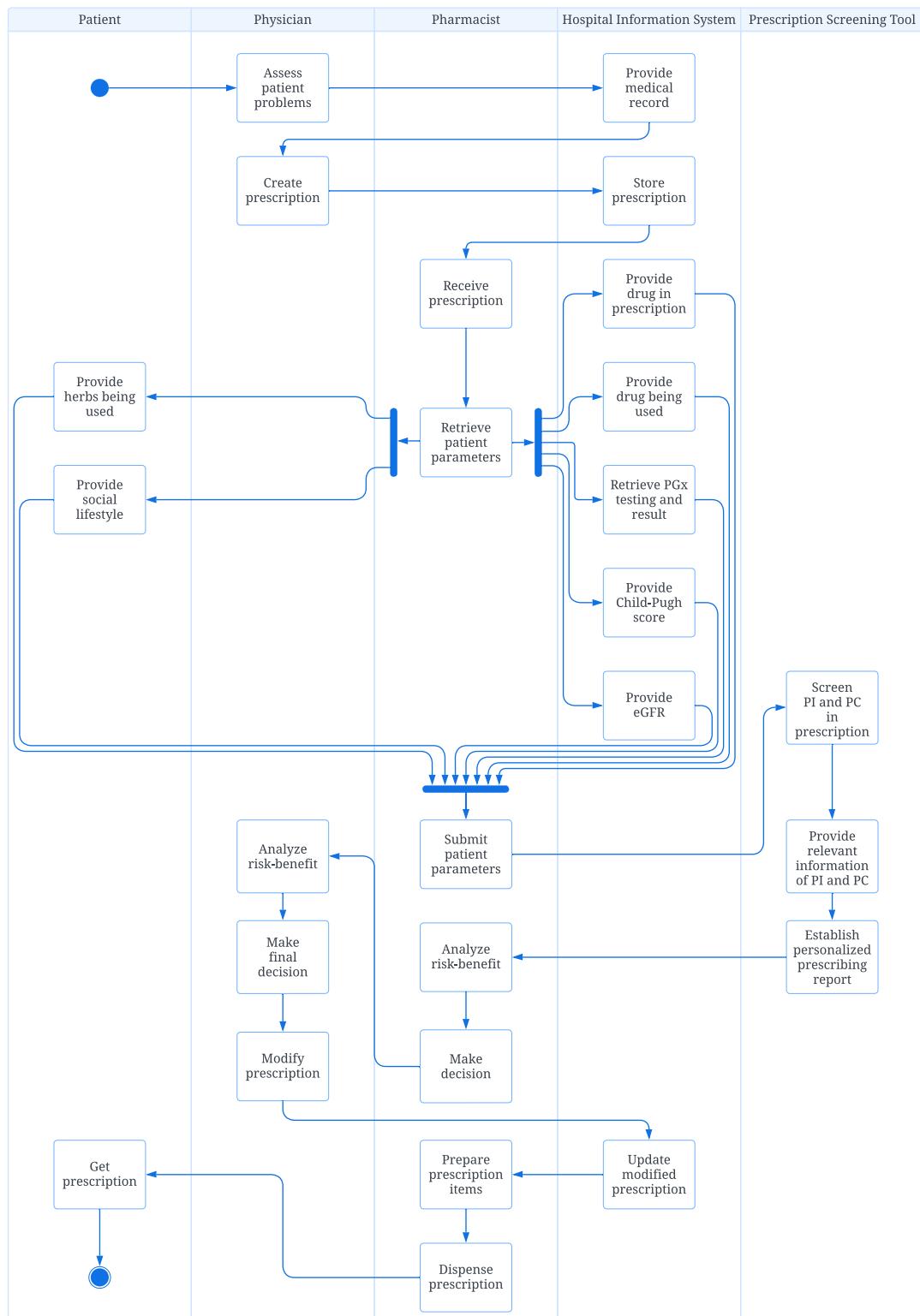


Fig. 5. The UML activity diagram for describing the step-wise activities in the prescribing process.

