A Knowledge-based System for Intelligent Support in Pharmacogenomics Evidence Assessment: Ontology-driven Evidence Representation, Retrieval, Classification and Interpretation

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Abstract

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Pharmacogenomics is the study of how genetic variants affect a person's response to a drug. With great advances to date, pharmacogenomics holds promise as one of the approaches to precision medicine. Yet, the use of pharmacogenomics in routine clinical care is minimal, partly due to the misperception that there is insufficient evidence to determine the value of pharmacogenomics and the lack of efficient and effective use of already existing evidence. Enormous efforts have been directed to develop pharmacogenomics knowledge bases; however, none of them fulfills the functionality of providing effective and efficient evidence assessment that supports decisions on adoption of pharmacogenomics in clinical care.

In this context, my overall hypothesis was that a knowledge-based system that fulfills three critical features, including clinically relevant evidence, providing an evidence-based approach, and using semantically computable formalism, could facilitate effective and efficient evidence assessment to support decisions on adoption of pharmacogenomics in clinical care. My overarching research question has been: How can we exploit state-of-the-art knowledge representation and reasoning in developing a knowledge-based system with the intended features and applications as specified above.

The first aim of this research was to develop a conceptual model to address the information needs and heterogeneity problem for the domain of pharmacogenomics evidence assessment. Faceted analysis and fine-grained characterization of clinically relevant evidence acquired from empirical pharmacogenomics studies were deployed to identify 3 information entities, 9 information components, 30 concepts, 49 relations and approximately 250 terms as building blocks of the conceptual model. These building blocks were then organized into a model, which features a layered and modular structure so that heterogeneous information content of pharmacogenomics evidence could be expressed to reflect its intended meaning. The developed conceptual model was validated against a general ontology of clinical research (OCRe) to show its strength in modeling pharmacogenomics publications, studies and evidence in an extensible and easy-to-understand way.

The second aim of this research was to exploit OWL 2 DL to build a knowledge-based system that enables formal representation and automatic retrieval of pharmacogenomics evidence for systematic review with meta-analysis. The conceptual model developed in Aim 1 was encoded into an OWL 2 DL ontology using Protégé. The constructed ontology provides approximately 400 formalized vocabularies, which were used in turn to formally represent 73

individual publications, 82 individual studies and 445 individual pieces of evidence, and thereafter formed a knowledge base. After a series of subsumption checking and instance checking using HermiT reasoner, the implemented knowledge-based system was verified as consistent and correct.

The third aim of this research was to use the implemented knowledge-based system to provide four applications in pharmacogenomics evidence assessment. The first application focused on the ontology-driven evidence retrieval for meta-analysis. A total of 33 meta-analyses selected from 9 existing systematic reviews were used as test cases. The results showed that the ontology-based approach achieved a 100% precision of evidence retrieval in a very short time, ranging from 9 to 23 seconds. The second application addressed the evidence assessment of the clinical validity of CYP2C19 loss-of-function variants in predicting efficacy of clopidogrel therapy. The third application addressed the evidence assessment of the comparative effectiveness of genotype-guided versus non-genotype-guided warfarin therapy. These two applications focused on ontology-driven evidence classification to provide useful information to assist in the planning, execution, and reporting of a multitude of meta-analyses. The fourth application focused on ontology-driven interpretation of a multitude of synthesized evidence that was enabled by formal representation of synthesized evidence and typology of clinical significance in the context of assessing clinical validity and clinical utility of pharmacogenomics.

In conclusion, the major contributions of this research include: deriving an extensible conceptual model that expresses heterogeneous information content, constructing an ontology that exploits the advanced features of OWL 2 DL, and implementing a knowledge-based system that supports ontology-driven evidence retrieval, classification and interpretation. Future research would focus on (1) enhancing the system's applicability in pharmacogenomics evidence

assessment by representing evidence of other sub-domains of pharmacogenomics such as cancer drugs, and (2) expanding the system's capability beyond pharmacogenomics evidence assessment by representing individuals' genomic profiles and providing evidence-based interpretation based on their individual genomic profiles. With the enhanced applicability, the pharmacogenomics knowledge-based system might improve pharmacogenomics evidence assessment as well as evidence-based interpretation of pharmacogenomics at the point of care, and ultimately increase the adoption of pharmacogenomics in routine clinical care.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

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Chapter 1. EXECUTIVE SUMMARY

1.1 OVERVIEW

The vision of precision medicine is to improve people's health by providing effective disease treatment and prevention based on individual variability in genetic, phenotypic, environmental and lifestyle factors. Pharmacogenomics is the study of how genetic variants affect a person's response to a drug. With great advances to date, pharmacogenomics holds promise as one of the approaches to precision medicine. Yet, the use and adoption of pharmacogenomics in routine clinical care is slow, partly due to the misperception of insufficient evidence to determine the value of pharmacogenomics and the lack of efficient and effective use of already existing evidence.

One approach to make effective use of existing evidence in clinical medicine is systematic review. Systematic review is a critical formal methodology used in evidence-based medicine that assesses and evaluates the findings of a collection of research studies that address a particular research question described by a set of specific criteria. Generally, the review process involves the following steps: conducting a comprehensive literature search, screening articles to identify relevant studies, extracting quantitative data and other essential elements from included studies, synthesizing the extracted data when they are sufficiently similar, rating the quality and strength of evidence, and interpreting the results. Systematic reviews with meta-analyses have the advantage of providing a more precise estimate of the effect of interventions or risk factors on patients' outcomes than any individual study, therefore, the evidence generated from a systematic review is one of the key resources in evidence-based medicine. Informatics approaches such as natural language processing, machine learning and text mining have been

applied to improve the efficiency of conducting a systematic review by reducing the burden of manual screening and data extraction in reviews; however, there remains considerable room for further improvement. Informatics approaches that focus on computational representation and knowledge management are promising to enhance the efficiency of the systematic reviews process.

The vision of artificial intelligence is to understand the nature of intelligence and cognition so that computers can demonstrate human-like abilities. Knowledge representation and reasoning is a sub-domain of artificial intelligence that is concerned with encoding the knowledge into logic- or non-logic-based formalisms that can be efficiently manipulated by reasoning programs. Web Ontology Language (OWL) has been developed by combining the Semantic Web technologies and logic-based representation formalisms to advance the computer interpretability of information on the Web. OWL-encoded ontologies provide shared conceptualizations of a domain of interest and controlled vocabularies which allow for formal representation and automatic reasoning. Because of its expressive power and reasoning capabilities, more research efforts are encouraged to further exploit the advanced features of OWL in developing more complex ontology-based applications.

1.2 Motivation for This Dissertation

Considering the time consuming and labor-intensive nature of pharmacogenomics evidence assessment, the idea of developing a knowledge-based system for intelligent support in evidence assessment emerges intuitively from the perspective of biomedical informatics. I hypothesized that a knowledge-based system with the following features can facilitate effective and efficient evidence assessment, and therefore assist timely decision on adoption of pharmacogenomics in clinical practice. First, the information provided by the knowledge-based system should be

clinically relevant evidence, which means that evidence related to clinical validity and clinical utility of pharmacogenomics should be accumulated in the system. Second, the information provided by the knowledge-based system should be acquired through an evidence-based approach, which means that primary evidence acquired from empirical research should be collected and synthesized through methodologies established in a comprehensive systematic review. Third, the information provided by the knowledge-based system should be semantically computable, which means that a knowledge-based system's ability to provide reasoning services should take full advantage of the expressive power and reasoning capabilities available for logic-based knowledge representation formalisms such as OWL DL. After reviewing existing pharmacogenomics databases or knowledge bases, none of them fully meets all the critical features of my envisioned pharmacogenomics knowledge-based system. This gap motivates me to design and develop a knowledge-based system toward intelligent assistance for pharmacogenomics evidence assessment.

1.3 Research Aims and Questions

My overarching research goal was to build a knowledge-based system that fulfills three critical features, briefly, clinically relevant evidence, evidence-based approach, and semantically computable formalism, to facilitate effective and efficient evidence-based assessment of pharmacogenomics evidence. My overarching research question has been: How can we exploit state-of-the-art knowledge representation and reasoning in developing a knowledge-based system with the intended features and applications as specified in the overarching research goal. I formulated three aims to achieve the overarching research goal.

Aim 1: Conceptual modeling of pharmacogenomics evidence assessment

Research questions: What building blocks are essential to express evidence-based assessment of clinical validity and utility of pharmacogenomics? What structure is appropriate for modeling the domain of pharmacogenomics evidence assessment, which by itself is heterogeneous in nature? Are there existing conceptual models that could be applied to the domain of pharmacogenomics evidence assessment?

Specific sub-aims:

1. Characterize empirical research that reported pharmacogenomics evidence regarding to clinical validity and utility of pharmacogenomics to identify building blocks i.e., concepts, relations and terms that are essential for modeling the domain of pharmacogenomics evidence assessment.
2. Derive a conceptual model that organizes the identified building blocks in a flexible and extensible manner to accommodate pharmacogenomics knowledge, which by itself is heterogeneous in nature.
3. Verify the developed conceptual model in terms of the intended uses of the envisioned knowledge-based system, i.e., annotation of clinically relevant pharmacogenomics evidence as well as inclusion criteria for evidence-based assessment and validate the developed conceptual model against an external model, OCRe (Ontology of Clinical Research – OCRe).

Aim 2: Adoption of OWL 2 DL to construct a knowledge-based system to enable formal representation and automatic retrieval of pharmacogenomics evidence for systematic review

Research questions: What advanced features of OWL 2 DL can be used to assert complex and heterogeneous individuals involved in pharmacogenomics evidence assessment? What are the logical consequences of different representation patterns? Does the formal representation of individual publication, study, evidence and inclusion criteria for meta-analysis match its intended meaning? Are formally represented individuals inferred and retrieved as expected? Is there a good balance between expressive representation and efficient inference?

Specific sub-aims

1. Construct an OWL 2 DL ontology based on the previously developed conceptual model to provide essential vocabularies for formal representation of heterogeneous pharmacogenomics evidence and inclusion criteria for systematic review with meta-analysis.
2. Develop a knowledge base that provides pharmacogenomics individual publications, studies and evidence that are formally represented using the developed OWL ontology to enable automatic retrieval of pharmacogenomics evidence.
3. Design verification mechanisms to verify whether the developed knowledge-bases system is consistent and correct.

Aim 3: Applications of the developed pharmacogenomics knowledge-based system: ontology-driven evidence retrieval, classification and interpretation in systematic reviews with meta-analysis

Specific applications

1. Precise and efficient evidence retrieval for systematic review with meta-analysis: focus mainly on retrieving pharmacogenomics evidence from the developed knowledge base

using test cases that are inclusion criteria applied in a collection of 33 existing meta-analyses. Precision and computing time taken by the HermiT reasoner to perform instance checking are used to evaluate the effectiveness and efficiency of the evidence retrieval task enabled by the developed pharmacogenomics knowledge-based system.

2. Effective and efficient assessment of the effects of *CYP2C19* loss-of-function variants on various outcomes among patients treated with clopidogrel and assessment of the comparative effectiveness of genotype-guided versus non-genotype-guided dosing of warfarin: involve a series of steps in conducting a systematic review with meta-analysis. First, predefined classification schemes which consist of a large number of necessary and sufficient conditions are used to examine the current status of available evidence at the knowledge-based system before embarking on a systematic review with meta-analysis. Thereafter, decisions about which meta-analyses to conduct and which individual evidence to include in meta-analyses are made. Then data for meta-analyses are acquired from the knowledge base and R and package 'meta', open sources for statistical computing, are incorporated with the system to provide a pooled, quantitative estimation of the effects of *CYP2C19* loss-of-function variants and genotype-guided dosing of warfarin on patents' outcome respectively.
3. Automatic inference of the clinical significance of *CYP2C19* loss-of-function variants and genotype-guided dosing of warfarin: attempt to formally represent synthesized evidence that is yielded from meta-analyses so that clinical significance of *CYP2C19* loss-of-function variants and genotype-guided dosing of warfarin can be automatically inferred from the synthesized effect estimates once the results of meta-analyses have been accumulated in the knowledge base.

1.4 OUTLINE OF THIS DISSERTATION

Chapter 2: Background and significance of developing a knowledge-based system to facilitate pharmacogenomics evidence assessment

This chapter first addresses the need for developing a knowledge-based system to overcome the informational barrier that hinders timely decision making and widespread adoption of pharmacogenomics into clinical practice. Based on the recognized need, I specify 3 critical features consisting of 10 requirements that my envisioned knowledge-based system should have in order to assist in effective and efficient pharmacogenomics evidence assessment. I review 5 existing pharmacogenomics databases or knowledge bases and identify the gaps between the current status of existing pharmacogenomics knowledge bases and my envisioned knowledge-based system. To fill the identified gaps, I formulate three research aims to address the questions related to the overarching research goal.

Chapter 3: Conceptual Modeling of Pharmacogenomics Evidence Assessment (Aim 1)

This chapter focuses on the design of a conceptual model for modeling the domain of pharmacogenomics evidence assessment at a higher level of abstraction, which is viewed as the blueprint to construct my envisioned knowledge-based system. I elaborate several key issues including problems of heterogeneity and inconsistency encountered in pharmacogenomics evidence assessment, information structure of the conceptual model, and the possibility of reusing an existing general ontology of clinical research (OCRe). Based on these considerations, I present a fine-grained characterization of a collection of empirical pharmacogenomics research articles to identify concepts, relations and terms that are essential to describe 3 information entities (i.e., publications, studies, and evidence) in the domain of pharmacogenomics evidence assessment. Subsequently, how these building blocks of the conceptual model are organized into

9 information components (bibliographical information of publication, study population, study design, drug therapy, risk of bias assessment, comparison, genetic variation, outcome, and effect) is explained in detail. Then, verification of the developed conceptual model is provided, particularly, by cross-validation against OCRe. At the end of this chapter, I discuss the strengths of my developed conceptual model to deal with heterogeneity encountered in pharmacogenomics evidence assessment.

Chapter 4: Adoption of OWL 2 DL to construct a knowledge-based system to enable formal representation and automatic retrieval of pharmacogenomics evidence for systematic review (Aim 2)

This chapter focuses on the design, development, implementation and verification of a pharmacogenomics knowledge-based system based on the conceptual models derived in Chapter 3. I start with a brief overview of the evolution of knowledge representation and reasoning to explain why OWL 2 DL is adopted as the formal language to develop the ontology, which is the core of the envisioned knowledge-based system. I concisely recapitulate the basic notions and advanced features of OWL 2 DL to explain the semantic meaning and the logical consequence of their uses. Subsequently, I present the principles of mapping the building blocks of developed conceptual model to appropriate OWL 2 DL ontology constructs. Based on the constructed OWL 2 DL ontology, I present the design of common and special representation patterns to assert complex and heterogeneous individual information entities. Next, I present the implementation of a knowledge base by providing formally represented individual pharmacogenomics publications, studies and evidence asserted using appropriate representation patterns which consist of vocabularies declared in ontology and constructors available for OWL 2 DL. The verification of the implemented knowledge-based system is presented, particularly, the

mechanisms used to check semantic consistency and logical consequences of some special representation patterns are described in detail. Finally, the advantages and limitations of adopting OWL 2 DL as the formal language to construct the envisioned pharmacogenomics knowledge-based system are discussed as well.

Chapter 5: Applications of the developed pharmacogenomics knowledge-based system: ontology-driven evidence retrieval, classification and interpretation in systematic reviews with meta-analysis (Aim 3)

This chapter provides step-wise implementation of four applications to demonstrate that the developed knowledge-based system is capable of providing intelligent support in pharmacogenomics evidence assessment by ontology-driven retrieval, classification and interpretation of evidence. The first application focused on the ontology-driven evidence retrieval for meta-analysis, a collection of 33 existing meta-analyses is used as test cases to evaluate the precision and efficiency of the ontology-driven retrieval for meta-analyses. The ontology-based retrieval was accomplished by (1) formal representation of inclusion criteria for meta-analyses into defined classes using the OWL ontology, (2) a knowledge base serves as a repository of formalized primary evidence, and (3) a DL reasoner reasons over the ontology and the knowledge base to retrieve all the evidence that satisfies the defined necessary and sufficient conditions. The second and the third application focused on the ontology-driven evidence classification that supports the planning, execution and reporting of a multitude of meta-analyses. More specifically, two systematic reviews are conducted, one regards to clinical validity of *CYP2C19* loss-of-function variants in predicting the efficacy of clopidogrel therapy, and the other regards to clinical utility of genotype-guided dosing of warfarin in improving patients' outcome. The key to implement these two applications is the design of evidence classification

schemes that subdivides a collection of relevant and retrieved evidence into groups were considered homogeneous and amenable to meta-analyses. The classification schemes took full advantages of the developed knowledge-bases system, including: (1) well-designed representation patterns that enable quick and easy creation of a large number of inclusion criteria, and (2) highly efficient OWL 2 DL reasoner that enables iterative instance checking over a large number of defined classes. The fourth application focused on the ontology-driven interpretation of overall findings acquired form a number of comprehensive pharmacogenomics evidence assessments. The implementation of this application involved four key tasks: (1) extend initially developed ontology to enable formal representation of synthesized evidence, (2) design and formal representation of a typology of clinical significance to enable automatic inference of clinical significance of individual synthesized evidence, (3) derive a typology of interpretation in the context of assessing clinical validity of genetic variants and clinical utility of genotype-guided drug therapies, and (4) mapping the typology of clinical significance to the typology of interpretation. After demonstration of four applications, I highlight the strengths and limitations of using a knowledge-based system as an informatics approach to assist in conducting efficient evidence assessment in support of pharmacogenomics clinical adoption decision.

Chapter 6: Conclusions

In this concluding chapter, I summarize the major findings from each aim as well as overall findings from this dissertation to see if they address the research questions concerned in this research. I discuss the limitation of the generalizability of these findings. I also discuss the limitation of this research because of the lack of participation of stakeholders who are involved in pharmacogenomics evidence assessment. In spite of these limitations, I discuss the contributions of my dissertation to biomedical informatics and evidence-based medicine. Finally,

directions for future research are provided, including enhancing the system's applicability in the domain of cancer pharmacogenomics or expanding the system's capability to provide evidence-based interpretation based on individuals' genomic profiles.

1.5 CONTRIBUTIONS

This dissertation contributes to the field of biomedical informatics and evidence-based medicine. Aim 1 delivers an extensible and easy to understand conceptual model, which is able to express heterogeneous information content in the domain of pharmacogenomics evidence assessment. The conceptual model enables two different types of pharmacogenomics evidence, i.e., clinical validity and clinical utility, to be expressed in a unified model. This important feature fills the gap identified from PharmGKB because PharmGKB provides a large amount of evidence obtained from genetic association studies but lacks evidence obtained from genetic sub-studies of clinical trials or comparative effectiveness research. Furthermore, the conceptual model fills the gap identified from OCRe because neither the study results nor the domain-specific concepts such as genetic variants have been modeled using OCRe. From the perspective of biomedical informatics, Aim 2 delivers an ontology and a number of representation patterns, which exploit the advanced constructors of OWL 2 DL with novel ideas. These representation patterns allow complex and heterogeneous pharmacogenomics evidence to be unambiguously represented and differentiated from each other. The ideas and methods that underlie the design of an OWL ontology and the implementation of an ontology-driven knowledge base could be used by others who are interested in applying knowledge representation and reasoning to biomedical knowledge management. From the perspective of evidence-based medicine, Aim 3 delivers four ontology-driven applications and ultimately provides a proof-of-concept of that a knowledge-based system as an informatics approach is capable of providing intelligent support in pharmacogenomics

evidence assessment by ontology-driven retrieval, classification and interpretation of evidence. Findings from Aim 3 suggest innovative informatics approaches expediting or radically changing conventional systematic review approach are essential to satisfy the growing needs for evidence-based practice in genomic medicine.

Chapter 2. BACKGROUND AND SIGNIFICANCE OF DEVELOPING A KNOWLEDGE-BASED SYSTEM TO FACILITATE PHARMACOGENOMICS EVIDENCE ASSESSMENT

2.1 Potential of Pharmacogenomics to Contribute to the Vision of Precision Medicine

The vision of precision medicine is to allow doctors and researchers to predict more accurate treatments and effective prevention strategies for patients based on individual variability in genetic, phenotypic, environmental and lifestyle factors. Pharmacogenomics, an important component in the success of precision medicine, is the study of how genetic variants affect a person's response to a drug. The rapid advances in pharmacogenomics research have made pharmacogenomics one of the genomics-based innovations that contribute to improving people's health and reducing health care costs by increasing drug efficacy and safety [Green & Guyer, 2011; Secretary's Advisory Committee on Genetics, Health, and Society, 2008]. More specifically, pharmacogenomics helps to improve effective and safe medication use by personalized drug prescribing and dose adjustment once it is adopted and incorporated into routine care [Schildcrout et al., 2012].

Various projects in support of using preemptive pharmacogenomics testing to guide the choice of medications and dose adjustments have been implemented. For example, the Vanderbilt PREDICT (Pharmacogenomic Resource for Enhanced Decisions in Care & Treatment) Project initiates prospective genotyping for personalized medicine [Pulley et al., 2012]. The 1200 Patients Project provides preemptive pharmacogenomics testing to patients receiving care at the University of Chicago and aims to evaluate the utility of pharmacogenomics

in routine care [O'Donnell et al., 2012]. St. Jude Children's Research Hospital developed the protocol, PG4KDS, which incorporates pharmacogenomics testing into the electronic health record to tailor drug choice [Hoffman et al., 2014]. The Mayo Clinic Center has designed the RIGHT Protocol to individualize treatment by giving the right patient, the right drug, at the right dose, at the right time [Bielinski et al., 2014].

2.2 Informational Barriers to Clinical Adoption of Pharmacogenomics

Though a preemptive pharmacogenomic testing approach does not delay the initiation of drug therapy, widespread integration of pharmacogenomics information in everyday clinical practice is still lacking [Relling & Klein, 2011]. There have been many discussions of barriers to the clinical adoption of pharmacogenomics. One of the most frequently mentioned barriers is insufficient evidence to recommend clinical validity and clinical utility of a genetic test [Nadkarni & Wiepert, 2005; Pirmohamed, 2010; Sadee, 2011; Pirmohamed, 2011]. To address the barrier of insufficient genomic evidence, the need for development of knowledge bases has been well recognized over the years. The National Institutes of Health initiated the Pharmacogenomics Knowledgebase in 2000 and with the aim of creating a publicly available repository of primary evidence of associations between genes and drugs [Thorn, Klein, & Altman, 2010]. In 2011, the National Center for Biotechnology Information launched the ClinVar Project, with the aim of developing a public resource to provide evidence for supporting the interpretations of the relationship between human variation and phenotype in general [Landrum et al., 2014], and pharmacogenomics more specifically. ClinicalTrials.gov is a publicly available database that registers study protocol and reports study results of clinical studies of human participants. According to the statistics of ClinicalTrials.gov as of June 1, 2015, the results of large numbers of clinical trials (approximately 17,000 studies) have been posted

since the ClinicalTrials.gov results database was launched in September 2008 (see **Figure 2.1**). Moreover, drug or biological interventions are the most commonly studied interventional types (see **Table 2.1**)

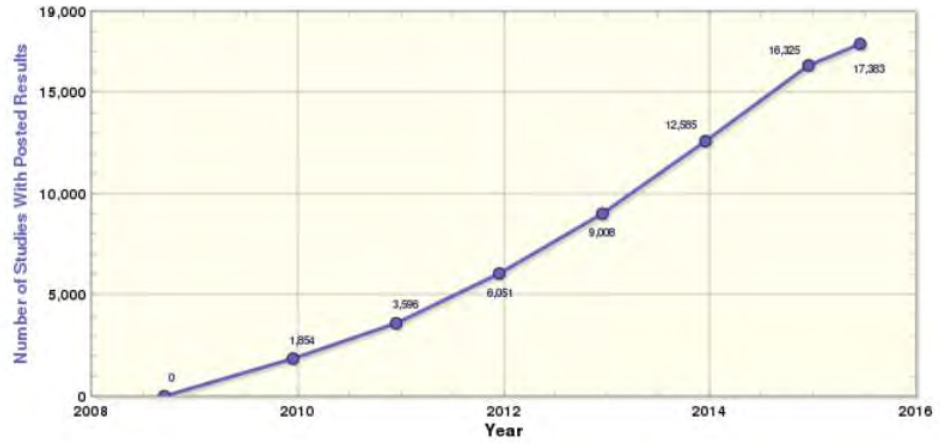

Figure 2.1: Number of registered studies with posted results in ClincialTrials.gov.
Data Source: http://ClinicalTrials.gov, as of June 1, 2015,

Table 2.1: Numbers and types of clinical studies registered in ClinicalTrials.gov

Type of study and intervention		Number of registered studies	Number of studies with posted results
Total		191, 583	17, 383
Interventional study		154, 396	16, 294
Type of intervention	Drug or biologic	98,262	13,354
	Behavioral, other	42,068	2,459
	Surgical procedure	16,765	834
	Device	15,917	1,725
Observational study		36, 323	1,089

Data Source: http://ClinicalTrials.gov, as of June 1, 2015

From a biomedical informatics perspective, the availability of evidence, per se, is thus no longer a big issue. The real challenge now is how to make effective use of existing study results as evidence to support timely decision making and adoption of pharmacogenomics into clinical practice. The decision making to adopt a pharmacogenomics-based drug therapy into clinical practice is a time consuming process involving evidence retrieval, synthesis and assessment. For

example, the Vanderbilt PREDICT Project initiated prospective genotyping for personalized medicine in 2010 [Pulley et al., 2012]. 'CYP2C19*2/*2 – clopidogrel' was the genetic variant–drug pair first selected for implementation. The selection was based on a process of a series of systematic reviews, evidence synthesis and approval by the Pharmacy and Therapeutics Committee of the institution. The process relies heavily on human effort, that is, domain experts and their knowledge of the domain of interest. Moreover, more than 60 articles related to the pair of 'CYP2C19*2/*2 – clopidogrel' have been published since the launch of the PREDICT Project. Due to the rapid growth of research in this field, evidence assessment by domain experts might seriously lag far behind the report of research findings. This is a concern particularly because practices and approaches that are supported by the evidence may change over time.

2.3 Hypothesis of Exploiting Knowledge-based System to Address Timely and Effective Evidence Assessment in Support of Clinical Adoption of Pharmacogenomics

I hypothesized that a knowledge-based system is an appropriate informatics approach to assist in conducting efficient evidence assessment in support of pharmacogenomics clinical adoption decision. A knowledge-based system is an information system that is built on a knowledge base wherein there is a collection of symbolic statements representing what the system knows about the domain of interest. The reason this is an appropriate approach to the pharmacogenomics evidence assessment problem is that, the knowledge-based system provides reasoning services to draw inferences or answer questions from the explicitly represented knowledge in the knowledge base [Brachman & Levesque, 2004].

If a knowledge-based system is intended to assist efficient and effective pharmacogenomic evidence assessment for use in pharmacogenomics clinical adoption decision support, then, three

important questions arise: (1) What pharmacogenomic information is essential to support effective evidence assessment? (2) What pharmacogenomic information is useful to support effective evidence assessment in practice? (3) What knowledge representation formalism can be used to represent essential and useful pharmacogenomic information curated in the system and to make this information semantically computable for automatic reasoning? These questions are elaborated as follows.

2.3.1 Feature of clinically relevant evidence: essential pharmacogenomic information to support effective evidence assessment needs to include clinically relevant findings from diverse pharmacogenomics studies

Since the study of pharmacogenomics attempts to understand how genetic variants affect a person's response to a drug, it relies on pharmacogenomic testing to identify variations that are involved in drug response. The results of pharmacogenomic testing only indicate that specific variations are present or absent. However, two measures, clinical validity and clinical utility, aid in interpreting the testing results. First, clinical validity interprets the predictive value of the pharmacogenomic testing for a given drug response, for example, the increased risk of bleeding will occur in a person with positive test result of a particular genetic variant. Clinical utility refers to improved outcome resulting from interventions offered to a person with positive test results, for example, the decreased risk of bleeding is observed when genotype-guided warfarin dosing is offered to the person with certain variations predisposing to bleeding using standard warfarin dosing. Testing of pharmacogenetic variants or pharmacogenomics-guided drug therapies will remain substantially underutilized in practice unless the interpretations of clinical validity or clinical utility are provided to support their appropriate use. Therefore, the clinically relevant findings, that is, clinical validity and utility of pharmacogenomics testing from diverse

pharmacogenomics studies, are considered as part of the essential pharmacogenomics information to support effective evidence assessment.

2.3.2 Feature of evidence-based approach: useful pharmacogenomic information to support effective evidence assessment needs to include evidence-based synthesized statements along with risk of bias assessments, and track of accumulated evidence over time

It is not surprising that many clinicians are not familiar with the concepts and terminology used in pharmacogenomics testing and research. A pharmacogenomics usability study observed that communicating genomics and pharmacogenomics information to clinicians is challenging because they are not trained to interpret the information [Devine et al., 2014]. Rather than using personal experience or judgment, clinicians are today encouraged to use evidence-based medicine when facing unfamiliar situations.

Evidence-based medicine requires the integration of clinical expertise and the best available evidence from systematic research [Sackett, Rosenberg, Gray, Haynes & Richardson, 1996]. Systematic review is a critical formal methodology used in evidence-based medicine that assesses and evaluates the findings of a collection of research studies that address a particular research question described by a set of specific criteria. The best available evidence generated from a systematic review is one of the key resources in evidence-based medicine. Two analytic methods, meta-analysis and cumulative meta-analysis, are commonly used in systematic reviews to create valuable and useful summaries of the current available scientific evidence. Meta-analysis is a quantitative method for pooling data from a collection of research studies that addresses a particular research issue. The synthesized result from meta-analysis is advantageous in that it provides a more precise estimate of the effect of interventions or risk factors on patients' outcomes than any individual study [Haidich, 2010]. While pooling the data from a

collection of research studies, the assessment of the risk of bias in each primary study needs to be taken into consideration as well [Jorgensen & Williamson, 2008]. The assessment of risk of bias in each included study is necessary to explain whether the available scientific evidence is valid enough to inform clinical practice. An extension of traditional meta-analysis, cumulative meta-analysis, is useful in recognizing the cumulative nature of scientific evidence [Impellizzeri & Bizzini, 2012]. The results of cumulative meta-analysis provide a track of evidence over time and help to identify the point at which accumulated evidence becomes statistically significant. Therefore, the ideal pharmacogenomic evidence supporting effective evidence assessment for use in pharmacogenomics clinical decision support is an evidence-based synthesized statement with risk of bias assessment and tracking of accumulated evidence over time, to account for and show the shifting back and forth of evidence over time.

2.3.3 Feature of semantically computable formalism: creation of a knowledge-based system with automatic question answering capability requires use of a logic-based knowledge representation formalism in constructing the basic components of a knowledge-based system (i.e., ontology, knowledge base, and reasoner)

A typical knowledge-based system is composed of three components, i.e., TBox (Terminology Box), ABox (Assertion Box), and reasoner. **Figure 2.2** illustrates a simple architecture of a knowledge-based system using description logics as knowledge representation formalism [Baader & Nutt, 2010].

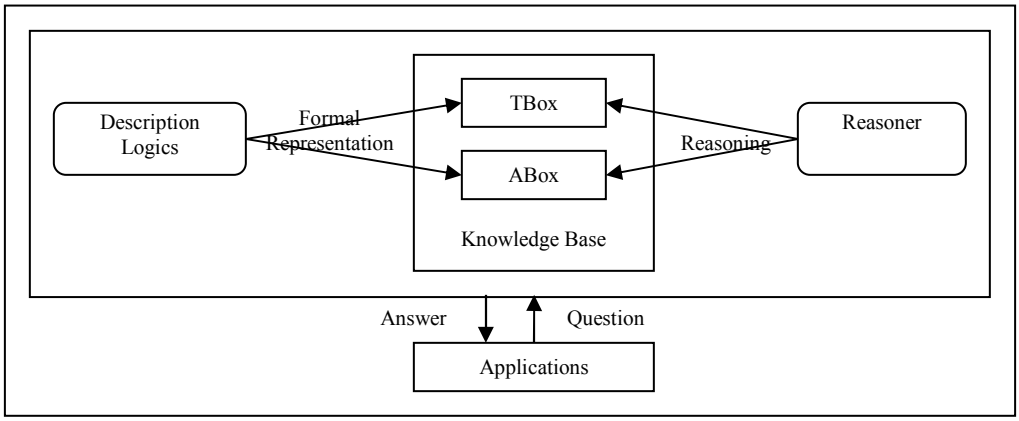

Figure 2.2: Fundamental architecture of a knowledge-based system.
Adapted from [Baader & Nutt, 2010].

A TBox corresponds to an ontology that enumerates concepts and roles (i.e., terminology) to describe the domain of interest. An ABox contains instances asserted using concepts and roles declared in the TBox. A TBox and an ABox collectively form the knowledge base. A reasoner performs inference drawn from TBox and ABox to answer questions posed by various applications. A knowledge-based system can demonstrate its ability to answer questions only when the domain of interest is built through the use of formal languages. Formal languages, also known as knowledge representation formalisms, can be broadly divided into logic-based formalisms and non-logic-based formalisms. How efficiently a knowledge-based system can perform reasoning to answer questions depends mainly on which knowledge representation formalism is selected. In general, in contrast to non-logic-based formalisms, logic-based formalisms can provide precise semantics along with associated inference rules, thus form the basis of a knowledge-based system that is required to carry out automatic reasoning. For example, Description Logics (DL) is a logic-based formalism with sound and complete reasoning services. OWL (Web Ontology Language) is a knowledge representation language for the Web. OWL DL is one species of OWL that aims to bring the expressive and reasoning power of description logic to the Semantic Web. Therefore, OWL DL is now widely used to represent

biomedical knowledge in various applications that require automatic reasoning. In summary, if a knowledge-based system is capable of automatic reasoning, it means that the system has three essential components, i.e., domain ontology encoded in a logic-based formalism, knowledge instances instantiated based on a logic-based ontology, plus sound and complete reasoning support.

Through the elaboration on the three important questions above, the knowledge-based system that I conceived for this dissertation has 3 critical features which include 10 requirements (see **Table 2.2**).

Table 2.2: Specification of the features and requirements of the envisioned knowledge-based system

Purpose	To assist efficient and effective pharmacogenomics evidence assessment for the purpose of decision making to adopt genotype-guided drug therapy into routine clinical practice.		
Critical Feature	The information provided by the KBS is **clinically relevant**	The information provided by the KBS is **evidence-based**	The question answered by the KBS is automatic reasoning over **logic-based semantic representation of knowledge**
Requirement	**1. Clinical validity** The KBS provides information that is relevant to the association of genetic variants with drug response **2. Clinical utility** The KBS provides information that is relevant to the effectiveness of genotype-guided drug therapy in improving clinical efficacy and safety of drug therapy	**3. Primary evidence** The KBS provides primary evidence that is extracted from empirical studies **4. Sufficient information for meta-analysis** The primary evidence contains the information required for conducting meta-analysis **5. Risk of bias assessment** The primary evidence is annotated with information of risk of bias assessment **6. Synthesized evidence** The KBS provides evidence that is synthesized from primary evidence by meta-analysis **7. Explicit inclusion criteria** The synthesized evidence is annotated with explicitly specified selection criteria of including primary evidence in the meta-analysis	**8. Formal ontology of the domain** The KBS provides ontology that formalizes in logic-based representation of concepts and relations for modeling the domain of interest. **9. Ontology-committed knowledge base** The KBS instantiates individual information entities in a knowledge base according to the formally represented domain ontology. **10. Question answering using automatic reasoning** The knowledge representation formalism is supported by automatic reasoning tool.

KBS: knowledge-based system

2.4 State of the Art of Pharmacogenomics Knowledge Bases

I conducted a review of current pharmacogenomics knowledge-based systems to see if they meet the features and requirements proposed in **Table 2.2**. An extensive search of current pharmacogenomics ontologies and/or knowledge bases was conducted by searching the following online resources: the National Center for Biomedical Ontology BioPortal, the Open Biological and Biomedical Ontologies Foundry, the Nucleic Acid Research online Molecular Biology Database Collection, PubMed and the Google Scholar search engine. These online resources were searched using the keywords: (pharmacogenomics OR pharmacogenetics) AND (knowledge base OR ontology). Seven pharmacogenomics ontologies or knowledge bases were found. After initial screening, the Pharmacogenomics Relationships Ontology and the Pharmacogenetic Effect Database were excluded because they do not provide information about genetic variants or drug responses (see **Figure 2.3**).

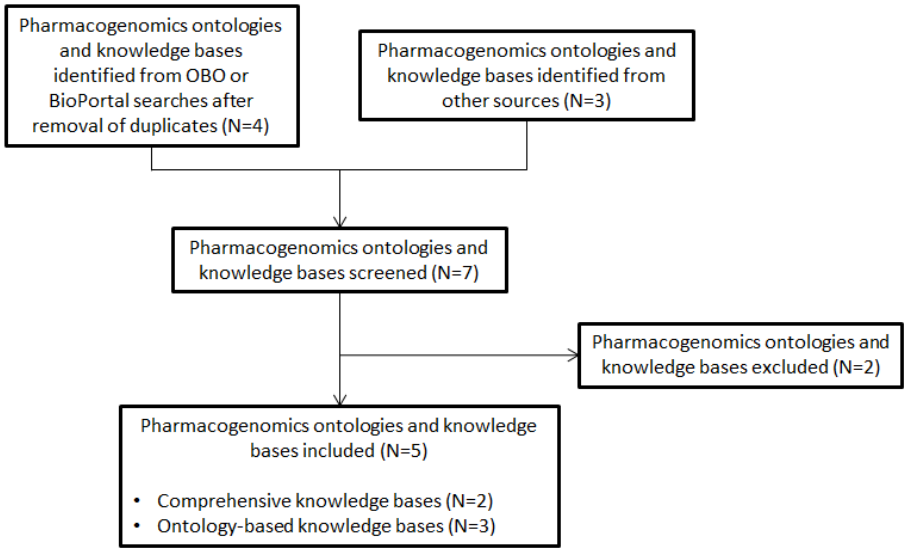

Figure 2.3: Flow of selection of pharmacogenomics ontologies and knowledge bases for a focused review

Five pharmacogenomics knowledge bases were selected and reviewed as follows.

2.4.1 PharmGKB (The Pharmacogenomics Knowledge Base)

Pharmacogenomics Knowledge Base (PharmGKB), a publicly available knowledge-sharing web-site, provides pharmacogenomics knowledge manually curated from the pharmacogenomics literature [Whirl-Carrillo et al., 2012; Thorn, Klein & Altman, 2013]. PharmGKB provides knowledge in different forms.

- Literature Annotation (also known as relationship file) captures concise pharmacogenomics knowledge that contains pair-wise relationships, e.g. gene-drug, gene-disease, variant-drug, etc., that are reported in a single published article. The relationship file is a relational table that contains a set of tuples. Each tuple consists of 9 data fields. Controlled vocabularies or standard codes are used as fillers of the data fields. The relationship file is widely downloaded for research uses, especially in knowledge discovery such as drug target discovery [Tau, Sun, Zheng, Chen & Xu, 2015] or drug repurposing [Zhu, Tao, Shen & Chute, 2014]. When the relationship file is used to discover new knowledge, it is usually transformed into formats conforming to the Semantic Web standards such as RDF (Resource Description Framework) or OWL in order to take advantage of sophisticated reasoning supported by the ontologies built by researchers according to their research interests.
- Variant Annotation (VA) curates the association between a variant and a drug response from a published article. Like the relationship file, the VA data file consists of inter-related relational tables and contains nearly 30 data fields. Although the VA is rich in information content, it is still insufficient for meta-analysis and information relating to risk of bias assessment is not provided. Moreover, some of the data field fillers are free text phrases or

sentences, rather than controlled vocabularies or standard codes. Thus, VA is not sufficient to allow for efficient reasoning.

- Clinical Annotation (CA) describes summarized genotype-phenotype relationships of a specific variant-drug pair and aims to assist pharmacogenomics implementation programs regarding which pharmacogenomics variants could be adopted into clinical practice. Like VA, the CA data file is comprised of relational tables consisting of approximately 20 data fields. In addition, CA is manually synthesized from the in-house curated VA. The synthesis process does not strictly follow the methodology of meta-analysis, and neither effect size nor selection criteria of supporting evidence is provided.
- Drug-centered pathway (PW) is the knowledge about genes involved in the pharmacokinetics or pharmacodynamics of a particular drug. It is manually synthesized from multiple publications and displayed as diagrams on the web along with a free text summary. In addition, the drug-centered pathway is captured and stored in a Biopax compatible format so that it can be downloaded and used in pathway analysis packages.
- Very Important Pharmacogene (VIP) is a free text summary article that describes all the drug responses relevant to a specific gene. VIP is manually synthesized from a collection of publications.
- Dosing Guidelines (DG) provide knowledge that is useful for clinicians, including the assignment of likely phenotypes based on genotypes and recommendations of dose adjustments or drug selections based on an individual's genotype. DGs are published by the Clinical Pharmacogenetics Implementation Consortium (CPIC) to help clinicians understand how an individual's genotype can be used to optimize drug therapy if the patient's genetic information is already available [Relling & Klein, 2011].

In summary, PharmGKB does provide primary and synthesized pharmacogenomics evidence. A large amount of clinical validity and only a small amount of clinical utility information is annotated within variant annotations and clinical annotations. Both variant annotations and clinical annotations are presented in a semi-structured format rather than a machine understandable semantics. Due to lack of formal semantics, the knowledge curated in PharmGKB cannot be efficiently manipulated by computer-assisted applications.

2.4.2 DrugBank

DrugBank is a publically available database that contains extensive information about drugs, drug targets and molecules involved in absorption, distribution, metabolism and elimination of drugs [Law et al., 2014]. DrugBank aims to support a wide range of applications such as *in silico* drug target discovery, drug design, drug docking or screening, drug metabolism prediction, and drug interaction prediction. Since its first release in 2006, DrugBank has rapidly evolved and expanded, with data fields increased from 88 to 208 of the latest update. The pharmacogenomics information was first added to DrugBank in 2008 [Knox et al., 2011], which provides genetic variant and drug response relationships of two categories: namely, SNP-mediated therapeutic effects (SNP-FX) and SNP-mediated adverse drug reactions (SNP-ADR). The relationship is described by 7 data fields: namely, drug, interacting gene/enzyme, reference SNP ID, allele name, defining sequence change, therapeutic effect/adverse reaction, and reference. Data are manually curated from primary literature sources by an in-house expert curation team. DrugBank employs a relational database system for data management and has converted the data to XML for data exchange [Wishart et al., 2008].

In summary, DrugBank does provide rich information about drugs. But it only provides limited information on the clinical validity of pharmacogenomics, that is, SNP-mediated

therapeutic effects, adverse drug reactions and their references. Neither clinical utility nor synthesized information is provided. Furthermore, since data are modeled as relational tables, reasoning data that lack precise semantic meaning cannot be carried out efficiently.

2.4.3 PO (Pharmacogenomics Ontology)

Pharmacogenomics Ontology (PO) is an OWL ontology developed for formal representation of pharmacogenomics knowledge. [Dumontier & Villanueva-Rosales, 2009] It includes essential concepts such as genes, gene variants, drugs, drug treatments, drug-gene interactions, drug-induced side effects, diseases and outcome measures. The investigators who created PO initially populated its knowledge base with data from the relationship file created by PharmGKB. However, the lack of explicit semantics in the relationship file makes it challenging to reuse the knowledge converted from PharmGKB. In order to demonstrate the use case of clinical decision support in practicing pharmacogenomics of depression, additional pharmacogenomics knowledge of depression is manually extracted from publications. The instantiation of additional knowledge makes it possible to answer the question: *"What is the most effective and safe drug treatment for an individual with a given genetic profile that suffers from depression?"* For example, for an elderly patient who is diagnosed with depression and has genotypes *ABCB1_3435C/C* and *CYP2D6*4/*6*, the system recommends: drug (*Nortriptyline*) and dose (103±25 *mg*) with a known side effect rate of postural hypotension (*less than 5%*). This recommendation is based on a piece of evidence extracted from a study that examined *ABCB1(3435C>T)* in patients with major depression enrolled in a randomized antidepressant trial of nortriptyline and fluoxetine, and observed that in the genotype group of *ABCB1_3435C/C*, the rate of postural hypotension was 0% at the completion of adequate 6-week

trial and the nortriptyline dosage at 6 weeks was 103±25 mg [Roberts, Joyce, Mulder, Begg & Kennedy, 2002].

In summary, the Pharmacogenomics Ontology experience suggests that knowledge-based systems for clinical decision support require rich information populated in the knowledge base. Although the PO ontology is not designed to address the need of pharmacogenomics evidence assessment, the ontology plus manually curated knowledge instances with respect to antidepressant treatment outcomes and specific genetic variants proved to answer questions posed by clinicians at the point-of-care.