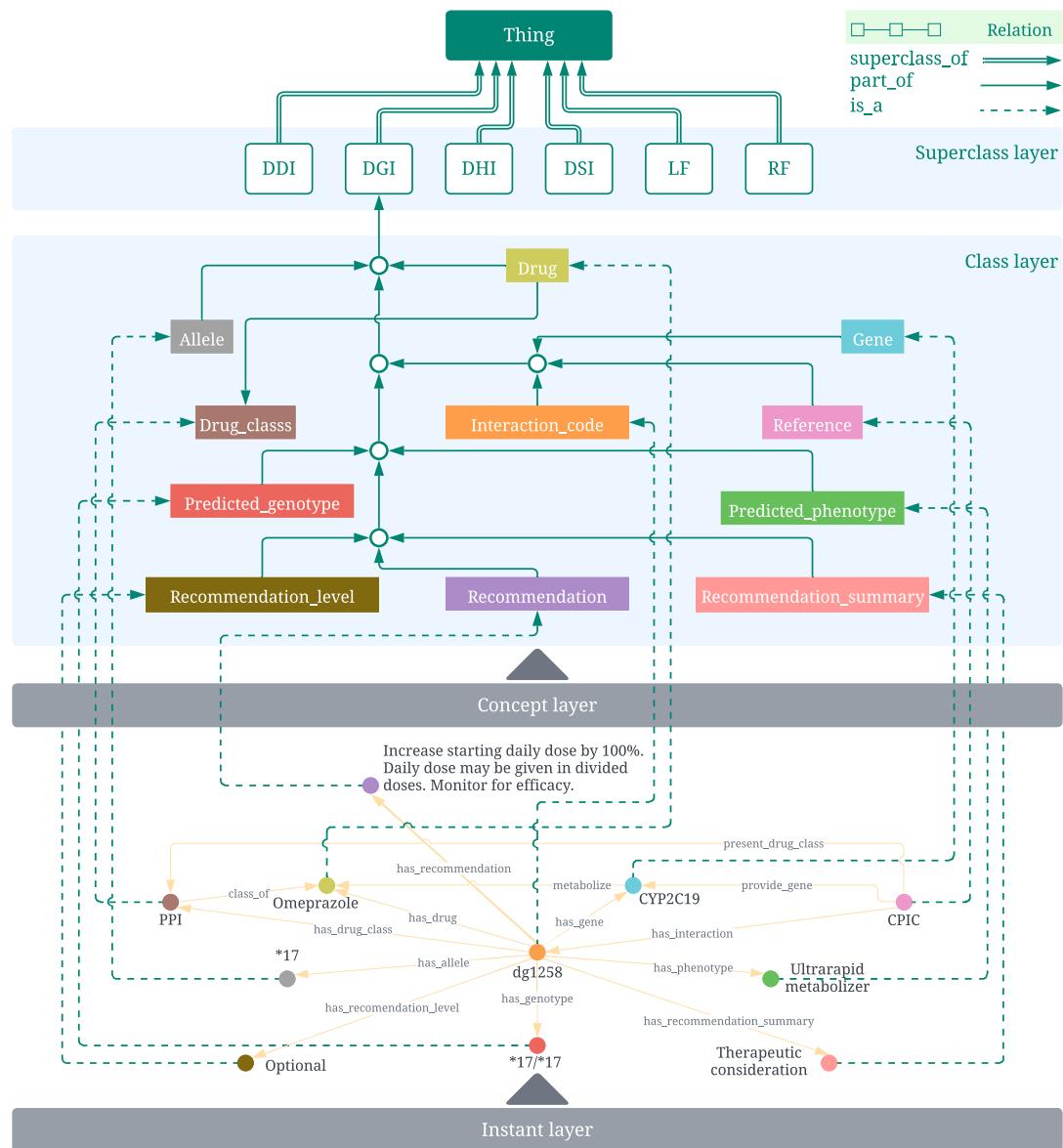


Fig. 6. Basic diagram of KM2PS model. It consists of two layers, including the concept layer and the instant layer. The concept layer is divided into superclass and class layers. The instant layer is a knowledge graph that explores entities and their respective relations.

evidence related PI and PC of the newest drugs for decision-making. The screening logic of this tool is divided into two modules, i.e., the detection module and the inference module.

The detection module is a part of the system that identifies potential drug interactions based on the patient's drug list, Pharmacogenes, predicted genotype, herbs list, social lifestyle, liver function, and renal function. The module creates pairs of considered drug-related interactions (PCDI) for each parameter and retrieves them from the knowledge model. The PCDI set is then compared with pairs of all explicit PI and PC in the KM2PS to identify exactly the detected PI and PC in the prescription (PIPC). Finally, relevant information on PIPC is queried for PPR establishment.

Seven patient parameters are denoted as definitions following.

- *D*: the drug list, including the drug being used and those that doctors consider at that visit
- *P*: the Pharmacogenes

- *A*: the predicted genotype as alleles (diplotypes format)
- *H*: the list of herbs being used
- *S*: the social lifestyle (including consumption lifestyle of alcohol, smoking, and caffeine)
- *L*: Liver function as Child-Pugh class
- *R*: Renal function as the class of eGFR

P and *A* are inputs from PGx testing, and are combined to create *G* for pairing. *D*, *G*, *H*, *S*, *L*, and *R* are paired to create Pairs of Considered Drug-related Interaction, *I_p*, for potential interactions and potential considerations. There are six sets of *I_p* including four sets of PI, namely Drug–Drug Interactions, *I_{dd}*, Drug–Gene Interactions, *I_{dg}*, Drug–Herb Interactions, *I_{dh}*, and Drug–Social Lifestyle Interactions, *I_{ds}*, as well as two sets of PC, namely Drug–Status of Liver Function, *F_{dl}*, and Drug–Status of Renal Function, *F_{dr}*. Each set is represented by equations as follows.

$$I_{dd} = \{x | x = d_i \times d_j, d_i \wedge d_j \in D, i \neq j\}, \quad (1)$$

Personalized Prescribing Tool

Form

Predicted genotype

Gene / HLA

(ii) HLA-B
CYP2C19
SLCO1B1

Allele

(iii) *58:01
*1
*3
*5
*1
*2
*3
*4
*5

Gene Add Delete

Medication

Drug

Amiodarone
 Esomeprazole
 Naproxen
Checkbox

Herbs

Ginger
Vitamin E

Select Add Delete

Social lifestyle

Smoking (vi) Drinking Coffee

Liver & Renal Status

Liver Status

(vii) Normal (Child-Pugh Score: <5)
 Mild (Child-Pugh Score: 5-6)
 Moderate (Child-Pugh Score: 7-9)
 Severe (Child-Pugh Score: 10-15)

Renal Status

(viii) Normal
 Dialysis
 CrCl < 15
 CrCl 15-29
 CrCl 30-44
 CrCl 45-59

Analysis

Fig. 7. Input interface screen.

$$I_{dg} = \{x | x = d \times g, d \in D, g \in G\}, \quad (2)$$

$$I_{dh} = \{x | x = d \times h, d \in D, h \in H\}, \quad (3)$$

$$I_{ds} = \{x | x = d \times s, d \in D, s \in S\}, \quad (4)$$

$$F_{dl} = \{x | x = d \times L, d \in D\}, \quad (5)$$

$$F_{dr} = \{x | x = d \times R, d \in D\}. \quad (6)$$

Then, the set of I_p is defined as

$$I_p = I_{dd} \cup I_{dg} \cup I_{dh} \cup I_{ds} \cup F_{dl} \cup F_{dr}. \quad (7)$$

To detect PI and PC in prescription, I_p is retrieved from knowledge model. The PI and PC that are exactly detected in prescription is described as

$$I_d = I_{km} \cap I_p. \quad (8)$$

Finally, relevant information of PIPC is queried for PPR establishing.

The results from the detection module may cause health experts to overlook minor details that may cause harm to patients, especially when prescribing the newest drugs for patient treatment. The inference module attempts to extrapolate the PI and PC using simple inductive reasoning. Our inductive reasoning observes the PI and PC of drugs in

the same physicochemical properties or mechanism of action (MOA) from knowledge resources such as PGx guidelines. The PI and PC of drugs with similar physicochemical properties or MOA are frequently similar [60]. There are various reasoning algorithms to capture the inferred results that are absent from semantic networks. To understand the logic of the inference module, we demonstrate simple inductive reasoning details with an inference of DGI as follows.

Considering the example of DGI as GPC [60], Proton Pump Inhibitors is a name of a drug class and also called PPI. Six drugs assigned to PPIs are Omeprazole, Esomeprazole, Lansoprazole, Rabeprazole, Pantoprazole, and Dexlansoprazole. Most PPIs are metabolized by cytochrome P450 2C19 enzyme, CYP2C19, as a major pathway. Thus, the genetic polymorphism of CYP2C19 can affect efficacy and be adverse during treatment. We found management information on Omeprazole, Lansoprazole, Pantoprazole, and Dexlansoprazole that is available on guidelines, but lacking evidence on Esomeprazole and Rabeprazole has become an obstacle to a systematic review for actionable recommendations. Therefore, the relations between Esomeprazole, Rabeprazole, and this guideline do not directly appear in KM2PS. Because KM2PS is a semantic representation as a graph, the data is presented as instances in the form of a set of entities, E , and relations, R , also known as triples.

Table 3

Clinical background of the virtual case study.