2.4.4 TMKB (Translational Medicine Knowledge Base)

The Translational Medicine Knowledge Base (TMKB) is an ontology-driven knowledge base aiming to integrate patient data acquired from medical information systems with knowledge acquired from biomedical research, and therefore, facilitate translational research, pharmaceutical drug discovery and development, and clinical practice [Luciano et al., 2011]. TMKB does not curate domain knowledge but acquires data from publicly available databases such as ClinicalTrials.gov, DailyMed, DrugBank, PharmGKB, etc. The external datasets are acquired through the Linking Open Drug Data (LODD) project and mapped to the Translational Medicine Ontology (TMO), an OWL-based ontology developed as a framework to integrate and map various external data sources. All data from external databases is transformed into RDF (Resource Description Framework) representation. TMKB provides SPARQL (a query language for RDF) endpoint to answer competency questions, such as, *"An APOE variant is strongly correlated with Alzheimer's disease predisposition. Are there drug classes and drugs that target APOE?"*, and *"Which marketed drugs might potentially be re-purposed for use in the treatment of Alzheimer's disease because they modulate Alzheimer's disease implicated genes?"*

In summary, the design of TMO and TMKB is to integrate and reuse various external data sources in order to answer competency questions for knowledge discovery; however, these competency questions are irrelevant to pharmacogenomics evidence assessment.

2.4.5 SO-Pharm (Suggested Ontology for Pharmacogenomics)

SO-Pharm is an ontology developed with the aim to support data integration for pharmacogenomic knowledge discovery, particularly discovery of genotype-phenotype relationship [Coulet, Smaïl-Tabbone, Napoli & Devignes, 2006]. SO-Pharm reuses a number of existing ontologies, such as SNP-Ontology, Disease Ontology, ChEBI, Pharmacogenetics Ontology, etc., and their instances to form a knowledge base that covers domain knowledge in pharmacogenomics. SO-Pharm proposes a conceptual model to represent individual patients' genotypes and phenotypes involved in pharmacogenomic clinical studies, thereby the patient-level data acquired from a study can be formatted into a dataset that conforms to the designed patient conceptual model. By this design, SO-Pharm interacts with patient dataset and domain knowledge during the process of data mining. SO-Pharm and the external ontologies incorporated in the system are all encoded in OWL. The reasoning capability enabled by OWL was demonstrated by a case study that reported ontology-guided data selection within a data mining process, whose objective was to discover genotype-phenotype relationships in a familial hypercholesterolemia dataset [Coulet, Smaïl-Tabbone, Benlian, Napoli & Devignes, 2008]. Two scenarios showed selection of subsets of SNPs, which were guided by the type and properties of SNPs asserted in the ontology. The third scenario showed a selection of subsets of patients based on their genotype and phenotype attributes asserted in the ontology.

In summary, SO-Pharm does not provide relevant and useful pharmacogenomics knowledge in the context of pharmacogenomics evidence assessment. However, the case study of ontology-

guided data selection upon a patient dataset suggests that the reasoning capability enabled by OWL is strong.

2.5 Gaps in Current Pharmacogenomics Knowledge Bases as Compared to Specified Requirements of the Envisioned Knowledge-based System

The review of five pharmacogenomics databases or knowledge bases indicates that none of them fully meets all the critical features and requirements of my envisioned pharmacogenomics knowledge-based system (see **Table 2.3**).

Table 2.3: Overview of identified gaps in current pharmacogenomics knowledge bases

Requirements of the Envisioned Pharmacogenomics Knowledge-Based System	Comprehensive Knowledge Base		Ontology-Driven Knowledge Base		
	PharmGKB	DrugBank	PO	TMKB	SO-Pharm
1. Clinical validity	Y	Y	N	N	N
2. Clinical utility	Y	N	N	N	N
3. Primary evidence	Y	Y	N	N	N
4. Sufficient information for meta-analysis	N	N	N	N	N
5. Risk of bias assessment	N	N	N	N	N
6. Synthesized evidence	Y	N	N	N	N
7. Explicit inclusion criteria	N	N	N	N	N
8.Logic-based formalized ontology	N	N	Y	Y	Y
9. Ontology-committed knowledge base	N	N	Y	N	Y
10. Question answering by automatic reasoning	N	N	Y	N	Y

PharmGKB: Pharmacogenomics and Pharmacogenetics Knowledge Base, PO: Pharmacogenomics Ontology for Depression, TMKB: Translational Medicine Knowledge Base, SO-Pharm: Suggested Ontology for Pharmacogenomics.
Y: the requirement listed in the first column is satisfied, N: the requirement listed in the first column is not satisfied.

In general, the selected pharmacogenomics knowledge bases could be divided into two types. The first type of knowledge bases, such as PharmGKB and DrugBank, aim to be comprehensive knowledge resources for multiple application purposes. Both PharmGKB and DrugBank put a lot

of human efforts into curating evidence and assuring the quality of the curated evidence. However, the large amount of knowledge is organized in structures that lack of formal semantic meaning, thereby, limiting the system's ability to reason over curated knowledge.

The second type of knowledge base, such as PO, TMKB, and SO-Pharm, are ontology-driven knowledge bases that aim to leverage as much as possible the existing knowledge resources. They focus on developing ad hoc ontologies to integrate various external knowledge sources, so that implicit knowledge can be inferred over explicit represented knowledge. These ontology-driven knowledge bases are designed for purposes that differ from pharmacogenomics evidence assessment. The lack of essential knowledge for synthesis makes these ontology-driven knowledge bases incapable of facilitating effective pharmacogenomics evidence assessment. However, these experiences expose the power of OWL in expressing and reasoning pharmacogenomics knowledge and lay the basis of implementing the envisioned knowledge-based system with OWL.

2.6 Research Aims and Questions

The research focus of my dissertation is motivated by the visions of precision medicine to improve healthcare. With great advances to date, pharmacogenomics holds promise as one of the approaches to precision medicine. Yet, the use and adoption of pharmacogenomics into routine clinical care is slow, partly due to the misperception of insufficient evidence to determine the value of pharmacogenomics and the lack of efficient and effective use of already existing evidence. Considering the knowledge-intensive nature of pharmacogenomics evidence assessment, the idea of building a knowledge-based system to assist in the intellectual work involved in evidence-based assessment emerges intuitively from the perspective of informatics. Moreover, in the context of supporting timely decision or policy making, my envisioned

knowledge-based system should satisfy the following three critical features: clinically relevant pharmacogenomics evidence (domain knowledge), evidence-based assessment methodology (domain rules), and logic-based knowledge representation formalisms to enable automatic and semantic computation of domain rules over domain knowledge. In contrast to a knowledge base that contains comprehensive domain knowledge but lacking in formal semantics, my envisioned knowledge-based system is a more appropriate and effective informatics approach to store, retrieve and manipulate pharmacogenomics knowledge, so that complex questions can be answered in an efficient way.

Due to the wide gap between the current status of existing pharmacogenomics knowledge bases and my envisioned knowledge-based system, this dissertation will develop a pharmacogenomics knowledge-based system *de novo*. The overall goal of my research is to design and develop a prototype of a knowledge-based system that satisfies 3 critical features and 10 requirements listed in **Table 2.2**, and therefore, fill gaps in existing systems. To achieve the overall goal, three aims and research questions being addressed are identified and presented as follows.

The first aim of this research is to **develop a conceptual model to address the information needs and heterogeneity problem encountered in the domain of pharmacogenomics evidence assessment**. The following research questions are explored: What building blocks are essential to express evidence-based assessment of clinical validity and utility of pharmacogenomics? What structure is appropriate for modeling the domain of pharmacogenomics evidence assessment which by itself is heterogeneous in nature? Are there existing conceptual models that could be applied to the domain of pharmacogenomics evidence

assessment? The research work undertaken to address the first aim and related research questions is provided in Chapter 3.

The second aim of this research is to **exploit OWL 2 DL to build a knowledge-based system that enables formal representation and automatic retrieval of pharmacogenomics evidence for systematic review with meta-analysis**, which explores the following questions: What advanced features of OWL 2 DL can be used to assert complex and heterogeneous individuals involved in pharmacogenomics evidence assessment? What are the logical consequences of different representation patterns? Does the formal representation of individual publication, study, evidence and inclusion criteria for meta-analysis match its intended meaning? Are formally represented individuals inferred and retrieved as expected? Is there a good balance between expressive representation and efficient inference? The research work undertaken to address the second aim and related research questions is provided in Chapter 4.

The third aim of this research is to **provide three independent yet inter-related applications involved in pharmacogenomics evidence assessment using the implemented knowledge-based system:** (1) precise and efficient evidence retrieval, (2) effective and efficient systematic review regarding the clinical validity and utility of pharmacogenomics, and (3) automatic inference of clinical significance from formally represented individual synthesized evidence. The research work undertaken to address the third aim and related use cases is provided in Chapter 5.

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Chapter 3. CONCEPTUAL MODELING OF PHARMACOGENOMICS EVIDENCE ASSESSMENT

3.1 INTRODUCTION

My overall research goal was to build a knowledge-based system that fulfills three critical features including clinically relevant evidence, evidence-based approach, and semantically computable formalism to facilitate effective and efficient evidence assessment, and ultimately to support timely decision making and adoption of pharmacogenomics into clinical practice. After reviewing existing pharmacogenomics databases or knowledge bases, none of them fully meets the critical features and requirements that my envisioned pharmacogenomics knowledge-based system should have (see Chapter 2, **Table 2.2** and **Table 2.3**). This gap motivated me to design and develop my envisioned knowledge-based system *de novo*, starting from conceptual modeling which aimed at describing the domain of pharmacogenomics evidence assessment at a higher level of abstraction.

The research in this chapter aims to construct a conceptual model that realizes two critical features i.e., clinically relevant evidence and evidence-based approach. In order to achieve the research goal, I propose the following three specific sub-aims:

1. Characterize empirical research that reported pharmacogenomics evidence regarding to clinical validity and clinical utility of pharmacogenomics to identify building blocks i.e., concepts, relations and terms that are essential for modeling the domain of pharmacogenomics evidence assessment.
2. Derive a conceptual model that organizes the identified building blocks in a flexible and extensible manner to accommodate different types of pharmacogenomics evidence which by itself is heterogeneous in nature.

3. Verify the developed conceptual model in terms of the intended uses of the envisioned knowledge-based system, i.e., annotation of primary pharmacogenomics evidence as well as inclusion criteria for retrieving relevant evidence and validate the developed conceptual model against an external model, OCRe (Ontology of Clinical Research).

In the following sections of this chapter, I provide in Section 3.2 the considerations in designing conceptual model, including (1) heterogeneity problems encountered in pharmacogenomics evidence assessment, (2) information structure of the conceptual model, (3) two pre-specified features i.e., clinically relevant evidence and evidence-based approach, and (4) a focused review of OCRe. In Section 3.3, I provide the characterization of empirical research that reported pharmacogenomics evidence regarding to clinical validity and clinical utility of pharmacogenomics to identify essential building blocks for modeling the domain of pharmacogenomics evidence assessment. In Section 3.4, I present the derived conceptual model consisting of building blocks identified in Section 3.3. In Section 3.5, I present the verification and validation of the developed conceptual model. I conclude this chapter by discussing the major findings when the domain of pharmacogenomics evidence assessment is being modeled from the beginning, the limitations of the developed model, and the next steps toward developing my envisioned knowledge-based system.

3.2 CONSIDERATIONS IN CONCEPTUAL MODELING

A conceptual model is fundamentally important for the development of a knowledge-based system because the developed conceptual model will be transformed later into an ontology. Thus, how the conceptual model developed is crucial whether the knowledge-based system is able to effectively manipulate pharmacogenomics knowledge to support decision making. In this

section, I elaborate issues considered when modeling the domain of pharmacogenomics evidence assessment.

3.2.1 Problem of heterogeneity encountered in pharmacogenomics evidence assessment

Systematic review with meta-analysis is a well-established methodology in evidence assessment. It is an overview of primary research that seeks to identify, select and synthesize all relevant evidence that fits pre-specified eligibility criteria, in order to answer specific research questions (see **Figure 3.1**) [Green et al., 2011]. Though systematic reviews with meta-analyses represent one of the important approaches to the presentation of evidence-based conclusions and inform decision-making, the subjective judgments made in the review process illustrated in **Figure 3.1** might potentially result in inconsistent conclusions among reviews on similar research questions.

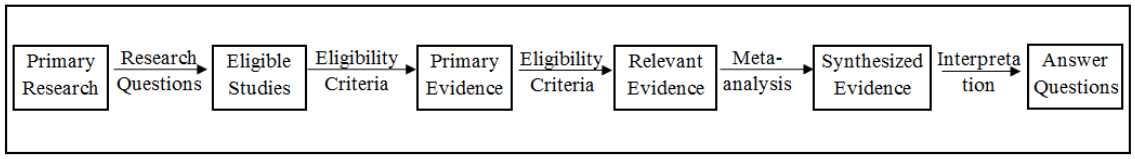


Figure 3.1: Process of systematic review with meta-analysis

Recently, a few reviews of systematic reviews did find that systematic reviews conducted in the field of pharmacogenomics reported inconsistent conclusions about the association between the carriage of genetic variants and drug responses [Sorich et al., 2013; Osnabrugge et al., 2015], or about the clinical utility of genotype-guided drug therapy over current standard therapy [Pirmohamed et al., 2015]. Sorich et al. [2013] reviewed 9 systematic reviews that explored the association between CYP2C19 loss-of-function variants and the risk of adverse cardiovascular events in patients receiving standard clopidogrel therapy [Sorich et al., 2013]. They found that the reviews yielded different conclusions due to the heterogeneity of patient populations and

cardiovascular end points used across studies included in the reviews. To further explore the possible contributors that cause contradictory conclusions among reviews, Osnabrugge et al. [2015] conducted an evaluation by examining 11 systematic reviews on the same topic of clopidogrel efficacy and CYP2C19 loss-of-function variants and found significant between-study heterogeneity on the clinical end point [Osnabrugge et al., 2015]. Pirmohamed et al. [2015] also evaluated 4 systematic reviews that explored the clinical utility of genotype-guided warfarin dosing and found that the results of two reviews suggested reduced bleeding risk by genotype-guided warfarin dosing, while the other two reviews showed no significant difference in bleeding risk between genotype-guided warfarin dosing and non-genotype-guided warfarin dosing [Pirmohamed et al., 2015]. The recurrent inconsistencies may confuse stakeholders and defer the adoption of pharmacogenomics to guide drug therapy decisions until more is known about its clinical usefulness.

In order to further explore the issue of heterogeneity, I reviewed 10 systematic reviews that investigated the association between CYP2C19 loss-of-function variant and the efficacy of clopidogrel therapy [Hulot et al., 2010; Mega et al., 2010; Sofi et al., 2011; Jin et al., 2011; Bauer et al., 2011; Holmes et al., 2011; Zabalaza et al., 2012; Jang et al., 2012; Singh et al., 2012; Yamaguchi et al., 2013]. MACE (major adverse cardiac events) is a commonly used composite outcome measure in cardiovascular pharmacogenomics research; however, no standard definition of composite MACE has been established. Consequently, the definitions of composite MACE are highly variable among primary studies as shown in **Table 3.1**. Among studies included in the 10 systematic reviews, a total of 9 different cardiac events were considered major adverse cardiac events, including death, myocardial infarction, stroke, stent thrombosis, revascularization, transient ischemic attack, unstable angina, angina pectoris and hospitalization due to ischemia.

Moreover, various numbers and types of events were included in composite MACE, ranging from a set of two to six events. As a result, 12 different combinations of composite MACE were defined as composite MACE across studies.

Table 3.1: Heterogeneity in primary studies and systematic reviews: major adverse cardiac events as an example

Heterogeneity in primary studies: different components included in MACE as outcome measure*												
Component of MACE	N=2		N=3			N=4				N=5	N=6	
Death	●	●	●	●	●	●	●	●	●	●	●	●
Myocardial Infarction		●	●	●	●	●	●	●	●	●	●	●
Stroke			●			●	●	●			●	●
Stent Thrombosis	●			●			●		●	●	●	
Revascularization					●	●			●	●	●	●
Transient Ischemic Attack												●
Unstable Angina								●				●
Angina Pectoris										●		
Hospitalization due to ischemia											●	
**N: the number of components included in composite MACE*												
Heterogeneity in inclusion criteria: different free-text statements of MACE extracted from systematic reviews												
…occurrence of death, non-fatal myocardial infarction, stroke, or urgent revascularization [Hulot 2010]												
…incidence of cardiovascular death, myocardial infarction, and ischemic stroke, as well as the composite of these endpoints [Mega 2010]												
…any cardiovascular event (fatal and non-fatal myocardial infarction, stroke, unstable angina), death from cardiovascular causes, ischemic recurrences, stent thrombosis and death from any causes [Sofi 2011].												
…composite of death from cardiovascular causes, non-fatal myocardial infarction, and non-fatal stroke; or the composite of death from any cause, non-fatal myocardial infarction, and non-fatal stroke; death from cardiovascular causes; and fatal and non-fatal myocardial infarction. …studies reporting only all cause mortality were excluded; studies reporting only composite end points including the clinician driven proxy outcomes of revascularization or admission to hospital were excluded. [Bauer 2011]												
…consisted 1 or more of the following: all-cause mortality, fatal and nonfatal coronary heart disease, fatal and nonfatal stroke, stent thrombosis, target vessel revascularization, and hospitalization for acute coronary syndrome. …studies reported stent thrombosis and no other outcome were excluded. [Holmes 2011]												
…occurrence of death, nonfatal myocardial infarction, stent thrombosis, or stroke. [Jang 2012]												
…any cardiovascular event (fatal and non-fatal myocardial infarction, stroke, unstable angina), recurrent ischemia (needing hospital readmission and coronarography), or death from other cardiovascular causes [Zabalaza 2012]												
…comprised all-cause death, myocardial infarction, stent thrombosis, stroke, and target vessel revascularization. [Yamaguchi 2013]												
not specified [Singh 2012], [Jin 2011]												

MACE: major adverse cardiac events

On the other hand, looking into the statements extracted from each systematic review that describes the inclusion criteria for choosing major adverse cardiac events to be included in reviews, the stated inclusion criteria are not sufficiently clear to readers owing to its text heavy and unstructured format (see **Table 3.1**). The ambiguous inclusion criteria might potentially lead to more subjective decisions regarding the selection of evidence among studies. Moreover,

heterogeneity also exists in the inclusion criteria adopted among the systematic reviews, which might be caused by the definition of MACE, which can be broad and narrow at the same time. It poses challenges in interpreting conclusions drawn from different systematic reviews, particularly when inconsistent conclusions occurred.

In summary, using a composite MACE outcome measure as an example, the extent and nature of the problem of heterogeneity encountered in pharmacogenomics evidence assessment is presented and summarized in **Table 3.1** and **Figure 3.2** respectively.

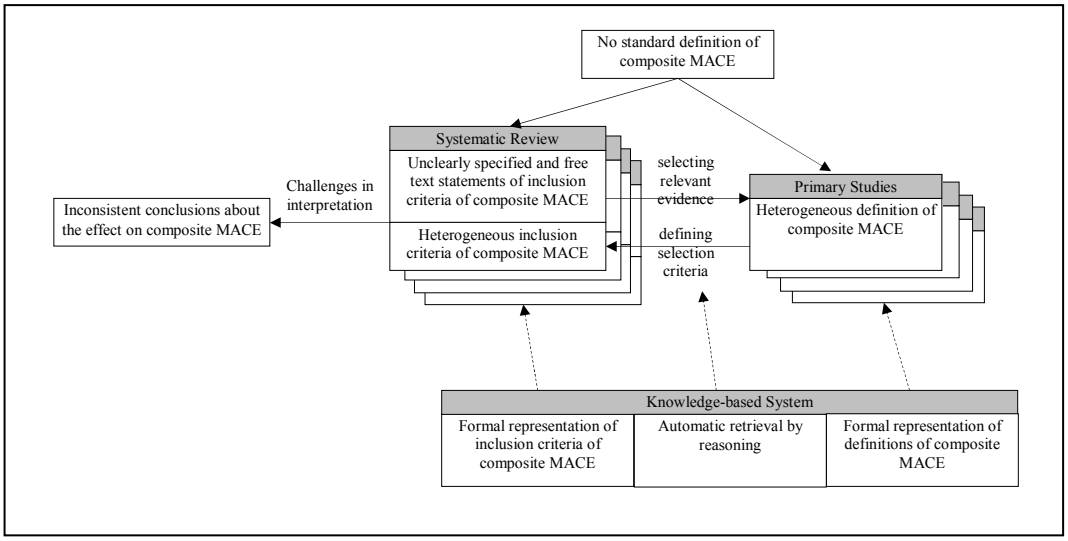


Figure 3.2: Nature of heterogeneity problem encountered in pharmacogenomics evidence assessment. MACE: major adverse cardiac event. A knowledge-based system is envisioned to address the problem through formal representation of definitions and inclusion criteria of composite outcome measures, and the automatic reasoning to assist retrieving relevant evidence.

There are certainly other contributors to the heterogeneity problems as well, such as study population, choice of drug therapy and genetic variation. These contributory factors collectively would cause problems for subsequent analyses. Therefore, the problem of heterogeneity should be considered throughout this research. Moreover, the problems of heterogeneity are not unique to pharmacogenomics research. Model such as OCRe (Ontology of Clinical Research) has being

developed to address similar issues in reporting clinical trial results. I provide a focused review of OCRe in Section 3.2.3. How OCRe addresses the heterogeneity problem is explored in Section 3.5.3.

Since heterogeneity among primary studies included in systematic reviews is inevitable, from an informatics perspective, it is essential to design a sophisticated model, not only to allow explicit evidence annotation but also to accommodate different types of evidence. Meanwhile, the same conceptual model can be used to explicitly annotate inclusion criteria, so that they can be unambiguously applied to retrieve relevant and well-annotated evidence for systematic reviews. With explicit representation, the heterogeneity inherent in the meaning of both primary evidence and inclusion criteria for systematic reviews can be faithfully revealed. Moreover, once the conceptual model is encoded using formal representation formalisms that allow for semantic computing, it can be used to improve a computer system's ability to precisely and objectively retrieve relevant evidence, and therefore, reduce the possibility of inconsistency among reviews due to subjective judgments around what is relevant (see **Figure 3.2**).

3.2.2 Design of basic information structure of the conceptual model

Conceptual modeling is concerned with the construction of information bases in the real-world domain of interest [Borgida & Brachman, 2007]. Given the heterogeneous nature of pharmacogenomics evidence assessment (see **Figure 3.2**) and two pre-specified features i.e., clinically relevant evidence and evidence-based approach (see Chapter 2, **Table 2.2**), I propose the following requirements that a conceptual model should satisfy: (1) a flexible and extensible information structure to accommodate heterogeneous pharmacogenomics knowledge as well as inclusion criteria for systematic review with meta-analysis, and (2) the information structure is instantiated using domain-dependent concepts, relations and terms related to clinical validity and

utility of pharmacogenomics evidence and strategies for systematic review with meta-analysis. Issues related to a flexible and extensible information structure are addressed next and issues related to information structure instantiation are addressed in Section 3.3.

3.2.2.1 Adoption of faceted analysis to develop a conceptual model

From an operational perspective, conceptual modeling is a process that allows identification of basic concepts and relationships between these concepts so that entities central to the domain of interest can be expressed in an abstract form. Considering the complexity inherent in the domain of pharmacogenomics evidence assessment, faceted analysis was adopted to develop a conceptual model. Faceted analysis was first introduced in library and information science to address the problems of library classification in an axiomatic way [Ranganathan, 1967]. As reviewed in [Hjørland, 2013], the facet-analytic approach has principles of logical division as its theoretical basis to provide structures in the knowledge organization system, and enables complex entities expressed in a number of perspectives. A facet can be regarded as a generic term used to denote any component of a compound subject; therefore, the faceted analysis can be applied to different domains to articulate their information needs [La Barre, 2006]. Owing to its applicability, faceted analysis has been in wide use and applied across different domains. For example, Tang [2007] designed a faceted display to facilitate query construction for PubMed users [Tang, 2007]. The study showed that users preferred the query submission methods that were associated with a faceted display, particularly when users' information needs were vague.

Various terms were used to express the notion of facet, e.g., category, attribute, class, group, dimension, etc. No matter what terminology is used, the central notion of faceted analysis is to analyze an entity from every conceivable angle. The faceted analysis follows three steps to abstract entities of domains of interest; the three steps are: choose facets, develop facets and

analyze entities using facets [Kwasnik, 1999]. In choosing facets, first, they are important components to the entities being modeled. Secondly, the chosen facet must be homogeneous and mutually exclusive, that is, the contents of any two facets cannot overlap. Next, the facet is developed by identifying basic concepts, in other words, identified basic concepts can be formed into a structure to express the facet. It is worth noting that a concept is a homogenous group of terms, and each term denotes a primitive atomic concept. In the final step, analyzing entities using facets means that the entities are expressed by combining the relevant facets, and each facet has its own structure of concepts and terms.

The faceted analysis has several features that motivated me to adopt it as the approach to modeling the domain of pharmacogenomics evidence assessment. First, it allows users to model the domain of interest from many different perspectives. Secondly, it is flexible enough to accommodate new entities. Thirdly, as opposed to enumeration which exhaustively lists all the components, concepts, relations and terms that fall under the entities in question, users do not need to know all the domain knowledge before modeling. These features make faceted analysis useful for modeling a fast changing field such as pharmacogenomics research.

3.2.2.2 Basic information structure of the conceptual model

Following the essence, principles and steps of faceted analysis, I proposed a conceptual model comprised of 5 building blocks (see **Figure 3.3**). The proposed conceptual model specifies that an information entity is composed of information components, an information component is expressed by relation-concept pairs, and a relation-concept pair is substantiated by terms.

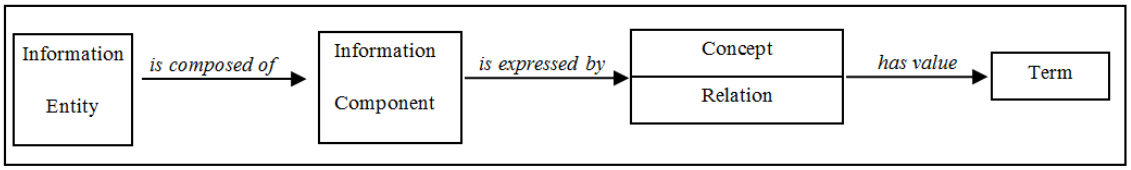


Figure 3.3: Basic structure of theconceptual model and its building blocks for conceptualization of the domain of pharmacogenomics evidence assessment

Since pharmacogenomics evidence assessment is the domain to be modeled, I considered the information needs and search strategies of systematic review with meta-analysis in choosing information entities and information components. Publications, studies, and evidence are commonly retrieved for systematic review with meta-analysis; therefore, they are regarded as the information entities in the model. In addition to information entities, information components (facets) have to be relevant to the systematic review with meta-analysis as well. Therefore, authoritative guidelines developed by Cochrane Collaboration and AHRQ (Agency for Healthcare Research and Quality) for systematic review were reviewed [Higgins & Green, 2011; AHRQ, 2012 & 2014] and 9 information components were identified. The information components relevant to the systematic review and evidence-based synthesis are: study population, drug therapy, comparison, outcome, genetic variation, study design, effect, risk of bias assessment and publication. Why these information components are important for systematic review with meta-analysis is briefly described in **Table 3.2**.

Table 3.2: Information components included in the conceptual model to describe pharmacogenomics evidence assessment

Information Component		Why it is important for systematic review with meta-analysis?
1	Study Population	It describes the characteristics of the studied population. It is required for interpreting applicability of research findings and assessing heterogeneity of study subjects across different studies.
2	Drug Therapy	In interventional studies, it describes the drug therapy of interest and the compared drug therapy. In observation studies, it describes the drug therapy under observation.
3	Comparison	It describes the features that divide study subjects into sub-groups for comparison. For examples, drug therapy and genetic variation are commonly used features in pharmacogenomics studies to divide study subjects to compare their measured outcome.
4	Outcome	It describes the end points used to measure the effects of drug therapies.
5	Genetic Variation	It is specifically required in pharmacogenomics studies. It describes the genetic variants considered in genotype-guided drug therapy. It also describes the genotypes that divide study subjects for comparison in genetic association studies.
6	Study Design	It describes the methodological issues of how the study is conducted. It is important in determining the quality of the evidence acquired from the study.
7	Effect	It is a set of summary quantities related to a comparative metric. It expresses the estimated treatment effect on outcomes. It contains necessary data for meta-analysis
8	Risk of Bias Assessment	It reflects the extent to which the study design and conduct of a study are likely to have prevented bias. It is indispensable information to judge whether the evidence is valid enough to inform clinical practice
9	Publication	It specifies the source that provides full description of the primary evidence and the original research as well.

3.2.3 Lessons learnt from the Ontology of Clinical Research (OCRe)

The Ontology of Clinical Research (OCRe) is an OWL 2 ontology that models human studies. OCRe serves as a common semantic framework for informatics approaches that intend to support a broad spectrum of scientific tasks involved in the lifecycle of a human study beginning with formulation of study questions, design of a study, execution of a study, report of study results, and interpretation and application of study results to clinical care or policy [Sim et al., 2014]. Since my envisioned pharmacogenomics knowledge-based system intends to store, retrieve and assess relevant evidence for clinical adoption of pharmacogenomics, I reviewed OCRe in depth in order to investigate the feasibility of reusing OCRe in developing my envisioned system. The review focused on the proposed motivating use cases as well as the underlying ontological structure and content of OCRe. Then, I identified the gaps for OCRe reuse.

3.2.3.1 OCRe motivating use cases

OCRe investigators identified a variety of motivating uses cases in each phase of the lifecycle of a study (see **Table 3.3**) [Sim et al., 2014]. Briefly, the use cases presented in **Table 3.3** can be roughly divided into two kinds: retrieval and reasoning. For example, use cases of retrieval include a retrieval of prior studies for formulating a research or policy question; a retrieval of a body of evidence from studies for answering a research or policy question; or a retrieval of eligible patients from electronic medical records for participation in clinical trials. As for the use cases of reasoning, they are mainly about checking completeness and consistency of data collected by study registries, and assessing risk of bias assessment subjected to various study designs.

Table 3.3: Motivating uses cases of OCRe

Phase of the lifecycle of a study	Use cases
Formulation of study question	- retrieval of prior studies for targeted literature review to support the formulation or refinement of research hypothesis
Design of a study	- decision support in determination of study design type, eligibility criteria of study population, and sample size - identification of potential bias, and confounding factors
Execution of a study	- matching eligibility criteria of a study to patients' data in electronic medical records for eligible cohort identification - matching a patient's medical record to databases of studies for eligible study determination
Registry of a study and report of study results	- assurance of completeness and consistency of reported data - federated data query across dispersed databases and external terminology
Interpretation and application of synthesized results to clinical care or policy	- retrieval of entire body of evidence for evidence synthesis - decision support for risk of bias assessment based on PICO features and study design characteristics - decision support for appraising applicability to a targeted patient population

Summarized from Section 2 in [Sim et al., 2014].

To accomplish the above mentioned use cases, OCRe focuses on providing a unifying semantics to describe a study's PICO (population, intervention, comparison and outcome) components as well as its design characteristics. The OCRe model is summarized as follows.

3.2.3.2 Structure and content of OCRe

The main structure and content of OCRe illustrated in **Figure 3.4** is abridged from the most updated version (Revision 315) released through the National Center for Biomedical Ontologies (NCBO) BioPortal.

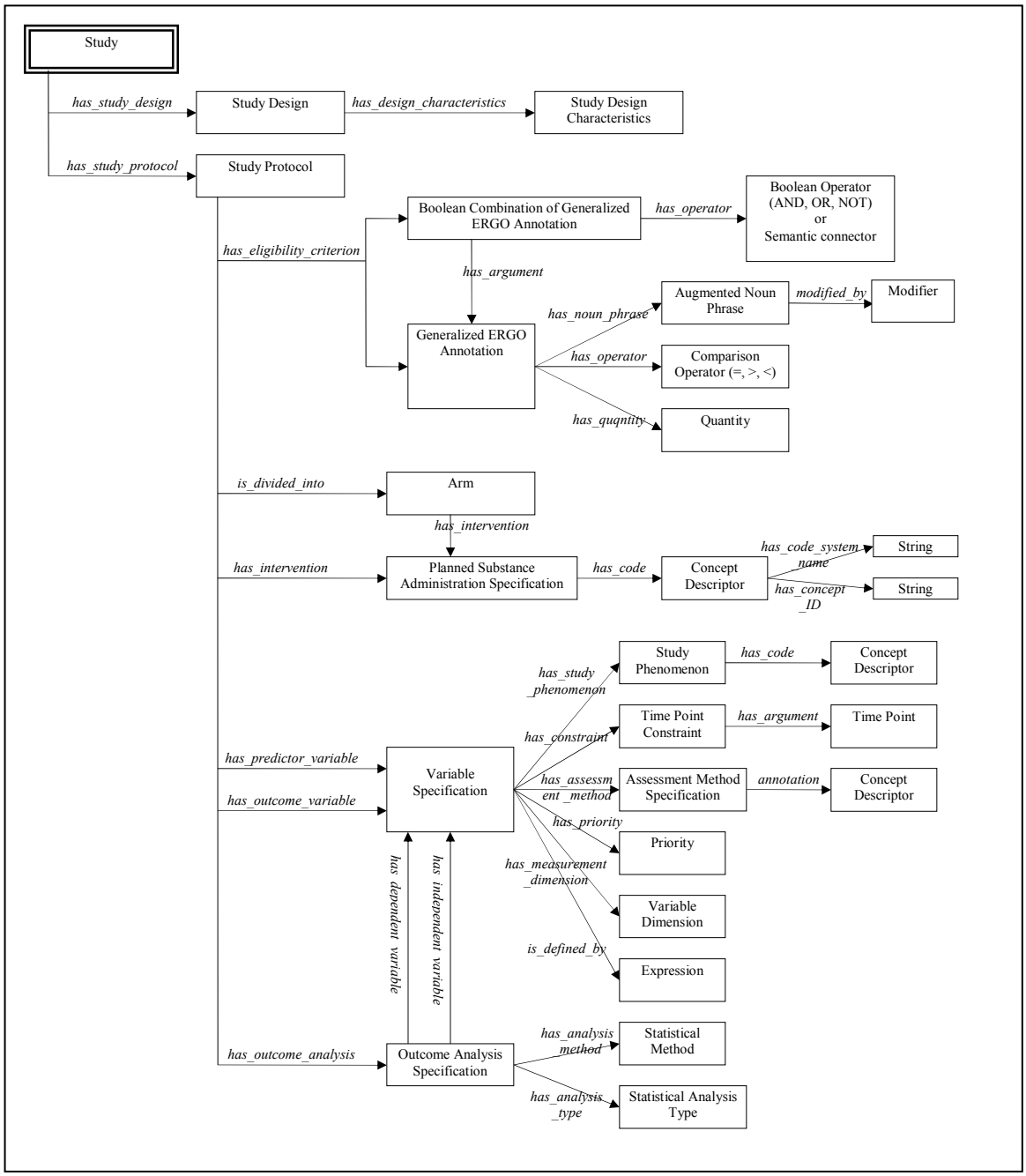


Figure 3.4: Abridged structure and content of OCRe. Source: OCRe (Revision 315) released through NCBO BioPortal, available at: https://bioportal.bioontology.org/ontologies/OCRE

As shown in **Figure 3.4**, **`Study`** is the root concept of the entire ontology and it is described by two concepts: **`Study Design`** and **`Study Protocol`**. The concept of **`Study Design`** represents a typology of study designs. In other words, each type of study design is defined by design characteristics so that different study designs can be organized into a hierarchy. For example, "`Parallel group study design`" is a subtype of "`Interventional study design`" with additional design characteristics including "`Multiple regimen`" and "`Main comparison across experimental units`". The concept of **`Study Protocol`** describes PICO components of a study. First of all, it models eligibility criteria using an information model called ERGO (Eligibility Rule Grammar and Ontology) Annotation [Tu et al., 2011]. Briefly, the ERGO Annotation models eligibility criteria as simple statement, comparison statement, or complex statement. A simple statement such as "tuberculosis of intrathoracic lymph nodes, confirmed histologically" is composed of a root noun (`tuberculosis`) modified by location (`intrathoracic`) and confirmation (`histology`). A comparison statement such as "white blood cell counts greater than 5000" is a triplet composed of a noun phrase (`white blood cell count`), a comparison operator (`greater than`), and a quantity (`5000`). A complex statement is composed of multiple statements connected by Boolean operators or semantic connectors. For example, the following complex statement "elevated blood pressure defined by systolic blood pressure > 140 mmHg and diastolic blood pressure > 80 mmHg" is modeled as "`elevated blood pressure` defined by (`systolic blood pressure`, `greater than`, `140mmHg`) and (`diastolic blood pressure`, `greater than`, `80mmHg`)". Secondly, OCRe models interventions and comparators using a generic concept called **`Planned Substance Administration Specification`**, of which clinical content is substantiated by linkages to external terminology codes. Thirdly, outcome is modeled by two concepts. One concept is **`Variable Specification`**

which specifies the phenomenon being assessed (e.g., `death`), the time points of assessment (e.g., `6 months after index myocardial infarction`), the assessment method (e.g., `death certificate`), etc. The other concept is **`Outcome Analysis Specification`** which specifies the variable of outcome measure (e.g., `incidence of death`), the type of statistical analysis being performed (e.g., `dependent variable dichotomous and independent variable dichotomous`), the statistical methods being used (e.g., `Chi-square test`), etc.

It is worth mentioning that OCRe is a domain-independent ontology. It means that the semantics of clinical content is expressed through references to external controlled terminologies such as SNOMED-CT. As shown in **Figure 3.5**, an outcome variable specification has study phenomenon `acute myocardial infarction phenomenon`, which is referred to a SNOMED concept with display name `acute myocardial infarction (disorder)` and concept identifier ***`57054005`***.

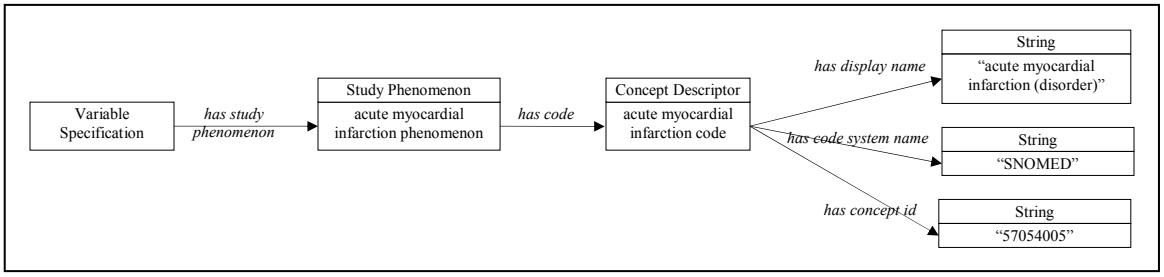


Figure 3.5: Reference of clinical content in OCRe to external terminology. `acute myocardial infarction phenomenon` is expressed through references to SNOMED.

3.2.3.3 Real-world applications of OCRe

Although a variety of motivating applications have been described in [Sim et al., 2014], only a couple of them had been empirically demonstrated. One notable application is OCRe-based federated query which retrieves human studies stored in three disparate institutional databases that participate in the Human Studies Database (HSDB) project [Sim et al., 2012]. This

application involves a series of tasks including: (1) transforming OCRe's OWL model into an XSD (XML Schema Definition) data model, (2) acquiring XSD compliant data from local relational databases, and (3) using Query Integrator to issue queries over the three data sources and the OCRe and SNOMED-CT exposed in BioPortal as well. As a result, an example query such as "*find all placebo-controlled trials in which a macrolide (a type of antibiotic) was used as an intervention*" is able to retrieve studies which satisfy the interventions of interest from three disparate databases.

3.2.3.4 Gaps for OCRe reuse

According to the OCRe ontology metrics shown in **Table 3.4**, its constructs could be roughly divided into four broad categories: statistical concept, study design concept, generic concept of PICO components and the others. Among them, approximately three-fourths classes are related to statistical concepts, study design concepts and generic concepts referring to PICO elements.

Table 3.4: Content of OCRe by ontology constructs and concepts of study characteristics

Ontology construct	Total	Statistical concept	Study design concept	Generic concept referring to PICO element	Others
Class	388	122 (31.4%)	94 (24.2%)	71 (18.3%)	101 (26.0%)
Property	220	9 (4.1%)	16 (7.3%)	62 (28.2%)	133 (60.4%)
Individual	39	--	--	13 (33.3%)	26 (66.7%)

Source: OCRe (Revision 315) released through NCBO BioPortal, available at: https://bioportal.bioontology.org/ontologies/OCRE

OCRe has not modeled study results to date [Sim et al., 2014], particularly the study results reported in journal publications. Thus OCRe does not include two information entities of my interest, namely, publication and evidence. Furthermore, information components including bibliographical information, risk of bias assessment of a study, comparison, genetic variation and effect are not modeled in OCRe either [Sim et al., 2014]. Due to the gaps between OCRe and my proposed information structure (i.e., three types of information entities and nine information components, see Section 3.2.2), it is necessary to develop a conceptual model *de novo* to address

the information need involved in evidence assessment for clinical adoption of pharmacogenomics. Although OCRe is not suitable for reuse, some of its concepts such as study design, study population, drug therapy and outcome measures will be validated against the developed conceptual model. The cross-mapping results are presented in Section 3.5.2.

3.3 Characterization of Pharmacogenomics Evidence

To address the information need of a knowledge-based system to assist in pharmacogenomics evidence assessment, the aim in this chapter was to develop a conceptual model that describes the domain of pharmacogenomics evidence assessment in an abstraction level. Taking heterogeneity and one of the critical features (i.e., evidence-based approach) into consideration, I have designed a basic information structure for the conceptual model (see section 3.2.2 and **Figure 3.3**). The information structure is composed of 5 building blocks, namely, 3 information entities (i.e., publication, study and evidence), 9 information components (i.e., study population, drug therapy, comparison, outcome, genetic variation, study design, effect, risk of bias assessment and bibliographical information of publication), concepts, relations, and terms. The subsequent work on conceptual modeling was to identify concepts, relations and terms that describe the 9 information components from empirical research articles that reported pharmacogenomics evidence regarding the clinical validity and clinical utility of pharmacogenomics. This section provides the materials, methods and results of the fine-grained characterization of clinically relevant pharmacogenomics evidence.

3.3.1 Materials and Methods

3.3.1.1 Selection of original research articles for extraction of concepts, relations and terms

Clinical guidelines summarize clinical knowledge that is essential in practice. Rigorous approaches including evidence review and expert consensus are used to inform guideline development, thus, clinical guidelines are considered an important knowledge resource. References cited by clinical guidelines were considered adequate sources for my research to find original research articles from which to develop the conceptual model of my envisioned knowledge-based system. A number of review articles in guidelines' references were used for backward citation tracking to identify relevant articles that are not directly cited in the guidelines' reference list, e.g. conference proceedings or letters of refereed journals.

In 2011, the Clinical Pharmacogenetics Implementation Consortium (CPIC) published its first guideline for genotype-guided thiopurine dosing and, as of 2013, there were 11 pharmacogenetics clinical guidelines published by CPIC. The scope of the research was narrowed to two cardiovascular drugs, i.e., clopidogrel and warfarin. The references of the two selected guidelines, a total of 313 publications, were used as the primary literature sources for selection of publications.

Publications were selected based on two inclusion criteria in order to meet the requirements of the envisioned system: i.e., clinically relevant research related to clinical validity and clinical utility of pharmacogenomics, and empirical research that provides primary evidence for evidence-based synthesis. Operational definitions of clinical validity and utility evidence (see **Table 3.5**) was derived from EGAPP (Evaluation of Genomic Application in Practice and Prevention initiative) evaluation framework [Teutsch et al., 2009] and CPIC guideline development process [Caudle et al., 2014].

Table 3.5: Definition of clinically relevant pharmacogenomics evidence

Clinical Relevant Pharmacogenomics Evidence		Operational Definition
Clinical Validity		• Research findings that demonstrate association between carriage of genetic variants and drug responses in terms of clinical endpoints • Research findings that demonstrate association between carriage of genetic variants and drug responses in terms of surrogates of clinical endpoints, e.g., dose requirement, pharmacodynamics and pharmacokinetics parameters.
Clinical Utility	Comparative Effectiveness	• Research findings that demonstrate improved drug dosing accuracy by using genotype-guided dosing algorithms • Research findings that demonstrate clinical benefits (i.e., increased clinical efficacy or decreased adverse drug reaction) by using genotype-guided strategy in drug therapy
	Genetic Modification	• Research findings that demonstrate drug treatment effect is modified by genotype

After initial screening, a total of 44 publications were selected directly from references of the CPIC guidelines. A number of conference abstracts cited in systematic reviews were also selected. To address the problem of small numbers of articles with evidence of clinical utility, recently published trials were included to increase the number of collected pharmacogenomics clinical trials. Ultimately, a total of 73 publications were selected (see Appendix 1 for the list of the selected publications). **Figure 3.6** illustrates the selection process and results described above. Interestingly this figure closely resembles the figures in a systematic review for selection of papers to include in a meta-analysis but in the current example the papers are not used per se as an evidence source but as a source of patterns used to develop the conceptual model.

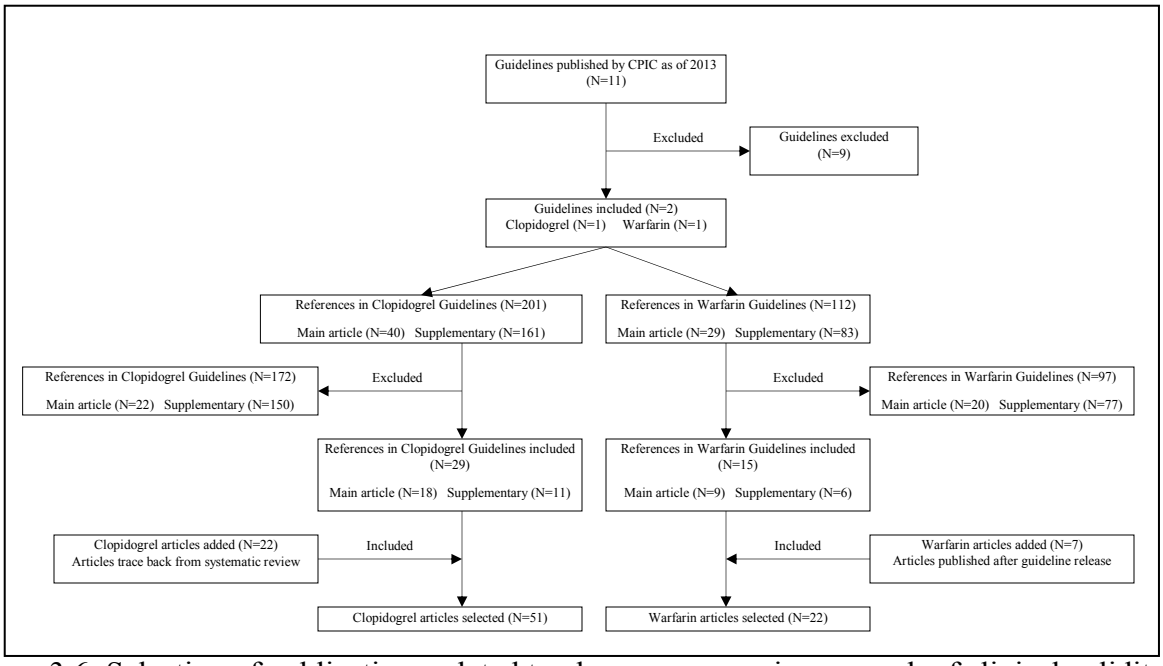


Figure 3.6: Selection of publications related to pharmacogenomics research of clinical validity and clinical utility.

3.3.1.2 Identifying terms and concepts relevant to 9 information components

I reviewed the full-text of 73 publications manually. I identified any sentences that describe the 9 information components. These identified sentences were organized in a tabular presentation and divided into 3 entities and subsequent components, that is, publication entity (including component of bibliographical information of publication), study entity (including components of study population, drug therapy, study design, and risk of bias assessment) and evidence entity (including components of outcome, comparison, genetic variant, and effect). Next, I examined the organized sentences in a fine-grained manner to identify relevant terms. The identified terms with similar meaning were grouped. A concept was created for each aggregated group of terms and a label was given to a concept, therefore, a concept is an abstract notion of the terms with similar meaning. In other words, terms are regarded as fillers to explicitly express the meaning of each concept. For example, **drug therapy** concept filled with

(clopidogrel therapy) means that the drug therapy is a clopidogrel therapy. Terms that have the same meaning were unified to standardized vocabularies or biomedical terminologies such as MeSH. In contrast to original research articles, concept and terms for the component of risk of bias assessment were identified from the Cochrane handbook [Higgins, Altman & Sterne, 2011] and AHRQ Methods Guide [Santaguida, Riley & Matchar, 2012].

3.3.1.3 Structuring concepts under information components

I assigned each identified and labeled concept to the information component it described. The extracted concepts and terms were thus assembled under the component where they belong. Relations were created to link the interrelated concepts and each relation was given a verb phrase to describe the relationship between two concepts. For example, the following expression **drug therapy** (clopidogrel therapy) *has_drug_therapy_strategy* **drug therapy strategy** (genotype-guided drug selection) means that **drug therapy** concept is linked to **drug therapy strategy** concept via the relation *has_drug_therapy_strategy*, clopidogrel therapy is a term to substantiate the meaning of **drug therapy**, genotype-guided drug selection is a term to substantiate the meaning of **drug therapy strategy**, overall, the expression means that the drug therapy described is a clopidogrel therapy that adopts a drug therapy strategy which is genotype-guided drug selection.

3.3.2 Results

I reviewed the full-text of 73 empirical research publications manually (covering 82 studies) and I identified 445 pieces of evidence that fit the operational definition of clinical validity and utility. **Table 3.6** summarizes the results of extraction according to pharmacogenomics fields,

publication year and publication types. It is not surprising that the number of publications, studies and evidence has increased dramatically since 2010.

Table 3.6: Number of pharmacogenomics publications, studies and pieces of evidence extracted for charactering pharmacogenomics evidence

	No. of publications	No. of studies	No. of pieces of evidence
Total	73	82	445
Pharmacogenomics field			
Warfarin	22	25	160
Clopidogrel	51	57	285
Publication Year			
1999	1	1	6
2000-2009	25	28	151
2010-2013	47	53	288
Publication Type			
Journal Article	67	76	438
Full Article	65	74	424
Letter	2	2	14
Conference Abstract	6	6	7

3.3.2.1 Terms

Table 3.7 presents the collection of terms organized by concepts and information components. Terms are used to substantiate the meaning of concepts. With so many terms identified in the modeling process, the variability across concrete information entities is inevitable. Terms that have a subsumptive relationship (those marked with ● and |- in **Table3.7**) are organized into a specialization hierarchy. The subsumptive relationship between terms provides a mechanism that describes the same concept with broad or narrow meaning. However, it inevitably leads to heterogeneity across concrete information entities.

In general, the identified terms can be broadly divided into four categories. Some of the terms are vocabularies or symbols commonly used in biomedical domains, such as clopidogrel, myocardial infarction, percutaneous coronary intervention, and *CYP2C19*2*. Some are modifiers used to qualify biomedical vocabularies or symbols, such as stable and elective, they are used to

qualify disease and procedure respectively. Some are categorical terms used to partition different meanings of a concept into disjoint categories. For example, terms of PGx drug therapy and non-PGx drug therapy represent two disjoint drug therapy strategies of the concept **`Drug Therapy Strategy`**. Others are identifiers such as PubMed ID or measurement unit such as mg/day. Attributes of terms have implications for ontology design and these implications will be discussed in Chapter 4, Section 4.3.

Table 3.7: Terms organized by concepts and information components

Information Component: Publication

Publication Type	PMID
● Refereed Journal Article |- Full Article |- Letter ● Conference Abstract	♦ pmid (adopted from PubMed)

Information Component: Study Design

Study Type	Study Design		Time Perspective	Allocation Scheme
● Observational Study ● Interventional Study ● Simulation Study ● Secondary Analysis	● Cohort ● Case Control ● Case Cohort ● Parallel assignment ● Cross-Over ● Before-After	● Intervention Vs Usual Care |- Intervention Vs Concurrent Usual Care |- Intervention Vs Historical Usual Care ● Intervention Vs Simulation ● Single Group ● Simulation Vs Simulation	● Prospective ● Retrospective	● Randomization ● Non-Randomization

Information Component: Study Population

Person	Drug	Disease	Disease Status	Procedure	Procedure Descriptor
● Patient ● Healthy Subject	● Warfarin ● Phenprocoumon ● Acenocoumarol ● Clopidogrel ● Prasugrel ● Ticagrelor ● Cilostazol	● Cardiovascular Disease |- Thromboembolism |- Pulmonary Embolism |- Deep Vein Thrombosis |- PE/DVT |- Heart Disease |- Atrial Fibrillation |- Rheumatic Heart Disease |- Dilated Cardiomyopathy |- Coronary Artery Disease |- Acute Coronary Syndrome |- Myocardial Infarction |- Fatal MI |- Nonfatal MI |- STE MI |- NSTE MI |- Angina Pectoris |- Stable Angina |- Unstable Angina ● Cerebrovascular Disorder |- Stroke |- Transient Ischemic Attack	● Acute ● Stable	● Heart Valve Replacement ● Orthopedic Surgery |- Knee Arthroplasty |- Total Hip Arthromplasty ● Percutaneous Coronary Intervention |- PCI with stent |- PCI with Drug Eluting Stent	● Elective

Information Component: Drug Therapy

Drug Therapy	Drug Therapy Strategy	Genetic Variant	PD Parameter	Drug Regimen
● Warfarin Therapy |- Standard Warfarin Therapy ● Acenocoumarol Therapy ● Phenprocoumon Therapy ● Clopidogrel Therapy |- Standard ClopidogrelTherapy |- Clopidogrel Dose Escalation ● Prasugrel Therapy ● Ticagrelor Therapy ● Cilostazol Therapy ● Placebo	● PGx Drug Therapy |- Genotype-Guided Drug Dosing |- Genotype-Informed Drug Dosing |- Genotype-Guided Drug Selection ● Non-PGx Drug Therapy |- Clinically-Guided Drug Dosing |- Pharmacologically-Monitored Drug Dosing |- Fixed Drug Dose	● CYP2C19*2 ● CYP2C19*3 ● CYP2C9*2 ● CYP2C9*3 ● VKRC1-1639G/A ● VKORC11 1173C/T ● rs2108622	● INR	● Warfarin Initial Dose 2.5mg/day ● Warfarin Initial Dose 5mg/day ● Warfarin Initial Dose 10mg/day ● Warfarin Initial Dose Standard ● Clopidogrel MD 75mg/day ● Clopidogrel MD 150mg/day ● Clopidogrel MD 225mg/ ● Clopidogrel MD 300mg ● Clopidogrel LD 300mg once ● Clopidogrel LD 600mg once ● Clopidogrel LD 600mg twice ● Clopidogrel LD 900mg once ● Prasugrel LD 60mg once ● Prasugrel MD 10mg ● Ticagrelor LD 180mg once ● Ticagrelor MD 90 mg/bid

Information Component: Risk of bias assessment

Risk of Bias Assessment Value
♦ high ♦ low ♦ unclear

Table 3.7 (Continued): Terms organized by concepts and information components

Information Component: Outcome

Outcome Measure	Disease	Adverse Event	Procedure	Pharmacodynamics Parameter
● Clinical Efficacy Measure ● Clinical Safety Measure ● Pharmacodynamics Measure ● Pharmacokinetics Measure ● Drug Dose Measure ● Composite Efficacy or Safety Measure ● Composite Efficacy or Safety or PD Measure	● Acute coronary syndrome |- Unstable angina ● Myocardial infarction ● Angina pectoris ● Thromboembolism ● Stroke ● Transient ischemic attack	● Death |- All cause death |- CV death ● Bleeding |- Major bleeding |- Minor bleeding |- Major or minor bleeding |- Bleeding of all types ● Stent thrombosis |- Definite ST |- Definite or probable ST |- Definite or probable or possible ST |- ST unspecified ● Hospitalization |- Hosp due to ischemia |- Hosp of all cause ● Use of Vitamin K	● Revascularization |- Target vessel revas |- Target lesion revas |- TVR or TLR |- NonTVR or TVR |- Revas unspecified	● Anticoagulation Parameter |-INR in therapeutic range |-INR out of therapeutic range |-Achieving stable dose |-Excessive anticoagulation |-Insufficient anticoagulation |-Dose adjustment |-INR test ● Antiplatelet Parameter |- On-treatment platelet reactivity |- OTPR_MPA |- OTPR_PRI |- OTPR_PRU |- High on-treatment platelet reactivity |-HOTPR_MPA |-HOTPR_PRI |-HOTPR_PRU

Pharmacokinetics Parameter	Drug Dose Parameter	Measurement Type	
● Plasma conc. of drug active metabolite |- Area Under Curve 0-t	● Drug dose requirement parameter |- Mean maintenance dose ● Drug dosing accuracy parameter |- Correct prediction of high dose requirement |- Correct prediction of low dose requirement |- Ideal dose prediction |- Dosing error |- Percentage of dose variation explained	● Incidence of Event ● Time to Event ● Percentage of Time with Event ● Time Required to Event ● Duration of Time with Event ● Count of Event ● Percentage of Encounter with Event	● Absolute Difference to Final Dose ● Relative Difference to Final Dose ● Absolute Reduction from Baseline ● Relative Reduction from Baseline ● Primary Value

Information Component: Comparison

Comparison	Drug Regimen	Drug Therapy Status	Interventional Strategy
● Comparison between genotypes |- Comparison between genotypes within drug therapy observe |- Comparison between genotypes within drug therapy experiment |- Comparison between genotypes within drug therapy comparator ● Comparison between drug therapies |- Comparison between drug therapies without genotype |- Comparison between drug therapies within genotype |- Comparison between drug therapies and between genotype	● Clopidogrel Regimen |- Clopidogrel LD over 300mg |- Clopidogrel LD below 300mg	● Ongoing Drug Therapy	● Invasive ● Non-invasive

Information Component: Genetic Variation

Genetic Contrast	Genotype	Genetic Variant	
● Carrier of 1 vs. Noncarrier ● Carrier of 2 vs. Noncarrier ● Carrier of at least 1 vs. Noncarrier ● Carrier of 2 vs. Carrier of 1 or Noncarrier ● Risk vs. Wild-type Allele	● Carrier |- Carrier of 1 |- Carrier of 2 |- Carrier of 3 |- Carrier of 4 |- Carrier of at least 1 ● Noncarrier	● Variant in CYP2C19 |- Loss-of-function variant in CYP2C19 |- CYP2C19*2 |- CYP2C19*3 |- CYP2C19*4 |- CYP2C19*5 |- CYP2C19*6 |- CYP2C19*8 |- Gain-of-function variant in CYP2C19 |- CYP2C19*17 ● Variant in ABCB1 |- ABCB1 3435C/T	● Variant in CYP2C9 |- CYP2C9*2 |- CYP2C9*3 |- CYP2C9*5 |- CYP2C9*6 |- CYP2C9*11 |- CYP2C9*12 ● Variant in CYP4F2 |- rs2108622 C/T ● Variant in VKORC1 |- VKORC1-1639G/A |- VKORC11173C/T

Information Component: Effect

Effect Metric				Effect Size Unit
● Difference |- Absolute Difference Group Rate |- Absolute Difference Group Mean |- Absolute Difference Group Median |- Absolute Difference Group R Square |- Relative Difference Group Mean	● Ratio |- Odds Ratio (OR) |- Unadjusted OR |- Adjusted OR	|- Hazard Ratio (HR) |- Unadjusted HR |- Adjusted HR	|- Relative Risk (RR) |- Unadjusted RR |- Adjusted RR	♦ percentage point ♦ percentage ♦ mg/day ♦ mg/week ♦ day ♦ count number

3.3.2.2 Concepts, relations and data types

Concepts are the abstraction of terms that have similar meaning. Each concept is paired with a relation to link to an information entity or another concept. Each of the information components has its specific set of concepts, whereas 5 concepts (**`Disease`**, **`Procedure`**, **`Pharmacodynamics Parameter`**, **`Drug Regimen`** and **`Genetic Variant`**) are shared by more

than one information component. When the same concept is used in different information components, different relations are created to pair with the concept used in different information components, in order to differentiate different meanings. For example, the **`Disease`** concept has two meanings, e.g., patients having a specific disease or an outcome that measures the incidence of a specific disease. Two relations are created, i.e., *`has_disease`* and *`has_component`*, where the former and the latter specifies the meaning of disease when it is used to annotate study populations and outcome, respectively. Thus the meaning is explicitly expressed by a specific relation-concept pair where the concept is filled with terms and restricted with relations.

It is also noted that if a relation links to a data type instead of a concept, it means that the relation represents an attribute that has numerical value. For example, *`has_effect_size`* is linked to a double data type to express the double-precision value of effect size.

3.4 Organization of Information Entities, Information Components, Concepts, Relations and Terms into A Conceptual Model

This section provides the developed conceptual model of pharmacogenomics evidence assessment, which is organized by 5 building blocks, i.e., information entities, information components, concepts, relations and terms.

3.4.1 The conceptual model and its building blocks

The characterization of 73 publications, 82 studies and 445 pieces of evidence yielded 30 concepts, 49 relations, and approximately 250 terms to describe 3 information entities and 9 information components. From these building blocks I derived the final conceptual model as shown in **Figure 3.7**.

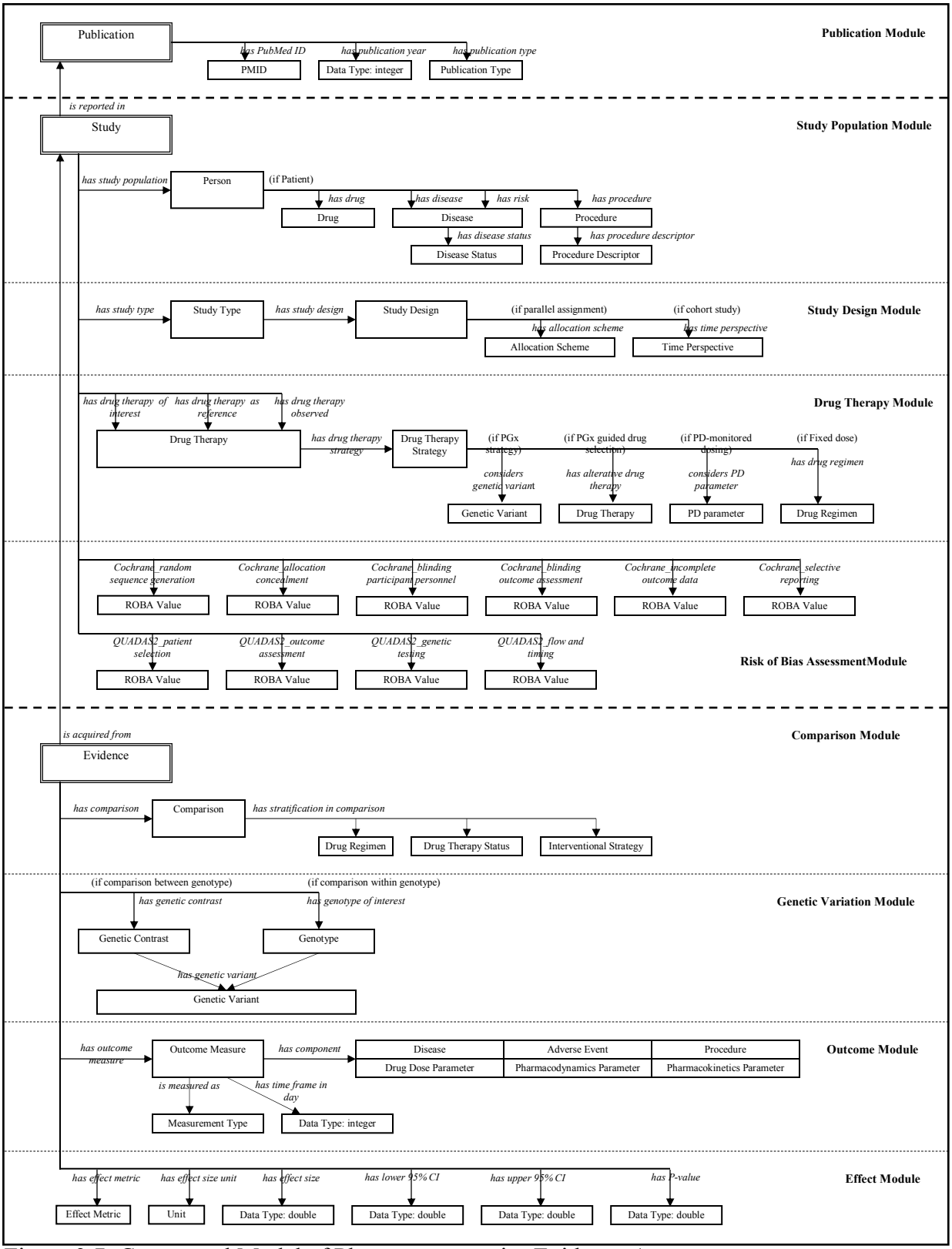


Figure 3.7: Conceptual Model of Pharmacogenomics Evidence Assessment. double-lined squares: information entities, single-lined squares: concepts, arrows: relations. Dotted lines divide the entire model into 9 modules, each corresponding to one information component.

3.4.2 Modules of information components

Figure 3.7 is a graphical presentation of the resultant conceptual model with its building blocks, where double-lined squares indicate information entities, single-lined squares indicate concepts, arrows indicate relations, and the dotted-lines divide the model into 9 information components. The conceptual model contains 9 modules, each corresponding to one of the 9 information components. Each module is represented as a directed acyclic graph where nodes denote concepts and directed edges denote relations. The modules of the 9 information components are elaborated separately below.

3.4.2.1 Publication Module

The publication module specifies three bibliographical information of the publication, i.e., publication types, publication year, and PMID if it is indexed by PubMed (see **Figure 3.8**).

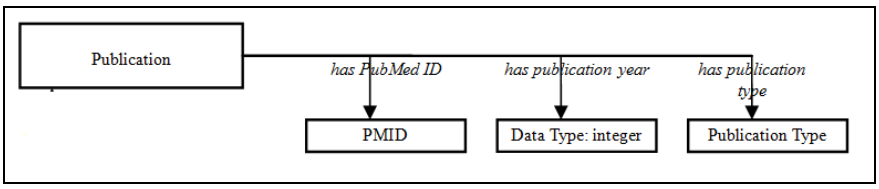


Figure 3.8: Publication module

3.4.2.2 Study Population Module

The study population module aims to specify types of person (either healthy subjects or patients) included in the study, and if patients are included, the characteristics of patients are further described (see **Figure 3.9**). To describe patient populations, the use of relation-concept pairs, (*has_drug* **Drug)**, (*has_disease* **Disease)**, (*has_procedure* **Procedure)**, and (*has_risk* **Disease)**, helps specify the presence of drug administration, the presence of disease, the presence of procedure underwent, and at risk of a disease in patient population, respectively.

The **`Disease`** concept can be further specified by **`Disease Status`** concept to qualify the disease, such as ("`myocardial infarction`" *`has_status`* "`acute`"). Also, the **`Procedure`** concept can be further specified by **`Procedure Descriptor`** concept, such as ("`percutaneous coronary intervention`" *`has_procedure_descriptor`* "`elective`").

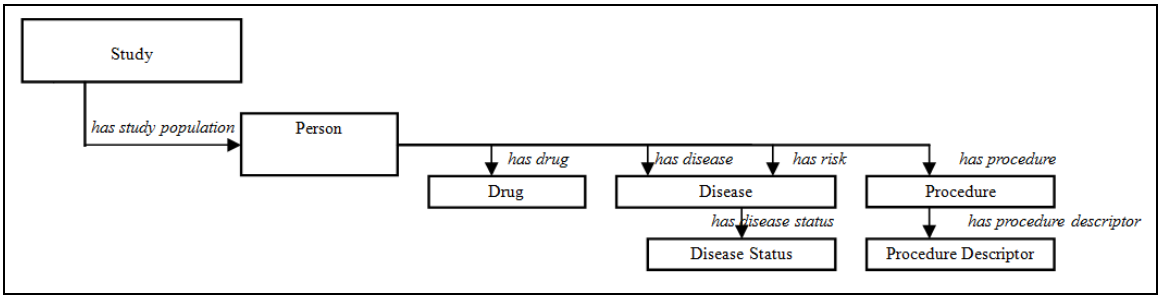


Figure 3.9: Study population module

3.4.2.3 Study Design Module

Study design module aims to specify the methodological aspects of a study (see **Figure 3.10**). Four different types of study were identified through characterization process. In addition to observational and interventional studies, the other two special study types are simulation study and secondary analysis. [Finkelman et al., 2011] is a simulation study that hypothetically applied genotype-based warfarin dosing to a patient cohort to evaluate the accuracy of drug dose predicted by dosing algorithm as compared to the patient's actual maintenance dose. [Sorich et al., 2010] is a secondary analysis that used published study-level data to estimate the genetic modification on clinical efficacy of prasugrel therapy vs. clopidogrel therapy. By this study design module, each study is specified and categorized into one of the four different types of study. Moreover, an observational study can be specified further by **`Study Design`** concept to indicate its design (i.e., cohort, case-cohort or case-control). The cohort study design can be further specified by **`Time Perspective`** concept (i.e., prospective or retrospective). Likewise, an

interventional study can be further specified by **`Study Design`** concept to indicate its design (i.e., parallel assignment, cross-over, before-after, intervention vs. usual care, intervention vs. simulation, or single group). The parallel assignment design can be further specified by **`Allocation Scheme`** concept (i.e., randomization or non-randomization).

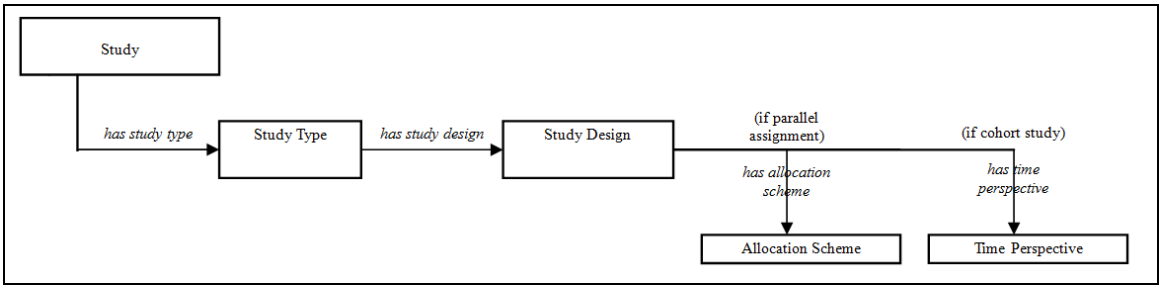


Figure 3.10: Study design module

3.4.2.4 Drug Therapy Module

Drug therapy module not only specifies types of drug therapies included in a study, but also the groups of study subjects receiving the drug therapies. For example, in a two-arm interventional study that included two types of drug therapies, it is required to specify what types of drug therapies are allocated to the experimental and the control arms respectively. Therefore, three different relations can be used to pair with **`Drug Therapy`** concept (see **Figure 3.11**).

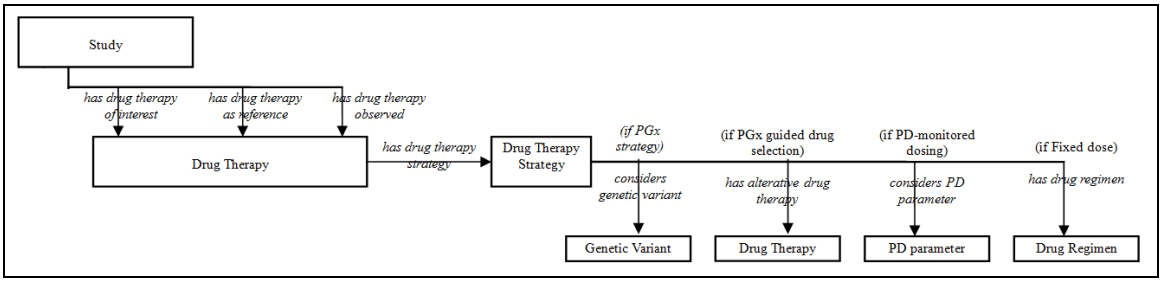


Figure 3.11: Drug therapy module

Drug Therapy concept is specified further by **Drug Therapy Strategy** concept. Six different strategies were identified, namely, genotype-guided drug dosing, genotype-informed drug dosing, genotype-guided drug selection, clinically-guided drug dosing, pharmacologically-monitored drug dosing and fixed drug dose, and grouped into two disjoint categories, PGx-based drug therapy or non-PGx-based drug therapy. PGx-based drug therapy can be further specified by **Genetic Variant** concept to indicate the genetic variants considered in drug therapy decision. For PGx-guided drug selection, the alternative drug therapy can be specified further. For example, ("clopidogrel therapy" *has_drug_therapy_strategy* "genotype-guided drug selection") and ("genotype-guided drug selection" *has_alternative_drug_therapy* "prasugrel therapy") means that clopidogrel therapy is a PGx-guided drug therapy and its alternative drug therapy is prasugrel therapy. Drug therapy that monitors pharmacodynamics parameter to adjust drug dose can be further specified by **PD parameter** concept, e.g., (*monitors_PD_parameter* "International Normalized Ratio") indicates that the non-PGx-guided warfarin therapy is monitored by a pharmacodynamics parameter, INR. Fixed dose drug therapy can be specified by **Drug Regimen** concept to describe drug dose information such as loading dose, initial dose, or maintenance dose.

3.4.2.5 Risk of Bias Assessment (ROBA) Module

Two assessment tools are modeled to assess the risk of bias in interventional or diagnostic accuracy studies respectively. The Cochrane Collaboration's tool for assessing risk of bias of interventional study has 6 criteria including random sequence generation, allocation concealment, blinding of outcome assessment, blinding of participants and personnel, incomplete outcome data, and selective reporting [Higgins et al., 2011]. The QUADAS-2 checklist (Quality Assessment of Diagnostic Accuracy Studies), recommended by AHRQ to assess risks of bias of

medical test studies, has 4 criteria regarding patient selection, genetic testing, outcome assessment, and flow and timing [Santaguida et al., 2012]. The assessment results of the above-mentioned 10 criteria are constrained to the same value-set of "`high`", "`low`" or "`unclear`", thus, 10 relations (labeled in italic in **Figure 3.12**) representing different assessment tool and criteria were created to link to the same concept **`ROBA Value`**.

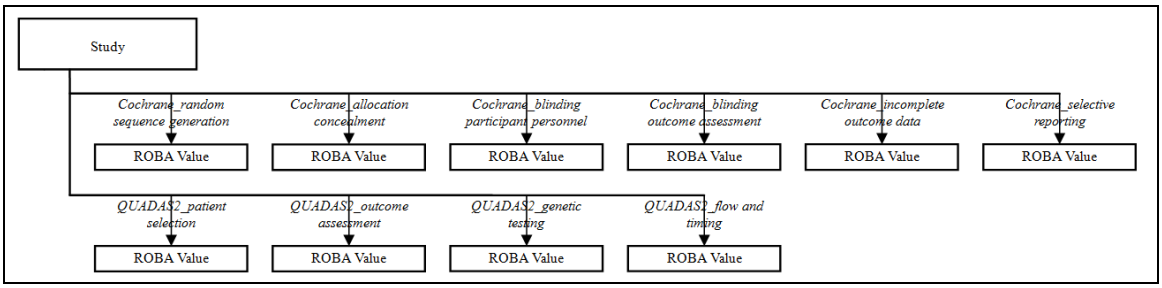


Figure 3.12: Risk of bias assessment module

3.4.2.6 Comparison Module

Pharmacogenomics studies involve two basic types of comparisons, namely a comparison between genotypes and a comparison between drug therapies. A comparison between two genotypes (e.g., carriers of risk allele vs. non-carriers) assesses the association between drug response and the risk allele of interest and helps identify the genotype that predicts risks of unintended drug response. A comparison between genotypes is conducted in observational studies and interventional studies, as well. For example, **Figure 3.13** shows that a group of participants is divided into carriers versus non-carriers to judge whether carrier of *CYP219*2* predicts clopidogrel response. In other words, the comparison is between carriers of *CYP2C19*2* and non-carriers of *CYP219*2*.

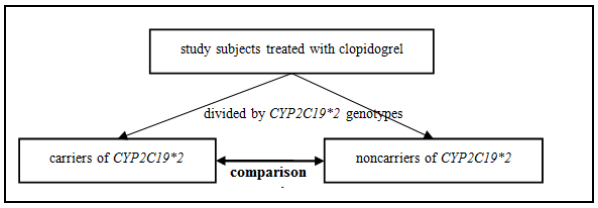


Figure 3.13: Comparison between genotypes in observational studies

Genetic sub-studies of clinical trials also provide evidence related to genetic association with drug response. In **Figure 3.14** Example 1, subjects are assigned to receive prasugrel or clopidogrel therapy so that the drug effects can be evaluated. The data of the clinical trial are further analyzed by dividing participants recruited in each arm into *CYP2C19*2* carriers versus non-carriers to evaluate whether genotype predicts prasugrel or clopidogrel efficacy. In other words, it is a type of comparison regarding the clinical validity of pharmacogenomics.

Another type of comparison is between drug therapies within the same genotype, for example, a comparison between *CYP2C19*2* carriers receiving prasugrel and *CYP2C19*2* carriers receiving clopidogrel. This type of comparison assesses whether alternative drug therapy is more effective than conventional drug therapy in patients carrying certain risk variants. Therefore, it is a type of comparison regarding the impact of genetic modification on drug treatment effect.

Another type of comparison is comparison between treatments without genotype. **Figure 3.14** Example 2 is a controlled trial that compares the impact of genotype-guided warfarin therapy with non-genotype-guided warfarin therapy on patient outcome. This type of comparison provides the ultimate proof of a clinical usefulness of genotype-guided drug therapy and it is a type of evidence regarding comparative effectiveness.

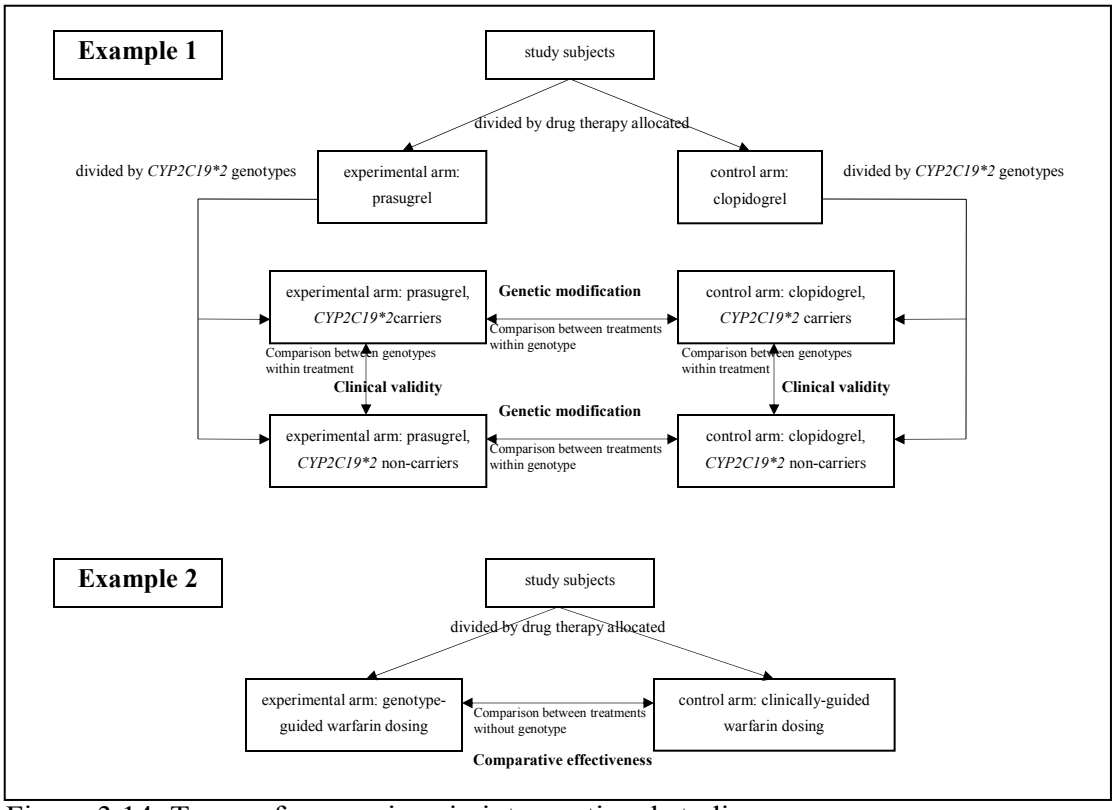


Figure 3.14: Types of comparison in interventional studies

Different types of comparisons mentioned above can be specified by the **`Comparison`** concept. If the comparison is stratified by certain stratification factors, the relation *has_stratification_in_comparison* can be used to specify the stratification factors (see **Figure 3.15**).

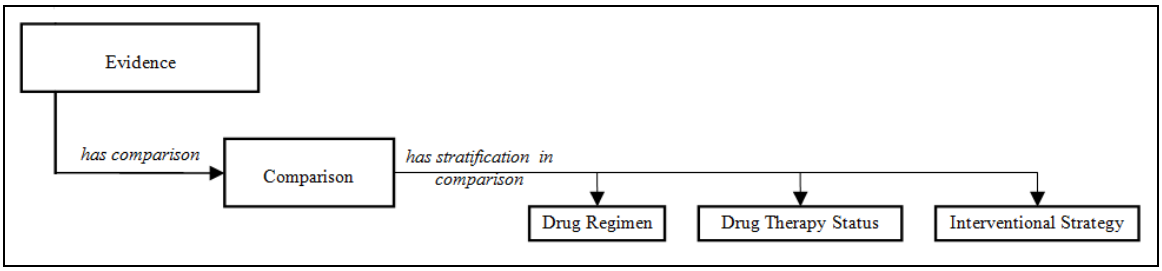


Figure 3.15: Comparison module

3.4.2.7 Genetic Variation Module

The genetic variation module provides three concepts to describe the genotype involved in the comparison of pharmacogenomics studies (see **Figure 3.16**). The **`Genotype`** concept was used to denote the presence of the allelic variant and it can be broadly classified into carrier or non-carrier. If it is a carrier, it could be further specified by the number of alleles, e.g., "`carrier of 1`" or "`carrier of 2`". The **`Genetic Contrast`** concept is used to denote the genotype-pair compared, e.g., "`carrier of 2 vs. non-carrier`". The **`Genetic Variant`** concept is used to specify the carried genetic variant e.g., "*`CYP2C9*2`", "`CYP2C19*17`"*. For example, ("`carrier of 2`" *has_genetic_variant* "*`CYP2C19*2`*") means that the genotype is CYP2C19*2/*2.

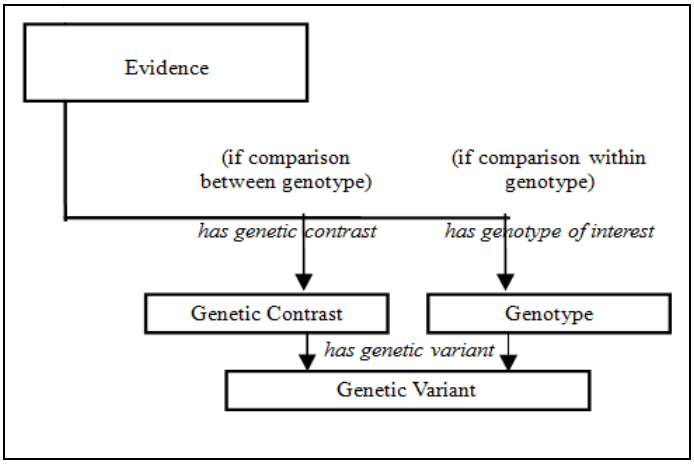


Figure 3.16: Genetic variation module

3.4.2.8 Outcome Module

Outcome module aims to specify the measurements used to determine the effect of drug therapy on study subjects. Six different outcome measure categories were identified, including efficacy, safety, pharmacodynamics, pharmacokinetics, drug dose, and composite outcome. The outcome measure category is further specified by the outcome measure components. Six

concepts are used as components of outcome: **`Disease`**, **`Adverse Event`**, **`Procedure`**, **`Drug Dose Parameter`**, **`Pharmacodynamics Parameters`**, and **`Pharmacokinetics Parameter`**. In addition, each outcome measure can be further specified by **`Measurement Type`** concept and *`has_time_frame`* relation that links to a numerical data type (see **Figure 3.17**).

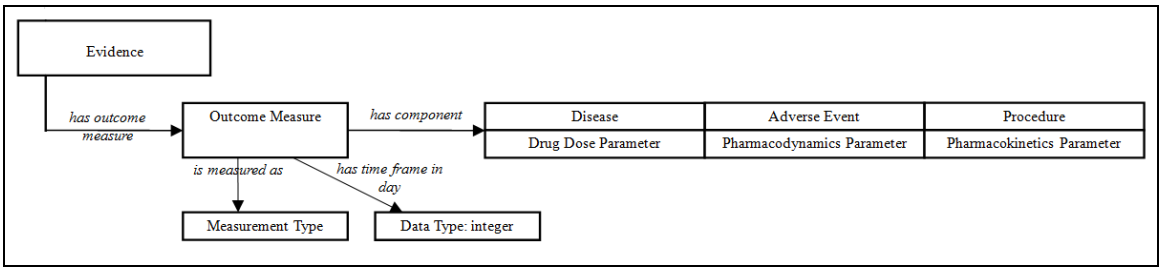


Figure 3.17: Outcome measure module

The outcome module is more complicated than other modules because multiple concepts are used as outcome components. For example, ("`clinical efficacy measure`" *`has_component`* "`myocardial infarction, death, revascularization`") refers to a composite efficacy measures including "`myocardial infarction`" from **`Disease`** concept, "`death`" from **`Adverse Event`** concept and "`revascularization`" from **`Procedure`** concept. Moreover, *`has_component`* relation can be further classified into *`has_single_component`* or *`has_multiple_component`*, and *`has_multiple_component`* can be further divided into sub-relations that denote the exact number of components included in the composite outcome measures. In considerations of the support of precise evidence retrieval, the use of sub-relations will be discussed in the next chapter.

3.4.2.9 Effect Module

Effect module aims to describe estimate of drug effect on outcome (see **Figure 3.18**). The **`Effect Metric`** concept specifies the summary statistics used to express effect size, e.g., risk

ratio or mean difference. **`Unit`** concept specifies the unit of measurement e.g. "`day`", or "`percentage`". In addition, 4 relations using data type as values, namely, *`has_effect_size`*, *`has_lower_95%_CI`*, *`has_upper_95%_CI`* and *`has_P_Value`*, are used to specify the estimated effect size, uncertainty and statistical significance of the effect, which provide useful information in interpreting clinical significance of pharmacogenomics evidence.

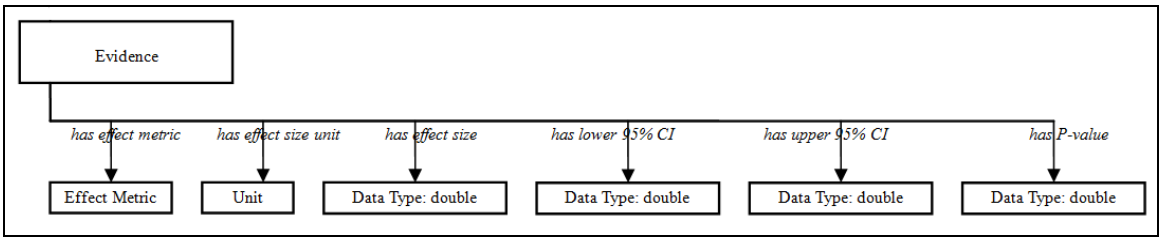


Figure 3.18: Effect module

3.5 Verification of the Developed Conceptual Model

This section presents verification of the developed conceptual in terms of the intended uses of the envisioned knowledge-based system, i.e., annotation of primary pharmacogenomics evidence as well as inclusion criteria for systematic review. The validation of the developed conceptual model against OCRe is provided as well.

3.5.1 Verification of the capability of annotating primary pharmacogenomics evidence

In order to illustrate the capability of the developed conceptual model to annotate primary pharmacogenomics evidence regarding clinical validity and clinical utility, two articles were selected from the collection of 73 publications as test cases to verify the model. The developed conceptual model was regarded as verified if the relevant information extracted from these two articles could be fitted into the structures of 9 information component modules.

[Kimmel et al., 2013] is a randomized controlled trial that compared a genotype-guided warfarin initial dose with a clinically-based warfarin initial dose during the first five days among patients initiating warfarin treatment. The purpose was to evaluate the comparative effectiveness of genotype-guided dosing of warfarin on anticoagulation control and drug safety. **Figure 3.19** shows the annotations of one publication, one study and one piece of evidence extracted from this article. The selected piece of evidence is using percentage of time with INR in therapeutic range as an surrogate outcome measure to assess the effectiveness of genotype-guided warfarin dosing that considers *CYP2C9*2, CYP2C9*3,* and *VKORC1-1639G/A*.

[Wallentin et al., 2010] is a genetic sub-study of the PLATO (Platelet Inhibition and Patient Outcomes) trial that investigated ticagrelor therapy vs. clopidogrel therapy on antiplatelet effect and drug safety. In the study, effect of *CYP2C19* and *ABCB1* genotypes on outcomes of treatment with ticagrelor vs. clopidogrel for acute coronary syndromes was investigated. **Figure 3.20** shows the annotations of one publication, one study and two pieces of evidence. One piece of evidence represents clinical validity evidence that compared the risk of recurrence of myocardial infarction, stroke or death between carriers and non-carriers of *CYP2C19 loss-of-function variants*, who received clopidogrel therapy. The other piece of evidence represents genetic modification evidence that compared recurrence of myocardial infarction, stroke or cardiovascular death in carriers of *CYP2C19 loss-of-function variants* treated with ticagrelor or clopidogrel.