Demographics	60 years old/male/Thai, weight 69 kg, height 172 cm
Chief complaint	14 days PTA: joint pain and swollen big toe joints
Past medical history	3 months PTA: Paroxysmal Atrial Fibrillation, Acute decompensated heart failure, ST-elevation myocardial infarction (DVT S/P PCI) 2 years PTA: Stage 3 Chronic kidney disease 8 years PTA: Hypertension, Hyperlipidemia, Diabetes mellitus
Current medications	1. Amiodarone 200 mg 1/2 * 1 tablet orally once daily 2. Clopidogrel 75 mg 1 tablet orally once daily 3. Aspirin 81 mg 1 tablet orally once daily 4. Carvidiolol 6.25 mg 0.5 tablet orally once daily 5. Enarapril 5 mg 1 tablet orally once daily 6. Warfarin 3 mg 1 tablet orally once daily take at bedtime 7. Atorvastatin 40 mg 1 tablet orally once daily take at bedtime 8. Metformin 500 mg 1 tablet orally twice a day 9. Senokot 2 tablets orally once daily take at bedtime 10. Esomeprazole 20 mg 1 tablet orally once daily take before meal
Allergy	NKDA
Laboratory tests	INR 3.71 Scr 1.9 mg/dL Serum uric 8 mg/dL CrCl 31.14 mL/min/1.73 m ²
Pharmacogenomics tests	SLCO1B1: Poor function (*5/*5) CYP2C9: Intermediate metabolizer (*1/*3) CYP2C19: Intermediate metabolizer (*1/*3)
Diagnosis	1st Gout attack
Prescription	1. Colchicine 0.6 mg 2 tab stat then 1 tab in 1 h 2. Naproxen 500 mg 1 × 2 pc 3. Allopurinol 100 mg 1 × 1 pc

Notes: Prior To Admission (PTA), No Known Drug Allergy (NKDA), International Normalized Ratio (INR), Serum Creatinine (SCr), Creatinine Clearance (CrCl).

The i th triple is denoted as T_i and can be expressed as

$$T_i = (h, r, t), \quad (9)$$

where h and t are members of E , r is member of R .

From the given information, we can construct the KM2PS as shown in Fig. 8, in which the instants represented by nodes in various colors are entities. Six olive green nodes represent drug names, including Omeprazole, Esomeprazole, Lansoprazole, Rabeprazole, Pantoprazole, and Dexlansoprazole. These entities are assigned to the class Drug (x_5). Four interaction codes, including dg1276, dg1289, dg1263, and dg1258, are represented by pastel orange nodes. These entities are assigned to the class Interaction_code (x_2). There is a pink node as CPIC is assigned to the class Reference (x_1). The instant PPI as a brown node is also assigned to the class Drug_class (x_3). There is also a seafoam blue node as CYP2C19 is assigned to the class Gene (x_4). CPIC, PPI, and CYP2C19 are the instances of x_1 , x_3 and x_4 , respectively. Six direct relations are represented as solid lines to connect explicit knowledge in KM2PS, including has_drug (r_1), has_interaction (r_2), class_of (r_3), metabolize (r_4), present_drug_class (r_5), and provide_gene (r_6). The dashed blue is represented the hidden relation, such as the should_guide relation used to explain the logic of the inference module. Moreover, from Fig. 8, we can construct the triples to explain the association, such as

$$T_1 = (\text{CPIC}, \text{present_drug_class}, \text{PPI}) \Rightarrow (x_1, r_5, x_3), \quad (10)$$

$$T_2 = (\text{PPI}, \text{class_of}, \text{Lansoprazole}) \Rightarrow (x_3, r_3, x_5), \quad (11)$$

$$T_3 = (\text{CPIC}, \text{provide_gene}, \text{CYP2C19}) \Rightarrow (x_1, r_6, x_4), \quad (12)$$

and

$$T_4 = (\text{CYP2C19}, \text{metabolize}, \text{Lansoprazole}) \Rightarrow (x_4, r_4, x_5). \quad (13)$$

Based on inductive reasoning, we can infer the Recommendation_summary class for drugs that do not have any recommendation in

KM2PS due to two conditions. First, the reference in KM2PS contains PI or PC that provides drugs from the same drug class as the drug in question. In this case, the Recommendation_summary can be inferred from the recommendations for other drugs in the same class. Second, the reference in KM2PS contains PI or PC that provides information about genes that metabolize the drugs. In this case, if the drug in question is metabolized by the same gene as other drugs with recommendations, it can be inferred that the drug should also have similar recommendations. Suppose a drug is the newest in its drug class and is metabolized by the same gene as other drugs within the class. In that case, the Recommendation_summary should be recommended similarly to the other drugs in the class. We can see from Fig. 8 that GPC provides DGI information for four drugs from the PPI drug class, which satisfies the first condition for inferring the Recommendation_summary. Additionally, GPC provides information that all four drugs from the PPI drug class are metabolized by the same gene, CYP2C19, satisfying the second condition. Therefore, since both Esomeprazole and Rabeprazole belong to the PPI drug class and do not have an explicit DGI on CPHARM, they should be guided by the same Recommendation_summary as other drugs in the same PPI class. To infer relations that are not directly stored in KM2PS, we can give a simple inference rule, which can be represented as follows.

$$\forall x_i, \forall r_i : \{T_1 \wedge T_2\} \wedge \{T_3 \wedge T_4\} \Rightarrow (x_1, r_7, x_5). \quad (14)$$

Eq. (14) becomes true if there exists x_i and r_i that satisfy the two conditions described above. An example of an inference module that can predict hidden relations is the prediction of the relation should_guide from existing entities and relations. For example, the triples $\{(\text{CPIC}, \text{present_drug_class}, \text{PPI}) \wedge (\text{PPI}, \text{class_of}, \text{Rabeprazole}) \wedge (\text{CPIC}, \text{provide_gene}, \text{CYP2C19}) \wedge (\text{CYP2C19}, \text{metabolize}, \text{Rabeprazole})\}$ can be used to infer the triple $(\text{CPIC}, \text{should_guide}, \text{Rabeprazole})$, even though the direct relation should_guide between Rabeprazole and CPIC does

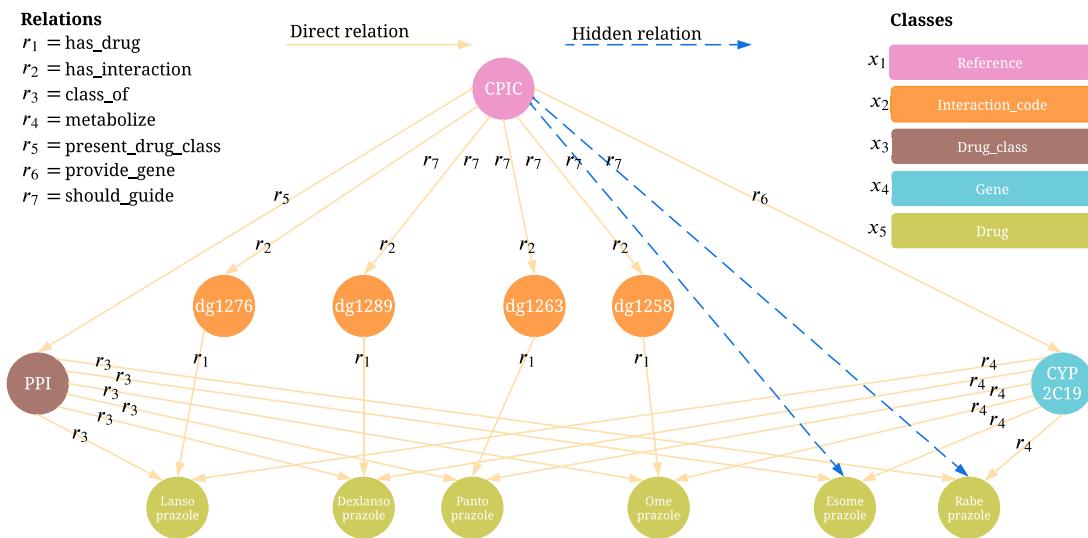


Fig. 8. An example of instance layer for the Guideline for Proton Pump Inhibitors and CYP2C19.

not exist in KM2PS. Based on the operation of the screening logic described above, the structure depicted as a UML class diagram in Fig. 11 of Appendix A provides a clear representation of the objects involved in the screening logic, aiding in understanding and communicating the system's design in the system development process. In the class diagram, the "Screening" class serves as one of the main classes, while other classes like "DDI", "DGI", "DHI", "DSI", "LF", "RF", "Drug", "Gene", "GenePrediction", "Herb", "Lifestyle", "LiverFunction", and "RenalFunction" represent concepts related to the screening process. The "Screening" class coordinates with several of those classes. Additionally, each class in this diagram presents its attributes and operations. The diagram also illustrates how these classes are coordinated and interconnected with each other.

4.1.5. Personalized prescribing report

After processing the detection module and inference module, the PI and PC information are established to output as PPR. PPR is presented to quickly and conveniently make decisions as shown in Fig. 9. Five sections in PPR contain medication overview, metabolic function overview, herb and social lifestyle overview, PGx function overview, and prescription screening overview. The medication overview shows drug classes and categories, both drugs being used and those that doctors consider at that visit. This section aids the initial interaction screening from the standpoint of drug classes or categories. The metabolic function overview shows liver and renal functions with interpretation. The herb and social lifestyle overview shows a list of herbs being used and the status of social lifestyle. The PGx function overview displays the predicted genotype and its interpretation, known as the predicted phenotype. Furthermore, this section provides the phenomenon of genotype–phenotype mismatch called "Phenoconversion factor" in terms of inhibitor, substrate, or inducer to assist health professionals in determining the true phenotype of a patient. The prescription screening overview presents the judgment results from screening logic for risk–benefit analysis.

From Fig. 9, the prescription screening overview contains two display modes. The first display mode shows the results of important factors that health professionals are most concerned about, including DGI, DDI, LF, and RF, and another one presents other associated factors, i.e., DHI and DSI, with the purple background color. The data within the column of PPR is the result of prescription screening. The data within the same row are called "Summary row" and

present a recommendation summary of the drug, i.e., Contraindication, Therapeutic consideration, and Use as directed. Using icons and colors can help make the PPR report more visually understandable and easier to interpret. The green check mark can represent a Use as directed recommendation, while the red cross mark can indicate a Contraindication recommendation. The orange exclamation mark can indicate Therapeutic consideration recommendation. The asterisk (*) can indicate a result from the inference module to be aware of each result. These icons are called "Recommendation summary icon" and help users to view the interaction detail by clicking on these icons. The relevant information from both the detection and inference modules in the screening logic is presented in pop-up windows, as shown in Fig. 10. The number of icons increases according to the number of PI and PC retrieved from KM2PS. Each DGI, LF, and RF has only one summary icon per interaction. However, each DDI, DHI, and DSI can have two summary icons per interaction, appearing in both the summary row of the drug, herb, or social lifestyle that is the root cause of the interaction.

4.2. Validation results

4.2.1. The validation of the approach by a virtual case study

A virtual case study has demonstrated the effectiveness and usefulness of our approach for personalized screening in the prescribing process. Background information of this virtual case study is as follows.

A 60-year-old Thai man has joint pain at the big toe joint. This pain had been exacerbated for two weeks until he could not tolerate the pain. He decided to go to the hospital that treated his underlying diseases. His symptom was screened, and the hospital supporting staff took him to meet a physician in the arthritis and rheumatic clinic. The clinical background of this case study appears in Table 3. After consulting with a physician, he was taken to the outpatient department (OPD). Before dispensing, a pharmacist took additional patient's history. This patient reported consuming ginger lemon tea at a rate of 1–2 sachets per day and engaging in social drinking with friends at a frequency of 3–4 times per week.

Ten drugs from current medications and three drugs that the physician prescribes for treating his 1st Gout attack are entered into input Medication. The drugs in consideration are marked to classify from the current drugs. The PGx testing and its predicted genotypes are input data for the predicted genotype. The input choice for liver status is

Personalized Prescribing Report

Display switch Include Herb and Dietary lifestyle

Medication overview

Class	Category	Drug	Status
CARDIAC THERAPY	Antiarrhythmics, class III	Amiodarone	Continue
ANTIGOUT PREPARATIONS	Preparations with no effect on uric acid metabolism	Colchicine	Continue
ANTIINFLAMMATORY AND ANTRHEUMATIC PRODUCTS	Propionic acid derivatives	Naproxen	Continue
ANTIGOUT PREPARATIONS	Preparations inhibiting uric acid production	Allopurinol	Consider

Metabolic function overview

Metabolic parameter	Input data	Interpretation
Liver function	Child-Pugh Score: <5	Normal function
Renal function	CrCl < 30-44 mL/min/1.73 m ²	Stage 3b Chronic kidney disease

Herb and Social lifestyle overview

Herb	Pharmacologic effect	Evidence level	Reference
Ginger (Zingiber officinale)	Antiflatulent Medplant	High	Click
Ginger (Zingiber officinale)	Antiplatelet	Low	Click
Ginger (Zingiber officinale)	Antimutagenic	Low	Click
Ginger (Zingiber officinale)	Antibiotic	Moderate	Click

Smoking Drinking Coffee

PGx function overview

Predicted phenotype and genotype	Phenoconversion factor		
	Inhibitor	Substrate	Inducer
CYP2C9 Intermediate metabolizer (*1/*3)	Amiodarone, Ginger	Naproxen	-

Prescription screening overview

Medication	Drug-Drug Interaction	Drug-Gene Interaction	Drug-Liver Consideration	Drug-Renal Consideration	Drug-Herb Interaction	Drug-Social Lifestyle Interaction
Amiodarone	!	N/A	✓	N/A	N/A	N/A
Colchicine	Same interaction	N/A	✓	!	N/A	N/A
Naproxen	!	!*	✓	!	N/A	N/A
Allopurinol	N/A	✗	✓	!	N/A	N/A
Ginger	N/A	N/A	N/A	N/A	N/A	N/A

Recommendation summary icons
 ✗ = Contraindication ! = Therapeutic consideration ✓ = Use as directed N/A = Not available * = Result from inference module

Fig. 9. An example of personalized prescribing report.

Table 4

Clinical background of the real case study.