In summary, the two test cases provided preliminary verification of the developed conceptual model. The results show that the developed conceptual model not only allows explicit annotation of publication, study and evidence but also accommodates three different types of evidence regarding comparative effectiveness, genetic modification and clinical validity.

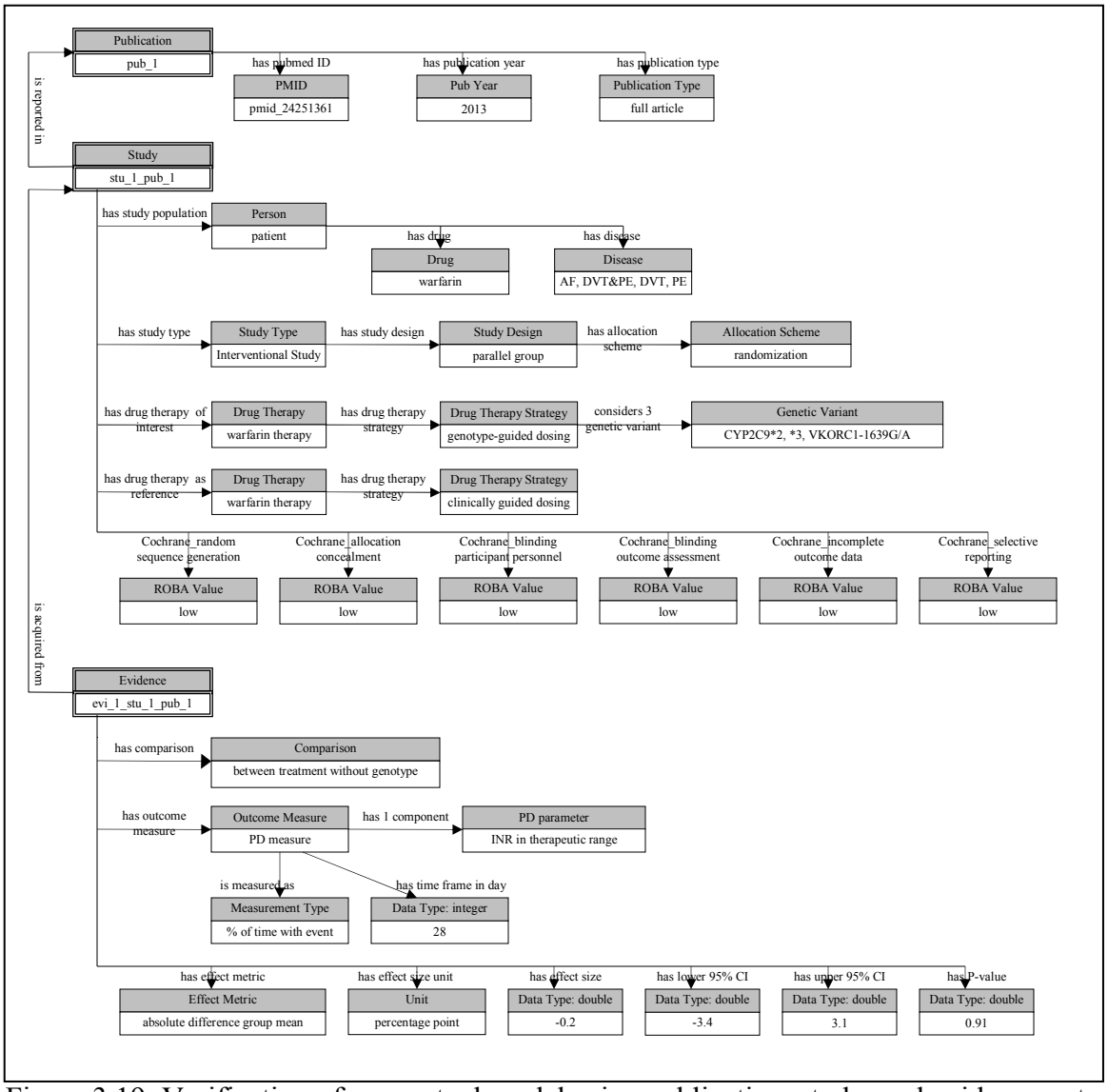


Figure 3.19: Verification of conceptual model using publication, study, and evidence extracted from a study of pharmacogenomics comparative effectiveness [Kimmel 2013]

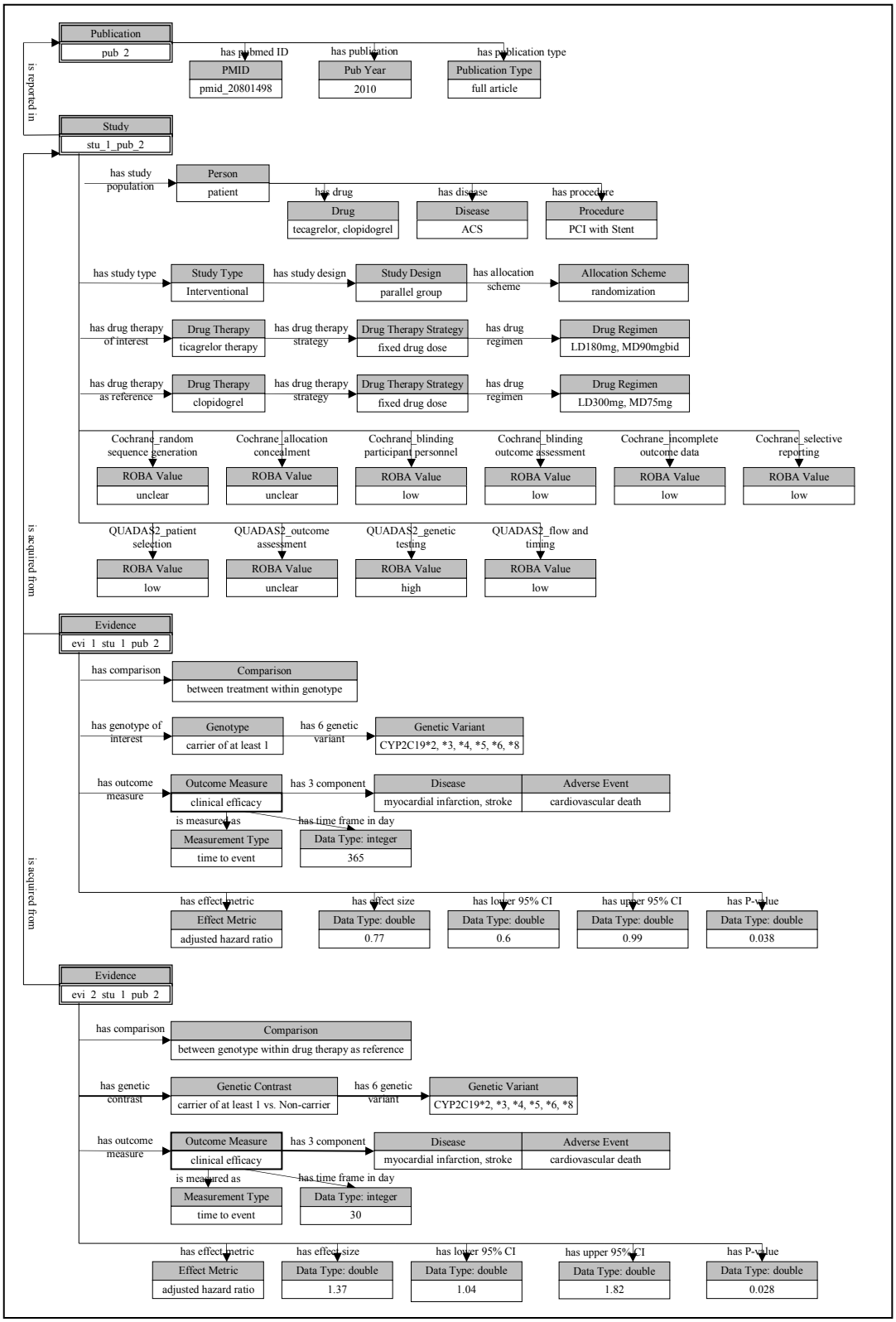


Figure 3.20: Verification of conceptual model using publication, study, evidence extracted from a pharmacogenomics study with evidence of genetic modification and clinical validity [Wallentin et al. 2010]

3.5.2 Verification of the capability of annotating inclusion criteria to retrieve primary pharmacogenomics evidence for conducting meta-analysis

To verify if inclusion criteria for systematic reviews with meta-analyses can be annotated by the same developed conceptual model, two systematic review articles were selected and their inclusion criteria were used as test cases. Inclusion criterion is referred to the statements that specify a set of criteria to identify relevant evidence. The developed conceptual model is verified if a set of criteria, such as PICO (population, intervention, comparison and outcome) can be instantiated inside the conceptual model.

[Stergiopoulos & Brown, 2014] is a systematic review with 4 meta-analyses aimed to compare genotype-guided initial dosing of warfarin and its analogues with clinical dosing protocols. **Figure 3.21** shows the result of annotating inclusion criteria of 4 meta-analyses based on the original statements listed in **Table 3.8**. Missing annotations include publication type, genetic variant to be considered in genotype-guided dosing, and measurement time frame of outcome measure. These annotations are missing because they were not provided in the inclusion criteria of the systematic review.

Table 3.8: Decomposition of inclusion criteria of systematic review with meta-analysis into information components – using comparative effectiveness of genotype-guided warfarin therapy as an example*

Information Components	Original text extracted from review article
Study Population	patients with indications for oral anticoagulation with warfarin, acenocoumarol, or phenprocoumon
Drug Therapy	genotype-guided dosing algorithms vs. clinical dosing algorithms
Study Design	randomized clinical trial
Comparison	comparison between treatment without genotype
Genetic Variation	genetic variants considered in genotype-guided dosing was not specified
Outcome	Meta-analysis 1: percentage of time the international normalized ratio (INR) was within the therapeutic range (TTR)
	Meta-analysis 2: incidence of INR greater than 4
	Meta-analysis 3: incidence of major bleeding
	Meta-analysis 4: incidence of thromboembolic events

*The exemplary inclusion criteria were extracted from [Stergiopoulos & Brown 2014]

Stergiopoulos and Brown [2014] selected 9 studies based on the inclusion criteria listed in **Table 3.8** and concluded that there's no significant difference between genotype-guided warfarin dosing and clinical dosing algorithms in improving percentage of time with INR within therapeutic range, incidence of INR over 4, major bleeding, and thromboembolism. I manually checked the studies included in each of the meta-analysis. However, it was found that 4 studies that compared genotype-guided warfarin dosing with fixed initial warfarin dose were included in the review. The selection of fixed initial warfarin dose did not meet the stated inclusions of drug therapy, which is supposed to be genotype-guided dosing algorithms vs. clinical dosing algorithms. This test case demonstrates that text-heavy, unclearly specified and heterogeneous inclusion criteria lead to incorrect retrieval.

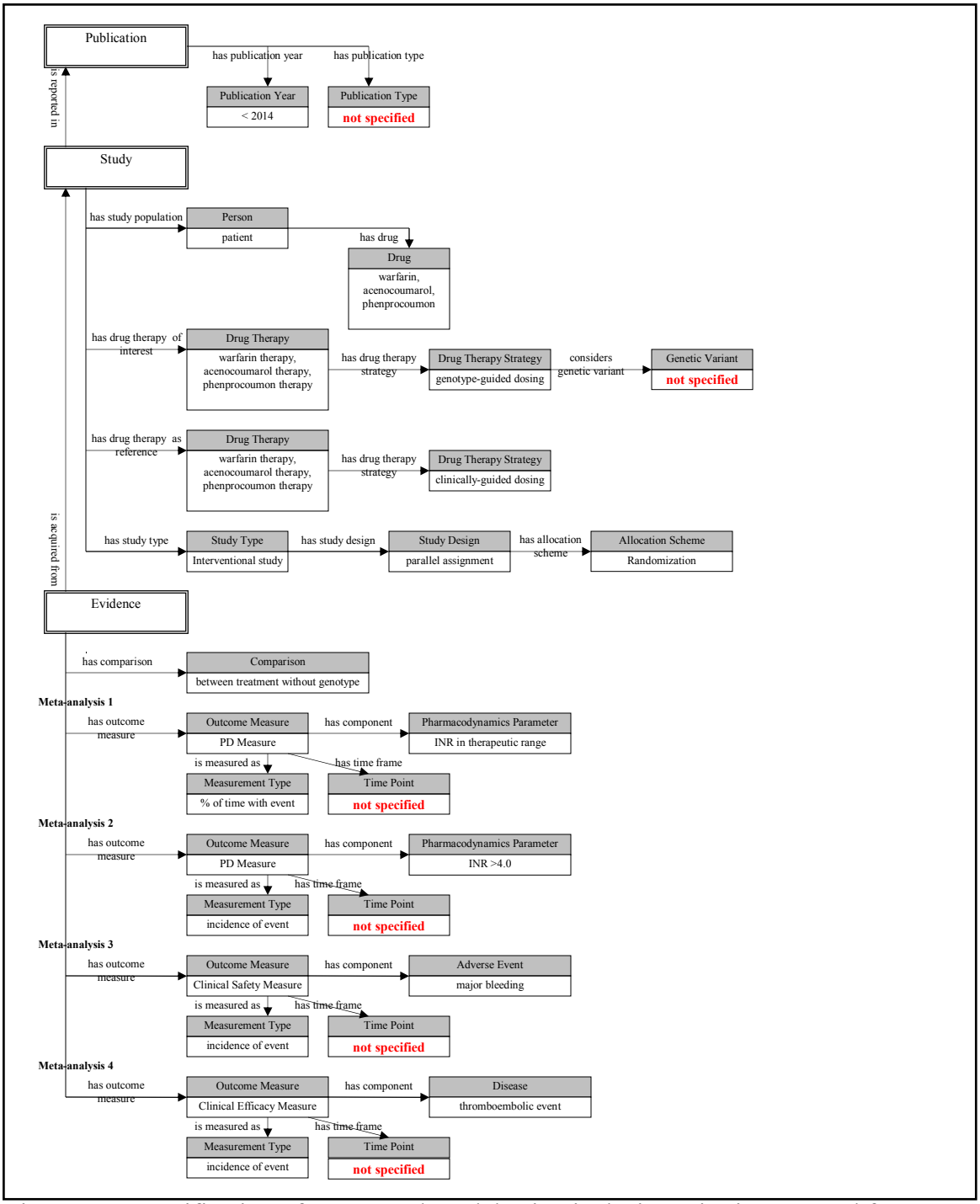


Figure 3.21: Verification of conceptual model using inclusion criteria extracted from a systematic review with meta-analysis that assessed comparative effectiveness of genotype-guided warfarin therapy [Stergiopoulos and Brown, 2014]

[Hulot et al. 2010] is a systematic review with the objective to assess the association between carriage of *CYP2C19*2* and adverse cardiovascular events in patients treated with clopidogrel.

Three meta-analyses were performed and concluded that carriage of *CYP2C19*2* increased the risk of cardiovascular event in clopidogrel-treated patients. **Figure 3.22** shows the result of annotating inclusion criteria of 3 meta-analyses based on the original statement listed in **Table 3.9**. Drug regimen and time frame are missing annotations because they were not provided in the inclusion criteria of the review article.

Table 3.9: Decomposition of inclusion criteria of systematic review with meta-analysis into information components – using clinical validity of *CYP2C19*2* and clopidogrel therapy as an example*

Information Components	Original text extracted from review article
Study Population	patients with coronary artery disease who were treated with clopidogrel
Drug Therapy	clopidogrel therapy
Study Design	randomized or cohort studies (prospective cohort or historical cohort)
Comparison	comparison between genotype within treatment
Genetic Variation	carriers of CYP2C19*2 compared with non-carriers
Outcome	Meta-analysis 1: occurrence of MACE, as defined in each study by the occurrence of death, nonfatal myocardial infarction, stroke, or urgent revascularization.
	Meta-analysis 2: mortality, which was defined either as cardiovascular or overall mortality.
	Meta-analysis 3: incidence of stent thrombosis, which was defined either as definite or definite or probable stent thrombosis

*The exemplary inclusion criteria were extracted from [Hulot et al., 2010]

I manually checked the evidence included in three meta-analyses. In the meta-analysis of MACE, two pieces of evidence from two studies did not match the definition of MACE which is supposed to be "occurrence of death, nonfatal myocardial infarction, stroke, or urgent revascularization". One piece of evidence obtained from [Shuldiner et al. 2009] satisfies the definition of MACE which is "occurrence of cardiovascular death, definite thrombosis, stroke, myocardial infarction, target and non-target vessel revascularization, and hospitalization due to ischemia" while another piece of evidence obtained from [Giusti et al. 2009] satisfies the definition of MACE which is "occurrence of cardiovascular death, definite or probable stent thrombosis". The underlined events including definite thrombosis, hospitalization due to ischemia and definite or probable stent thrombosis clearly did not match the defined major adverse cardiac events described in **Table 3.9**.

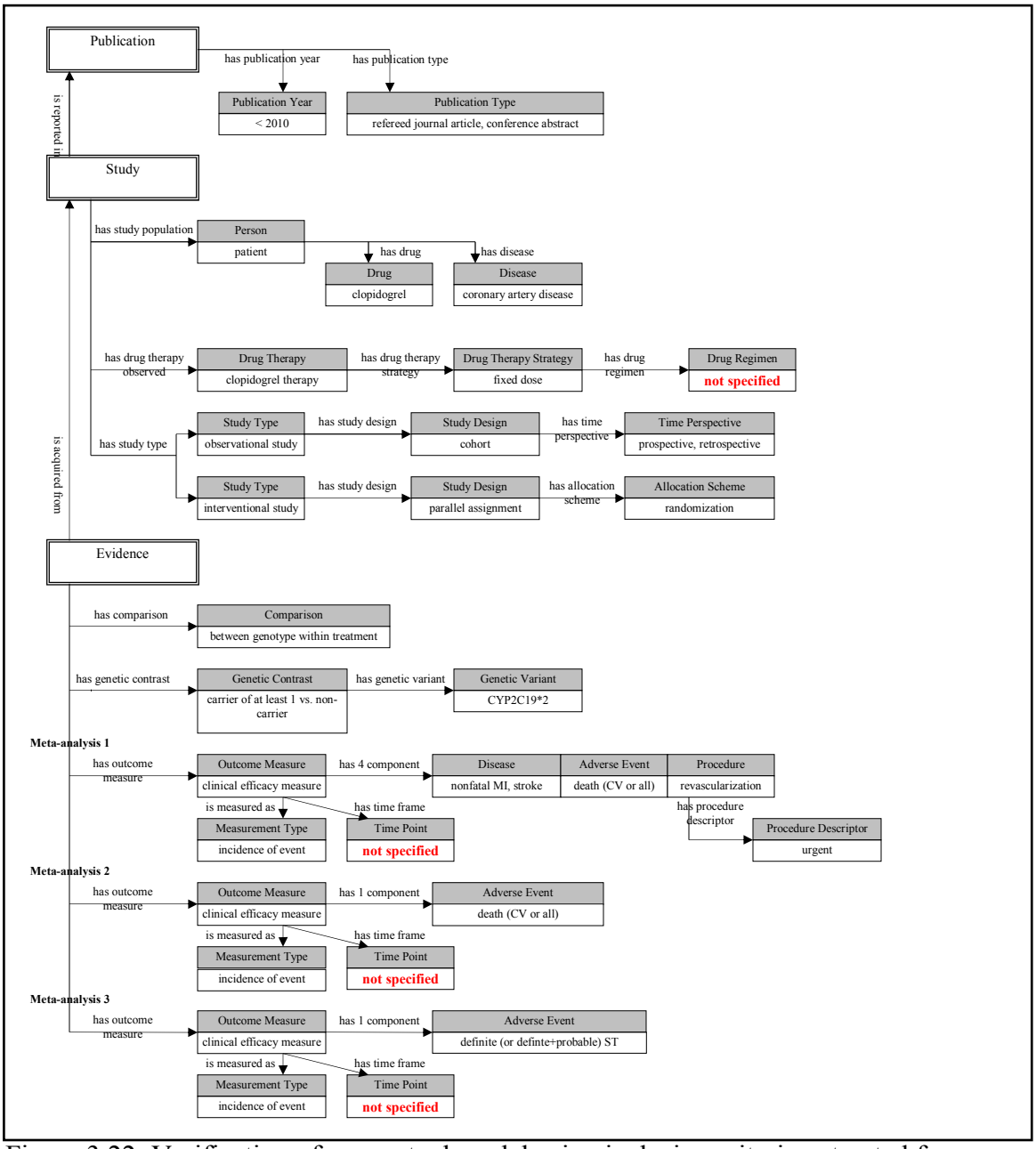


Figure 3.22: Verification of conceptual model using inclusion criteria extracted from a systematic review with meta-analysis that assessed clinical validity of *CYP2C19*2* and clopidogrel therapy [Hulot et al., 2010].

In summary, the conceptual model is adequate in annotating inclusion criteria for systematic reviews. Particularly, different drug strategies such as "clinically guided dosing" and "fixed drug dose" can be specified by **`Drug Therapy Strategy`** concept built in the conceptual model. Moreover, various definitions of composite MACE can be further specified if qualifiers, such as

exact, *at least* or *at most*, and set operators, such as *union* or *intersection*, are added in the model to annotate and restrict the relations between a set of events.

3.5.3 Validation of the developed conceptual model against OCRe

The structure and content of the conceptual model developed by me were compared with OCRe. The comparison was done by mapping my model to OCRe to see which concepts or relations were present with OCRe or absent from OCRe. The comparison between my developed conceptual model (referred as CM-PGEA hereafter) and OCRe is presented in **Figure 3.23**, where concepts and relations absent from OCRe are highlighted in red, concepts and relations indirectly present with OCRe are highlighted in green, and concepts and relations directly present with OCRe are highlighted in black. If a concept or relation is indirectly present with OCRe, it means that this concept or relation is expressed through references to external controlled terminologies. The comparison between two models in terms of their building blocks is also summarized in **Table 3.10**.

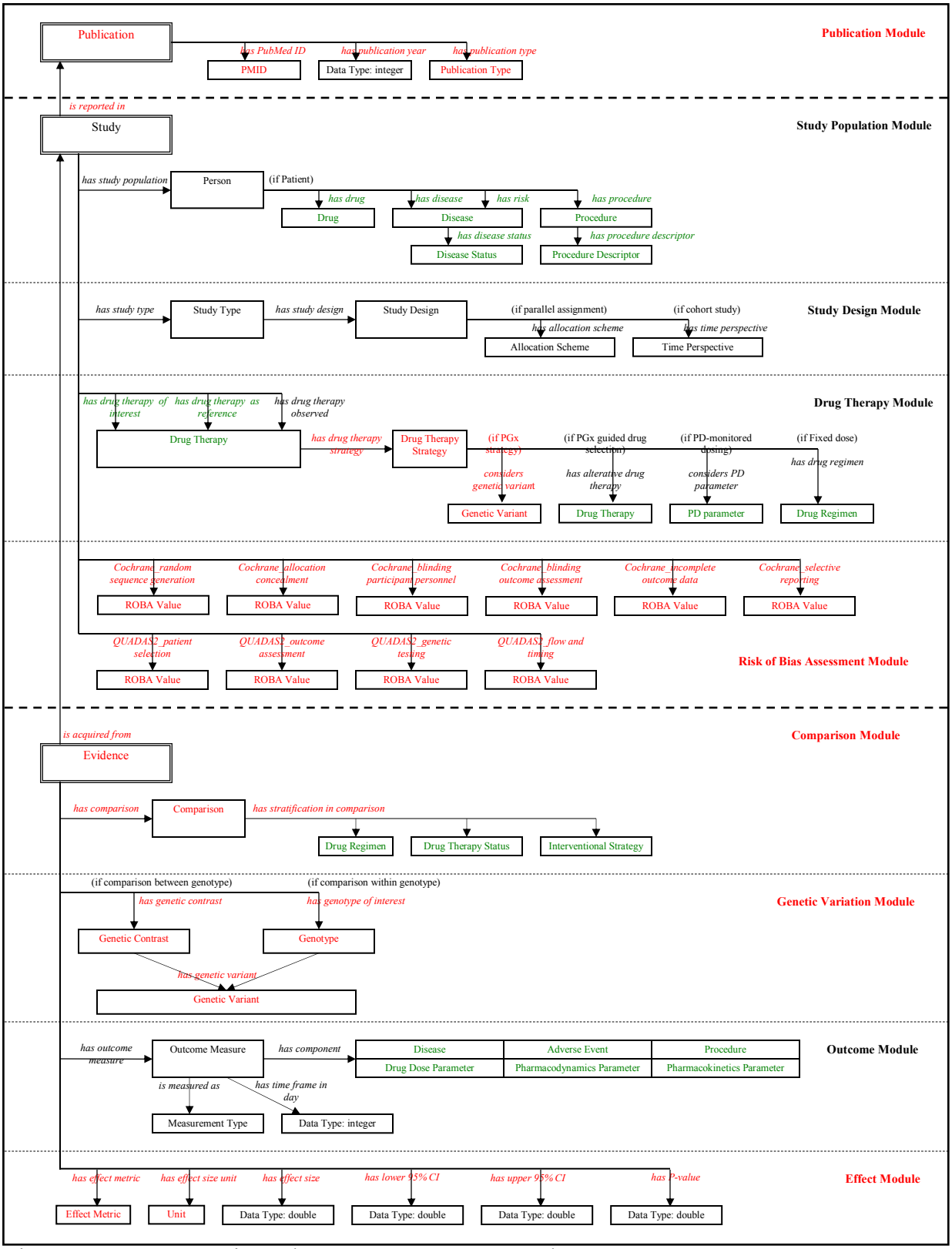


Figure 3.23: Comparison between CM-PGEA and OCRe. CM-PGEA: Conceptual model of pharmacogenomics evidence assessment developed by this research, OCRe: Ontology of Clinical Research. red: absent from OCRe, green: indirect present with OCRe, black: direct present with OCRe

Considering the building block of information entity, CM-PGEA models `Evidence` (representing study results), `Study` (representing characteristics of a study) and `Publication` (representing sources of study results) to provide information required in conducting a pharmacogenomics evidence assessment. Although OCRe has modeled `Study` in great details, important entities such as `Evidence` and `Publication` have not yet been modeled [Sim et al., 2014].

Table 3.10: Comparison between CM-PGEA and OCRe in terms of building blocks modeled in CM-PGEA

Building Block		CM-PGEA	OCRe
Information Entity	Publication	○	×
	Study	○	○
	Evidence	○	×
Information Component	Bibliographical Information	○	×
	Study Design	○	○
	Study Population	○	○ (modeled as ERGO annotation)
	Drug Therapy	○	○ (modeled as Intervention)
	Risk of Bias Assessment	○	×
	Comparison	○	×
	Outcome	○ (modeled in Evidence)	○ (modeled in Study)
	Genetic Variation	○	×
	Effect	○	×
Concept, Relation and Term		• Direct representation • On-demand	• Domain-specific concepts: indirect representation (expressed through references to external controlled terminologies) • Study design concept: direct and extensive representation • Statistical method and analysis: direct and extensive representation

CM-PGEA: conceptual model of pharmacogenomics evidence assessment developed by this research, OCRe: Ontology of Clinical Research, ○ denotes presence, × denotes absence.

Considering the building block of information component, five information components i.e., bibliographical information, risk of bias assessment, comparison, genetic variation, and effect have not been modeled either.

Considering the building block of concepts, relations and terms, CM-PGEA directly instantiates concepts and relations by vocabularies extracted from 73 published empirical articles reported clinically relevant pharmacogenomics evidence. On the other hand, OCRe uses two approaches to create instantiations. Instantiations are created either through references to external controlled terminologies (see **Figure 3.5**) or by vocabularies declared in OCRe. The difference between OCRe and CM-PGEA is that the role of OCRe is to serve as a reference ontology that is independent from specific domain and application, while CM-PGEA is developed to serve as an application ontology that supports the specific domain of pharmacogenomics evidence assessment.

The difference between CM-PGEA and OCRe in modeling methods is elaborated below, using examples that represent study design, study population, drug therapy and outcome respectively.

3.5.3.1 Cross validation of study design module between CM-PGEA and OCRe

A randomized parallel group study is instantiated using CM-PGEA and OCRe and the result is shown in **Figure 3.24**. OCRe includes approximately 100 concepts to describe types of study designs as well as their characteristics. Most of the study design concepts in OCRe are absent from CM-PGEA because concepts included in CM-PGEA are derived from 73 selected empirical pharmacogenomics publications. However, it is found that some study designs are unable to be represented using OCRe. For example, a study design of “interventional vs. concurrent usual care” was represented using CM-PGEA to describe a clinical effectiveness trial reported in

[Anderson et al., 2012], which compared two groups, where the experimental group received genotype-guided warfarin dosing and the control group under concurrent usual care setting received standard warfarin dosing. This particular study design found in pharmacogenomics research cannot be instantiated using OCRe.

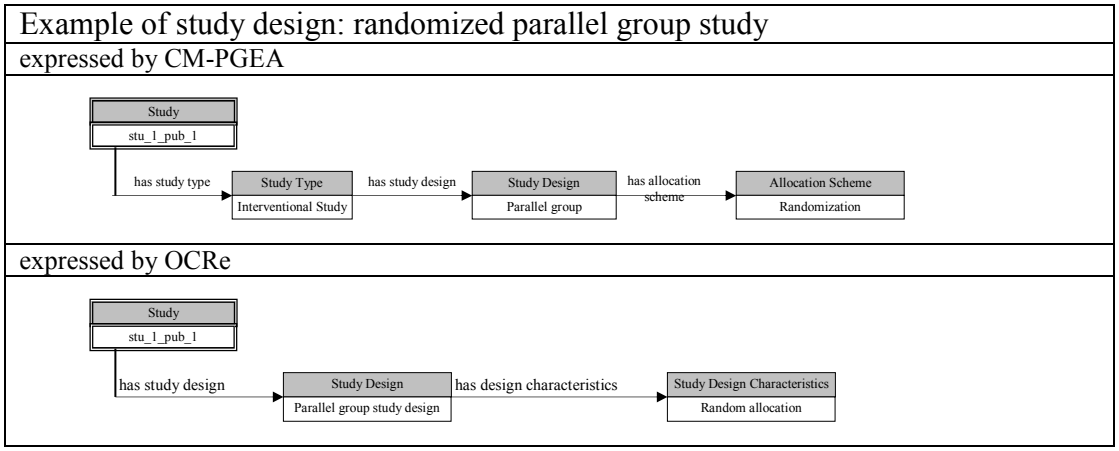


Figure 3.24: Comparison of representation of study design between CM-PGEA and OCRe.
CM-PGEA: conceptual model of pharmacogenomics evidence assessment developed by this research,
OCRe: Ontology of Clinical Research.

3.5.3.2 Cross validation of study population module between CM-PGEA and OCRe

A study population which warfarin is indicated for use in patients with atrial fibrillation, deep venous thrombosis or pulmonary embolism is instantiated using CM-PGEA and OCRe and the result is shown in **Figure 3.25**.

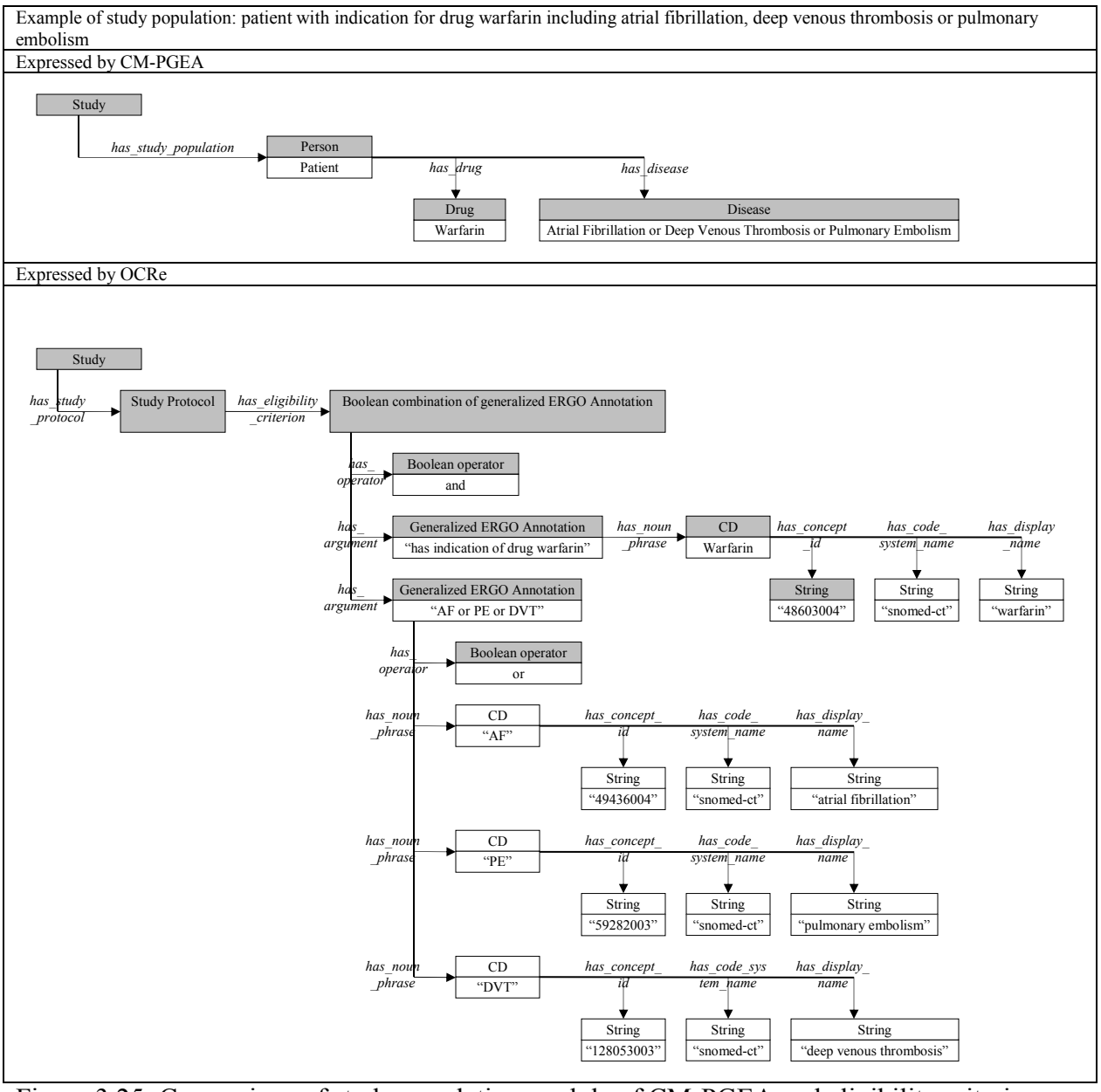


Figure 3.25: Comparison of study population module of CM-PGEA and eligibility criterion module of OCRe. CM-PGEA: conceptual model of pharmacogenomics evidence assessment developed by this research, OCRe: Ontology of Clinical Research.

The differences between CM-PGEA and OCRe in modeling study populations are elaborated as follows. First, CM-PGEA regards study population as a group of persons who are enrolled in a particular study. The characteristics of this group of persons can be used to reveal the

heterogeneity inherent in studies. On the other hand, OCRe regards study population as important eligibility criterion described in a study protocol which can be used to identify eligible patients for participation in clinical trials. In order to achieve this particular aim, OCRe models the study population as detailed as possible. Secondly, OCRe represents study population through references to external controlled terminologies such as SNOMED-CT. Unlike OCRe, CM-PGEA directly represents study population by vocabularies extracted from 73 published empirical articles. Because of the direction representation, CM-PGEA models study population in a natural and easy to understand way.

3.5.3.3 Cross validation of drug therapy module between CM-PGEA and OCRe

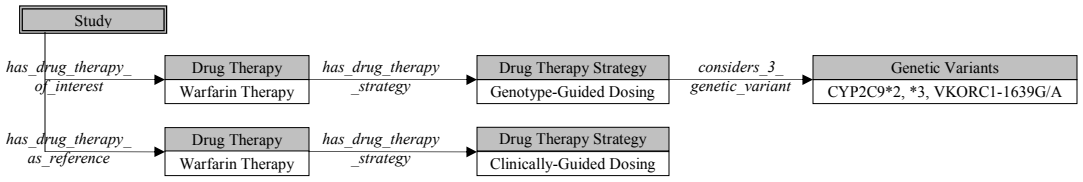
Two instantiations are provided, one is a two-arm interventional study that included two types of drug therapies i.e., genotype-guided warfarin dosing that considers three specific genetic variants versus clinically-guided warfarin dosing (see **Figure 3.26.A1 and A2**), and the other one is an observational study that studied the effects of clopidogrel standard dose (see **Figure 3.26.B1 and B2**). As shown in **Figure 3.26.A1 and B1**, CM-PGEA specifies not only the types of drug therapies included in a study but also the groups of study subjects receiving the drug therapies via three sub-relations including *`has_drug_therapy_of_interest`*, *`has_drug_therapy_as_reference`*, and *`has_drug_therapy_observed`*. The complete module has been illustrated in **Figure 3.11** and described in Section 3.4.2.

As shown in **Figure 3.26.A2 and B2**, OCRe represents drug therapies in interventional studies and observational studies as `Planned Substance Administration Specification` and `Planned Observation Specification` respectively. An interventional study is linked to `Arm` to denote two groups (i.e., experimental or control). SNOMED-CT is also referred to specify the drug i.e., warfarin. However, it is found that some drug therapies are unable to be further

specified in OCRe. For example, the question mark shown in **Figure 3.26.A2** indicates that it is yet unable to represent a genotype-guided warfarin therapy when this particular drug therapy considers specific genetic variants such CYP2C9*2, CYP2C9*3 and VKORC1-1639G/A. How to integrate genomic concepts into OCRe is not discussed yet, however, it may be achieved through references to external controlled terminologies such as Gene Ontology

A. Expression of drug therapy in interventional study to assess comparative effectiveness
Example: genotype-guided warfarin dosing vs. clinically-guided warfarin dosing

A1. Expressed by CM-PGEA



A2. Expressed by OCRe

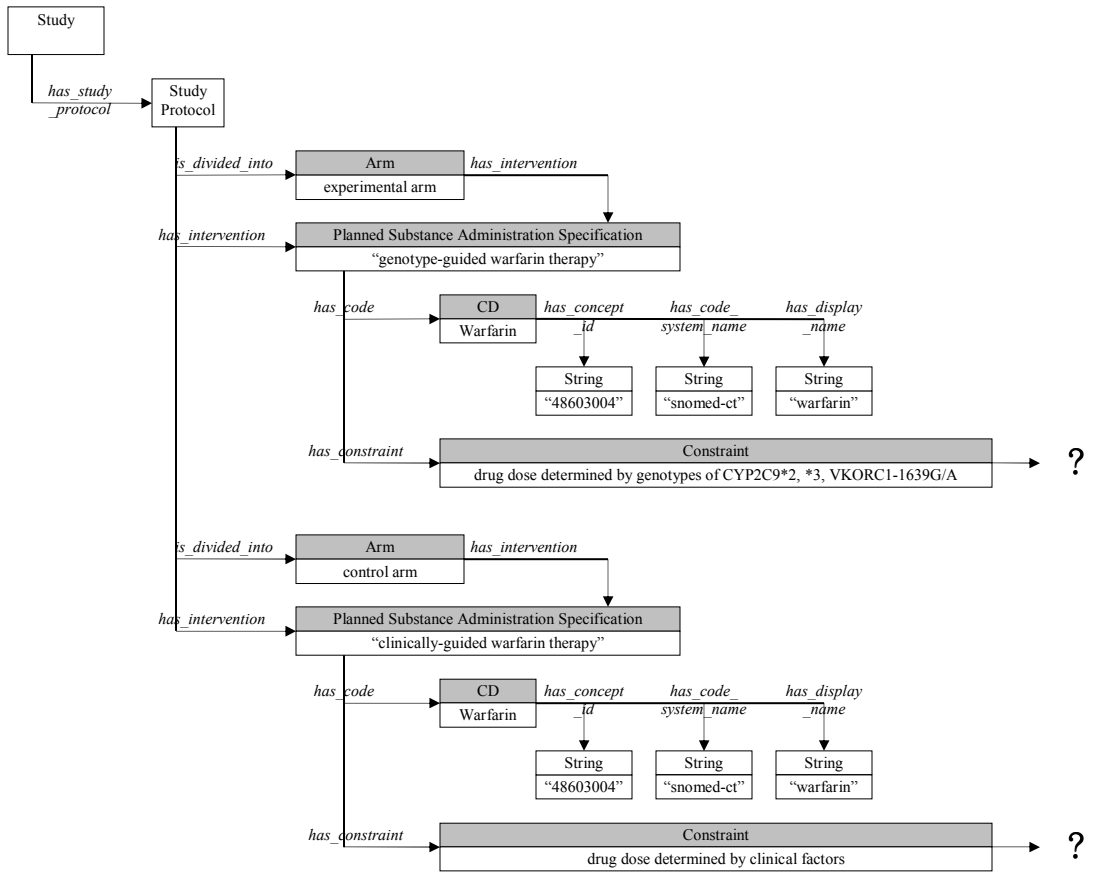


Figure 3.26: Comparison of drug therapy module of CM-PGEA and OCRe
CM-PGEA: conceptual model of pharmacogenomics evidence assessment developed by this research,
OCRe: Ontology of Clinical Research.

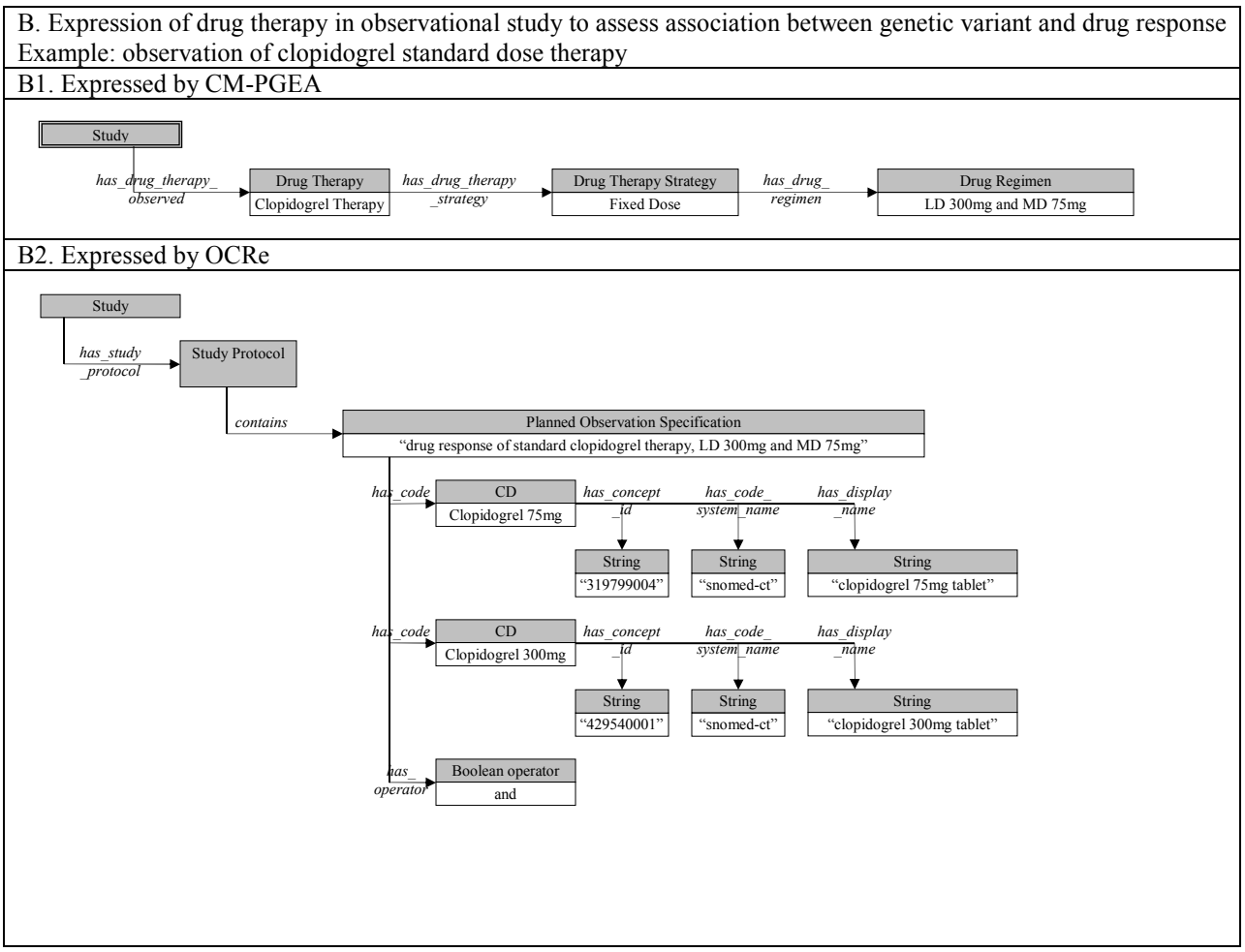


Figure 3.26 (continued): Comparison of drug therapy module of CM-PGEA and OCRe.
CM-PGEA: conceptual model of pharmacogenomics evidence assessment developed by this research,
OCRe: Ontology of Clinical Research.

3.5.3.4 Cross validation of outcome module between CM-PGEA and OCRe

CM-PGEA associates outcome measure with `Evidence`, because it belongs in study results. As shown in **Figure 3.27.A**, CM-PGEA specifies a particular outcome measure using four concepts, namely, outcome category, outcome component, outcome measurement type, and follow-up time frame. The outcome module has been illustrated in **Figure 3.17** and described in Section 3.4.2.8.

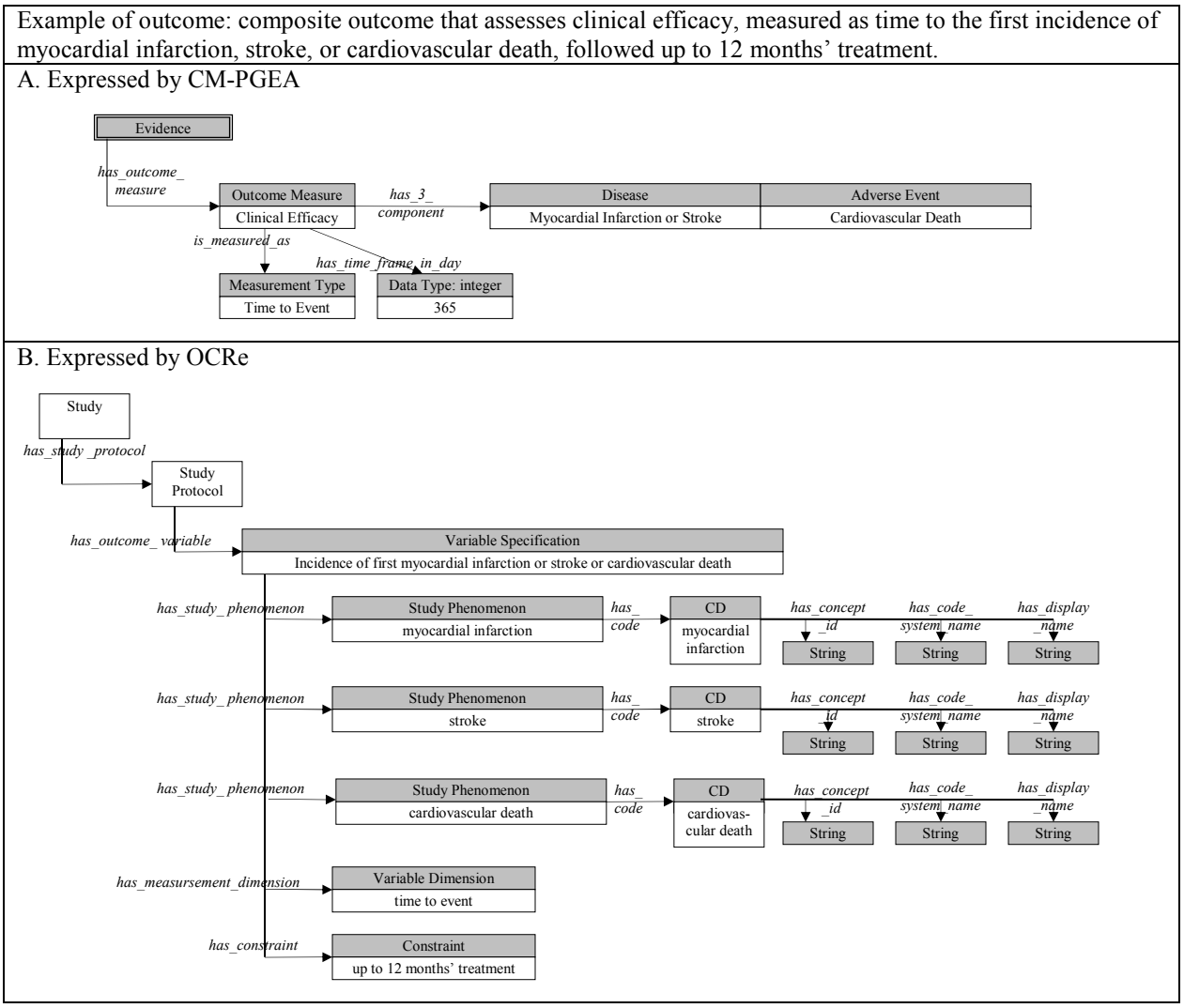


Figure 3.27. Comparison of outcome module between CM-PGEA and OCRe.
CM-PGEA: conceptual model of pharmacogenomics evidence assessment developed by this research,
OCRe: Ontology of Clinical Research.

OCRe expresses outcome by a generic concept of `Variable Specification`, which is associated with study protocol through *`has_outcome_variable`* relation (see **Figure 3.27.B**). Since an outcome can be measured in a variety of ways, OCRe models outcome featuring a concept of `Study Phenomenon`, which disambiguates the event of interest per se (e.g., myocardial infarction) from variables that are the measurement of the event (e.g., time to event, up to 12 months' treatment). OCRe identifies a number of concepts that enable in-detail description of outcome; however, important concept such as effect sizes for outcomes is not modeled yet.

3.6 DISCUSSION

3.6.1 Major findings

The study presented in this chapter aimed to develop a conceptual model for modeling the domain of pharmacogenomics evidence assessment. The model was developed to specifically address (1) the issue of heterogeneity encountered in pharmacogenomics evidence assessment, and (2) two critical features i.e., clinically relevant evidence and evidence-based approach that have been pre-specified for my envisioned knowledge-based system. The modeling process adopted faceted analysis and followed the general principle of systematic review with meta-analysis to identify the basic information structure to accommodate information needs of pharmacogenomics evidence assessment. A fine-grained characterization of 73 publications, 82 studies, and 445 pieces of evidence extracted from empirical articles related to clinical validity and clinical utility of pharmacogenomics yielded 30 concepts, 49 relations, and approximately 250 terms. As a result, I developed a conceptual model that contains 3 independent yet inter-related information entities, namely, publication, study and evidence. These 3 information entities carry information modeled as 9 information components: study population, drug therapy, outcome, genetic variation, comparison, effect, study design, risk of bias assessment, and publication. Each module of information component was expressed in a layered structure composed of relations-concept pairs where the concepts were directly substantiated by terms related to empirical and clinically relevant pharmacogenomics evidence. Thus, the meaning of each information component could be explicitly and precisely expressed. I validated the conceptual model through 2 selected primary studies. The validation results showed that the developed conceptual model was able to accommodate 3 types of pharmacogenomics evidence including clinical validity, comparative effectiveness, and genetic modification. Thus, the feature

of clinically relevant evidence is satisfied. I validated the conceptual model through inclusion criteria extracted from 2 systematic reviews consisted of 7 meta-analyses. The validation results showed that the developed conceptual model was able to accommodate heterogeneous inclusion criteria to retrieve primary evidence for conducting meta-analysis. Thus, the feature of evidence-based approach is also satisfied.

I validated the conceptual model against OCRe which is an external model. The roles and modeling methods are different between OCRe and CM-PGEA. OCRe is developed to serve as a reference ontology that is independent of specific domain and application, while CM-PGEA is developed to serve as an application ontology that supports the specific domain of pharmacogenomics evidence assessment. Several gaps prevented me from reusing OCRe. First, OCRe does not model study results yet, which are critical information involved in evidence assessment. How to describe domain-specific concepts (e.g., genotype-guided drug therapies, genotypes, and genetic variants) in OCRe is unclear. The concepts and relations described in OCRe are too generic and from my perspective, they are not straightforward enough. OCRe refers some domain-specific concepts such as medical terms through external terminologies, which might cause inefficiency in reasoning.

The conceptual model I developed is organized in a layered structure. The layered structure allows developers to add incremental specifications to a concept by expanding the number of layers or increasing the number of relation-concept pairs at the same layer. That is, adding depth or breadth to the concept being specified. In general, the more layers and relation-concept pairs in a module, the more explicit the concept. Furthermore, the terms filled in the concepts enable expressing the meaning of a concept at different levels of specialization. The layered conceptual model not only is useful in incrementally and explicitly specifying evidence and inclusion

criteria, but also faithfully reveals the heterogeneity among studies. For example, in **Figure 3.28**, three study populations were illustrated with layered structure. The heterogeneity due to different number of layers, different relation-concept pairs and different terms in describing disease, disease status and procedure is clearly observed.

Furthermore, the advantage of using an inter-related layered structure to incrementally specify inclusion criteria is that, in the context of evidence synthesis, the criteria for considering types of evidence to be included in an analysis should be sufficiently broad to cover the likely diversity of studies, but sufficiently narrow to ensure a meaningful answer to the research question. For example, **Figure 3.28** presents three inclusion criteria that are annotated with different numbers of layers, different numbers of relation-concept pairs and different terms for retrieving relevant study populations. The use of less layers, relation-concept pairs or broader terms in inclusion criteria, such as the inclusion criteria_3, results in a broader retrieval. However, the variability among retrieved studies inevitably increases while more studies are retrieved.

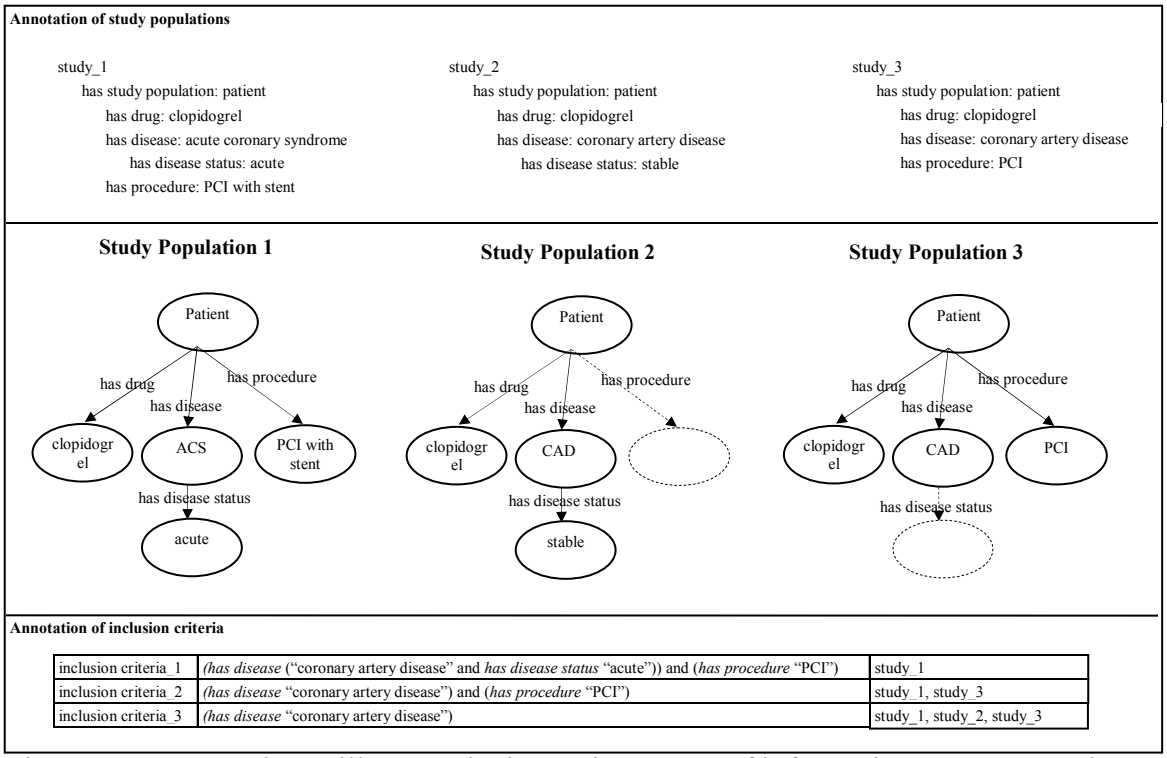


Figure 3.28: Examples to illustrate the layered structure of information component, the heterogeneity of information content, and the level of specialization in inclusion criteria

Not only relation-concept pairs are useful in specifying inclusion criteria, qualifiers and logic operators are helpful to prevent the inconsistent retrieval results caused by vague inclusion criteria. For example, a retrieval of relevant studies that considers three genetic variants, *CYP2C9*2*, *CYP2C9*3* **and** *VKORC1-1639* in genotype-guided warfarin dosing has been conducted in **Figure 3.29**, scenario A. Though inconsistent retrieval results have been found, it does not mean that the retrieval results are incorrect. **Figure 3.29**, Scenario B explains the different retrieval results when both qualifiers i.e. *exact*, *at least*, *at most* and logic operator, i.e. *and (conjunction)* are added to specify the retrieved scope and relations between a set of genetic variants, respectively.

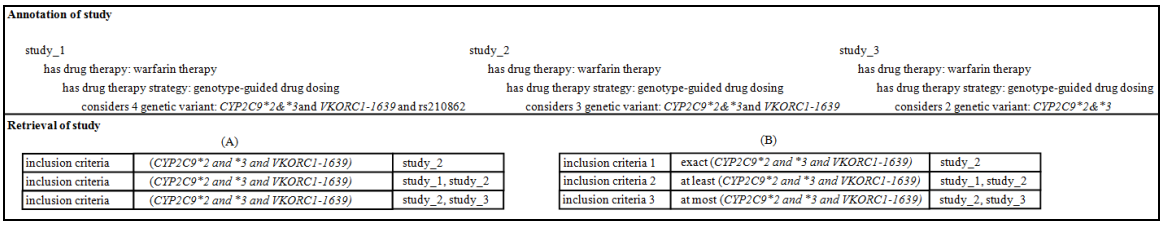


Figure 3.29: Examples to illustrate the heterogeneity of genetic variants considered in genotype-guided warfarin dosing

Meanwhile, the appropriate use of qualifiers to specify the retrieved scope is critical in order to ensure meaningful retrieval results. For example, a retrieval of relevant evidence that measures the composite incidence of cardiovascular death, myocardial infarction **or** stroke was conducted in **Figure 3.30**. Though evidence relevant to at least one of the defined outcomes is correctly retrieved, the resultant high variability on efficacy outcomes among evidence may influence the subsequent analysis. On the other hand, an adequate set of evidence is retrieved when "*at most"* qualifier is applied.

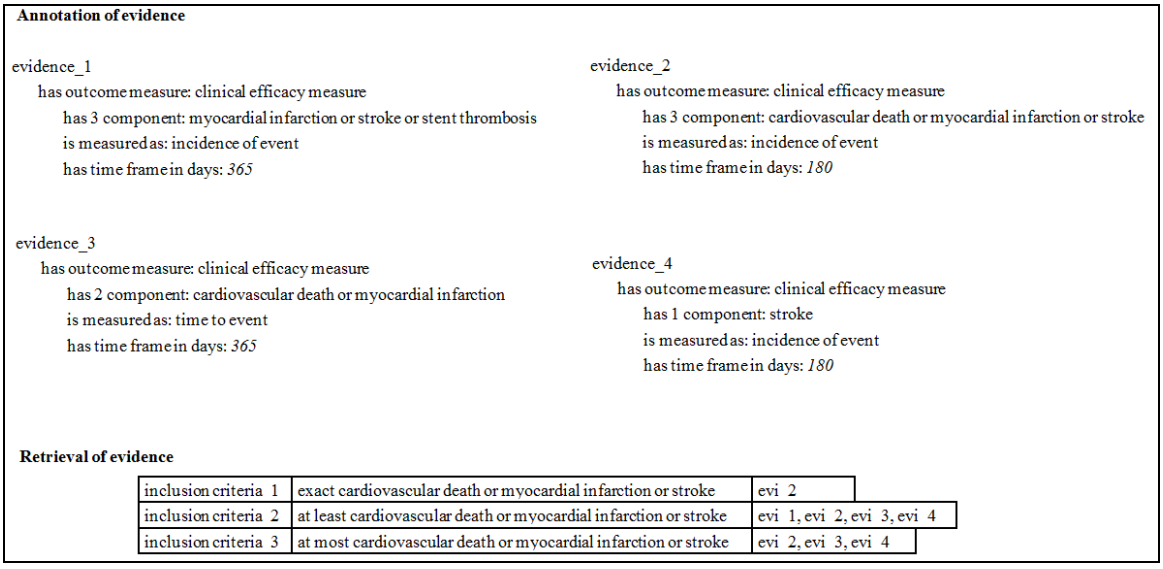


Figure 3.30: Examples to illustrate the heterogeneity of adverse cardiac events considered in composite outcome measure

3.6.2 Limitations

When considering the generalizability of the developed model, the model should be tested against other pharmacogenomics research such as cancer pharmacogenomics. However, the scope of the developed conceptual model was limited to pharmacogenomics research that is related to clinical validity and utility of clopidogrel and warfarin therapy. The comparison module only provides a comparison between two groups. However, a comparison across three groups, such as carriers of 1, carriers of 2 and non-carriers of a genetic variant of interest, is not uncommon in pharmacogenomics studies. This type of comparison is informative for evidence assessment as well and it should be modeled in the future research. The study population module did not include demographic characteristics of study subjects, such as age, body mass index, and ethnicity. This information provides critical modifying factors that affect the association between genetic variation and drug response and should be modeled in the future research, as well.

3.6.3 Contributions

The research work in Aim 1 delivers an extensible and easy to understand conceptual model, which is able to express heterogeneous information content in the domain of pharmacogenomics evidence assessment. The conceptual model also enables two different types of pharmacogenomics evidence, i.e., clinical validity (i.e., the association between genetic variants and drug response) and clinical utility (i.e., comparative effectiveness of genotype-guided drug therapy versus non-genotype-guided drug therapy), to be expressed in a unified model. This important feature fills the gap identified from PharmGKB (see Chapter 2, Section 2.4.1) because PharmGKB provides a large amount of evidence obtained from genetic association studies but lacks evidence obtained from genetic sub-studies of clinical trials or comparative effectiveness research. Furthermore, the conceptual model fills the gap identified from OCRe because neither

the study results nor the domain-specific concepts such as genetic variants have been modeled using OCRe. Thus, to my best knowledge, the conceptual model developed by this research is the first one that considers different dimensions of information needs in a unified model: (1) annotation of primary evidence and inclusion criteria to address the need for evidence retrieval, (2) annotation of clinical validity and utility evidence to address the need for integration of pharmacogenomics in clinical practice, and (3) annotation of three information entities i.e., publication, study and evidence to address the need for systematic review with meta-analysis.

3.7 CONCLUSIONS

This chapter has illustrated the development of a conceptual model which expresses the information needs in the context of pharmacogenomics evidence assessment and addresses the problems of heterogeneity and inconsistency encountered in the domain. These problems collectively make precise and meaningful evidence assessment more complex and challenging. These findings provide a compelling justification for the need of a knowledge-based system to assist in assessing pharmacogenomics evidence.

In the next chapter, I describe the conversion of the conceptual model that I developed into an ontology that is encoded in logic-based representation formalism to enable reasoning over it. The ontology is the core of my envisioned knowledge-based system which is aimed to assist in the time-consuming and labor-intensive tasks involved in evidence assessment. In the next chapter, I will explore the challenges posed by ontology construction, review state-of-the-art knowledge representation technologies, adopt an appropriate knowledge representation formalism to implement a prototype of knowledge-based system, and evaluate the knowledge-based system against its intended uses.

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Chapter 4. ADOPTION OF OWL 2 DL TO CONSTRUCT A KNOWLEDGE-BASED SYSTEM TO ENABLE FORMAL REPRESENTATION AND AUTOMATIC RETRIEVAL OF PHARMACOGENOMICS EVIDENCE FOR SYSTEMATIC REVIEW

4.1 INTRODUCTION

My overall research goal was to build a knowledge-based system that fulfills three critical features including clinically relevant evidence, evidence-based approach, and semantically computable formalism to facilitate effective and efficient evidence assessment that supports decisions on adoption of pharmacogenomics in clinical practice. In Chapter 3, a conceptual model has been developed to provide the conceptualization of the domain of pharmacogenomics evidence assessment. Briefly, The model addressed the feature of evidence-based approach by decomposing the informational structure into 3 information entities (i.e., publication, study, and evidence), 9 information components (i.e., bibliographical information, study design, study population, drug therapy, risk of bias assessment, comparison, outcome, genetic variation, and effect), concepts, relations and terms (see Chapter 3, Section 3.1.2). In addition, the conceptual model addressed the feature of clinically relevant evidence by characterizing empirical evidence concerning the clinical validity and utility of clopidogrel and warfarin pharmacogenomics to derive the rest building blocks (i.e., 30 concepts, 49 relations and around 250 terms) that could be used to substantiate the information content of the 3 types of information entities (see Chapter 3, Section 3.3.1).

Built on the conceptual model developed in Chapter 3, the research in this chapter focused on the realizing the feature of semantically computable formalism and constructing the envisioned

knowledge-based system. The primary aim was to build a knowledge-based system that enables formal representation and automatic retrieval of pharmacogenomics evidence for systematic review with meta-analysis. OWL 2 DL, a highly expressive and semantically computable web ontology language, was adopted to implement the envisioned knowledge-based system in order to overcome the inherent heterogeneity of pharmacogenomics evidence. To achieve the primary aim, I conceived three specific sub-aims as follows.

1. Construct an OWL 2 DL ontology based on the previously developed conceptual model to provide essential vocabularies for formal representation of heterogeneous pharmacogenomics evidence and inclusion criteria for systematic review with meta-analysis.
2. Develop a knowledge base that provides individual publications, studies and evidence that are formally represented using the developed OWL ontology to enable automatic retrieval of pharmacogenomics evidence.
3. Design verification mechanisms to verify whether the developed knowledge-based system is consistent and correct.

In the subsequent sections of this chapter, I first explain in Section 4.2 why OWL 2 DL was adopted as the formal language to develop my envisioned knowledge-based system. Then, in Section 4.3 I present the construction of an OWL 2 DL ontology by encoding the building blocks derived in Chapter 3. Subsequently, I used the constructed ontology to design representation patterns for formal representation of concrete individual information entities and inclusion criteria for evidence retrieval. The considerations in the design of representation patterns are elaborated in Section 4.4. Built on the constructed OWL 2 DL ontology and representation patterns, I constructed the envisioned knowledge base by formally asserting the individual

publications, studies and evidence extracted in Chapter 3. The constructed knowledge base is presented and discussed in Section 4.5. To verify the consistency and correctness of the constructed ontology and knowledge base, I designed test cases that exploit the automatic reasoning of an OWL 2 DL reasoner to implement the checking mechanisms. The design of test cases and the results of verification are provided in Section 4.6. Finally, I conclude this chapter by providing major findings and lessons learnt from applying OWL 2 DL to develop a pharmacogenomics knowledge-based system, and the next steps toward applying the implemented knowledge-based system to assist in pharmacogenomics evidence assessment.

4.2 Adoption of OWL 2 DL as Formal Representation Language to Construct the Envisioned Knowledge-based System

The research in this chapter focused on realizing the feature of semantically computable formalism when constructing the envisioned knowledge-based system. OWL 2 DL, a highly expressive and semantically computable web ontology language, was adopted to implement the envisioned knowledge-based system. In this section, I provide a brief review of the evolution of knowledge representation and reasoning to explain why OWL 2 DL was adopted as the formal representation language to construct my envisioned knowledge-based system. Subsequently, I provide a concise recapitulation of basic notions and advanced features of OWL 2 DL to explain the semantic meaning and logical consequences of their uses in formal representation, as well as how the features of OWL 2 DL are useful in formalizing the domain of pharmacogenomics evidence assessment. At the end of the section, I highlight major concerns to be considered as OWL 2 DL is used to build my envisioned knowledge-based system.

4.2.1 A brief review of the evolution of knowledge representation and reasoning

The vision of artificial intelligence is to understand the nature of intelligence and cognition so that computers can demonstrate human-like abilities [Lifschitz, Morgenstern, & Plaisted, 2008]. Knowledge representation and reasoning is an area of artificial intelligence research that concerns with encoding the knowledge into certain formalisms that can be efficiently manipulated by reasoning programs [Brachman & Levesque, 2004]. A number of representational formalisms have been developed based on two different schools of thought on how to best capture knowledge. One school of thought lies at the root of philosophy of mathematics and intends to "express a sentence through written signs in a more precise and clear way than it is possible to do through words" [Lifschitz et al., 2008]. Therefore, the syntax of declarative knowledge should be unambiguously structured by formulas that combine logical symbols such as predicates, functions, variables, logical connectives (e.g., *and*, *or*, *not*) and quantifiers (e.g., *for all*, *there exists*). The use of logical formulas does capture some of the essence of human inference. However, the inference may be undecidable because the increasing expressivity of logic-based languages results in higher complexity in computation.

The other school of thought, with roots in psychology and linguistics, was based on the assumption that the understanding of knowledge involves complex cognitive processes; therefore, knowledge should be expressed by a network-shaped cognitive structure [Nardi & Brachman, 2007]. For example, the intuition behind two non-logic-based representation formalisms, i.e., semantic networks and frames, is that the knowledge should be organized and represented by nodes and connected by arcs. In a network-based structure, nodes are either concrete individuals of the domain of interest or general categories (a.k.a. concepts) that group concrete individuals with certain characteristics in common; and arcs represent relations between these nodes [Lehmann, 1992; Minsky, 1975]. A graphical structure that consists of nodes and

arcs provides an intuitive and straightforward way to structure the knowledge. However, the non-logic-based formalisms have been frequently criticized due to the lack of a formal semantics. The lack of a formal semantics results in the insufficiency to precisely and explicitly represent complex knowledge in a network-based structure and the poor performance on reasoning over it.

Due to the need to improve the formal semantics of network-based formalisms and the trade-off between language expressivity and inferential complexity in logic-based formalisms, Description Logics were developed [Nardi & Brachman, 2007]. Description Logics are a family of logic-based representation formalisms that adopt decidable fragments of first-order logic constructors to describe concepts, roles (a.k.a. relations) and individuals at different levels of expressivity [Badder & Nutt, 2007]. The most expressive Description Logic to date is named as Description Logic $\mathcal{SROIQ}(\mathcal{D})$, where the letters used in the name stand for the adoption of particular constructors. For example, the letter $\mathcal{S}$ means that Boolean operators (AND, OR, NOT) are adopted to combine basic concepts into complex concepts and role value restriction (ONLY, SOME) are adopted to restrict the type of value of a given role. The letter $\mathcal{Q}$ means that qualified cardinality restriction (MIN, MAX, EXACTLY) are adopted to restrict the number and the type of value of a given role. The letter $\mathcal{D}$ means that datatype is supported. A number of reasoners, e.g., FaCT++, HermiT, Pellet and RacerPro, have been developed to provide reasoning service if knowledge is represented by Description Logic $\mathcal{SROIQ}(\mathcal{D})$.

Inspired by the vision of the Semantic Web, Description Logics were adapted and combined with standard web languages to provide formal semantics and reasoning services for the Web. The idea of Semantic Web was first introduced by Tim Berners-Lee with the vision to advance the computer interpretability of information stored on the Web and enable the exchange of information between automated web services [Berners-Lee, 1999; Berners-Lee, Hendler &

Lassila, 2001]. To realize the Semantic Web vision, the information that is stored on the Web needs to be annotated and organized by ontologies. From a Semantic Web perspective, ontologies refer to a collection of formalized vocabularies that explicitly specify a shared conceptualization of a domain of interest [Gruber, 1993; 1995]. In other words, ontologies are not only the simplified and abstract views of the domain that we wish to represent for certain purposes, but also the computational artifacts that encode the abstract views of the domain into computer processable forms which are suitable for automated reasoning. OWL (Web Ontology Language) is the standard web ontology language recommended by the World Wide Web Consortium (W3C), an international community that develops open standards to ensure the long term growth of the Web. OWL 2, the latest revision of OWL, became a W3C recommendation in 2009 [Hitzler, Krötzsch, Parsia, Patel-Schneider, & Rudolph, 2012]. OWL 2 provides sub-languages (a.k.a. profiles) with different levels of expressivity, i.e., OWL 2 EL, OWL 2 QL, OWL 2 RL, OWL 2 DL and OWL 2 Full, to satisfy different expressivity and reasoning requirements [Motik, Grau, Horrocks, Wu, Foloue, & Lutz, 2012]. OWL 2 DL is a very expressive but still decidable language among the OWL 2 family. The semantics of OWL 2 DL is based on $\mathcal{SROIQ}(\mathcal{D})$, which facilitates OWL 2 DL ontologies for reusing the well-developed Description Logics reasoners.

Due to the extension of the expressivity and the availability of ontology editors and reasoners, the OWL 2 family has been vigorously adopted in various application scenarios. In biomedical fields, numerous OWL ontologies have been released in the National Center for Biomedical Ontology (NCBO) BioPortal, which is a comprehensive repository of biomedical ontologies [Salvadores, Alexander, Musen, & Noy, 2013]. As of November 2015, the BioPortal repository (accessed at http://bioportal.bioontology.org/ontologies) contains much more

ontologies in OWL format than ontologies in other formats such as OBO (Open Biomedical Ontologies), UMLS (Unified Medical Language System) and SKOS (Simple Knowledge Organization Systems). According to the analysis conducted by Horridge and colleagues, OWL and OWL-compatible biomedical ontologies in BioPortal repository are largely represented in less-expressive profiles such as OWL 2 EL [Horridge, Parsia, & Sattler, 2011]. OWL 2 EL profile plays a prominent role in developing large-scale terminological ontologies and reasoning with them. For example, the concepts defined in the SNOMED CT (Systematized Nomenclature of Medicine, Clinical Terms) can be captured by features of OWL 2 EL so that the subsumption relations between clinical terms can be inferred [Dentler, Cornet, ten Teije, & de Keizer, 2011]. However, the use of OWL profiles should not be limited to the development of terminological ontologies. More research efforts are needed to further exploit the advanced features of OWL in order to support more complex ontology-based applications.

In summary, OWL 2 DL has been developed to have the desirable features of both the network-based semantics and the logic-based formalisms. The considerations which have led me to adopt OWL 2 DL as the representation formalism to fulfill the feature of semantically computable formalism for my envisioned knowledge-based system are: (1) OWL 2 DL is a very expressive but still decidable formal language, (2) ontology editors and reasoners that support OWL 2 DL are readily available, (3) OWL 2 DL is a standard web ontology language recommended by W3C, (4) OWL 2 DL is increasingly adopted in biomedical application scenarios, and (5) the use of advanced OWL 2 DL features in developing complex ontology-based applications is still a field requiring further exploration. In the following subsection, I elaborate in-depth on how the advanced features of OWL 2 DL are useful in the context of representing the complex domain i.e., pharmacogenomics evidence assessment.

4.2.2 A concise recapitulation of basic notions and advanced features of OWL 2 DL

This section highlights how OWL 2 DL is used to achieve the aim of developing a semantically computable knowledge-based system. OWL 2 is a language designed for representing and reasoning knowledge about a domain of interest [Hitzler et al., 2012]. OWL 2 represents domain knowledge as an ontology which is a collection of declared axioms. An axiom is a statement composed of basic OWL 2 constructs, i.e., classes, properties and individuals. Classes, properties and individuals are used to refer to real-world objects of the domain of interest, in that, individuals denote objects, classes denote categories of objects, object properties denote the relations between objects, and datatype properties denote the relations between objects and data values. The critical feature of OWL 2 DL is that the basic language constructs (i.e., classes, properties, and individuals) can be arbitrarily connected by advanced constructors to form complex expressions which are able to address the heterogeneous and complicated information contents implied in real-world objects.

To achieve the aim of developing a semantically computable knowledge-based system, the real-world objects involved in pharmacogenomics evidence-based assessment have been identified, conceptualized and described in Chapter 3 (see Section 3.4.1). The requirements of transforming the conceptual model into an ontology are summarized as follows.

(1) Use basic constructs of OWL ontology to refer to 4 building blocks of the conceptual model (i.e., information entities, concepts, relations and terms).

(2) Use complex class expressions to represent information components that are modeled as a layered structure composed of relation-concept pairs where the concept is substantiated by terms related to empirical and clinically relevant pharmacogenomics evidence.

(3) Use multiple complex class expression connected by set operators to enable detailed representation of heterogeneous and complex information components.

(4) Use restrictions on properties to allow for specification when multiple terms are used to substantiate one relation-concept pair.

(5) Use a chain of properties to infer relations between information entities.

(6) Use a DL reasoner to enable class subsumption checking and instance checking based on the explicitly defined classes.

(7) Use various classification schemes to satisfy the needs for evidence retrieval.

The basic constructs and advanced constructors of OWL 2 DL that could be used to address the above-mentioned requirements are selected from [Hitzler et al., 2012] and summarized in **Table 4.1**. To better understand the features of OWL 2 DL, two running examples that are adapted from [Hitzler et al., 2012] and [Noy, 2005] respectively, are used to explain the semantic meaning and the logical consequence of using OWL 2 DL constructs and constructors in formal representation. In addition, how the features of OWL 2 DL are useful in representing the domain of pharmacogenomics evidence assessment is illustrated while walking through the running examples.

Table 4.1: Summary of basic constructs and advanced constructors of OWL 2 DL

Construct	Syntax	Meaning
Atomic class	Class: C	declare a class by the name of C
Atomic object property	ObjectProperty: P	declare an object property by the name of P
Atomic datatype property	DatatypeProperty: T	declare an datatype property by the name of T
Individual	Individual: I	declare an individual by the name of I
Class Expression (CE)		
Class union	C_1 or C_2 or … or C_n, where n is an integer >= 2	describe a class that consists of individuals which are instances of at least one of the classes C_1, C_2, … C_n
Class conjunction	C_1 and C_2 and … and C_n, where n is an integer >= 2	describe a class that consists of individuals which are instances of the classes C_1, C_2, … C_n concurrently
Existential restriction	P some C	describe a class of individuals that have at least one property P and the value of property P is restricted to individuals of class C
Qualified exactly cardinality restriction	P exactly n C, where n is an integer >= 1	describe a class of individuals that have exactly n property P and the value of each property P is restricted to individuals of class C
Qualified minimal cardinality restriction	P min n C, where n is an integer >= 1	describe a class of individuals that have at least n property P and the value of each property P is restricted to individuals of class C
Qualified maximal cardinality restriction	P max n C, where n is an integer >= 1	describe a class of individuals that have at most n property P and the value of each property P is restricted to individuals of class C
Class Axiom		
Subclass axiom	$C_1 \subseteq C_2$	class C_2 is more general than class C_1, meaning that individuals of C_1 must be individuals of C_2
Partially defined class axiom	$C \subseteq CE$	CE describes the necessary but not the sufficient conditions for class C, meaning that individuals of C are always individuals of CE, whereas it is not sufficient to say that individuals of CE are individuals of C.
Fully defined class axiom	$C \equiv CE$	CE describes the necessary and sufficient conditions for defining class C, meaning that individuals of C are always individuals of CE, and vice versa.
Object Property Axiom		
SubProperty axiom	$P_1 \subseteq P_2$	If an individual I_1 is connected with another individual I_2 through property P_1, then I_1 is connected with I_2 through property P_2 as well.
Object property chain	$P_1 \circ P_2 \subseteq P_3$	If an individual I_1 connected with another individual I_2 through a chain from P_1 over P_2, then I_1 is connected with I_2 through P_3 as well.
Datatype Property Axiom		
SubProperty axiom	$T_1 \subseteq T_2$	If an individual I_1 is connected with a value v through T_1, then I_1 is connected with v through T_2 as well.
Individual Assertion		
Class assertion	$I \in C$ or $I \in CE$	Individual I is an instance of the named class C or individual I is an instance of an anonymous class that is expressed using class expression CE
Object property assertion	I_1 P I_2	An individual I_1 is related to another individual I_2 via P
Data property assertion	I T "value"^^xsd:datatype	An individual I is related to a value that has a specified datatype via datatype property T

Note: The content of this table is excerpted from [Hitzler et al., 2012]

4.2.2.1 Running example 1: Description and retrieval of individuals using a family ontology

The first running example is an ontology of family adapted from [Hitzler et al., 2012]. The example is used to demonstrate how an individual can be described by OWL 2 DL constructors and retrieved by instance checking supported by OWL 2 DL reasoners. This example helps to understand how individual publications, studies and evidence could be represented in semantically computable formalism and retrieved by automatic reasoning based on an OWL 2 DL ontology.

The running example starts with describing an individual named `Mary` (see **Figure 4.1**).

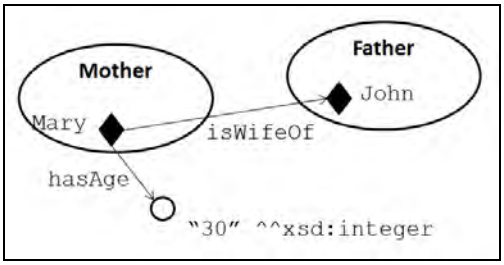

Figure 4.1: Three ways to describe an individual by OWL 2 DL

First, the individual `Mary` is described via the following class assertion:

`Mary` ∈ **`Mother`** ----- [Axiom 1: Class Assertion] (Note: `Mary` is an individual, **`Mother`** is a class)

The formal meaning of the statement is that `Mary` is an instance of the class named **`Mother`**. Such a statement specifies the intended real world meaning, i.e., Mary is a mother. Second, the individual `Mary` is described via the following object property assertion:

`Mary` ***`isWifeOf`*** `John` ----- [Axiom 2: Object Property Assertion] (Note: ***`isWifeOf`*** is an object property, `John` is an individual)

The statement means that `Mary` is related to another individual named `John` via the object property named *`isWifeOf`*; in other words, it implies that Mary is John's wife. Third, the individual `Mary` is described via the following datatype property assertion:

`Mary` *`hasAge`* "`30`"^^`xsd:integer` ----- [Axiom 3: Datatype Property Assertion] (Note: *`hasAge`* is a datatype property, `xsd:integer` is a datatype; `30` is a data value)

The statement means that `Mary` is related to a data value `30` that belongs to the `integer` datatype via a datatype property named *`hasAge`*, and it simply implies that Mary is 30 years old.

Besides simple classes, e.g., **`Mother`**, OWL 2 DL provides set operators and property restrictions to describe complex classes by class expressions. A complex class can consist of atomic classes cemented together using set operators, i.e., "`and`", "`or`", "`not`". For example, the following class expression

`Mother` `or` **`Father`** ----- [Class Expression 1] (Note: **`Father`** is a class)

describes a complex and anonymous class that is the union of two simple classes **`Mother`** and **`Father`**. This complex class contains every individual that belongs to either the class **`Mother`** or the class **`Father`** if two classes are disjoint (see **Figure 4.2**).

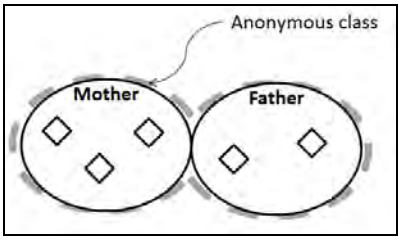

Figure 4.2: A complex and anonymous class described by a class expression denoting the union of two simple classes

The use of property restrictions is another way to describe a complex class. The idea is that a complex class can consist of a set of individuals which can be described by the relations that they participate in. For example, the following class expression

hasChild some **Boy** ----- [Class Expression 2]
(Note: *hasChild* is an object property, some is an existential restriction constructor, **Boy** is a class)

describes a complex and anonymous class of which every individual has at least one *hasChild* relation to an individual that is an instance of the class **Boy** (see **Figure 4.3**). It refers to a group of individuals who have some children and at least one of them is a boy.

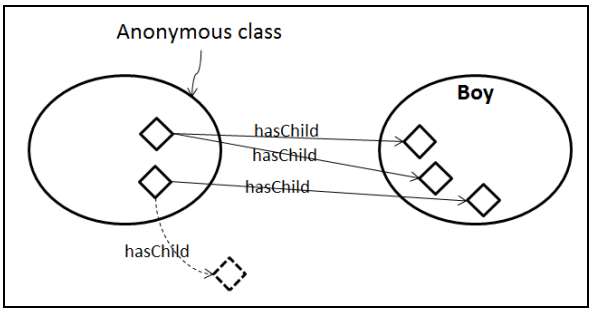

Figure 4.3: A complex and anonymous class described by a class expression denoting an existential restriction on object property

The property restriction can be further specified by the number of relations involved in the restriction, such as the following expressions:

hasChild exactly 2 **Boy** ----- [Class Expression 3]
hasChild min 2 **Boy** ----- [Class Expression 4]
hasChild max 2 **Boy** ----- [Class Expression 5]
(Note: exactly, min and max are cardinality restriction constructors)

Three class expressions differ from each other based on the number of *hasChild* relations to the class **Boy** that they participate in. [Class Expression 3] means that individuals of this anonymous class have exactly 2 *hasChild* relations to individuals that are instances of the class **Boy**, while [Class Expression 4] and [Class Expression 5] mean that there are at least 2 and at most 2 *hasChild* relations involved with instances of the class **Boy**, respectively.

Class expressions can be used in class assertions to describe individuals, for example, [Class Expression 3] is used to assert the individual Mary in the following axiom.

Mary ∈ (*hasChild* exactly 2 **Boy**) ----- [Axiom 4: Class Assertion]

The statement describes Mary as an instance of the class of which every individual has exactly 2 *hasChild* relations to individuals that are instances of the class **Boy**, in other words, it implies that Mary has two children who are boys.

Class expressions can be used in defining classes as well. For example, [Class Expression 1] is used to define the class **Parent** in the following axiom.

Parent ≡ **Mother** or **Father** ----- [Axiom 5: Defined Class]

Generally speaking, the class expression on the right side of the equivalence symbol "≡" is the description of necessary and sufficient conditions and every individual that satisfies the necessary and sufficient conditions must be an instance of a named class which is on the left side of the symbol "≡". Thus, [Axiom 5] means that the class **Parent** is defined by the class expression (**Mother** or **Father**). It formally means that every individual of the class **Parent** is either an individual of the class **Mother** or an individual of the class **Father**, and vice versa. Therefore, every individual of the class **Mother** such as Mary and every individual of the class **Father** such as John are individuals of the class **Parent** as well (see **Figure 4.4**).

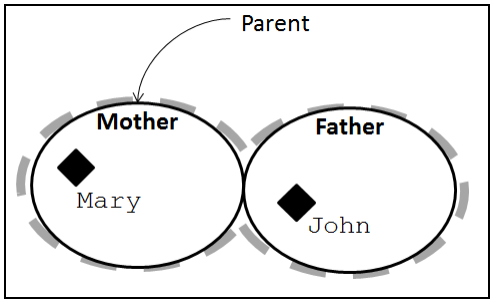

Figure 4.4: A named class defined by a class expression denoting the union of two simple classes

A defined class can be divided into more specific categories by adding additional properties to the definition. For example, the following axioms categorize parents based on the number of boys they have.

ParentHasExactly2Boy ≡ **Parent** and (*hasChild* exactly 2 **Boy**) ----- [Axiom 6: Defined Class]
ParentHasAtLeast2Boy ≡ **Parent** and (*hasChild* min 2 **Boy**) ----- [Axiom 7: Defined Class]
ParentHasAtMost2Boy ≡ **Parent** and (*hasChild* max 2 **Boy**) ----- [Axiom 8: Defined Class]

The structure of these axioms shows that each category of parents is defined by adding an additional class expression that specifies a group of individuals by the number of boys they have to the defined class **Parent**. Thus, one "and" operator is used to connect the class **Parent** and the added class expression. In other words, the defined class **Parent** [Axiom 5] and class expressions [Class Expression 3, 4 or 5] can be used together to further specify groups of individuals. For example, [Axiom 6] defines a class named **ParentHasExactly2Boy** that refers to a specific group of individuals who are either a mother of exactly 2 boys or a father of exactly 2 boys.

Given such individual assertions and class definitions, the OWL 2 DL reasoners can provide instance checking service to determine whether or not a given individual is an instance of a given defined class. This is achieved by checking if individual assertions match the necessary and sufficient conditions defined in a class. For example, as shown below, the individual Mary can be inferred as an instance of 4 defined classes based on the explicitly asserted axioms.

Mary ∈ **Parent** ----- [Axiom 9: Inferred Class Assertion], (Note: inferred from Axioms 1 and 5)
Mary ∈ **ParentHasExactly2Boy** ----- [Axiom 10: Inferred Class Assertion], (Note: inferred from Axioms 4, 6, and 9)
Mary ∈ **ParentHasAtLeast2Boy** ----- [Axiom 11: Inferred Class Assertion], (Note: inferred from Axioms 4, 7, and 9)
Mary ∈ **ParentHasAtMost2Boy** ----- [Axiom 12: Inferred Class Assertion], (Note: inferred from Axioms 4, 8, and 9)

Besides, an OWL 2 DL reasoner can automatically retrieve all the individuals that satisfy necessary and sufficient conditions described in three defined classes, **ParentHasAtMost2Boy**,

ParentHasExactly2Boy and **ParentHasAtLeast2Boy**. Suppose that two individuals, Jane and Tom, are added and asserted as follows:

Jane ∈ **Mother** ----- [Axiom 13: Class Assertion]
Jane ∈ *hasChild* exactly 1 **Boy** ----- [Axiom 14: Class Assertion]
Tom ∈ **Father** ----- [Axiom 15: Class Assertion]
Tom ∈ *hasChild* exactly 3 **Boy** ----- [Axiom 16: Class Assertion]

As shown in **Figure 4.5**, a DL reasoner can automatically infer that, the defined class **ParentHasAtMost2Boy** has two individuals, Jane and Mary, because Jane is a mother of one boy and Mary is a mother of two boys. Besides, John is not expected to be inferred as an instance of any one of three defined classes because John is not asserted with the *hasChild* property.