Demographics	59 years old/female/Thai, weight 69 kg, height 160 cm
Chief complaint	After taking antiplatelet: bruise at arm and leg, prolong bleeding time, no hematuria or melena
Past medical history	Type 2 DM, HTN, HLP, post embolization Stent Assist coiling superior hypophyseal non ruptured aneurysm for Rt small ICA aneurysm
Current medications	1. Aspirin 81 mg 1 tablet orally once daily 2. Clopidogrel 75 mg 1 tablet orally once daily 3. Manidipine 10 mg 1 tablet orally once daily 4. Metformin XR 750 mg 1 tablet orally once daily 5. (Empagliflozin 10 mg + Linagliptin 5 mg) 1 tablet orally once daily 6. Fenofibrate 145 mg 1 tablet orally once daily 7. Vitamin D2 20,000 IU 1 capsule every 1 week 8. Chlorophyll powder 9. Moringa capsules + Vitamin C
Allergy	- Sulfamethoxazole + trimethoprim: unknown reaction - Chloramphenicol: unknown reaction - Fluticasone furoate nasal spray: feel muscle spasms after applying nasal spray - Ofloxacin + prednisolone acetate: fever Side effect: - Meloxicam: Stomach upset - Orphenadrine citrate + paracetamol: stomach upset - Dextromethorphan hydrobromide: dry mouth - OTC drug (Paracetamol + Chlorpheniramine): palpitations - Avoid NSAIDs
Laboratory tests	HbA1c 6.8% CPK 70 U/L (range 29–168) Scr 0.63 mg/dL CrCl 77.55 mL/min BUN 19.9 mg/dL
Pharmacogenomics tests	SLCO1B1: Normal transporter function (*1/*1) CYP2C9: Normal metabolizer (*1/*1) CYP2C19: Normal metabolizer (*1/*1) CYP2D6: Ultrarapid metabolizer (*1 × 2/*1 × 2) VKORC1: Significantly reduced VKROCR1 enzyme level CYP1A2: Ultrarapid metabolizer (*1F/*1F) CYP3A4: Normal metabolizer (*1/*1) CYP3A5: Intermediate metabolizer (*1/*3) OPRM1: Intermediate opioid sensitivity (AG)
Management	- 10 Mar 2021 Management: Off Aspirin continue only Clopidogrel Monitor: Bruise disappeared but still prolong bleeding time - 11 June 2021 Management: Off Moringa capsule Interaction: Aspirin VS Clopidogrel VS Moringa capsule

Notes: Diabetes Mellitus (DM), Hypertension (HTN), Hyperlipidemia (HLP), Right (Rt), Internal Carotid Artery (ICA), Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Hemoglobin A1C (HbA1c), Creatine Phosphokinase (CPK), Serum Creatinine (Scr), Creatinine Clearance (CrCl), Blood Urea Nitrogen (BUN).

normal, while the input choice for renal status is CrCl 30–44. Ginger is input data for Herbs. The alcohol status is marked for Social lifestyle input. After processing, the complete version of the PPR for this case is available in Fig. 12 of Appendix B. The prescription screening overview is a highlighted section of this report.

Focusing on Recommendation summary icons Contraindication and Therapeutic considerations, PPR can detect one summary icon of Contraindication, at the DGI column, and 32 summary icons Therapeutic considerations, including two presented at DGI, four presented at RF, 16 presented at DDI, two presented at DHI, and eight DSI. These results are processed by the detection module. Based on the sample result of the inference module, there are three interactions with the recommendation summary icon of Therapeutic consideration in the DGI column, which include Aspirin, Esomeprazole, and Naproxen. This module can detect indirect interactions, such as the interaction between gene CYP2C9 and two NSAIDs drugs, Aspirin and Naproxen. This detection is possible due to the inclusion of DGI knowledge from Guideline for NSAIDs based on CYP2C9 genotype [65]. Additionally, it can identify the indirect interaction between the gene CYP2C9 and the PPIs drug Esomeprazole [60], even though these three drugs do not appear to have explicit recommendations from DGI resources.

4.2.2. The validation of the approach by a case report

The case report is a study that describes the medical condition, symptoms, diagnosis, treatment, outcomes, and follow-up of a patient with specific conditions [66]. The first stage of the Evidence-Based Medicine Pyramid initiates specific observations, new insights, or potential therapeutic ideas [67]. We selected a case report from Dybro et al. [68] to demonstrate the effectiveness and usefulness of our approach beyond the virtual case study. This case report presents the scenario of the contemporaneous effect of multiple drugs on cytochrome pathways, which can affect drug metabolism. The patient is a 47-year-old female admitted due to muscle pain. The additional background information of this patient is provided in the case report [68]. The PPR of this case is presented in Fig. 13 of Appendix B. According to this report, four drugs are presented in the section of the medication overview. Itraconazole is highlighted as a considered drug because it is assumed to be the possible root cause of this problem. This patient did not take any herbal medication or supplements. She did not smoke, drink alcohol, or consume caffeine. Furthermore, her PGx profile did not exist. The detection module detects two Therapeutic consideration icons at DDI, as shown in the section of the prescription screening overview. The result from the inference module is unavailable.

Contraindication				
Drug	Gene	Recommendation level	Reference	
Allopurinol	HLA-B*58:01	Strong	CPIC	
Close				

(a) Notification of contraindication

Therapeutic consideration				
Drug	Gene	Recommendation	Recommendation level	Reference
Clopidogrel	CYP2C19: IM	Avoid standard dose (75 mg) clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication	Strong	CPIC
Close				

(b) Notification of therapeutic consideration

Therapeutic consideration* (Inference)				
Drug	Gene	Recommendation level	Reference	
Aspirin	CYP2C9: IM	N/A	Inferred Mode	
Close				

(c) Inferential notification of therapeutic consideration

Use as directed				
Drug	eGFR (mL/min/1.73 m ²)	Recommendation	Recommendation level	Reference
Metformin	30-44	No adjust	Strong	DailyMed
Close				

(d) Notification of confirmation

Fig. 10. The example relevant information presented in pop-up windows. A pop-up window marked with an asterisk (*) displays interaction details from the inference module, while the others display interaction details from the detection module.

4.2.3. The validation of the approach by a real case study

Bumrungrad International Hospital (BH) is Thailand's leading preventive genomics and integrative medicine center, which offers PGx services with the most PGx panel tests [69]. A real case from BH is used to demonstrate the proof-of-concept of our approach. Background information of this case study is shown in Fig. 14 of Appendix B. The patient is a 59-year-old female of Thai ethnicity. She has a weight of 69 kg and a height of 160 cm. The patient told physicians and pharmacists that she took vitamin C, Chlorophyll powder, and Moringa capsules as dietary supplements. The PPR of this case is presented in Fig. 14 of Appendix B. The detection module detects ten Therapeutic consideration icons, including six presented at DDI, and four presented at DHI. For the

inference module result, there is only one Use as directed summary icon in the DGI column at the summary row of Aspirin because of the DGI knowledge from CPHARM [65].

5. Discussion

5.1. Clinical decision making for therapeutic interventions for the virtual case study

After personalized screening for PI and PC with the prescription screening tool, the presented information can reduce the time gathering data and facilitate the risk–benefit analysis by health professionals to cover all factors that may affect patients in terms of efficacy and harm. In a real setting at Thailand hospitals, the Contraindication icon is the first medical-related problem addressed. One Contraindication summary icon contains DGI between allopurinol and gene HLA-B*58:01. When users drill down the details of interactions hidden in this icon, DGI information is presented because there is no input of HLA-B*58:01, which means this case study may not be able to screen HLA genotyping. Nowadays, the HLA-B*58:01 screening is a part of the Universal Coverage Scheme in Thailand's universal healthcare coverage [69,70]. Physicians can order this screening before the Allopurinol prescription. The toxicity monitoring of Colchicine administration is an additional plan for this patient because the renal stage of this patient is moderate-severe (30–44 mL/min/1.73 m²) [71] and the elimination half-life of colchicine is the long duration around 27 to 31 h [56]. According to Fig. 12, the patient used ginger as a herbal supplement, and one of the pharmacologic effects of this herb is antiplatelet. This patient also takes Amiodarone, Clopidogrel, Aspirin, and Warfarin together. Unfortunately, these drugs have similar side effects, such as bruises and bleeding. As a result, health professionals can plan side effect monitoring for bruises and bleeding, or they can prevent side effects by discontinuing ginger use. According to our knowledge, alcohol is metabolized by the liver. As drinking status from PPR, when the patient consumes alcohol, the medication's metabolism is slowed. This factor influences the efficacy and side effects of the medication [72]. The prescription will also be tailored to the patient's social life.

5.2. Clinical decision making for therapeutic interventions for the case report

The concurrent drugs of this patient include Simvastatin as an antihyperlipidemic agent, Metformin as an antidiabetic agent, and Pregabalin as an antineuropathic agent. She was well-treated and showed good tolerance to these medications for several years. Three weeks before admission, she felt a red and itchy rash and visited the hospital to seek treatment for this symptom. She consulted with a general practitioner, who diagnosed it as a fungal infection. As a result, she was prescribed Itraconazole as an antifungal agent. Based on the medication profile and laboratory testing results, the cause of this admission was a DDI between Simvastatin and Itraconazole. This interaction occurred because Itraconazole can inhibit the metabolism of Simvastatin at enzyme CYP3A4 [68]. Simvastatin was discontinued, and she received immediate treatment following the discontinuation. Her symptoms improved markedly. This medication-related harm can still occur despite DDI being listed as a potential interaction in prescribing information [55] or drug information databases [22]. From Fig. 13, the approach presents the metabolism phenotype of each enzyme in the section of the PGx function overview. We can observe that Simvastatin is listed as a substrate of CYP3A4, while Itraconazole is listed as an inhibitor of CYP3A4. This section can provide an overview of the metabolism of drugs, herbs, or lifestyle factors that are considered. It can also facilitate the decision-making process of general practitioners. This aligns with the discussion of Dybro et al. who have suggested that systems should be capable of screening and detecting DDI during the prescribing process [68].

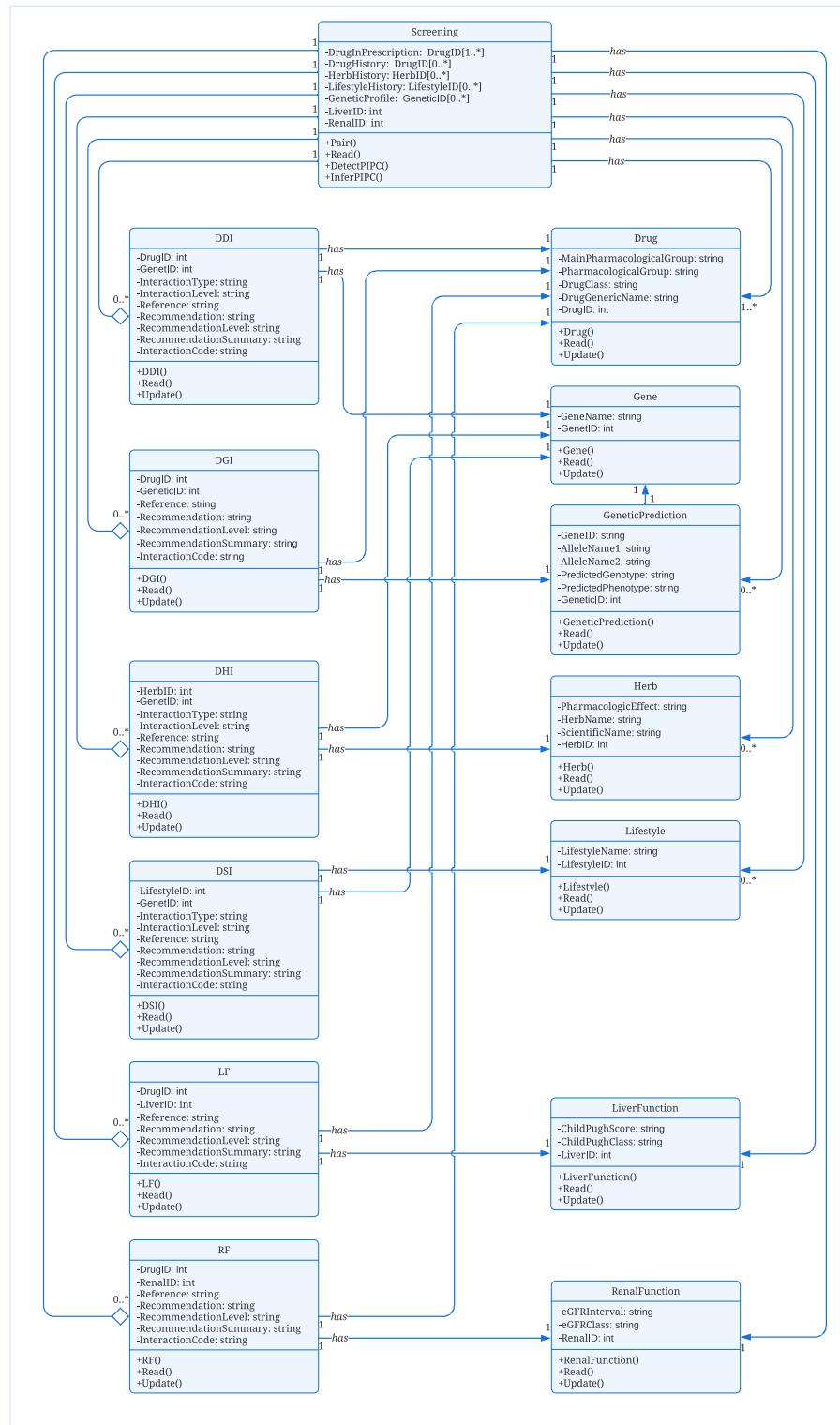


Fig. 11. The UML class diagram for describing the PI and PC screening in the proposed system. For example, the “Screening” class contains attributes such as arrays of DrugInPrescription, DrugHistory, HerbHistory, LifestyleHistory, and GeneticProfile, as well as integers for LiverID and RenalID. This class exhibits operations like Read() for retrieving data from submission, Pair() for creating possible pairs of PI and PC, DetectPIP() for screening PI and PC using the detection module, and InferPIP() for predicting PI and PC using the inference module.