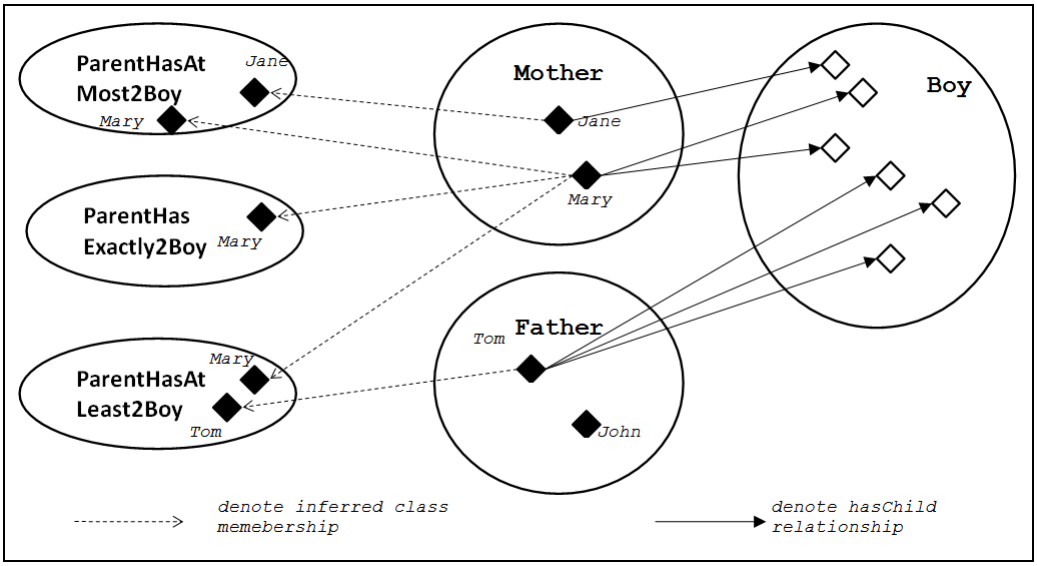

Figure 4.5: Simplified illustration of instance checking

In summary, the running example introduces several basic constructs and advanced features of OWL 2 DL to address the requirements of representation language to express the conceptual model into an ontology (see the list of requirements in the beginning of Section 4.2.2.). For example, the anonymous class expressions (e.g., [Class Expression 1 & 2]) iteratively connected

by set operator "and" could enable information components to be expressed with incremental specification. The qualified cardinality restrictions (e.g., [Class Expression 3, 4 & 5]) could enable the specification of the numbers and categories of classes used as values of a property. The `EquivalentClasses` axiom (e.g., [Axioms 6, 7 & 8]) could enable instance checking based on the explicitly expressed definitions of classes. The collection of the axioms and class expressions introduced in the running example forms a small ontology to identify individual parents based on the number of boy they have. This example addresses one of the intended uses of my envisioned knowledge-base system, that is, retrieval of relevant individual evidence for meta-analysis.

4.2.2.2 Running example 2: Class subsumption and instance checking using a book ontology

The second running example is a book ontology adapted from [Noy, 2005]. The example is used to introduce class subsumption checking provided by OWL 2 DL reasoners. The class subsumption checking helps organize a set of classes according to their level of generality-specificity relationship. It also helps in consistency checking of ontology.

The second running example demonstrates the class subsumption and instance checking based on the following asserted axioms:

Class: **Animal** ----- [Axiom 17: Class Declaration]
Class: **Lion** ----- [Axiom 18: Class Declaration]
Lion ⊆ **Animal** ----- [Axiom 19: Subclass Axiom]
Class: **AfricanLion** ----- [Axiom 20: Class Declaration]
AfricanLion ⊆ **Lion** ----- [Axiom 21: Subclass Axiom]
ObjectProperty: *hasSubject* ----- [Axiom 22: Object Property Declaration]
Class: **Book** ----- [Axiom 23: Class Declaration]
Class: **BookAboutAnimal** ----- [Axiom 24: Class Declaration]
BookAboutAnimal ≡ **Book** and (*hasSubject* some **Animal**) ----- [Axiom 25: Defined Class]
Class: **BookAboutLion** ----- [Axiom 26: Class Declaration]
BookAboutLion ≡ **Book** and (*hasSubject* some **Lion**) ----- [Axiom 27: Defined Class]
Class: **BookAboutAfricanLion** ----- [Axiom 28: Class Declaration]
BookAboutAfricanLion ≡ **Book** and (*hasSubject* some **AfricanLion**) ----- [Axiom 29: Defined Class]
Individual: TheAnimalBook ----- [Axiom 30: Individual Declaration]
TheAnimalBook ∈ **Book** ----- [Axiom 31: Class Assertion]

`TheAnimalBook` ∈ (*`hasSubject`* `some` **`Animal`**) ----- [Axiom 32: Class Assertion]
Individual: `TheBookOfTheLion` ----- [Axiom 33: Individual Declaration]
`TheBookOfTheLion` ∈ **`Book`** ----- [Axiom 34: Class Assertion]
`TheBookOfTheLion` ∈ (*`hasSubject`* `some` **`Lion`**) ----- [Axiom 35: Class Assertion]
Individual: `HuntingTheAfricanLion` ----- [Axiom 36: Individual Declaration]
`HuntingTheAfricanLion` ∈ **`Book`** ----- [Axiom 37: Class Assertion]
`HuntingTheAfricanLion` ∈ (*`hasSubject`* `some` **`AfricanLion`**) ----- [Axiom 38: Class Assertion]

An OWL 2 DL reasoner can perform automatic subsumption checking (see **Figure 4.6**) based on Axioms 17 to 38, particularly the Axioms 19 and 21 that describe the *`subClassOf`* relationships between classes of **`Animal`**, **`Lion`** and **`AfricanLion`**. Since classes of **`Animal`**, **`Lion`** and **`AfricanLion`** are used as restricted values of *`hasSubject`* property in describing necessary and sufficient conditions that define three different categories of books (see Axioms 25, 27 and 29), the implicit class subsumption relationships between three defined categories of books are inferred as follows.

`BookAboutAfricanLion` ⊆ **`BookAboutLion`** ----- [Axiom 39: Inferred Subclass Axiom], (Note: inferred from Axioms 21, 27 and 29)
`BookAboutLion` ⊆ **`BookAboutAnimal`** ----- [Axiom 40: Inferred Subclass Axiom], (Note: inferred from Axioms 19, 25, and 27)

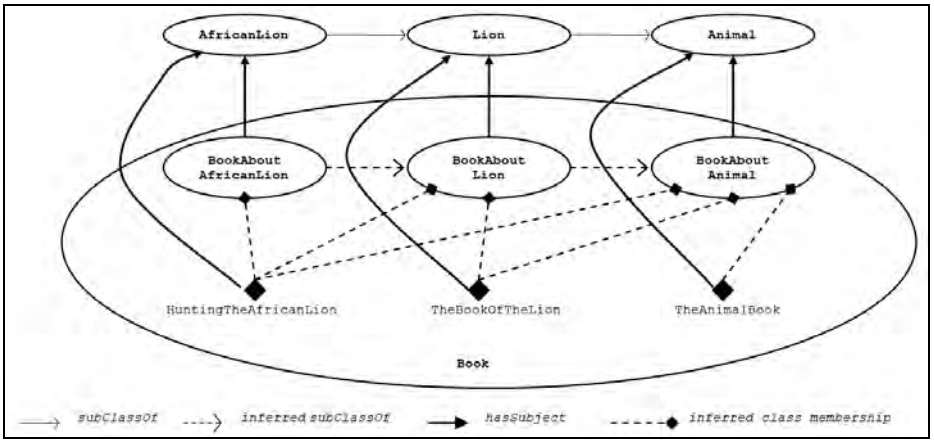

Figure 4.6: Simplified illustration of class subsumption and instance checking

The reasoner also performs instance checking (see **Figure 4.6**) and infers the following implicit class assertions. It is worth mentioning that the book `HuntingTheAfricanLion` is not

only inferred as an instance of the defined class of **BookAboutAfricanLion** but also inferred as an instance of the defined class of **BookAboutLion** and **BookAboutAnimal** respectively because a subclass (including its members) inherits descriptions or characteristics from its parent classes.

TheAnimalBook ∈ **BookAboutAnimal** ----- [Axiom 41: Inferred Class Assertion], (Note: inferred from Axioms 25, 31, 32)
TheBookOfTheLion ∈ **BookAboutLion** ----- [Axiom 42: Inferred Class Assertion], (Note: inferred from Axioms 27, 34, 35)
TheBookOfTheLion ∈ **BookAboutAnimal** ----- [Axiom 43: Inferred Class Assertion], (Note: inferred from Axioms 40, 42)
HuntingTheAfricanLion ∈ **BookAboutAfricanLion** ----- [Axiom 44: Inferred Class Assertion], (Note: inferred from Axioms 29, 37, 38)
HuntingTheAfricanLion ∈ **BookAboutLion** ----- [Axiom 45: Inferred Class Assertion], (Note: inferred from Axioms 39, 44)
HuntingTheAfricanLion ∈ **BookAboutAnimal** ----- [Axiom 46: Inferred Class Assertion], (Note: inferred from Axioms 40, 45)

In summary, the small ontology of book enables categories of book to be classified based on which kind of animal is the subject of a book. This example indicates that the subclass-of relationships among major concepts of the domain of pharmacogenomics evidence assessment are essential to enable the classifications of heterogeneous pharmacogenomics evidence from different perspectives and at different levels of specialization.

4.2.3 Major concerns in adopting OWL 2 DL to build a knowledge-based system

After a focused examination on the constructs and constructors of OWL 2 DL by two running examples, it showed that OWL 2 DL has sufficient expressive power and ability to represent and differentiate heterogeneous content. Particularly, the constructs and constructors of OWL 2 DL can be combined in a flexible way so that complex knowledge can be represented as precisely as possible to reflect its intended meaning. However, every coin has two sides. Since constructs and constructors of OWL 2 DL have logic-based semantics, the inference over axioms that are composed of various combinations of constructs and constructors might cause problems

including computational inefficiency and unexpected inference results. Therefore, constructors that combine multiple classes and properties to form a complex class expression should be used with caution. Major concerns for adopting knowledge representation formalisms in building a knowledge-based system are shown in **Figure 4.7**. They are "Does the formal representation of domain knowledge match its intended meaning?", "Are the results inferred as expected?" and "Is there a good balance between expressive representation and efficient inference?" These important issues will be explored and elaborated in the following sections in the context of adopting OWL 2 DL to design and develop a knowledge-based system that supports pharmacogenomics evidence assessment.

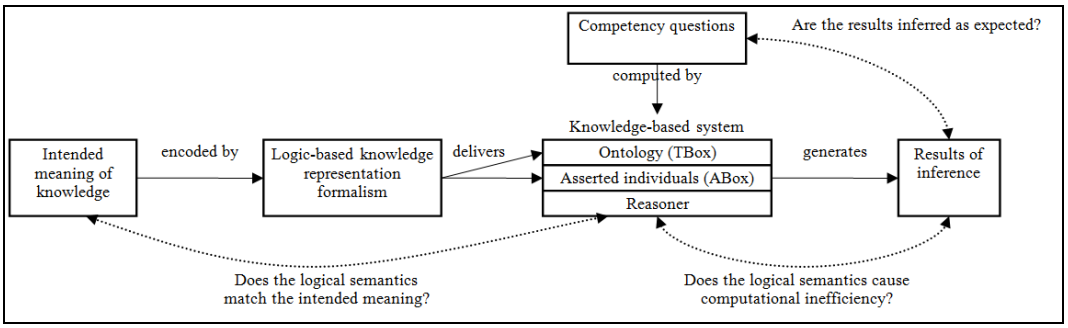

Figure 4.7: Major concerns in adopting OWL 2 DL to build a knowledge-based system

4.3 Construction of an OWL 2 DL Ontology as the Core of the Knowledge-based System

The primary aim of the study presented in this chapter was to build a knowledge-based system that enables formal representation and automatic retrieval of pharmacogenomics evidence to assist in systematic review with meta-analysis. After a brief review of the features of OWL 2 DL and a focused examination on the constructs and constructors of OWL 2 DL by two running examples, OWL 2 DL was adopted to implement the envisioned knowledge-based system in order to exploit its strength in expressivity of semantic meaning and decidability of logical

reasoning to overcome the inherent heterogeneity of pharmacogenomics knowledge. Therefore, I began the research work of constructing an OWL 2 DL ontology based on the conceptual model developed in Chapter 3. To address the primary aim of the study, the ontology was built with two intended uses: (1) to provide vocabularies for representation of pharmacogenomics evidence and inclusion criteria and (2) to enable automatic evidence retrieval for systematic review with meta-analysis. This section provides the construction of the ontology, including: the material and methods used in constructing the ontology, general principles of converting the building blocks into an OWL 2 DL ontology, and the results of the constructed ontology in terms of ontology metrics and ontology features.

4.3.1 Materials and Methods

The conceptual model of pharmacogenomics evidence assessment that has been developed in Chapter 3 (see Section 3.3.1) served as the blueprint for constructing the ontology. The building blocks of the conceptual model, that include 3 information entities (i.e., publications, studies and evidence), 9 information components, 30 concepts, 49 relations and around 250 terms served as the materials to construct the ontology.

OWL 2 DL was adopted as the formal language to implement the ontology. Protégé is an open-source ontology editor developed by the Stanford Center for Biomedical Informatics Research at the Stanford University School of Medicine. Protégé fully supports the latest OWL 2 Web Ontology Language and is supported by highly efficient OWL 2 DL reasoners such as HermiT [Glimm, Horrocks, Motik, Stoilos, & Wang, 2014]. Therefore, Protégé was used to build the ontology.

In order to encode the building blocks in a systemic way, I derived mapping principles based on a commonly cited guide for constructing OWL 2 ontology [Hitzler et al., 2012]. The mapping

principles and the underlying rationales are elaborated in Section 4.3.2. Subsequently, I manually encoded building blocks into an ontology using Protégé. I followed the mapping principles while declaring atomic classes, atomic properties, or individuals to refer to the information entities, concepts, relations and terms of the conceptual model. Besides, advanced classes or property axioms such as `SubClassOf`, `EquivalentClass`, `SubObjectPropertyOf`, `ObjectPropertyChain`, etc., were used to explicitly describe relations between atomic classes and between atomic properties, if the intentionally asserted knowledge is useful for reasoning or drawing inferences.

4.3.2 General principles of converting the conceptual model and its building blocks into an OWL 2 DL ontology

The first step into the formal representation of domain knowledge is to develop an OWL ontology (a.k.a. TBox) that comprises a collection of classes, properties and individuals which are declared using a collection of vocabularies of the domain. This task is challenging because there are usually no clear rules determining whether a vocabulary should be declared as a class, a property, or an individual in an OWL ontology. The judgment mainly depends on the intended meaning and the planned usage of each vocabulary. Since the building blocks of the conceptual model of pharmacogenomics evidence assessment are quite diverse in terms of their meanings and usages, I followed a commonly cited guide for constructing OWL 2 ontology [Hitzler et al., 2012] to derive the principles of converting these various building blocks into basic constructs of an OWL 2 DL ontology. The principles and the underlying rationales are elaborated below and summarized in **Table 4.2** for quick reference.

Table 4.2: Principles for mapping building blocks of conceptual model of pharmacogenomics evidence assessment to basic constructs of OWL 2 DL ontology

Building block	Construct of OWL 2 DL	Rationale
Concept	Class	Concepts are generic abstraction of a group of terms that have similar meanings
Term	Class	Subsumption relations exist between terms that belong to the same concept
	Individual	No subsumption relations exist between terms that belong to the same concept
Relation	Object property	Relations describe the relationship between two information entities, or between two concepts
	Datatype property	Relations link a concept or an individual to a numerical value
Information component	Complex class expression	Information components are modules that comprise multiple concepts and relations to describe essential information content of information entities
Information entity	Class	Information entities (i.e., publication, study, evidence) are sets of concrete individual publications, studies and evidence respectively

4.3.2.1 Concepts are mapped to classes

A concept in the conceptual model is regarded as a generic abstraction of terms that have similar meaning. Therefore, all the concepts identified in the conceptual model are mapped to classes. For example, **Figure 4.8** shows that the `Disease` concept is an abstraction of many specific diseases such as `thromboembolism`, `atrial fibrillation`, etc. Thus, the `Disease` concept will be converted into a **`Disease`** class when constructing the ontology.

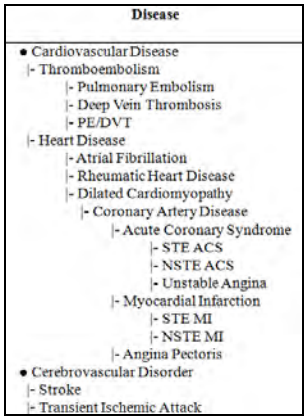

Figure 4.8: Disease concept and related terms identified in the conceptual model

4.3.2.2 Terms are mapped to either classes or individuals

Terms are vocabularies commonly appearing in the domain of pharmacogenomics evidence assessment. They substantiate the concrete meaning of the concepts they belong to. For example, terms in **Figure 4.8** are specific terms that substantiate the meaning of the `Disease` concept. Terms can be declared as classes or individuals. The decision depends on whether or not the subsumption relations exist between terms. Since the subsumption relations between terms provide a logical basis for inferring class hierarchy of defined classes (see Section 4.2.2.2, running example 2), in the context of pharmacogenomics evidence assessment, almost all terms are mapped to classes in order to declare `SubClassOf` axioms that describe subsumption relations between them. For example, when terms shown in **Figure 4.8** are converted into classes, `SubClassOf` axioms such as **`thromboembolism` ⊆ `cardiovascular disease`** can be declared in the ontology.

On the other hand, terms that have no subsumption relations between them are declared as individuals of the concepts they belong to. For example, the concept of `Risk of Bias Assessment Value` has three specific terms, i.e., `high`, `low` and `unclear`, and no subsumption relations exist between these terms; therefore, these terms are converted into individuals of **`Risk of Bias Assessment Value`** class.

4.3.2.3 Relations are mapped to either object properties or datatype properties

A relation in the conceptual model is a verb phrase that describes the relationship between two information entities, or between two concepts, or between a concept and a numerical data value. In general, if a relation describes a relationship that involves a numerical value, the relation is mapped to a datatype property in OWL ontology. For example, the

"*has_effect_size*" and "*has_P-Value*" relations are mapped to datatype properties in order to describe an individual piece of evidence with its data values of effect size and P-value. On the other hand, relations that do not involve numerical values are mapped to object properties. For instance, the "*is_reported_in*" relation is used to describe the relationship between an information entity (i.e., study) and another information entity (i.e., publication); therefore, it is mapped to an object property. In addition, relations between two concepts are mapped to object properties as well. For example, in **Figure 4.9**, all the relations (denoted by arrows) are used to link a concept to another concept, thus, they are mapped to object properties.

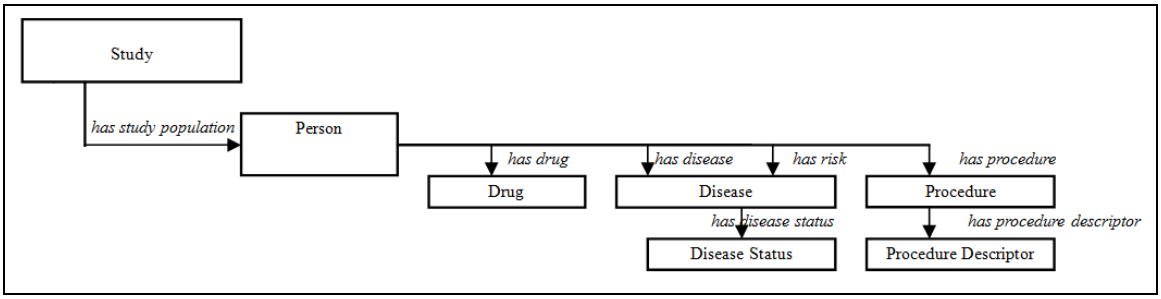

Figure 4.9: Study population module

4.3.2.4 Information components are mapped to complex class expressions

Information components in the conceptual model (i.e., Publication, Study Population, Study Design, Drug Therapy, Risk of Bias Assessment, Comparison, Genetic Variation, Outcome and Effect) are modules that intend to describe essential information content implied in information entities (i.e., Publication, Study and Evidence). Each module is composed of multiple relation-concept pairs in order to describe multiple features of an information component. For example, the **Study Population** module shown in **Figure 4.9** requires at most 7 relation-concept pairs to describe a study population enrolled in an individual study. Therefore, rather than mapping them to atomic named classes or properties, the information components are mapped to complex and anonymous classes, which are represented using class expressions.

4.3.2.5 Information entities are mapped to classes

Three different types of information entities (i.e., Publication, Study and Evidence) are regarded as sets of concrete individual publications, studies and evidence respectively. Therefore, they are mapped to classes when constructing the ontology. It is worth noting that the instances of these three classes cannot be described by basic constructs only. The representation of individual information entities requires the use of advanced OWL 2 DL constructors and this will be discussed in Section 4.4.

4.3.3 The constructed OWL 2 DL ontology

The conceptual model of pharmacogenomics evidence assessment developed in Chapter 3 was encoded into an OWL 2 DL ontology by following the mapping principles presented in **Table 4.2**. The constructed ontology is presented in terms of ontology metrics and ontology features in the following subsections.

4.3.3.1 Ontology metrics

Table 4.3 provides an overview of the ontology metrics that reflect the evolution of the ontologies constructed at different stages of the development of the envisioned knowledge-based system. The initial OWL ontology (referred as Ontology_1 hereafter) was converted from the conceptual model of pharmacogenomics evidence assessment. The other ontologies are extensions of Ontology_1 for different purposes. Ontology_2 was expanded with individual assertions to construct the envisioned knowledge base, which will be elaborated in Section 4.5. Ontology_3 to Ontology_6 were expanded with defined classes to implement the classification schemes designed in 4 test cases respectively, which will be elaborated in Section 4.6.

Table 4.3: Overview of ontology metrics at different stages of the development of the envisioned knowledge-based system

Ontology metrics	**Ontology_1**	**Ontology_2 (including KB)**	**Ontology_3 (including KB, test case 1)**	**Ontology_4 (including KB, test case1 & 2)**	**Ontology_5 (including KB, test case1 & 3)**	**Ontology_6 (including KB, test case 1 & 4)**
DL expressivity	*ALCRF(D)*	*ALCRQ(D)*	*ALCRQ(D)*	*ALCRQ(D)*	*ALCRQ(D)*	*ALCRQ(D)*
Class count	306	306	325	334	338	357
Object property count	69	69	69	69	69	69
Datatype property count	12	12	12	12	12	12
Individual count	9	676	676	676	676	676
SubClassOf axioms count	289	289	306	315	319	336
EquivalentClasses axioms count	9	9	28	37	41	60
SubObjectPropertyOf axioms count	27	27	27	27	27	27
SubPropertyChainOf axioms count	11	11	11	11	11	11
SubDatatypePropertyOf axioms count	5	5	5	5	5	5
FunctionalDatatypeProperty axioms count	7	7	7	7	7	7
DatatypePropertyRange axioms count	7	7	7	7	7	7
ClassAssertion axioms count	9	2679	2679	2679	2679	2679
ObjectPropertyAsserion axioms count	0	1187	1187	1187	1187	1187
DatatypePropertyAssertion axioms count	0	1522	1522	1522	1522	1522
Computing time	not applicable	not applicable	2,874ms (~3 seconds)	6,463,579ms (~108 minutes)	3,990ms (~4 seconds)	149,908ms (~ 2.5 minutes)

Ontology_1 provides around 400 vocabulary words for describing information entities involved in the domain of pharmacogenomics evidence assessment, including 306 classes (with depth of hierarchies from two to six levels), 69 object properties, 12 data properties, and 9 individuals. The *ALCRF(D)* expressivity of Ontology_1 means that conjunction of classes, union of classes, existential restrictions on properties, datatype property restrictions and object property chain were adopted to describe various axioms [Golbreich & Wallace, 2012]. Ontology_1 features several important axioms to explicitly describe the domain knowledge associated with classes and properties, to facilitate reasoning for class subsumption and instance checking, to enable expression of heterogeneous information content, and to reduce redundancy in curating individual information entities. How these axioms are useful in addressing the intended uses of the ontology is presented in the following subsection.

4.3.3.2 Ontology features

- `SubClassOf` *axioms*

`SubClassOf` axioms were heavily used in Ontology_1 to describe subsumption relations between classes in order to establish class hierarchies. As shown in **Figure 4.10**, classes in Protégé are denoted by yellow circles next to the class names and a class hierarchy can be expanded by clicking the grey arrowhead next to the yellow circle. A 6-level hierarchy of **`Disease`** class is illustrated in **Figure 4.11**. Each `SubClassOf` axiom declares an "is-a" relationship between two classes. In general, the bottom-level classes such as **`UnstableAngina`**, **`NonfatalMyocardialInfarction`** are more suitable for asserting individual study or evidence because they have a more specific meaning. On the other hand, the top-level classes such as **`CardiovascularDisease`** and **`CardiovascularDisorder`** are more suitable for expressing defined classes that aim to perform a broad range of retrieval to identify all relevant asserted individuals.

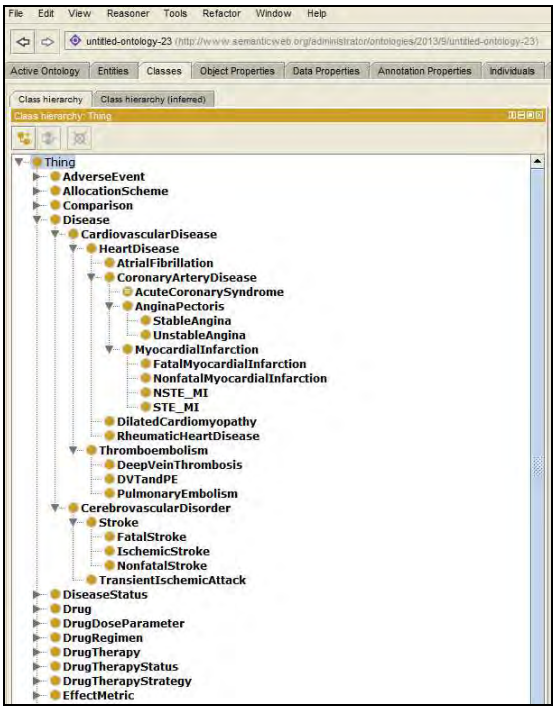

Figure 4.10: Screenshot of classes and class hierarchies shown in Protégé. Classes are denoted with yellow circles next to class names. Clicking on a grey arrowhead next to a class expands a class hierarchy.

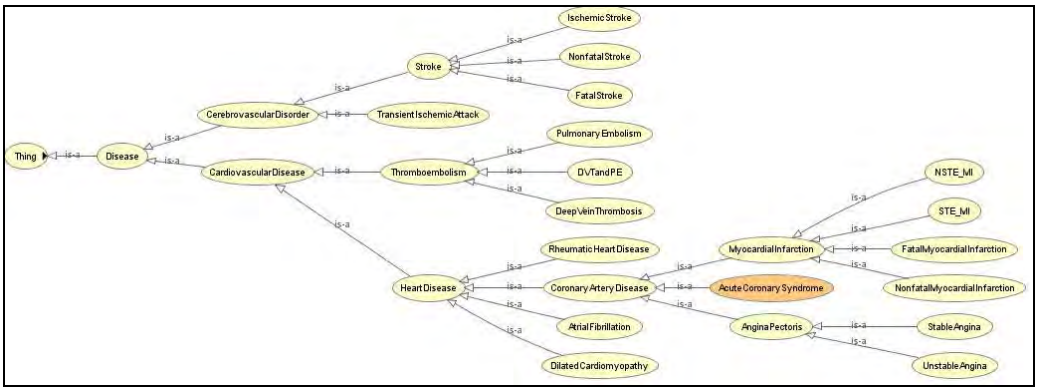

Figure 4.11: Visualization of the asserted `Disease` class hierarchy. Generated by Protégé plugged-in visualization tool OWLViz.

In addition to explicitly declare "is-a" relationships, `SubClassOf` axioms explicitly describe the necessary conditions of being a member of a class. For example, as shown in **Figure 4.12**, a specific drug regimen of clopidogrel maintenance dose 75 mg was represented by the class **`ClopidogrelMD75mg`**, which was declared as a subclass of the **`ClopidogrelRegimen`** class and a subclass of the class expression `hasMDInmg some [integer <= 75]`.

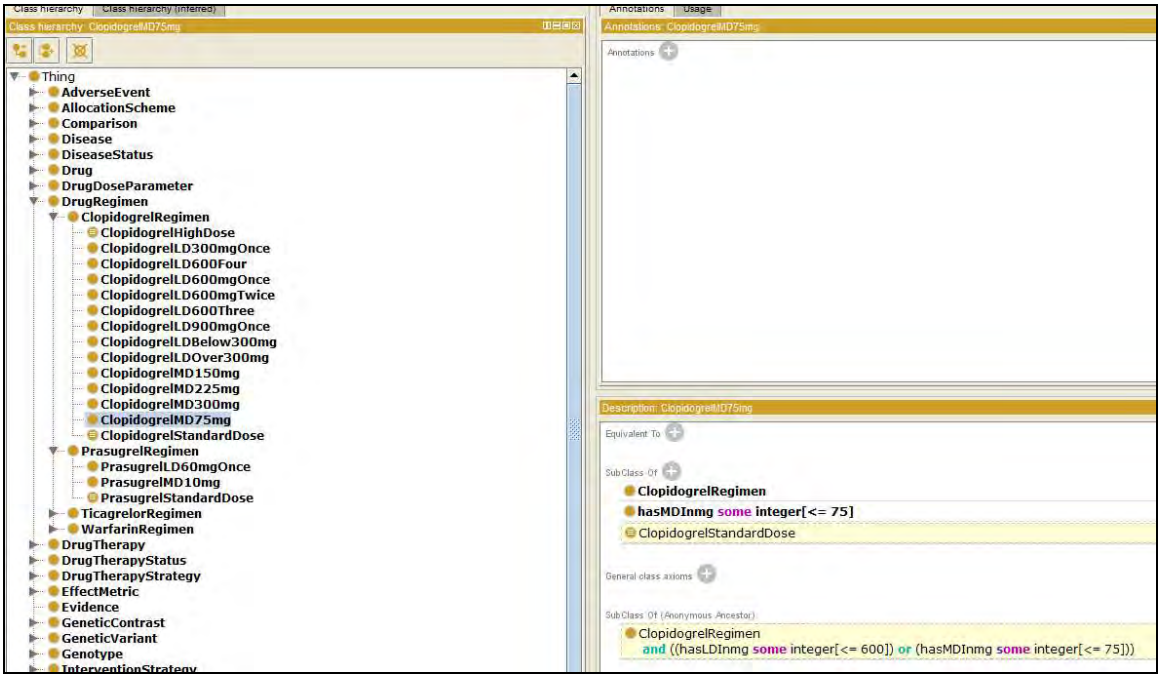

Figure 4.12: Formal representation of clopidogrel regimen of maintenance dose of 75 mg.

- `EquivalentClasses` *axioms*

`EquivalentClasses` axioms were used to declare defined classes with necessary and sufficient conditions. For example, acute coronary syndrome (ACS) is a commonly used disease term that refers to clinical presentations of ST-segment elevation myocardial infarction (STE_MI), non-ST-segment elevation myocardial infarction (NSTE_MI) or unstable angina. Therefore, **`AcuteCoronarySyndrome`** was defined by the following `EquivalentClasses` axioms: **`AcuteCoronarySyndrome`** ≡ **`(STE_MI`** `or` **`NSTE_MI`** `or` **`UnstableAngina)`**. Given the definition, three classes **`STE_MI`**, **`NSTE_MI`** and **`UnstableAngina`** are automatically inferred as subclasses of **`AcuteCoronarySyndrome`** (see **Figure 4.13**).

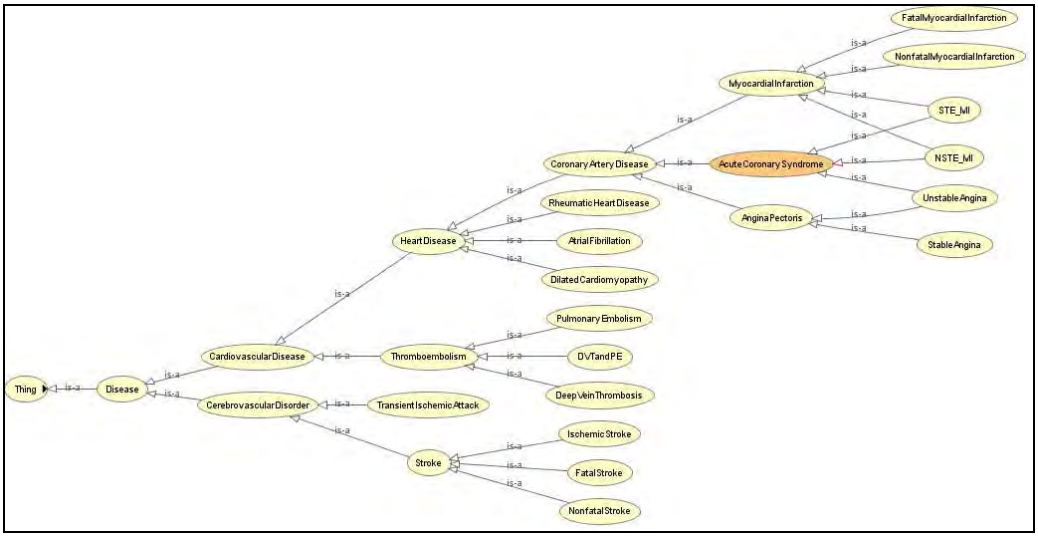

Figure 4.13: Visualization of the inferred `Disease` class hierarchy. Compared to Figure 4.11, **`STE_MI`**, **`NSTE_MI`**, and **`UnstableAngina`** are inferred as subclasses of **`AcuteCoronarySyndrome`**.

Similarly, the noun phrase "clopidogrel standard dose" is commonly used in journal articles to describe drug regimen of an observed clopidogrel therapy, without explicitly specifying the exact dosage. Thus, the class **`ClopidogrelStandardDose`** was created in ontology and defined by the following `EquivalentClasses` axiom,

ClopidogrelStandardDose ≡ **ClopidogrelRegimen** and ((*hasLDInmg* some integer[<= 600]) or (*hasMDInmg* some integer[<= 75]))

which means that clopidogrel standard dose is any clopidogrel regimen with loading dose less than or equal to 600 mg or with maintenance dose less than or equal to 75 mg, and vice versa. The advantage of `EquivalentClasses` axioms in inferring class subsumption relationship is further illustrated in **Figure 4.14**. Each clopidogrel regimen that is described with specific dosage (such as **ClopidogrelMD75mg** in **Figure 4.12**) and satisfies the definition of **ClopidogrelStandardDose** was automatically inferred as a subclass of **ClopidogrelStandardDose** via a OWL 2 DL reasoner.

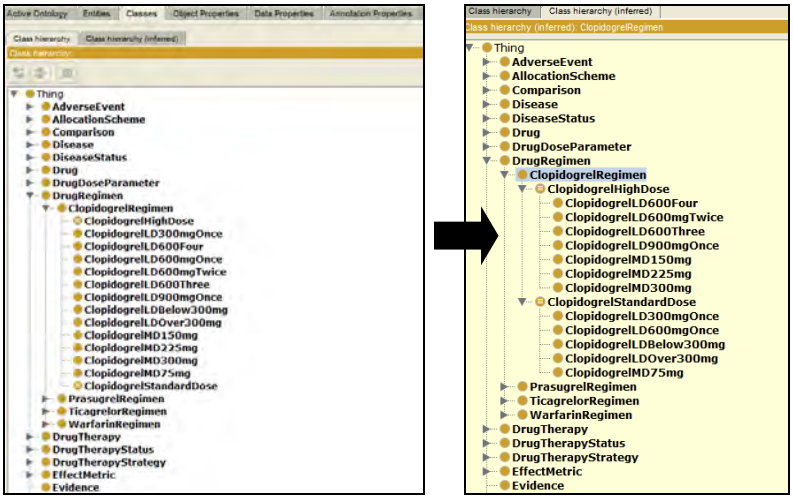

Figure 4.14: Asserted versus inferred class hierarchy of clopidogrel regimen. Asserted class hierarchy is on the left, inferred class hierarchy is on the right.

- `SubPropertyOf` *axioms*

Similar to `SubClassOf` axioms, `SubPropertyOf` axioms describes subsumption relations between properties and therefore establishes property hierarchies. As shown in **Table 4.4**, subproperties are useful in two scenarios. In the first scenario, subproperties were used to denote

the total number of involved classes when the values of an object property involved multiple classes. Three property hierarchies (i.e., *hasComponent*, *hasGeneticVariant*, *hasGenotypeOI*) were created to explicitly describe the total number of classes involved in describing an outcome measure, total number of variants involved in determining genotypes, and total number of genotypes involved in the genotypes of interest, respectively.

In the second scenario, subproperties were created to represent more specific relations. For example, the object property *hasDrugTherapy* represented a general relation between a study and a drug therapy under investigation in the study. Subproperties such as *hasDrugTherapyObserved* and *hasDrugTherapyCompared* were created to specify a drug therapy that was investigated under an observational study or an interventional study respectively. Subproperties such as *hasDrugTherapyOI* and *hasDrugTherapyRef* were created to specify a drug therapy that was given to subjects in the experimental arm or the control arm respectively. Similarly, all the subproperties of *hasDose*, *hasProcedure* and *hasTimeFrame* listed in **Table 4.4** were created to address the needs for describing more specific relations.

Table 4.4: Property hierarchies declared in ontology

Scenario 1: when the values of an object property involved multiple classes			
Object property hierarchy			
hasComponent |-*hasSingleComponent* |-*hasMultipleComponent* |-*hasTwoComponent* |-*hasThreeComponent* |-*hasFourComponent* |-*hasFiveComponent* |-*hasSixComponent* |-*hasSevenComponent*	*hasGeneticVariant* |-*hasSingleGeneticVariant* |-*hasMultipleGeneticVariant* |-*hasTwoGeneticVariant* |-*hasThreeGeneticVariant* |-*hasFourGeneticVariant* |-*hasFiveGeneticVariant* |-*hasSixGeneticVariant*	*hasGenotypeOI* |-*hasSingleGenotypeOI* |-*hasMultipleGenotypeOI* |-*hasTwoGenotypeOI* |-*hasThreeGenotypeOI* |-*hasFourGenotypeOI*	
Scenario 2: when a more specific relation is required			
Object property hierarchy			**Datatype property hierarchy**
hasDrugTherapy |- *hasDrugTherapyObserved* |- *hasDrugTherapyCompared* |- *hasDrugTherapyOI* |- *hasDrugTherapyRef*	*hasDose* |- *hasIDInmg* |- *hasLDInmg* |- *hasMDInmg*	*hasProcedure* |- *hasProcedureAll* |- *hasProcedureMajority* |- *hasProcedureMinority*	*hasTimeFrame* |- *hasTimeFrameInDays* |- *hasTimeFrameInHours*

- `SubPropertyChainOf` *axioms*

SubPropertyChainOf axioms allowed individuals to be automatically connected when they were linked by a chain of properties. As shown in **Figure 4.15**, given that an individual evidence is linked to an individual study via *isAcquiredFrom*, and an individual study is linked to an individual publication via *isReportedIn*, the *isExtractedFrom* property that linked an individual evidence to an individual publication was automatically inferred by defining a property chain of *isAcquiredFrom* o *isReportedIn* to be subsumed by the *isExtractedFrom* property. The advantage of this design is that, since multiple pieces of evidence are often extracted from one publication, rather than repeatedly asserting the *isExtractedFrom* relation between an individual piece of evidence and an individual publication, the inference that automatically generates this relationship reduces the burden of manual evidence annotation. Similarly, the following SubPropertyChainOf axiom: *isAcquiredFrom* o *hasROBA_Cochrane_RandomSequenceGeneration* ⊆ *hasROBA_Cochrane_RandomSequenceGeneration*, allowed a set of individual evidence to automatically have the assessed risk of bias value high, so that the labor-intensive evidence annotation process could be improved.

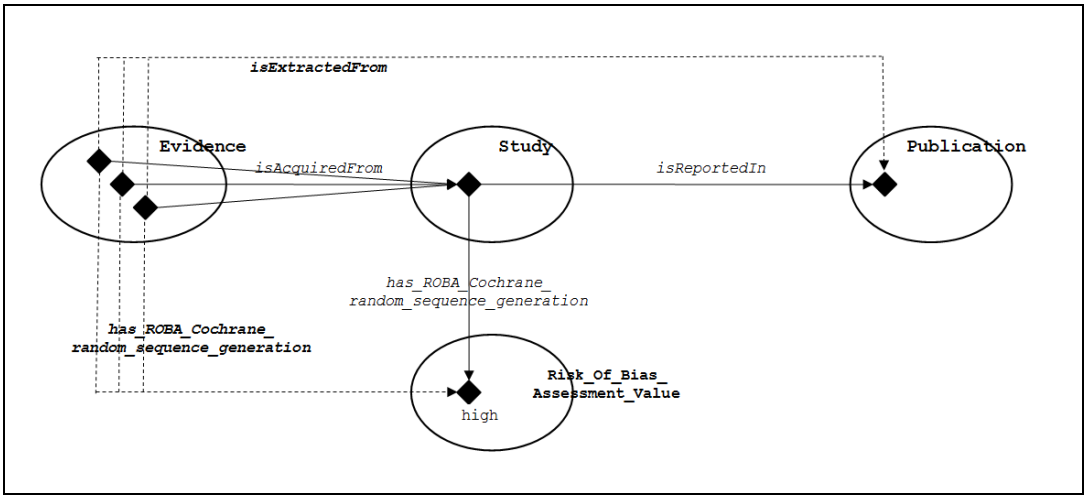

Figure 4.15: Illustration of the use of object property chains. The solid arrows indicate explicit property assertions. The dashed arrows indicate inferred property assertions.

4.4 Design of Representation Patterns for Formal Representation of Individual Information Entities

Once an OWL ontology (a.k.a. TBox) was developed, the next step is to assert each individual publication, study and evidence, that is, creating a knowledge base (a.k.a. ABox) using the OWL ontology [Nardi & Brachman, 2007]. The major consideration in asserting individual information entities is to faithfully reveal their intended meaning; meanwhile, formally represented individual information entities could be precisely differentiated from each other and efficiently retrieved based on various inclusion criteria. Specifically, it is important to avoid over or under representation of individual information entities because over representation of individual information entities may lead to computational inefficiency and under representation of individual information entities may lead to inaccurate or irrelevant retrieval. Based on this consideration, the general patterns in asserting individual information entities are presented first and some special representation patterns in describing heterogeneous information content such as genetic variation and outcome measure are presented next.

4.4.1 General patterns that represent individual information entities

Generally, individual information entities are formally represented through three types of assertions, i.e., class assertion, object property assertion, and datatype property assertion. As shown in **Table 4.5**, an individual publication (IE_p) is described by 2 class assertions, one specifies its information entity type and the other specifies its publication type; 1 object property assertion which specifies its PubMed ID; and 1 datatype property which specifies its publication year. An individual study (IE_s) is described by 4 class assertions, one specifies its information entity type and the other three specify its study population, study design and drug therapy; 1 object property assertion which specifies its related individual publication and at most 10 object

property assertions which specify the assessed risk of bias in study. An individual evidence (IE_e) is described by 5 class assertions, one specifies its information entity type and the other four specify its comparison, genetic variation, outcome and effect; 2 object property assertions, one specifies its related individual study and the other specifies the unit of effect size; and 5 datatype property assertions which specify the values of effect size, lower and upper 95% confidence interval, P-value and outcome measure time frame.