5.3. Clinical decision making for therapeutic interventions for the real case study

This patient was bruised on the arm and leg and had prolonged bleeding time after comedication concurrently time. We show the real management of this problem in the management section of clinical

background in **Table 4**. There are two actual decisions for the patient. The first decision occurred on March 10, 2021. Health experts decided to discontinue Aspirin. The bruise disappeared, but the patient still had prolonged bleeding time. The second decision occurred on June 11, 2021. Moringa capsule is stopped. The bruising and bleeding time side effect of this patient was improved. Although the PPR did not

Personalized Prescribing Report

Include Herb and Dietary lifestyle

Medication overview

Class	Category	Drug	Status
CARDIAC THERAPY	Antiarrhythmics, class III	Amiodarone	Continue
ANTITHROMBOTIC AGENTS	Platelet aggregation inhibitors excl. heparin	Clopidogrel	Continue
ANALGESICS	Salicylic acid and derivatives	Aspirin	Continue
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	ACE inhibitors and diuretics	Enasapril	Continue
BETA BLOCKING AGENTS	Alpha and beta blocking agents	Carvedilol	Continue
LIPID MODIFYING AGENTS	HMG CoA reductase inhibitors	Atorvastatin	Continue
ANTITHROMBOTIC AGENTS	Vitamin K antagonists	Warfarin	Continue
DRUGS FOR ACID RELATED DISORDERS	Proton pump inhibitors	Esomeprazole	Continue
DRUGS FOR CONSTIPTION	Contact laxatives	Sennokot	Continue
DRUGS USED IN DIABETES	Biguanides	Metformin	Continue
ANTIGOUT PREPARATIONS	Preparations with no effect on uric acid metabolism	Colchicine	Consider
ANTINFAMMATORY AND ANTI-RHEUMATIC PRODUCTS	Propionic acid derivatives	Naproxen	Consider
ANTIGOUT PREPARATIONS	Preparations inhibiting uric acid production	Allopurinol	Consider

Metabolic function overview

Metabolic parameter	Input data	Interpretation
Liver function	Child-Pugh Score: <5	Normal function
Renal function	CrCl < 30–44 mL/min/1.73 m ²	Stage 3b Chronic kidney disease

Herb and Social lifestyle overview

Herb	Pharmacologic effect	Evidence level	Reference
Ginger (Zingiber officinale)	Antiflammatory	High	Click
Ginger (Zingiber officinale)	Antiplatelet	Low	Click
Ginger (Zingiber officinale)	Antimutagenic	Low	Click
Ginger (Zingiber officinale)	Antibiotic	Moderate	Click

Smoking Drinking Coffee

PGx function overview

Predicted phenotype and genotype	Inhibitor	Substrate	Inducer	Phenoconversion factor
CYP2C9 Intermediate metabolizer (*1/*3)	Amiodarone, Ginger	Warfarin, Naproxen	-	-
CYP2C19 Intermediate metabolizer (*1/*3)	Ginger	Clopidogrel, Warfarin, Esomeprazole	-	-
CLO1B1 Poor function (*5/*5)	Ginger	Atorvastatin	-	-
CYP3A4 -	Ginger	Atorvastatin, Esomeprazole, Alcohol	-	-
CYP1A2 -	Ginger	Warfarin, Naproxen, Alcohol	-	-

Prescription screening overview

Medication	Drug-Drug Interaction	Drug-Gene Interaction	Drug-Liver Consideration	Drug-Bowel Consideration	Drug-Herb Interaction	Drug-Social Lifestyle Interaction
Amiodarone	!!	N/A	✓	N/A	N/A	N/A
Clopidogrel	!!	!	✓	✓	N/A	N/A
Aspirin	N/A	!	✓	!	N/A	N/A
Enasapril	N/A	N/A	✓	N/A	N/A	N/A
Carvedilol	N/A	N/A	✓	N/A	N/A	N/A
Atorvastatin	!	!	✓	N/A	!	!
Warfarin	!!!!!!	✓ ✓	✓	N/A	!	!
Esomeprazole	!!!	!	✓	✓	N/A	!
Sennokot	N/A	N/A	✓	N/A	N/A	N/A
Metformin	N/A	N/A	✓	✓	N/A	N/A
Colchicine	N/A	N/A	✓	!	N/A	N/A
Naproxen	!!!	!	✓	!	N/A	!
Allopurinol	N/A	X	✓	!	N/A	N/A
Ginger	N/A	N/A	N/A	N/A	!!	!!
Alcohol	N/A	N/A	N/A	N/A	!!	!!

Recommendation summary icons
■ = Contraindication ■ = Therapeutic consideration ■ = Use as directed N/A = Not available * = Result from inference module

Fig. 12. The personalized prescribing report for virtual case study.

detect any Contraindication summary icon, health professionals can become aware of the common side effects from the section of medication overview in Fig. 14. From the knowledge of pharmacology, this section provides about the drug class of Aspirin and Clopidogrel, which have similar side effects such as bruising and bleeding. Furthermore, the patient used Moringa capsules as an herbal supplement, and the pharmacologic effect of this herb is Antiplatelet. Suppose health professionals use this tool to plan the intervention. In that case, the patient's side effects will be reduced quickly, and report like PPR raises

Personalized Prescribing Report

Include Herb and Dietary lifestyle

Medication overview

Class	Category	Drug	Status
LIPID MODIFYING AGENTS, PLAIN	HMG CoA reductase inhibitors	Simvastatin	Continue
DRUGS USED IN DIABETES	Biguanides	Metformin	Continue
ANTIEPILEPTICS	Other antiepileptics	Pregabalin	Continue
ANTIMYCOTICS FOR SYSTEMIC USE	Triazole derivatives	Itraconazole	Consider

Metabolic function overview

Metabolic parameter	Input data	Interpretation
Liver function	Child-Pugh Score: <5	Normal function
Renal function	Normal function	Normal function

Herb and Social lifestyle overview

This patient did not take any herbal medications.
 Smoking Drinking Coffee

PGx function overview

This patient did not have any PGx profile.

Predicted phenotype and genotype	Inhibitor	Substrate	Inducer	Phenoconversion factor
CYP3A4 -	Itraconazole	Simvastatin	-	-

Prescription screening overview

Medication	Drug-Drug Interaction	Drug-Gene Interaction	Drug-Liver Consideration	Drug-Bowel Consideration	Drug-Herb Interaction	Drug-Social Lifestyle Interaction
Simvastatin	!!	N/A	✓	✓	N/A	N/A
Metformin	N/A	N/A	✓	✓	N/A	N/A
Pregabalin	N/A	N/A	✓	✓	N/A	N/A
Itraconazole	!!	N/A	✓	✓	N/A	N/A

Recommendation summary icons
■ = Contraindication ■ = Therapeutic consideration ■ = Use as directed N/A = Not available * = Result from inference module

Fig. 13. The personalized prescribing report for case report.

health professionals' awareness of prescribing and allows for early intervention planning with a multidisciplinary team.