Table 4.5: General representation patterns for individual publications, studies and evidence

Information entity	General representation patterns and syntax	
Individual publication (IE_p)	Class assertion	$IE_p \in$ **Publication**
		$IE_p \in$ CE(Publication Type)
	Object property assertion	IE_p *hasPMID* I(**PMID**)
	Datatype property assertion	IE_p *hasPublicationYear* "value"^^xsd:integer
Individual study (IE_s)	Class assertion	$IE_p \in$ **Study**
		$IE_s \in$ CE(Study Population)
		$IE_s \in$ CE(Study Design)
		$IE_s \in$ CE(Drug Therapy)
	Object property assertion	IE_s *isReportedIn* IE_p
		IE_s *hasROBA_method_criterion** I(**RiskOfBiasAssessmentValue**)
	Datatype property assertion	None
Individual evidence (IE_e)	Class assertion	$IE_p \in$ **Evidence**
		$IE_e \in$ CE(Comparison)
		$IE_e \in$ CE(Genetic Variation)
		$IE_e \in$ CE(Outcome)
		$IE_e \in$ CE(Effect)
	Object property assertion	IE_e *isAcquiredFrom* IE_s
		IE_e *hasEffectSizeUnit* I(**Unit**)
	Datatype property assertion	IE_e *hasTimeFrame* "value"^^xsd:integer
		IE_e *hasEffectSize* "value"^^xsd:double
		IE_e *hasLower95PercentCI* "value"^^xsd:double
		IE_e *hasUpper95PercentCI* "value"^^xsd:double
		IE_e *hasPvalue* "value"^^xsd:double

Note: IE_p denotes individual publication, IE_s denotes individual study, IE_e denotes individual evidence. I( ) denotes instances of the class which is specified in the parentheses. CE( ) denotes class expressions which aim to describe the information component module specified in the parentheses. *has_ROBA_method_criterion** denotes 10 object properties that describe different assessment methods and criteria.

It is worth mentioning that two object property assertions, IE_e *isAcquiredFrom* IE_s and IE_s *isReportedIn* IE_p, are critical assertions that allow an OWL 2 DL reasoner to find implicit knowledge about an individual evidence. The former assertion describes the relation between an individual piece of evidence and an individual study. It allows inference of a group of individual evidence based on the features of the individual studies to which they are linked. For example, a class that is defined as **Evidence** and *isAcquiredFrom* some (**Study** and *hasStudyType* some **InterventionalStudy**) can retrieve all the individual evidence that was acquired from interventional studies even though the study type is not explicitly stated when asserting an individual piece of evidence. Similarly, since the latter assertion describes the relation between an individual study and an individual publication, and a property chain has been defined as *isAcquiredFrom* o *isReportedIn* ⊆ *isExtractedFrom*, the *isExtractedFrom* relation between an individual piece of evidence and an individual publication can be automatically inferred. That is to say, a class that is defined as **Evidence** and *is_extracted_from* some (**Publication** and *hasPubYear* some integer[>= 2010, <= 2010]) can retrieve all the individual pieces of evidence that was published in 2010 even though the publication year is not explicitly stated when asserting an individual evidence.

It is observed that object and datatype property assertion are relatively straightforward because both assertions only require a property to describe a binary relation between an individual and another individual or a binary relation between an individual and a data value. On the other hand, class assertion is more complicated because it often requires complex class expressions (CE) to describe an information component. The general patterns of complex class expressions concerning 8 information components are presented in **Table 4.6** and elaborated below.

Table 4.6: General representation patterns for information components

Information component	Representation pattern
Publication Type	*hasPublicationType* some **PublicationType**
Study Population	*hasStudyPopulation* some (**Patient** and (*hasIndicationByDrug* some **Drug**) and (*hasDisease* some (**Disease*** and (*hasDiseaseStatus* some **DiseaseStatus**))) and (*hasProcedure* some (**Procedure*** and (*hasProcedurDescriptor* some **ProcedureDescriptor**))) and (*hasRisk* some **Disease**))
Drug Therapy	*hasDrugTherapy* some (**DrugTherapy*** and *hasDrugTherapyStrategy* some (**DrugTherapyStrategy** and (*considersGeneticVariant* some **GeneticVariant***) and (*hasAlternativeDrugTherapy* some **DrugTherapy***) and (*hasDrugRegimen* some **DrugRegimen***) and (*monitorsPharmacodynamicsParameter* some **PharmacodynamicsParameter**)))
Study Design	*hasStudyType* some (**StudyType** and *hasStudyDesign* some (**StudyDesign** and (*hasAllocationScheme* some **AllocationScheme**) and (*hasTimePerspective* some **TimePerspective**)))
Comparison	*hasComparison* some (**Comparison** and (*hasStratificationInComparison* some **Thing**))
Genetic Variation	*hasGeneticContrast* some (**GeneticContrast** and *hasGeneticVariant some* **GeneticVariant***)
	hasGenotypeOI some (**Genotype*** and *hasGeneticVariant some* **GeneticVariant***)
Outcome	*hasOutcomeMeasure* some (**OutcomeMeasure** and (*hasComponent* some (**Disease/Adverse Event/Procedure/DrugDoseParameter/PharmacodynamicsParameter/PharmacokineticsParameter**)*,#) and (*isMeasuredAs* some **MeasurementType**))
Effect	*hasEffectMetric* some **EffectMetric**

Note: * denotes that either a single class or multiple classes can be used as property values. # denotes that any of the classes in the parentheses can be used as value of *hasComponent* property.

Generally, the patterns of representing information components follow the previously developed conceptual model of pharmacogenomics evidence assessment in Chapter 3, where each information component is composed of interrelated and layered relation-concept pairs. The representation of a relation-concept pair into a simple class expression follows a general form, that is, an object property is followed by an existential restriction constructor "some" as property constraint which is in turn followed by a class as property value. The simple class expression is then connected by set operator "and" to another class which is intended to be described by this class expression. For example, the following complex class expression **Patient** and (*hasDisease* some **CoronaryArteryDisease**) describes a group of patients who have some diseases and at least one of them is coronary artery disease. More class expressions can be added to describe the class **Patient**. For instance, **Patient** and (*hasDisease* some

CoronaryArteryDisease) and (*hasProcedure* some **PercutaneousCoronaryIntervention**) indicates a group of patients who have at least a disease that is coronary artery disease and have undergone at least a procedure that is percutaneous coronary intervention.

Another pattern that describes a group of objects is a nested class expression. In a nested class expression, a complex class expression is used as a property value. For example, in the following nested class expression, **ClopidogrelTherapy** and (*hasDrugTherapyStrategy* some (**GenotypeGuidedDrugSelection** and (*considersGeneticVariant* some **CYP2C19star2**))), the complex class expression underlined is the value of the *hasDrugTherapyStrategy* property. It describes a group of clopidogrel therapies that adopt at least a drug therapy strategy that is genotype guided drug selection and the adopted genotype guided drug selection strategy considers at least a genetic variant that is *CYP2C19*2*. **InterventionalStudy** and (*hasStudyDesign* some (**ParallelGroup** and (*hasAllocationScheme* some **Randomization**))) is another example of nested class expression. It describes a group of interventional studies that adopt at least a study design that is parallel group and this parallel group design has at least an allocation scheme that is randomization. Suppose that an individual entity is asserted to belong to the class **Study** and the three complex and anonymous classes mentioned above as well, it means that this particular individual study is a randomized and paralleled clinical trial that aims to investigate a genotype-guided clopidogrel therapy that considers CYP2C19*2 in drug selection for patients with coronary artery disease undergoing percutaneous coronary intervention.

While using a single class or a single complex class expression as object property value is generally applicable to describe some essential content of information components, it is found that the description of some specific content often involves multiple property values (See the classes marked with * in **Table 4.6**). For example, a study population enrolls patients with 2 different diseases (i.e., atrial fibrillation or pulmonary embolism), a genotype-guided warfarin

therapy considers 3 genetic variants (i.e., *CYP2C9*2*, *CYP2C9*3* and *VKORC1-1639G/A*) in warfarin dosing, and a composite outcome measure includes 3 categories of events (i.e., death, myocardial infarction or stroke). The proper use of constructors to address the representation issues in the context of using multiple classes as object property values is discussed next.

4.4.2 Special patterns that represent class expressions with multiple classes as property values

Two scenarios are used to address the representation issues when object property values involve multiple classes. The first scenario discusses the representation of a genotype-guided drug dosing strategy that may consider either a single genetic variant or multiple genetic variants in deciding drug dose. The second scenario discusses the representation of an outcome measure that may have either a single category of event or multiple categories events as the components of the outcome measure. The representation patterns designed to address these two scenarios differ in the operators (i.e., `and` or `or`) used to connect multiple class expressions, and consequently the logical consequences of the resulting compound class expressions are different. Since genetic variation and outcome measure are the most commonly used criteria for pharmacogenomics evidence retrieval, it deserves to explore how the design of representation patterns for genetic variation and outcome measure affects the precision of pharmacogenomics evidence retrieval.

4.4.2.1 Scenario 1: Representation issue with regard to heterogeneous genotype-guided drug dosing strategies

An increasing number of studies that investigated the effect of genotype-guided drug therapies on drug treatment outcomes have been published, and a great variety of genetic variants have been considered for drug dose adjustment or drug selection. For example, suppose that 4 different genetic variants (i.e., *CYP2C9*2*, *CYP2C9*3*, *VKORC1-1639G/A*, and

rs2108622C/T) are available to guide warfarin dosing, this 4-member set of genetic variant will form 15 possible genotype-guided dosing strategies (see **Table 4.7**).

Table 4.7: Overview of types of genotype-guided drug dosing strategies in scenario 1

Type of GD*	Intended meaning	Discriminating factors	
		Genetic variant considered simultaneously	
		No.	Category
GD_1	A group of individuals that have **one** *considers_genetic_variant* relation with individuals of **CYP2C9*2** class	1	CYP2C9*2
GD_2	A group of individuals that have **one** *considers_genetic_variant* relation with individuals of **CYP2C9*3** class	1	CYP2C9*3
GD_3	A group of individuals that have **one** *considers_genetic_variant* relation with individuals of **VKORC1-1639G/A** class	1	VKORC1-1639G/A
GD_4	A group of individuals that have **one** *considers_genetic_variant* relation with individuals of **rs2108622C/T** class	1	rs2108622C/T
GD_5	A group of individuals that have **two** *considers_genetic_variant* relations, one with individuals of **CYP2C9*2** class and one with individuals of **CYP2C9*3** class	2	CYP2C9*2, CYP2C9*3
GD_6	A group of individuals that have **two** *considers_genetic_variant* relations, one with individuals of **CYP2C9*2** class and one with individuals of **VKORC1-1639G/A** class	2	CYP2C9*2, VKORC1-1639G/A
GD_7	A group of individuals that have **two** *considers_genetic_variant* relations, one with individuals of **CYP2C9*2** class and one with individuals of **rs2108622C/T** class	2	CYP2C9*2, rs2108622C/T
GD_8	A group of individuals that have **two** *considers_genetic_variant* relations, one with individuals of **CYP2C9*3** class and one with individuals of **VKORC1-1639G/A** class	2	CYP2C9*3, VKORC1-1639G/A
GD_9	A group of individuals that have **two** *considers_genetic_variant* relations, one with individuals of **CYP2C9*3** class and one with individuals of **rs2108622C/T** class	2	CYP2C9*3, rs2108622C/T
GD_10	A group of individuals that have **two** *considers_genetic_variant* relations, one with individuals of **VKORC1-1639G/A** class and one with individuals of **rs2108622C/T** class	2	VKORC1-1639G/A, rs2108622C/T
GD_11	A group of individuals that have **three** *considers_genetic_variant* relations, one with individuals of **CYP2C9*2** class, one with individuals of **CYP2C9*3** class and one with individuals of **VKORC1-1639G/A** class	3	CYP2C9*2, CYP2C9*3, VKORC1-1639G/A
GD_12	A group of individuals that have **three** *considers_genetic_variant* relations, one with individuals of **CYP2C9*2** class, one with individuals of **CYP2C9*3** class and one with individuals of **rs2108622C/T** class	3	CYP2C9*2, CYP2C9*3, rs2108622C/T
GD_13	A group of individuals that have **three** *considers_genetic_variant* relations, one with individuals of **CYP2C9*2** class, one with individuals of **VKORC1-1639G/A** class and one with individuals of **rs2108622C/T** class	3	CYP2C9*2, VKORC1-1639G/A, rs2108622C/T
GD_14	A group of individuals that have **three** *considers_genetic_variant* relations, one with individuals of **CYP2C9*3** class, one with individuals of **VKORC1-1639G/A** class and one with individuals of **rs2108622C/T** class	3	CYP2C9*3, VKORC1-1639G/A, rs2108622C/T
GD_15	A group of individuals that have **four** *considers_genetic_variant* relations, one with individuals of **CYP2C9*2** class, one with individuals of **CYP2C9*3** class, one with individuals of **VKORC1-1639G/A** class and one with individuals of **rs2108622C/T** class	4	CYP2C9*2, CYP2C9*3, VKORC1-1639G/A, rs2108622C/T

*GD denotes genotype-guided dosing strategies which are described by genetic variants considered in medication decision making. A total of 15 types of genotype-guided drug dosing strategies are possible when 4 different genetic variants are available for consideration in medication decision making.

As shown in **Table 4.7**, 15 possible genotype-guided dosing strategies (coded as GD_1 to GD_15, where GD denotes genotype-guided dosing) differ in the number and category of genetic variants they considered. For better understanding of the scenario, four different genotype-guided dosing strategies, GD_1, GD_5, GD_11 and GD_15, that consider the following genetic variants (*CYP2C9*2*), (*CYP2C9*2* and *CYP2C9*3*), (*CYP2C9*2* and *CYP2C9*3* and *VKORC1-1639G/A*) and (*CYP2C9*2* and *CYP2C9*3* and *VKORC1-1639G/A* and *rs2108622C/T*) respectively, are selected and illustrated in **Figure 4.16** for further discussion.

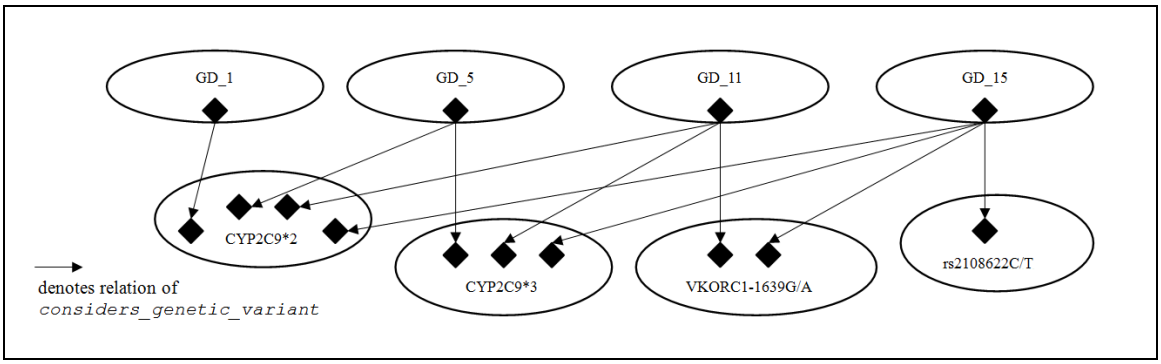

Figure 4.16: Graphic presentation of selected types of genotype-guided drug dosing strategies in scenario 1. GD_1, GD_5, GD_11 and GD_15 are classes that represent types of genotype-guided drug dosing strategies that consider 1, 2, 3 and 4 genetic variant(s) respectively. The arrows denote object property `considersGeneticVariant`, which links classes of genotype-guided drug dosing strategies to classes of genetic variants based on which specific variant(s) is considered in medication decision making.

The major consideration in representing heterogeneous genotype guided drug dosing strategies is to faithfully reveal their meaning so that they can be differentiated from each other and classified by different levels of specificity as well. Four representation patterns are designed to describe heterogeneous genotype-guided dosing strategies (i.e., **`GD_1`**, **`GD_5`**, **`GD_11`** and **`GD_15`**). Each representation pattern that adopts different OWL 2 DL constructors to form class expressions is summarized in **Table 4.8**.

Table 4.8: Formal representation of types of genotype-guided drug dosing strategy in scenario 1

Ontology			
Class		Object Property	
Thing |-**GeneticVariant** |- **VariantInCYP2C9** |- **CYP2C9*2** |- **CYP2C9*3** |- **VariantInVKORC1** |- **VKORC1-1639G/A** |- **VariantInCYP4F2** |- **rs2108622-C/T**		*considersGeneticVariant* |- *considers_1_variant* |- *considers_multiple_variant* |- *considers_2_variant* |- *considers_3_variant* |- *considers_4_variant*	
Pattern for Formal Representation			
Constructors	Type of GD	Syntax for class expression	Logical consequence
Existential restriction	GD_1	(*considers_genetic_variant* some **CYP2C9*2**)	GD_15 ⊆ GD_11 ⊆ GD_5 ⊆ GD_1
	GD_5	(*considers_genetic_variant* some **CYP2C9*2**) and (*considers_genetic_variant* some **CYP2C9*3**)	
	GD_11	(*considers_genetic_variant* some **CYP2C9*2**) and (*considers_genetic_variant* some **CYP2C9*3**) and (*considers_genetic_variant* some **VKORC1-1639G/A**)	
	GD_15	(*considers_genetic_variant* some **CYP2C9*2**) and (*considers_genetic_variant* some **CYP2C9*3**) and (*considers_genetic_variant* some **VKORC1-1639G/A**) and (*considers_genetic_variant* some **rs2108622-C/T**)	
Existential restriction + Subproperty	GD_1	(*considers_1_genetic_variant* some **CYP2C9*2**)	GD_1 ∩ GD_5 = Ø GD_1 ∩ GD_11 = Ø GD_1 ∩ GD_15 = Ø GD_5 ∩ GD_11 = Ø GD_5 ∩ GD_15 = Ø GD_11 ∩ GD_15 = Ø
	GD_5	(*considers_2_genetic_variant* some **CYP2C9*2**) and (*considers_2_genetic_variant* some **CYP2C9*3**)	
	GD_11	(*considers_3_genetic_variant* some **CYP2C9*2**) and (*considers_3_genetic_variant* some **CYP2C9*3**) and (*considers_3_genetic_variant* some **VKORC1-1639G/A**)	
	GD_15	(*considers_4_genetic_variant* some **CYP2C9*2**) and (*considers_4_genetic_variant* some **CYP2C9*3**) and (*considers_4_genetic_variant* some **VKORC1-1639G/A**) and (*considers_4_genetic_variant* some **rs2108622-C/T**)	
Qualified cardinality restriction	GD_1	(*considers_genetic_variant* exactly 1 **CYP2C9*2**)	GD_15 ⊆ GD_11 ⊆ GD_5 ⊆ GD_1
	GD_5	(*considers_genetic_variant* exactly 1 **CYP2C9*2**) and (*considers_genetic_variant* exactly 1 **CYP2C9*3**)	
	GD_11	(*considers_genetic_variant* exactly 1 **CYP2C9*2**) and (*considers_genetic_variant* exactly 1 **CYP2C9*3**) and (*considers_genetic_variant* exactly 1 **VKORC1-1639G/A**)	
	GD_15	(*considers_genetic_variant* exactly 1 **CYP2C9*2**) and (*considers_genetic_variant* exactly 1 **CYP2C9*3**) and (*considers_genetic_variant* exactly 1 **VKORC1-1639G/A**) and (*considers_genetic_variant* exactly 1 **rs2108622-C/T**)	
Refined Qualified cardinality restriction	GD_1	(*considers_genetic_variant* exactly 1 **GeneticVariant**) and (*considers_genetic_variant* exactly 1 **CYP2C9*2**)	GD_1 ∩ GD_5 = Ø GD_1 ∩ GD_11 = Ø GD_1 ∩ GD_15 = Ø GD_5 ∩ GD_11 = Ø GD_5 ∩ GD_15 = Ø GD_11 ∩ GD_15 = Ø
	GD_5	(*considers_genetic_variant* exactly 2 **GeneticVariant**) and (*considers_genetic_variant* exactly 1 **CYP2C9*2**) and (*considers_genetic_variant* exactly 1 **CYP2C9*3**)	
	GD_11	(*considers_genetic_variant* exactly 3 **GeneticVariant**) and (*considers_genetic_variant* exactly 1 **CYP2C9*2**) and (*considers_genetic_variant* exactly 1 **CYP2C9*3**) and (*considers_genetic_variant* exactly 1 **VKORC1-1639G/A**)	
	GD_15	(*considers_genetic_variant* exactly 4 **GeneticVariant**) and (*considers_genetic_variant* exactly 1 **CYP2C9*2**) and (*considers_genetic_variant* exactly 1 **CYP2C9*3**) and (*considers_genetic_variant* exactly 1 **VKORC1-1639G/A**) and (*considers_genetic_variant* exactly 1 **rs2108622-C/T**)	

*GD denotes types of genotype-guided dosing strategies defined in Table 4.7.

⊆ denotes subclass of relationship, Ø denotes empty set

The logical consequences of using different representation patterns to represent different genotype guided dosing strategies are also presented in **Table 4.8** to examine whether the designed patterns satisfy the above mentioned requirements.

- *Representation pattern 1: existential restriction connected by "*and*"*

The class expression (*considers_genetic_variant* some **CYP2C9*2**) simply indicates that a group of genotype-guided dosing strategies consider some genetic variants and at least one of them is CYP2C9*2. In more natural language, the conjunction of two class expressions (*considers_genetic_variant* some **CYP2C9*2**) and (*considers_genetic_variant* some **CYP2C9*3**) could be interpreted as considering some genetic variants, at least one is CYP2C9*2 and at least one is CYP2C9*3. Although the use of existential restriction more or less expresses the meanings of heterogeneous genotype-guided dosing strategies, its ability to differentiate heterogeneous genotype-guided dosing strategies is insufficient**.** As shown in **Table 4.8**, instead of the expected inference of four mutually disjoint classes, an inferred class hierarchy (**GD_15** ⊆ **GD_11** ⊆ **GD_5** ⊆ **GD_1**) is the logical consequence of using existential restriction class expressions connected by "and" to represent heterogeneous genotype-guided dosing strategies. The inferred class hierarchy indicates that these four classes have something in common.

- *Representation pattern 2: existential restriction with subproperties connected by "*and*"*

In order to differentiate heterogeneous genotype-guided dosing strategies, subproperties of *considers_genetic_variant* are additionally created to denote the numbers of variants that are considered in a genotype-guided dosing strategy. For example, the subproperty *considers_2_genetic_variant* means that 2 genetic variants are considered in a dosing strategy. The conjunction of two class expressions (*considers_2_genetic_variant* some

CYP2C9*2) and (*considers_2_genetic_variant* some **CYP2C9*3**) formally describes a group of genotype-guided dosing strategies that have at least one *considers_2_genetic_variant* relation to individuals of the class **CYP2C9*2**; and meanwhile, have at least one *considers_2_genetic_variant* relation to individuals of the class **CYP2C9*3**. In more natural language, it could be interpreted as considering 2 genetic variants, at least one is CYP2C9*2 and at least one is CYP2C9*3. The use of existential restriction with subproperty is sufficient for proper differentiation of heterogeneous genotype guided dosing strategies. As shown in **Table 4.8**, four different classes of genotype-guided dosing strategies are inferred as mutually disjoint classes rather than a class hierarchy.

- *Representation pattern 3: qualified cardinality restriction connected by "*and*"*

The class expression (*considers_genetic_variant* exactly 1 **CYP2C9*2**) adopts qualified cardinality restriction constructor "exactly 1" to formally describe a class of which every individual has exactly one *considers_genetic_variant* relation to an instance of the class **CYP2C9*2.** That is to say, it could be precisely interpreted as considering exactly 1 genetic variant that is CYP2C9*2. Although the use of qualified cardinality restriction is able to precisely describe the meanings of heterogeneous genotype-guided dosing strategies, its ability to differentiate heterogeneous genotype-guided dosing strategies is still insufficient. As shown in **Table 4.8**, subsumption relations exist between four different classes of genotype-guided dosing strategies. They are classified into a class hierarchy rather than mutually disjoint classes.

- *Representation pattern 4: refined qualified cardinality restriction connected by "*and*"*

In order to differentiate heterogeneous genotype-guided dosing strategies represented using qualified cardinality restriction, an additional class expression is added to specify the total

number of *considers_genetic_variant* relations involved in a genotype-guided dosing strategy. For example, the following conjunction of three class expressions, (*considers_genetic_variant* exactly 2 **GeneticVariant**) and (*considers_genetic_variant* exactly 1 **CYP2C9*2**) and (*considers_genetic_variant* exactly 1 **CYP2C9*3**), includes a class expression that specifies exactly two *considers_genetic_variant* relations involved in **GD_5**. It could be precisely interpreted as considering exactly two genetic variants that are CYP2C9*2 and CYP2C9*3. The logical consequence of the refined qualified cardinality restriction shown in **Table 4.8** indicates that its ability to differentiate heterogeneous genotype guided dosing strategies is sufficient.

In order to further explore the logical consequences of four different representation patterns, seven classification schemes (coded as **GD_CS_1** to **GD_CS_7**, where **CS** denotes classification scheme) corresponding to commonly used inclusion criteria for systematic review with meta-analysis are designed to classify heterogeneous genotype-guided dosing strategies regarding **GD_1** to **GD_15**. The purpose of each classification scheme and its expected classification results are summarized in **Table 4.9**. In general, classification schemes aim to test whether various genotype-guided dosing strategies can be classified by different constraints (i.e., any of, any single of, any multiple of, at least one of, at least two of, at most 3 of, and at least 2 and at most 3 of) on values (i.e., Genetic Variant) of the property of interest (i.e., *consider_genetic_variant*).

Table 4.9: Classification schemes of genotype-guided drug dosing strategies in scenario 1

Classification Scheme	Intended meaning	Expected results
GD_CS_1	Genotype-guided dosing strategies that considers any genetic variant (**CYP2C9*2** or **CYP2C9*3** or **VKORC1-1639G/A** or **rs2108622-C/T**)	GD_1 to GD_15
GD_CS_2	Genotype-guided dosing strategies that considers any single genetic variant (**CYP2C9*2** or **CYP2C9*3** or **VKORC1-1639G/A** or **rs2108622-C/T**)	GD_1 to GD_4
GD_CS_3	Genotype-guided dosing strategies that considers any multiple genetic variants (**CYP2C9*2** or **CYP2C9*3** or **VKORC1-1639G/A** or **rs2108622-C/T**)	GD_5 to GD_15
GD_CS_4	Genotype-guided dosing strategies that considers at least 1 genetic variant (**CYP2C9*2**)	GD_1, GD_5, GD_6, GD_7, GD_11, GD_12, GD_13, GD_15
GD_CS_5	Genotype-guided dosing strategies that considers at least 2 genetic variant (**CYP2C9*2** and **CYP2C9*3**)	GD_5, GD_11, GD_12, GD_15
GD_CS_6	Genotype-guided dosing strategies that considers at most 3 genetic variants (**CYP2C9*2** or **CYP2C9*3** or **VKORC1-1639G/A**)	GD_1, GD_2, GD_3, GD_5, GD_6, GD_8, GD_11
GD_CS_7	Genotype-guided dosing strategies that considers at least 2 and at most 3 genetic variants (**CYP2C9*2** or **CYP2C9*3** or **VKORC1-1639G/A**)	GD_5, GD_6, GD_8, GD_11

How the four above mentioned representation patterns are used to formally represent seven classification schemes are presented in **Table 4.10**. Given the limited expressivity of existential restriction and qualified cardinality restriction, only 3 classification schemes are expressible by these two expression patterns, which means, their capability of retrieving genotype-guided dosing strategies is limited to broad criteria that consider "any" or "at least" of some specified genetic variants. On the other hand, all of the seven classification schemes are expressible by either the existential restriction with subproperty or the refined qualified cardinality restriction.

Table 4.10: Formal representation of classification schemes of genotype-guided drug dosing strategies in scenario 1

Constructor	Classification Scheme	Formal representation of classification scheme
Existential restriction	GD_CS_1	(*considers_genetic_variant* some (**CYP2C9*2** or **CYP2C9*3** or **VKORC1-1639G/A** or **rs2108622-C/T**))
	GD_CS_2	not expressible
	GD_CS_3	not expressible
	GD_CS_4	(*considers_genetic_variant* some **CYP2C9*2**)
	GD_CS_5	(*considers_genetic_variant* some **CYP2C9*2**) and (*considers_genetic_variant* some **CYP2C9*3**)
	GD_CS_6	not expressible
	GD_CS_7	not expressible
Existential restriction with subproperty	GD_CS_1	(*considers_genetic_variant* some (**CYP2C9*2** or **CYP2C9*3** or **VKORC1-1639G/A** or **rs2108622-C/T**))
	GD_CS_2	(*considers_1_genetic_variant* some (**CYP2C9*2** or **CYP2C9*3** or **VKORC1-1639G/A** or **rs2108622-C/T**))
	GD_CS_3	(*considers_multiple_genetic_variant* some (**CYP2C9*2** or **CYP2C9*3** or **VKORC1-1639G/A** or **rs2108622-C/T**))
	GD_CS_4	(*considers_genetic_variant* some **CYP2C9*2**)
	GD_CS_5	(*considers_multiple_genetic_variant* some **CYP2C9*2**) and (*considers_multiple_genetic_variant* some **CYP2C9*3**)
	GD_CS_6	(*considers_1_genetic_variant* some (**CYP2C9*2** or **CYP2C9*3** or **VKORC1-1639G/A**)) or ((*considers_2_genetic_variant* some **CYP2C9*2**) and (*considers_2_genetic_variant* some **CYP2C9*3**)) or ((*considers_2_genetic_variant* some **CYP2C9*2**) and (*considers_2_genetic_variant* some **VKORC1-1639G/A**)) or ((*considers_2_genetic_variant* some **CYP2C9*3**) and (*considers_2_genetic_variant* some **VKORC1-1639G/A**)) or ((*considers_3_genetic_variant* some **CYP2C9*2**) and (*considers_3_genetic_variant* some **CYP2C9*3**) and (*considers_3_genetic_variant* some **VKORC1-1639G/A**))
	GD_CS_7	((*considers_2_genetic_variant* some **CYP2C9*2**) and (*considers_2_genetic_variant* some **CYP2C9*3**)) or ((*considers_2_genetic_variant* some **CYP2C9*2**) and (*considers_2_genetic_variant* some **VKORC1-1639G/A**)) or ((*considers_2_genetic_variant* some **CYP2C9*3**) and (*considers_2_genetic_variant* some **VKORC1-1639G/A**)) or ((*considers_3_genetic_variant* some **CYP2C9*2**) and (*considers_3_genetic_variant* some **CYP2C9*3**) and (*considers_3_genetic_variant* some **VKORC1-1639G/A**))
Qualified cardinality restriction	GD_CS_1	*considers_genetic_variant* some (**CYP2C9*2** or **CYP2C9*3** or **VKORC1-1639G/A** or **rs2108622-C/T**)
	GD_CS_2	not expressible
	GD_CS_3	not expressible
	GD_CS_4	(*considers_genetic_variant* some **CYP2C9*2**)
	GD_CS_5	(*considers_genetic_variant* some **CYP2C9*2**) and (*considers_genetic_variant* some **CYP2C9*3**)
	GD_CS_6	not expressible
	GD_CS_7	not expressible

Table 10 (Continued): Formal representation of classification schemes of genotype-guided drug dosing strategies in scenario 1

Constructor	Classification Scheme	Formal representation of classification scheme
Refined qualified cardinality restriction	GD_CS_1	*considers_genetic_variant* some (**CYP2C9*2** or **CYP2C9*3** or **VKORC1-1639G/A** or **rs2108622-C/T**)
	GD_CS_2	(*considers_genetic_variant* exactly 1 **GeneticVariant**) and (*considers_genetic_variant* exactly 1 (**CYP2C9*2** or **CYP2C9*3** or **VKORC1-1639G/A** or **rs2108622-C/T**))
	GD_CS_3	(*considers_genetic_variant* min 2 **GeneticVariant**) and (*considers_genetic_variant* some (**CYP2C9*2** or **CYP2C9*3** or **VKORC1-1639G/A** or **rs2108622-C/T**))
	GD_CS_4	*considers_genetic_variant* some **CYP2C9*2**
	GD_CS_5	(*considers_genetic_variant* some **CYP2C9*2**) and (*considers_genetic_variant* some **CYP2C9*3**)
	GD_CS_6	((*considers_genetic_variant* exactly 1 **GeneticVariant**) and (*considers_genetic_variant* exactly 1 (**CYP2C9*2** or **CYP2C9*3** or **VKORC1-1639G/A**))) or ((*considers_genetic_variant* exactly 2 **GeneticVariant**) and (*considers_genetic_variant* exactly 1 **CYP2C9*2**) and (*considers_genetic_variant* exactly 1 **CYP2C9*3**)) or ((*considers_genetic_variant* exactly 2 **GeneticVariant**) and (*considers_genetic_variant* exactly 1 **CYP2C9*2**) and (*considers_genetic_variant* exactly 1 **VKORC1-1639G/A**)) or ((*considers_genetic_variant* exactly 2 **GeneticVariant**) and (*considers_genetic_variant* exactly 1 **CYP2C9*3**) and (*considers_genetic_variant* exactly 1 **VKORC1-1639G/A**)) or ((*considers_genetic_variant* exactly 3 **GeneticVariant**) and (*considers_genetic_variant* exactly 1 **CYP2C9*2**) and (*considers_genetic_variant* exactly 1 **CYP2C9*3**) and (*considers_genetic_variant* exactly 1 **VKORC1-1639G/A**))
	GD_CS_7	((*considers_genetic_variant* exactly 2 **GeneticVariant**) and (*considers_genetic_variant* exactly 1 **CYP2C9*2**) and (*considers_genetic_variant* exactly 1 **CYP2C9*3**)) or ((*considers_genetic_variant* exactly 2 **GeneticVariant**) and (*considers_genetic_variant* exactly 1 **CYP2C9*2**) and (*considers_genetic_variant* exactly 1 **VKORC1-1639G/A**)) or ((*considers_genetic_variant* exactly 2 **GeneticVariant**) and (*considers_genetic_variant* exactly 1 **CYP2C9*3**) and (*considers_genetic_variant* exactly 1 **VKORC1-1639G/A**)) or ((*considers_genetic_variant* exactly 3 **GeneticVariant**) and (*considers_genetic_variant* exactly 1 **CYP2C9*2**) and (*considers_genetic_variant* exactly 1 **CYP2C9*3**) and (*considers_genetic_variant* exactly 1 **VKORC1-1639G/A**))

In summary, genotype-guided dosing strategies are heterogeneous because multiple genetic variants are commonly used together to guide drug therapy. Four representation patterns were designed to represent heterogeneous genotype-guided dosing strategies. Different representation patterns adopt different constructs and constructors of OWL 2 DL including: existential restriction constructor "some", subproperties (such as *considers_2_genetic_variant*) that denote the numbers of variants considered in dosing strategy, qualified cardinality restriction constructor "exactly", and additional class expression that denotes the total number of *considers_genetic_variant* relations involved in describing a dosing strategy. An overview

of the expressivity of the 4 representation patterns is summarized in **Table 4.11**. Though existential restriction and qualified cardinality restriction are limited in their ability to differentiate, they are easy to use and sufficient to infer subsumption relations between classes. That is to say, they are suitable for application scenarios that focus on inferring subsumption relations between classes of ontologies. On the other hand, the existential restriction with subproperty and the refined qualified cardinality restriction are capable of representing, differentiating and classifying heterogeneous information content. But they have disadvantage in representing the classification schemes with the intended meaning of "at most" (i.e., GD_CS_6 and GD_CS_7), since the syntax of the representation is somewhat cumbersome for a user.

Table 4.11: Overview of the expressivity of 4 representation patterns in the scenario of the formal representation of genotype-guided drug dosing strategies

Expressivity	Existential restriction	Existential restriction with subproperty	Qualified cardinality restriction	Refined qualified cardinality restriction
Differentiating ability	×	○	×	○
Multiplicity of classification				
GD_CS_1	○	○	○	○
GD_CS_2	×	○	×	○
GD_CS_3	×	○	×	○
GD_CS_4	○	○	○	○
GD_CS_5	○	○	○	○
GD_CS_6	×	Δ	×	Δ
GD_CS_7	×	Δ	×	Δ

×: insufficient, ○: sufficient, Δ: cumbersome

4.4.2.2 Scenario 2: Representation issue with regard to heterogeneous outcome measures

Scenario 2 differs from scenario 1 in that the "`or`" operators, rather than the "`and`" operator, is used to connect multiple class expressions that represent multiple values of a property of interest.

In this scenario, the property of interest is *hasComponent*. Various classes, such as **Disease**, **AdverseEvents**, **Procedures**, etc., are used as value(s) of the property to indicate the component(s) of an outcome measure. Composite outcomes are commonly used in cardiovascular studies and they usually comprise 3 to 4 categories of events [Lim, Brown, Helmy, Mussa, & Altman, 2008]. Suppose that 4 different event categories (i.e., death, myocardial infarction, stroke, and revascularization) are available for measuring an outcome, the combinations of 4 event categories will form 15 possible types of outcome measures. However, the representation issue in the outcome measure scenario is more complicated than in the genotype-guided drug therapy scenario. It is complicated because an event category usually contains several subcategories which imply different levels of specificity. For example, death contains subcategories such as cardiovascular death and death of all causes, stent thrombosis contains subcategories such as definite stent thrombosis and probable stent thrombosis, and these subcategories are frequently used as components of an outcome measure as well. Here, for simplicity, only 15 possible outcome measures that have components including death, cardiovascular death, myocardial infarction, stroke or stent thrombosis are selected for further discussion. As shown in **Table 4.12**, 15 possible outcome measures (coded as **OM_1** to **OM_15**, where **OM** denotes outcome measure) differ in the number and category of event(s) they measured.

Table 4.12: Overview of types of outcome measures in scenario 2

Type of OM*	Intended meaning	Discriminating factors	
		Outcome measure component	
		No.	Category
OM_1	A group of individuals that have one *has_component* relation with individuals of **CardiovascularDeath** class	1	Cardiovascular Death
OM_2	A group of individuals that have one *has_component* relation with individuals of **MyocardialInfarction** class	1	Myocardial Infarction
OM_3	A group of individuals that have one *has_component* relation with individuals of **Stroke** class	1	Stroke
OM_4	A group of individuals that have one *has_component* relation with individuals of **StentThrombosis** class	1	Stent Thrombosis
OM_5	Union of two groups, individuals of one group have one *has_component* relation with individuals of **CardiovascularDeath** class, and individuals of the other group have one *has_component* relation with individuals of **MyocardialInfarction** class	2	Cardiovascular Death, Myocardial Infarction
OM_6	Union of two groups, individuals of one group have one *has_component* relation with individuals of **Death** class, and individuals of the other group have one *has_component* relation with individuals of **Stroke** class	2	Death, Stroke
OM_7	Union of two groups, individuals of one group have one *has_component* relation with individuals of **Death** class, and individuals of the other group have one *has_component* relation with individuals of **StentThrombosis** class	2	Death, Stent Thrombosis
OM_8	Union of two groups, individuals of one group have one *has_component* relation with individuals of **MyocardialInfarction** class, and individuals of the other group have one *has_component* relation with individuals of **Stroke** class	2	Myocardial Infarction, Stroke
OM_9	Union of two groups, individuals of one group have one *has_component* relation with individuals of **MyocardialInfarction** class, and individuals of the other group have one *has_component* relation with individuals of **StentThrombosis** class	2	Myocardial Infarction, Stent Thrombosis
OM_10	Union of two groups, individuals of one group have one *has_component* relation with individuals of **Stroke** class, and individuals of the other group have one *has_component* relation with individuals of **StentThrombosis** class	2	Stroke, Stent Thrombosis
OM_11	Union of three groups, individuals of one group have one *has_component* relation with individuals of **Death** class, and individuals of one group have one *has_component* relation with individuals of **MyocardialInfarction** class, and individual of the remaining group have one *has_component* relation with individuals of **Stroke** class	3	Death, Myocardial Infarction, Stroke
OM_12	Union of three groups, individuals of one group have one *has_component* relation with individuals of **Death** class, individuals of one group have one *has_component* relation with individuals of **MyocardialInfarction** class, and individual of the remaining group have one *has_component* relation with individuals of **StentThrombosis** class	3	Death, Myocardial Infarction, Stent Thrombosis
OM_13	Union of three groups, individuals of one group have one *has_component* relation with individuals of **Death** class, individuals of one group have one *has_component* relation with individuals of **Stroke** class, and individual of the remaining group have one *has_component* relation with individuals of **StentThrombosis** class	3	Death, Stroke, Stent Thrombosis
OM_14	Union of three groups, individuals of one group have one *has_component* relation with individuals of **MyocardialInfarction** class, individuals of one group have one *has_component* relation with individuals of **Stroke** class, and individual of the remaining group have one *has_component* relation with individuals of **StentThrombosis** class	3	Myocardial Infarction, Stroke, Stent Thrombosis
OM_15	Union of four groups, individuals of one group have one *has_component* relation with individuals of **Death** class, individuals of one group have one *has_component* relation with individuals of **MyocardialInfarction** class, individuals of one group have one *has_component* relation with individuals of **Stroke** class, and individual of the remaining group have one *has_component* relation with individuals of **StentThrombosis** class	4	Death, Myocardial Infarction, Stroke, Stent Thrombosis

*OM denotes outcome measures which are described by categories of event included as the components of the outcome measure. A total of 15 types of outcome measures are selected in scenario 2, with 5 different categories of events available for consideration.

To better understand the meaning of outcome measure component, **Figure 4.17** illustrates four selected outcome measures, i.e., **OM_1**, **OM_5**, **OM_11** and **OM_15**. Take **OM_11** as an example, its formal semantics is the union of 3 groups of individuals, one group of individuals having one *hasComponent* relation with individuals of the **Death** class, one group of individuals having one *hasComponent* relation with individuals of the **MyocardialInfarction** class and the remaining group of individuals having one *hasComponent* relation with individuals of the **stroke** class. That is to say, a total of 3 *hasComponent* properties are involved in describing **OM_11**, and each *hasComponent* property has a different event category as its value. Thus, heterogeneous outcome measures could only be differentiated from each other by the total number of *hasComponent* relations and the event category involved in describing outcome measure components.

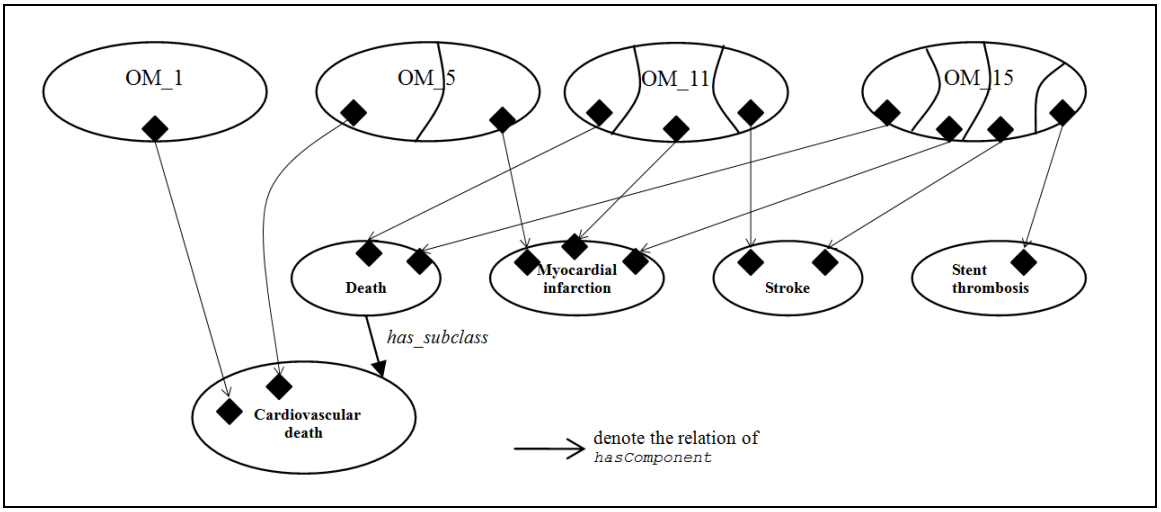

Figure 4.17: Illustration of selected types of outcome measures in scenario 2. OM_1, OM_5, OM_11 and OM_15 are classes that represent types of outcome measures that have 1, 2, 3, and 4 categories of event(s) respectively. The arrows denote object property *hasComponent*, which links classes of outcome measure to classes of adverse event based on which specific event(s) is considered in outcome measure.

Three representation patterns are designed to express heterogeneous outcome measures. The representation patterns of existential restriction, existential restriction with subproperties, and qualified cardinality restriction are summarized in **Table 4.13**. The refined qualified cardinality restriction pattern is not discussed in this scenario because of its cumbersome syntax.