5.4. Implementing precision medicine to personalized prescribing

After PM was declared in 2015 [9], PGx played a major role in individualizing therapy with medications. Knowledge from PGx is collected and synthesized into actionable knowledge, such as clinical guidelines for drug dosing based on genetic variation [25,26]. To facilitate the screening in prescribing, we need the actionable PGx knowledge to serve as CDST [33,35,37,50,51,73]. The outcome of the PGx perspective can reduce harm from inappropriate polypharmacy, especially in prescribing drugs that cause serious adverse drug reactions such as Allopurinol, Carbamazepine, and Abacavir [70]. However, only information from the PGx perspective cannot screen all harm from concurrent multiple drug use. The approaches to improve efficacy and reduce harm in patients by combining them with renal function, liver function, other biophysical markers, and PGx information in clinical decision-making are presented to revolutionize the therapy with medications with PM paradigm [17,38]. However, patients in a real-world setting may have unpredictable, complex conditions like the above case studies. Factors that affect treatment success rate should be considered from stratified results for precise treatment interventions. Unlike the typical PGx approaches that screen single drug-gene pairs, the proposed personalized prescribing system offers the comprehensive PGx panel for interpreting and reporting multiple drugs simultaneously [74]. This study presents the possibility of personalized prescribing by involving PGx factors and non-genetic factors from the guideline for design knowledge-based and implementation examples. Implementing this approach can address problems that health professionals encounter, like time-consuming when gathering related data for intervention planning, a higher number of health professionals per patient, or just-in-time intervention planning for urgent situations.

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Fig. 14. The personalized prescribing report for real case study.

5.5. Challenges when explicit knowledge is not available from existing knowledge resources

An ideal implementation of PM into personalized prescribing relies on integrating various knowledge resources into comprehensive knowledge. Generally, knowledge of medication therapy is retrieved and summarized by research studies based on patient stratification concepts [75]. It requires an amount of time to complete a research study. In addition, each knowledge resource rapidly grows to a level that humans cannot review all available knowledge. Expected knowledge from users at the point of care should be actionable in all scenarios they encounter, real-time updated, providing evidence for decision making, and curating knowledge to be conveniently used in a short time [76]. With an advancement of technology at present, knowledge for predicting drug responses in both efficacy and harm may have been driven by Artificial Intelligence [51,75]. Although AI's prediction seems less reliable than knowledge from research studies based on patient stratification concepts, it still presents possible interactions if

a clear conclusion of medication-related interactions is not available from existing resources for preliminary screening. This work presents a transformation of knowledge into a semantic knowledge-based which facilitates many AI applications, for example, an application to discover suitable drugs [77], a prediction of drug-drug interaction [78,79], or a prediction of adverse drug reactions [80]. All mentioned above are challenges in applying knowledge graphs into knowledge management, derived from genetic and non-genetic factors, based on precision medicine paradigm to facilitate screening for potential interactions in prescribing.

5.6. Limitation

This study has several limitations that should be acknowledged. Firstly, it is important to note that the work presented here is at the conceptual design stage and has not been implemented in a real-world setting. While the proposed KM2PS holds promise as a screening tool for personalized prescribing, its practical application and feasibility in clinical practice need to be further explored and validated.

Secondly, the number of test cases used for validation was limited. Only one virtual case, one case report, and one real case were employed to evaluate the performance and effectiveness of the KM2PS. This small sample size may restrict the generalizability of the findings. Future research should involve a larger and more diverse set of test cases to ensure a comprehensive assessment of the system's capabilities.

Another area for improvement is the absence of feedback from stakeholders, including healthcare professionals and patients. Their perspectives and insights are crucial in understanding the usability, practicality, and acceptability of the KM2PS in real-world healthcare settings. Therefore, involving stakeholders and incorporating their feedback in the design and development process is vital for creating a system that meets their needs and enhances its relevance and effectiveness.

To address these limitations, further work is needed. Future research should focus on implementing the KM2PS in real-world settings, conducting extensive testing with diverse cases, and actively engaging stakeholders to obtain their feedback and ensure the system's usability and relevance. By addressing these limitations, the potential of the KM2PS as a valuable tool for personalized prescribing can be further realized.

6. Conclusion

To better screening and decrease screening time for prescription screening based on PM, this work presents an approach to preventing harm from inappropriate polypharmacy by involving both genetic factors and non-genetic factors, transforming data into a curated knowledge-based. Knowledge from various resources is curated into a concept of four PIs and two PCs for prescription screening, namely DDI, DGI, DHI, DSI, LF, and RF. We describe an implementation guideline for facile decision-making in clinical practice. A semantic knowledge-based is proposed as an alternative to explore hidden knowledge by AI aiming to assist in decision-making together with the existing knowledge. PPR is established to assist with risk-benefit analysis when health professionals such as physicians or pharmacists plan any therapeutic intervention with medicine. This proof of concept needs collaboration from whether it be health professionals, clinical and biomedical researchers, bioinformatics specialists, IT developers, data scientists, or medical curators to further design, develop, and implement the concept in real-world settings.

CRediT authorship contribution statement

Samart Jamrat: Conceptualization, Methodology, Software, Knowledge-based design, Validation, Formal analysis, Resources, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Chonlaphat Sukasem:** Conceptualization, Methodology, Validation, Formal analysis, Resources, Writing – review & editing, Visualization. **Lawan Srathaphut:** Knowledge-based design, Writing – review & editing. **Yaowaluck Hongkaew:** Validation, Formal analysis, Resources, Writing – review & editing. **Taweesak Samanchuen:** Conceptualization, Methodology, Software, Knowledge-based design, Validation, Formal analysis, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration.

Declaration of competing interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

During the preparation of this work the authors used ChatGPT in order to correct grammatical mistakes. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

Acknowledgments

The authors wish to acknowledge the contributions of Putcharapon Ferngprayoon in clinical consulting and virtual case study preparation, Montinee Sangtian, Lalita Suwandumrong, Tanawat Khunlertkit, Pornchit Eiumurai, and Waree Jaturapattarapong in real case study preparation. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Mahidol University (protocol code MU-MOU 2022/175.2406, 27 August 2022). Informed Consent for the clinical background of real case study was waived due to the case study was completed data anonymization by Bumrungrad Genomic Medicine Institute, Bumrungrad International Hospital, Bangkok, Thailand. Also, this case study was not prepared specifically for the proposed research.

Appendix A. The UML class diagram of the proposed system

See Fig. 11.

Appendix B. The personalized prescribing reports

See Figs. 12–14.

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