Table 4.13: Formal representation of types of outcome measures in scenario 2

Ontology			
Class		Object Property	
Death **|- CardiovascularDeath** **MyocardialInfarction** **Stroke** **StentThrombosis**		*hasComponent* |- *has_1_Component* |- *has_Multiple_Component* |- *has_2_Component* |- *has_3_Component* |- *has_4_Component*	
Pattern for Formal Representation			
Constructor	Type of OM*	Syntax of class expression	Logical Consequence
Existential restriction	OM_1	(*hasComponent* some **CardiovascularDeath**)	OM_1 ⊆ OM_5 ⊆ OM_11 ⊆ OM_15
	OM_5	(*hasComponent* some (**CardiovascularDeath** or **MyocardialInfarction**))	
	OM_11	(*hasComponent* some (**Death** or **MyocardialInfarction** or **Stroke**))	
	OM_15	(*hasComponent* some (**Death** or **MyocardialInfarction** or **Stroke** or ST))	
Existential restriction with subproperty	OM_1	(*has_1_Component* some **CardiovascularDeath**)	OM_1 ∩ OM_5 = Ø OM_1 ∩ OM_11 = Ø OM_1 ∩ OM_15 = Ø OM_5 ∩ OM_11 = Ø OM_5 ∩ OM_15 = Ø OM_11 ∩ OM_15 = Ø
	OM_5	(*has_2_Component* some (**CardiovascularDeath** or **MyocardialInfarction**))	
	OM_11	(*has_3_Component* some (**Death** or **MyocardialInfarction** or **Stroke**))	
	OM_15	(*has_4_Component* some (**Death** or **MyocardialInfarction** or **Stroke** or **StentThrombosis**))	
Qualified cardinality restriction	OM_1	(*hasComponent* exactly 1 **CardiovascularDeath**)	OM_1 ⊆ OM_5 ⊆ OM_11 ⊆ OM_15
	OM_5	(*hasComponent* exactly 1 **CardiovascularDeath**) or (*hasComponent* exactly 1 **MyocardialInfarction**)	
	OM_11	(*hasComponent* exactly 1 **Death**) or (*hasComponent* exactly 1 **MyocardialInfarction**) or (*hasComponent* exactly 1 **Stroke**)	
	OM_15	(*hasComponent* exactly 1 **Death**) or (*hasComponent* exactly 1 **MyocardialInfarction**) or (*hasComponent* exactly 1 **Stroke**) or (*hasComponent* exactly 1 **StentThrombosis**)	

*OM denotes types of outcome measures defined in Table 10. ⊆ denotes subclass of relationship. Ø denotes empty set.

- *Representation pattern 5: existential restriction connected by "*`or`*"*

Since a composite outcome could be viewed as a union of multiple groups of individuals, the formal representation of a composite outcome measure is comprised of multiple class expressions which are connected by the operator "`or`". Take **`OM_5`** as an example, it could be described by the union of two class expressions (*`hasComponent`* `some` **`CardiovascularDeath`**) `or` (*`hasComponent`* `some` **`MyocardialInfarction`**). Therefore, it could be interpreted as having some outcome measure components, at least one is cardiovascular death or at least one is myocardial infarction. There is an advantage worth noting when operator "`or`" is used to connect multiple class expressions that are represented using existential restriction. The syntax is relatively clear and straightforward because the following two expressions "(`Property some` $\texttt{Class}_1$) `or` (`Property some` $\texttt{Class}_2$) `or`… `or` (`Property some` $\texttt{Class}_n$)" and "(`Property some` (`Class`$_1$ `or` `Class`$_2$ … `or` `Class`$_n$))" are logically equivalent. So, the concise representation of **`OM_5`** shown in **Table 4.13** is (*`hasComponent`* `some` (**`CardiovascularDeath`** `or` **`MyocardialInfarction`**)). It is not surprising that the use of existential restriction pattern shows poor differentiation ability because this pattern does not describe the total number of components of each outcome measure. As shown in **Table 4.13**, instead of mutually disjoint classes, a class hierarchy (OM_1 ⊆ OM_5 ⊆ OM_11 ⊆ OM_15) is the logical consequence of using existential restriction to represent heterogeneous outcome measures.

- *Representation pattern 6: existential restriction with subproperties connected by "*`or`*"*

Subproperties of the *`hasComponent`* are added to explicitly express the total number of components that are measured in an outcome. For example, the expression *`has_2_Component`* `some` (**`CardiovascularDeath`** `or` **`MyocardialInfarction`**) could be precisely interpreted as

having two components, at least one is cardiovascular death or at least one is myocardial infarction. The logical consequence of this representation pattern, as shown in **Table 4.13**, means that heterogeneous outcome measures can be clearly differentiated from each other.

- *Representation pattern 7: qualified cardinality restriction connected by "*`or`*"*

The following union of class expressions (*hasComponent* exactly 1 **CardiovascularDeath**) or (*hasComponent* exactly 1 **MyocardialInfarction**) only expresses that each group of individuals have exactly one *hasComponent* relation, but it does not express the total number of *hasComponent* relations involved. Therefore, the use of qualified cardinality restriction is unable to differentiate heterogeneous outcome measures from each other. Furthermore, since "((Property exactly 1 $Class_1$) or (Property exactly 1 $Class_2$) or …or (Property exactly 1 $Class_n$))" and "(Property exactly 1 ($Class_1$ or $Class_2$ or… or $Class_n$))" are not logically equivalent, the syntax of qualified cardinality restriction patterns is more cumbersome than existential restriction patterns.

Nine classification schemes (coded as **OM_CS_1** to **OM_CS_9**) are designed to further explore the logical consequence of three different representation patterns. The purpose of each classification scheme and its expected classification results are summarized in **Table 4.14**. In general, these classification schemes aim to test: (1) whether outcome measures that have single or composite component(s) can be correctly retrieved, (2) a comprehensive retrieval of outcome measures that consider any/at most/at least some components and (3) class subsumption checking, more specifically, if a criterion of evidence retrieval includes death as a component of outcome measure, then the expected retrieved outcomes should include those having a component of cardiovascular death; whereas if cardiovascular death is a component being

retrieved, then the expected retrieved outcomes should not include those having a component of death.

Table 4.14: Classification schemes of outcome measures in scenario 2

Classification Scheme	Intended meaning	Expected results
OM_CS_1	Outcome measure that has any component(s) (**Death** or **Myocardial Infarction** or **Stroke** or **Stent Thrombosis**)	OM_1 to OM_15
OM_CS_2	Outcome measure that has any single component (**Death** or **Myocardial Infarction** or **Stroke** or **Stent Thrombosis**)	OM_1 to OM_4
OM_CS_3	Outcome measure that has any multiple components (**Death** or **Myocardial Infarction** or **Stroke** or **Stent Thrombosis**)	OM_5 to OM_15
OM_CS_4	Outcome measure that has at least 1 component (**Death**)	OM_1, OM_5, OM_6, OM_7, OM_11, OM_12, OM_13, OM_15
OM_CS_5	Outcome measure that has at least 2 components (**Death** or **Myocardial Infarction**)	OM_5, OM_11, OM_12, OM_15
OM_CS_6	Outcome measure that has at most 3 components (**Death** or **Myocardial Infarction** or **Stroke**)	OM_1, OM_2, OM_3, OM_5, OM_6, OM_8, OM_11
OM_CS_7	Outcome measure that has at least 2 and at most 3 components (**Death** or **Myocardial Infarction** or **Stroke**)	OM_5, OM_6, OM_8, OM_11
OM_CS_8	Outcome measure that has at most 3 components (**Cardiovascular Death** or **Myocardial Infarction** or **Stroke**)	OM_1, OM_2, OM_3, OM_5, OM_8
OM_CS_9	Outcome measure that has at least 2 and at most 3 components (**Cardiovascular Death** or **Myocardial Infarction** or **Stroke**)	OM_5, OM_8

How the three representation patterns are used to represent 9 classification schemes are presented in **Table 4.15**. Given the limited expressivity of existential restriction and qualified cardinality restriction, only 3 classification schemes are expressible by these two representation patterns, which means, their capability of retrieving outcome measure is limited to representation of criteria that include "any" or "at most" of some specified categories of event. On the other hand, 7 classification schemes are expressible when patterns of existential restriction with subproperties are applied to class expressions. It is found that two classification schemes that aim to retrieve outcomes having "at least" a specific component (**OM_CS_4**) or "at least" some specific components (**OM_CS_5**) are not expressible by any patterns. They are not expressible because of the meaning of "at least" and the logical consequence of "or". For example, **OM_CS_4** aims to retrieve outcome measures that have at least a component of death. To be more specific, it aims to find not only outcome measure with a single component of **Death** itself but also

outcome measures with any other unspecified components as long as they are combined with **Death** via the operator "or". However, there is no way to retrieve unspecified components unless they are explicitly described or a new constructor corresponding to the meaning of "or else" is created to represent them.

Table 4.15: Formal representation of classification schemes of outcome measure in scenario 2

Constructor	Classification scheme	Formal representation of classification scheme
Existential restriction	OM_CS_1	(*hasComponent* some (**Death** or **MyocardialInfarction** or **Stroke** or **StentThrombosis**))
	OM_CS_2	not expressible
	OM_CS_3	not expressible
	OM_CS_4	not expressible
	OM_CS_5	not expressible
	OM_CS_6	(*hasComponent* some (**Death** or **MyocardialInfarction** or **Stroke**))
	OM_CS_7	not expressible
	OM_CS_8	(*hasComponent* some (**CardiovascularDeath** or **MyocardialInfarction** or **Stroke**))
	OM_CS_9	not expressible
Existential restriction with subproperty	OM_CS_1	(*hasComponent* some (**Death** or **MyocardialInfarction** or **Stroke** or **StentThrombosis**))
	OM_CS_2	(*has_1_Component* some (**Death** or **MyocardialInfarction** or **Stroke** or **StentThrombosis**))
	OM_CS_3	(*has_Multiple_Component* some (**Death** or **MyocardialInfarction** or **Stroke** or **StentThrombosis**))
	OM_CS_4	not expressible
	OM_CS_5	not expressible
	OM_CS_6	(*hasComponent* some (**Death** or **MyocardialInfarction** or **Stroke**))
	OM_CS_7	(*has_Multiple_Component* some (**Death** or **MyocardialInfarction** or **Stroke**))
	OM_CS_8	(*hasComponent* some (**CardiovascularDeath** or **MyocardialInfarction** or **Stroke**))
	OM_CS_9	(*has_Multiple_Component* some (**CardiovascularDeath** or **MyocardialInfarction** or **Stroke**))
Qualified cardinality restriction	OM_CS_1	(*hasComponent* some (**Death** or **MyocardialInfarction** or **Stroke** or **StentThrombosis**))
	OM_CS_2	not expressible
	OM_CS_3	not expressible
	OM_CS_4	not expressible
	OM_CS_5	not expressible
	OM_CS_6	(*hasComponent* some (**Death** or **MyocardialInfarction** or **Stroke**))
	OM_CS_7	not expressible
	OM_CS_8	(*hasComponent* some (**CardiovascularDeath** or **MyocardialInfarction** or **Stroke**))
	OM_CS_9	not expressible

An overview of the expressivity of the 3 representation patterns is summarized in **Table 4.16**. It shows that, the representation pattern of existential restriction with subproperties not only has sufficient ability to differentiate but also succeeds in returning expected results from most of the classification schemes. Furthermore, its syntax is relatively concise and straightforward for a

user. The patterns with only existential restriction or qualified cardinality restriction are incapable of differentiating heterogeneous outcome measures. However, they may be adequate for some application scenarios that require less expressivity.

Table 4.16: Overview of the expressivity of 3 representational patterns in the scenario of the formal representation of outcome measures

Expressivity	Existential restriction	Existential restriction with subproperties	Qualified cardinality restriction
Differentiating ability	×	○	×
Multiplicity of classification			
OM_CS_1	○	○	○
OM_CS_2	×	○	×
OM_CS_3	×	○	×
OM_CS_4	×	×	×
OM_CS_5	×	×	×
OM_CS_6	○	○	○
OM_CS_7	×	○	×
OM_CS_8	○	○	○
OM_CS_9	×	○	×

×: insufficient, ○: sufficient

4.4.3 Representation patterns for inclusion criteria to automate evidence retrieval from an ontology-based knowledge base for systematic review with meta-analysis

In this study, evidence retrieval refers to the process of using the developed OWL ontology to represent inclusion criteria and then using a OWL 2 DL reasoner to automatically reason over the OWL 2 DL ontology and the ontology-based knowledge base. Basically, the formal representation of inclusion criteria for systematic review with meta-analysis is similar to asserting individual information entities (See Section 4.4.1 and Section 4.4.2). It involves using class expressions to describe multiple information components. These class expressions are then regarded as necessary and sufficient conditions in a defined class. For example, a set of inclusion criteria for the systematic review conducted by Hulot and colleagues is summarized and formally represented in **Table 4.17** [Hulot et al., 2010].

Table 4.17: General patterns that represent inclusion criteria for systematic review with meta-analysis

Information expressed	General pattern of formal representation	Example representation of inclusion criteria of a meta-analysis*	Original text of inclusion criteria extracted from review article*
Information entities to be retrieved	**Evidence**	**Evidence**	-
Inclusion criteria related to publication	(and *isExtractedFrom* some (**Publication**	(and *isExtractedFrom* some (**Publication**	-
defined by publication type	and **CE(Publication Type)**))	and (*hasPublicationType* some (**Refereed Journal Article** or **Conference Abstract**))))	including journal article and conference abstract
Inclusion criteria related to study	(and isAcquiredFrom some (**Study**	(and isAcquiredFrom some (**Study**	-
defined by study population	and **CE(Study Population)**	and (*hasStudyPopulation* some (**Patient** and (*hasIndicationByDrug* some **Clopidogrel**) and (*hasDisease* some **CoronaryArteryDisease**)))	patients with coronary artery disease who were treated with clopidogrel
defined by study design	and **CE(Study Design)**	and ((*hasStudyType* some (**InterventionalStudy** and (*hasStudyDesign* some (**Parallel Group** and (hasAllocationScheme some **Randomization**))))) or (hasStudyType some (**ObservationalStudy** and (*hasStudyDesign* some (**Cohort** and (*hasTimePerspective* some (**Prospective** or **Retrospective**)))))))))	randomized or cohort studies (prospective cohort or historical cohort)
defined by drug therapy	and **CE(Drug Therapy)**))	and (*hasDrugTherapy* some (**ClopidogrelTherapy** and (*hasDrugTherapyStrategy* some (**FixedDrugDose** and (*hasDrugRegimen* some **ClopidogrelStandardDose**)))))	standard clopidogrel therapy
Inclusion criteria related to evidence	-	-	-
defined by comparison	and **CE(Comparison)**	and (*hasComparison* some **ComparisonBetweenGenotype WithinTreatment**)	comparison between two genotypes of patient with standard clopidogrel therapy
defined by genetic contrast	and **CE(Genetic Contrast)**	and (*hasGeneticContrast* some (**CarrierOfAtLeast1VsNoncarrier** and (*hasSingleGeneticVariant* some **CYP2C19star2**)))	carriers of CYP2C19*2 compared with noncarriers
defined by genotype of interest	and **CE(Genotype of interest)**	*not applicable*	-
defined by outcome	and **CE(Outcome)**	and (*hasOutcomeMeasure* some (**ClinicalEfficacyMeasure** and (*hasMultipleComponent* some (**Death** or **NonfatalMyocardial Infarction** or **Stroke** or (**Revascularization and** *hasProcedureDescriptor* some **Urgent**))) and (*isMeasuredAs* some **IncidenceOfEvent**)))	occurrence of MACE, as defined in each study by the occurrence of death, nonfatal myocardial infarction, stroke, or urgent revascularization.

***extracted from [Hulot et al., 2010]**

Seven complex class expressions corresponding to essential information components including publication, study population, study design, drug therapy, comparison, genetic contrast and outcome are expressed using different representation patterns, i.e., existential restriction or

existential restriction with subproperties. Then, with the use of the object properties of *isAcquiredFrom* and *is_acquired_from* and the set operator "and", those class expressions related to inclusion criteria of publications and studies are linked to the class **Evidence**. Finally, a named class can be declared in the ontology and defined by a conjunction of complex class expressions which are highlighted in blue in **Table 4.15**.

As shown in **Table 4.17**, the designed representation patterns so far are able to represent a set of inclusion criteria for identifying relevant individual publications, studies and evidence. Since a set of inclusion criteria for a meta-analysis can be transformed into a defined class that has necessary and sufficient conditions in an OWL 2 DL ontology, the automatic evidence retrieval can be achieved by leveraging a OWL 2 DL reasoner to reason and return all the relevant individuals that satisfy the defined necessary and sufficient conditions.

4.5 Construction of Knowledge Base by formal representation of Individual Information Entities

The primary aim of this study was to build a knowledge-based system that enables formal representation and automatic retrieval of pharmacogenomics evidence to assist in systematic review with meta-analysis. OWL 2 DL, a highly expressive and decidable web ontology language, is selected to implement the envisioned system in order to overcome the inherent heterogeneity of pharmacogenomics knowledge and inclusion criteria. After a comprehensive exploration of representation issues including "Does the formal representation of individual publications, studies, evidence and inclusion criteria for meta-analysis match their intended meaning?", "What is the logical consequence of different representation patterns?" and "Are the formally represented heterogeneous content inferred as expected based on various classification schemes?", the OWL 2 DL ontology constructed in Section 4.3.3 and the constructors of OWL 2

DL demonstrate sufficient expressive power and ability to represent and differentiate heterogeneous content as presented in Section 4.4. Therefore the subsequent research work focuses on developing an ontology-based knowledge base that provide heterogeneous pharmacogenomics knowledge in terms of individual publications, studies, and evidence that are formally represented using the developed OWL 2 DL ontology.

4.5.1 Materials and Methods

The characterization of empirical, clinical relevant and evidence-based pharmacogenomics knowledge extracted from pharmacogenomics research articles has been completed and described in Chapter 3. The fine-grained pharmacogenomics knowledge characterization yielded 3 types of information entities, including 73 publications, 82 studies and 445 pieces of pharmacogenomics evidence. This collection of concrete real-world individuals of information entities served as the materials to construct the knowledge base.

Protégé was used to implement the knowledge base. I manually instantiated the collection of individual information entities using the formal vocabularies encoded in Ontology_1 (see **Table 4.3**). The formal representation of individual publication, study and evidence followed the patterns presented in **Table 4.5 and Table 4.6**. The formal representation of heterogeneous content regarding study population, drug therapy, genetic variation and outcome followed the adoption of representation patterns presented in **Table 4.18**. The syntax of the selected representation patterns can be found in **Table 4.8** and **Table 4.13**.

Table 4.18: Adoption of representation patterns to describe complex class expressions in information components

Information component	Class expression		Adopted representation pattern	
	Object property	Class as property value	OWL 2 DL constructor	Operator
Study population	*hasDisease*	Disease	Existential restriction	or
	hasProcedure	Procedure	Existential restriction	or
Drug therapy	*hasDrugTherapy*	DrugTherapy	Existential restriction	or
	hasAlternativeDrugTherapy	DrugTherapy	Existential restriction	or
	hasDrugRegimen	DrugRegimen	Existential restriction	and
	considersGeneticVariant	GeneticVariant	Refined qualified cardinality restriction	and
Genetic variation	*hasGeneticVariant*	GeneticVariant	Existential restriction with Subproperties	and
	hasGenotypeOI	Genotype	Existential restriction with Subproperties	or
Outcome	*hasComponent*	Disease/Adverse Event/Procedure	Existential restriction with Subproperties	or

4.5.2 The constructed knowledge base

The constructed knowledge base contains formally asserted individual publications (see Appendix 2 for 73 pieces of asserted publications), studies (see Appendix 3 for 82 pieces of asserted studies) and evidence (see Appendix 4 for 445 pieces of asserted evidence) based on the ontology constructed in Section 4.3. After instantiation of individuals in the knowledge base, the expressivity of the OWL 2 DL ontology was changed from $\mathcal{ALCRF(D)}$ to $\mathcal{ALCRQ(D)}$ (See Ontology_2 in **Table 4.3**). It means that qualified cardinality restrictions were adopted in individual assertions to restrict the numbers and the types of classes used as values of a given property. As a result of individual assertions, Ontology_2 evolved with increased numbers of individual counts (from 9 to 676), `ClassAssertion` axioms counts (from 9 to 2679), `ObjectPropertyAsserion` axioms counts (from 0 to 1187) and `DatatypePropertyAssertion` axioms counts (from 0 to 1522). **Table 4.19** provides an overview of the sets of class expressions that have been created to formally represent 73 individual publications, 82 individual studies and 445 individual pieces of evidence. How diverse class expressions were used to address the heterogeneity among individual publications, studies and evidence are described below.

Table 4.19: Overview of individual assertions in formal representation of individual information entities

Individual	Individual assertion	Representation pattern	Count of class expressions set	Count of individual assertion axiom
Individual of **Publication** (IE_p) N=73	Class assertion	$IE_p \in$ **Publication**	1	73
		$IE_p \in$ **CE**(Publication Type)	3	73
	Object property assertion	IE_p *hasPMID* I_{pmid}	1	67
	Datatype property assertion	IE_p *hasPubYear* "value"^^xsd:integer	1	73
Individual of **Study** (IE_s) N=82	Class assertion	$IE_p \in$ **Study**	1	82
		$IE_s \in$ **CE**(Study Population)	49	82
		$IE_s \in$ **CE**(Study Design)	13	82
		$IE_s \in$ **CE**(Drug Therapy)	35	82
	Object property assertion	IE_s *isReportedIn* IE_p	1	82
		IE_s *has_ROBA_method_criterion** I(**Risk of Bias Assessment Value**)	30	374
	Datatype property assertion	None	-	-
Individual of **Evidence** (IE_e) N=445	Class assertion	$IE_p \in$ **Evidence**	1	445
		$IE_e \in$ **CE**(Comparison)	11	445
		$IE_e \in$ **CE**(Genetic Variation)	45	305
		$IE_e \in$ **CE**(Outcome)	108	445
		$IE_e \in$ **CE**(Effect Metric)	10	445
	Object property assertion	IE_e *isAcquiredFrom* IE_s	1	445
		IE_e *hasEffectSizeUnit* I(**Unit**)	6	286
	Datatype property assertion	IE_e *hasTimeFrame* "value"^^xsd:integer	2	422
		IE_e *hasEffectSize* "value"^^xsd:double	1	445
		IE_e *hasLower95PercentCI* "value"^^xsd:double	1	159
		IE_e *hasUpper95PercentCI* "value"^^xsd:double	1	159
		IE_e *hasPValue* "value"^^xsd:double	1	241
Individual of **PMID** (I_{pmid}) N=67	Class assertion	$I_{pmid} \in$ **PMID**	1	67

4.5.3 Individual publication assertion

The formal representation of an individual publication was relatively straightforward. As shown in **Figure 4.18**, an individual publication labeled as pub_24251361, referring to the article [Kimmel et al., 2013], was formally represented using 2 class assertions (denoted by yellow circles), 1 object property assertion (denoted by blue square), and 1 datatype property assertion (denoted by green square). As a result, the individual pub_24251361 could be interpreted as a full-text publication that was published in 2013 and its PubMed identifier is 24251361.

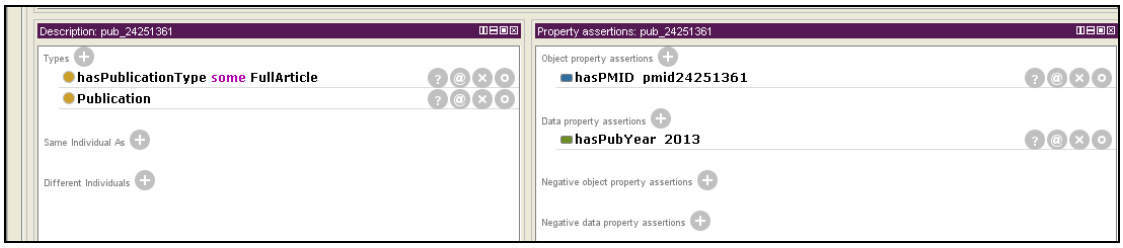

Figure 4.18: Example of assertion of individual publication. `pub_24251361` refers to the article [Kimmel et al, 2013].

- *Formal representation of publication types*

The publication types were represented by nested class expressions that involve existential restrictions (See **Table 4.6**). Since the heterogeneity in publication types among 73 asserted individual publications was minimal, it was found that 3 sets of class expressions (i.e., *hasPublicationType* some **FullArticle**, *hasPublicationType* some **Letter** and *hasPublicationType* some **ConferenceAbstract**) were enough to assert publication types of all 73 individual publications.

4.5.4 Individual study assertion

Figure 4.19 shows the assertions of an individual study `stu_1_pub_24251361`, which refers to the study that reported study results in an individual publication `pub_24251361`. As a result, the individual `stu_1_pub_24251361` could be interpreted as a randomized and paralleled clinical trial which aimed to investigate a genotype-guided warfarin therapy that considered three genetic variants (*CYP2C9*2* and *CYP2C9*3* and *VKORC1-1639G/A*) versus clinically guided warfarin dosing in patients with atrial fibrillation or deep vein thrombosis or pulmonary embolism or deep vein thrombosis & pulmonary embolism. In addition, the risk of bias in this particular study was assessed using Cochrane assessment tool, with low risk of bias in each of the six criteria (i.e.,

blinding of outcome assessment, incomplete outcome data, blinding of participants and personnel, random sequence generation, selective reporting and allocation concealment).

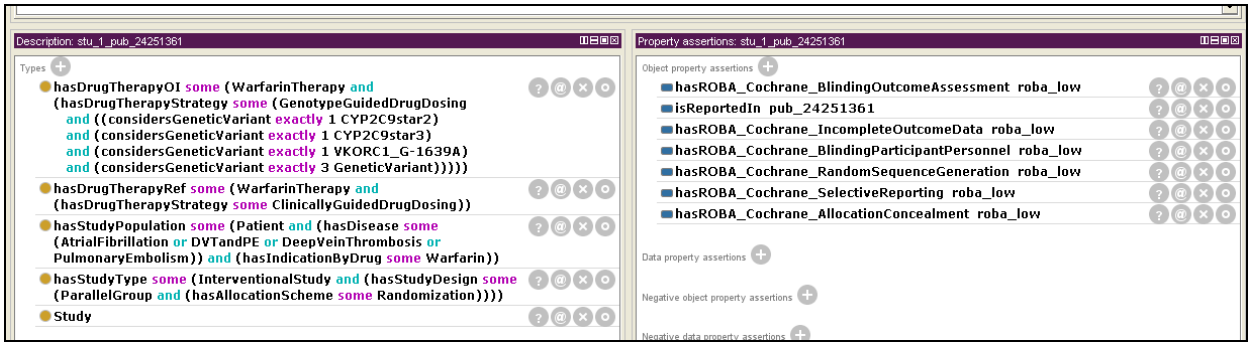

Figure 4.19: Example of assertion of individual study. `stu_1_pub_24251361` refers to the study reported in the article [Kimmel et al, 2013].

In the assertions of individual studies, the object property assertions are simple and straightforward, while the class assertions in formal representation of study design, drug therapy and study population are more complicated. The major points are highlighted as follows.

- *Formal representation of study design*

The study designs were represented by nested class expressions that involve existential restrictions (See **Table 4.6**). All of the 82 asserted individual studies could be broadly divided into four categories of study types (i.e., observational studies, interventional studies, simulation studies and secondary analysis studies) and specifically divided into 13 categories of study design. Therefore, a total of 13 sets of nested class expressions were found to describe the study design of 82 studies (see **Figure 4.20**, where arrows denote object properties and existential restriction constructor "`some`", rectangles denote classes as property values). The 13 sets of study design expressions are mutually exclusive and each of the 82 individual studies could be classified into one and only of the 13 categories of study design. Take the representation of

observational studies as an example, all 39 observational studies (highlighted in green) were described by one of the following class expressions: (1) *hasStudyType* some (**ObservationalStudy** and (*hasStudyDesign* some (**Cohort** and (*hasTimePerspective* some **Prospective**)))), (2) *hasStudyType* some (**ObservationalStudy** and (*hasStudyDesign* some (**Cohort** and (*hasTimePerspective* some **Retrospective**)))), (3) *hasStudyType* some (**ObservationalStudy** and (*hasStudyDesign* some **CaseControl**)), and (4) *hasStudyType* some (**ObservationalStudy** and (*hasStudyDesign* some **CaseCohort**)). In addition, once a set of class expression was used in a define class, it guaranteed that all the retrieved individuals were homogeneous. For example, the class expression (1) should enable a DL reasoner to retrieve a homogeneous group of 31 individual studies that are prospective cohort studies (See yellow highlight area in **Figure 4.20**). The results indicate that the representation pattern designed for the study design module is adequate in terms of expressing and differentiating heterogeneity in study design among different studies.

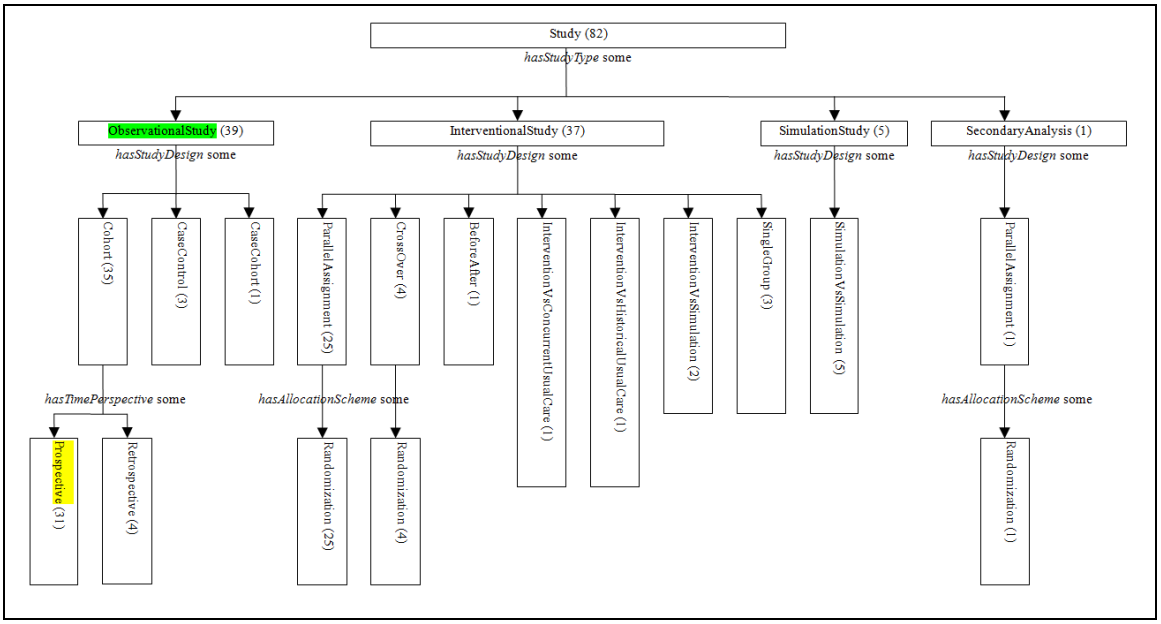

Figure 4.20: Class expressions that represent study designs. The numbers in parentheses denote the numbers of studies.

- *Formal representation of drug therapies*

The drug therapies were represented by nested class expressions that involve existential restrictions and refined qualified cardinality restrictions (see **Table 4.18**). All of the 82 asserted individual studies were broadly divided into two categories: studies relating to antiplatelet therapies (i.e., drug therapies with clopidogrel, cilostazol, prasugrel and ticagrelor) and studies relating to anticoagulation therapies (i.e., drug therapies with warfarin, acenocoumarol and phenprocoumon). A total of 35 sets of class expressions were created to describe the investigated drug therapies in 82 individual studies (see **Figure 4.21** and **Figure 4.22**). For example, the following set of class expression `hasDrugTherapyObserved some (ClopidogrelTherapy and (hasDrugTherapyStrategy some (FixedDrugDose and ((hasDrugRegimen some ClopiodgrelLD300mg) and (hasDrugRegimen some ClopiodgrelMD75mg)))))` was created to assert 6 individual studies (i.e., `stu_1_pub_19106083`, `stu_1_pub_21099121`, `stu_1_pub_21168310`, `stu_1_pub_21862109`, `stu_1_pub_22990067` and `stu_1_pub_23001453`) with the same drug therapy of clopidogrel therapy of fixed doses of 300 mg loading dose and 75 mg maintaining dose (see green highlight area in **Figure 3.21**). Because of the heterogeneity existed among drug therapies, it was also found that 22 of 35 sets of class expressions were created to assert only one individual study. The heterogeneity was most commonly found in the values of *hasDrugRegimen* property and *considersGeneticVariant* property. However, only the *considersGeneticVariant* property was used with the refined qualified cardinality restriction in order to precisely differentiate drug therapies with different genetic variants considered in medication decision.

- *Formal representation of study populations*

The study populations were represented by nested class expressions that involve existential restrictions (see **Table 4.18**). As illustrated in **Figure 4.23**, a total of 49 sets of class expressions were created to describe the highly heterogeneous study populations of the 82 individual studies, with 31 out of the 49 sets of class expression having been created to assert only one individual study. It was also found that the highly varied values of properties of *hasDisease*, *hasProcedure* and *hasRisk* all contributed to the heterogeneity in study populations.

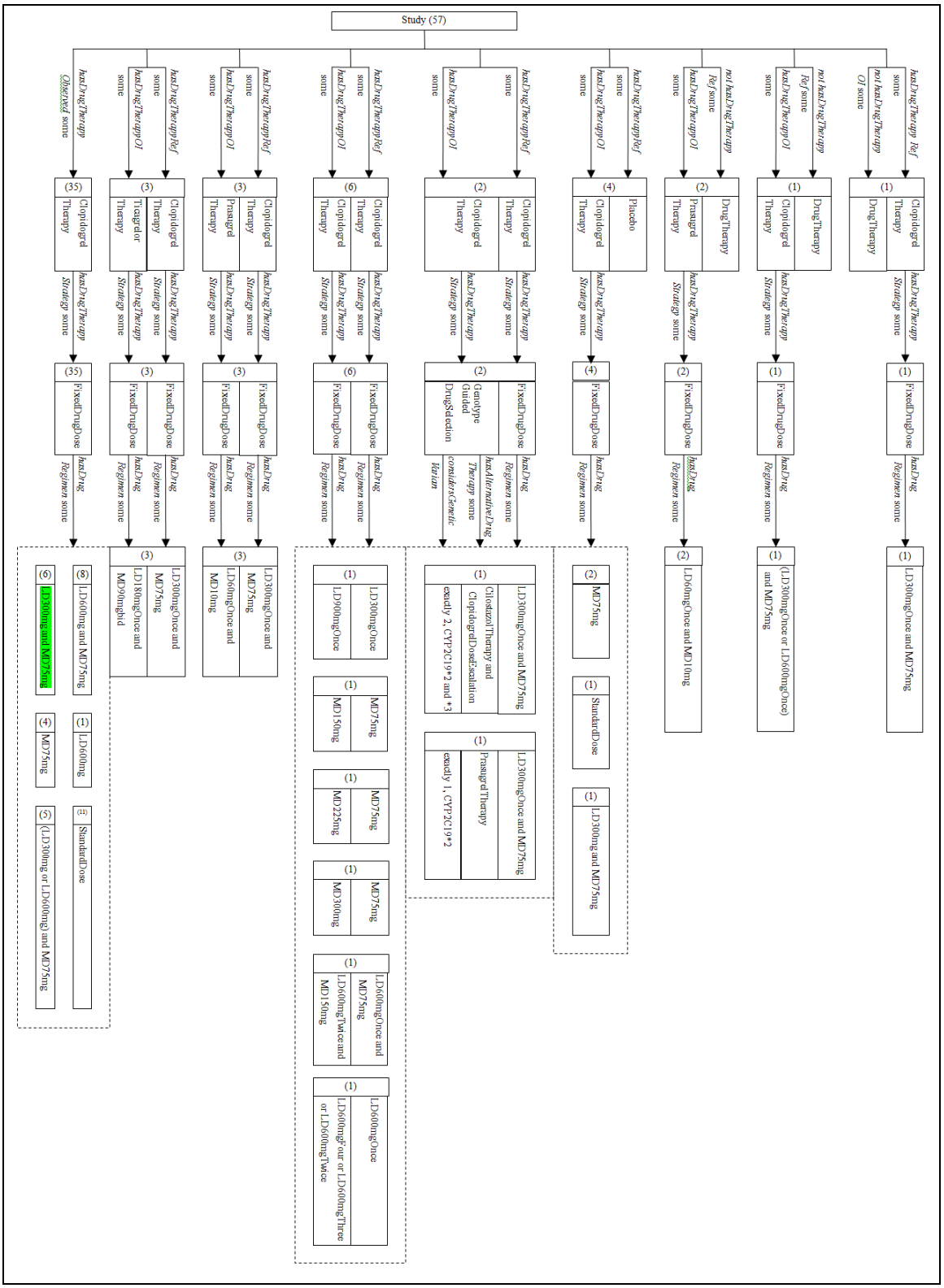

Figure 4.21: Class expressions that represent antiplatelet therapies. The numbers in parentheses denote the numbers of studies.

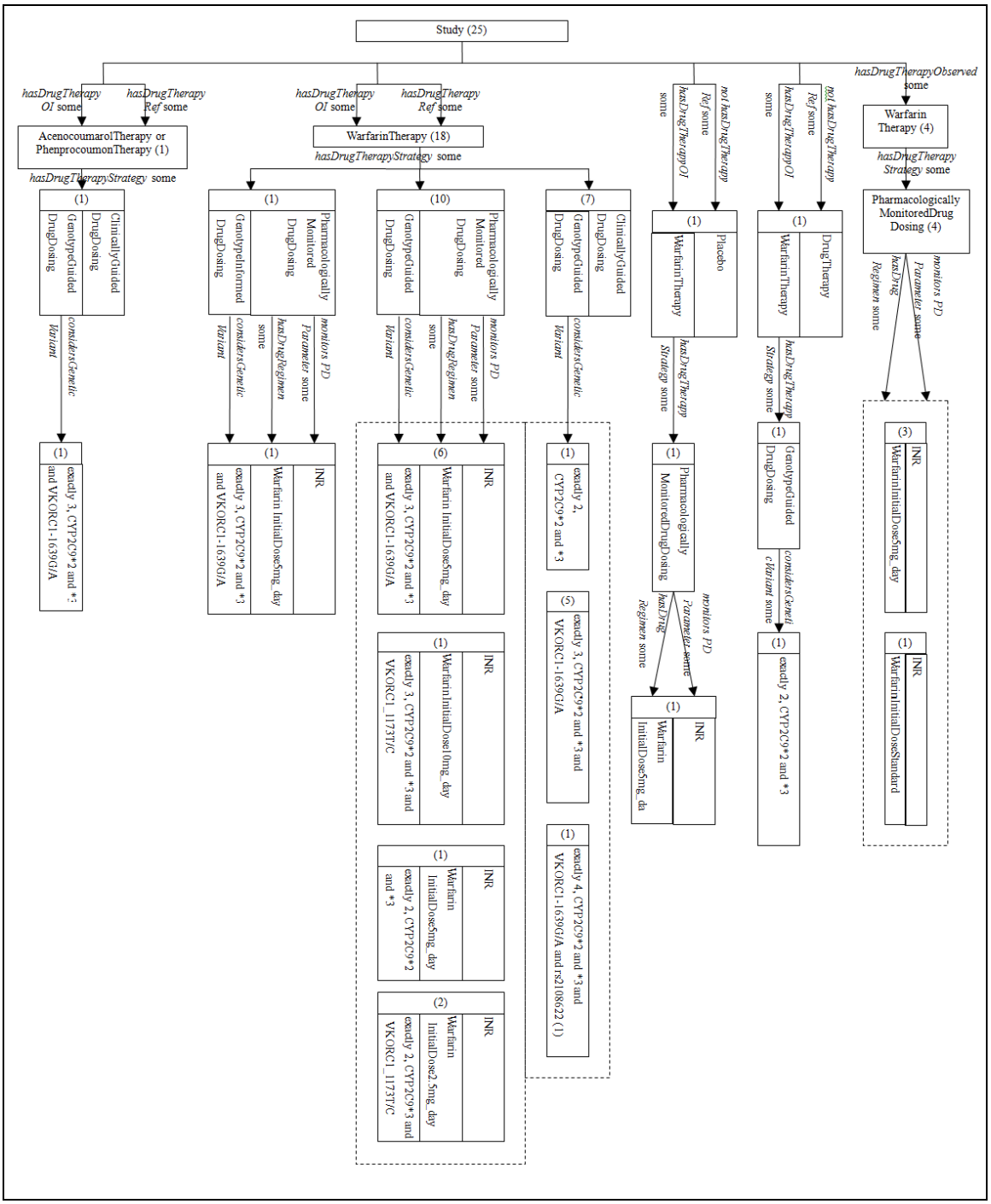

Figure 4.22: Class expressions that represent anticoagulation therapies. The numbers in parentheses denote the numbers of studies.

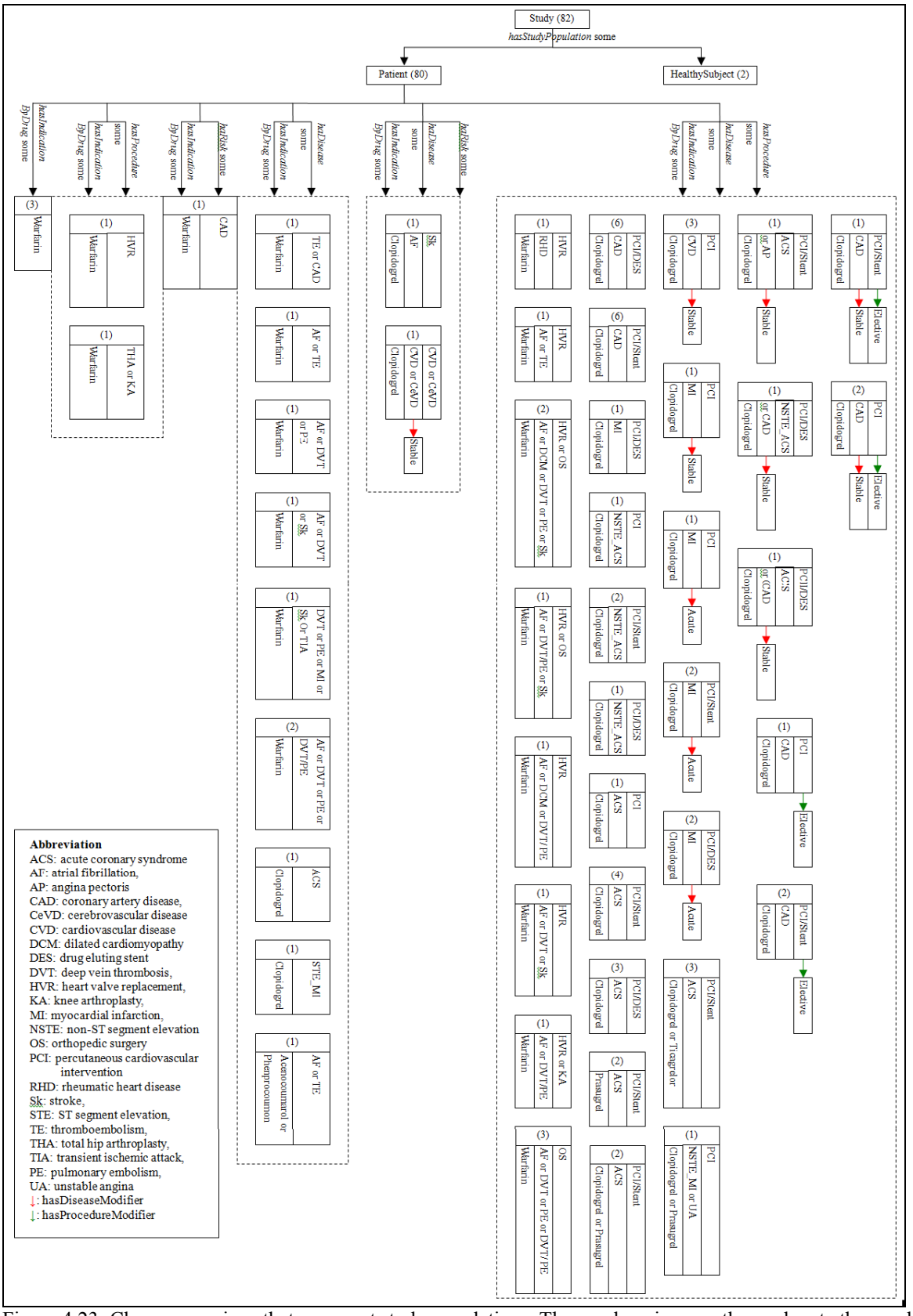

Figure 4.23: Class expressions that represent study populations. The numbers in parentheses denote the numbers of studies.

4.5.5 Individual evidence assertion

Figure 4.24 shows the assertions of an individual evidence `evi_01_pub_24251361_stu_1`, which refers to a piece of study result extracted from [Kimmel et al., 2013]. As a result, this individual evidence was explicitly represented with essential information related to a comparative effectiveness research, which included: The comparison was between two drug therapies (i.e., genotype-guided vs. clinically guided warfarin therapies) and this was known through the *`isAcquiredFrom`* relationship to the asserted individual study `stu_1_pub_24251361` (see **Figure 4.19**). The outcome measure was the percentage of time of international normalized ratio in the therapeutic range up to the follow-up of 28 days. The effect size was measured as absolute difference between the means of the two comparison groups, i.e., 45.2% in the genotype-guided group (standard deviation=26.6%, sample size=494) and 45.4% in the clinically-guided group (standard deviation=25.8%, sample size=471). The estimate of effect size was -0.2% with 95% confidence interval of -3.4% to 3.1% and P-value of 0.91. In addition, the inferred object property assertions also indicated implicit information which included: this piece of evidence was extracted from the individual publication `pub_24251361`; and it was associated with a low risk of bias in six assessment criteria via its relationship with the individual study `stu_1_pub_24251361`.

In the assertions of individual evidence, the class assertions in formal representation of genetic variation and outcome measure are more complicated than other assertions. The major points are highlighted as follows.

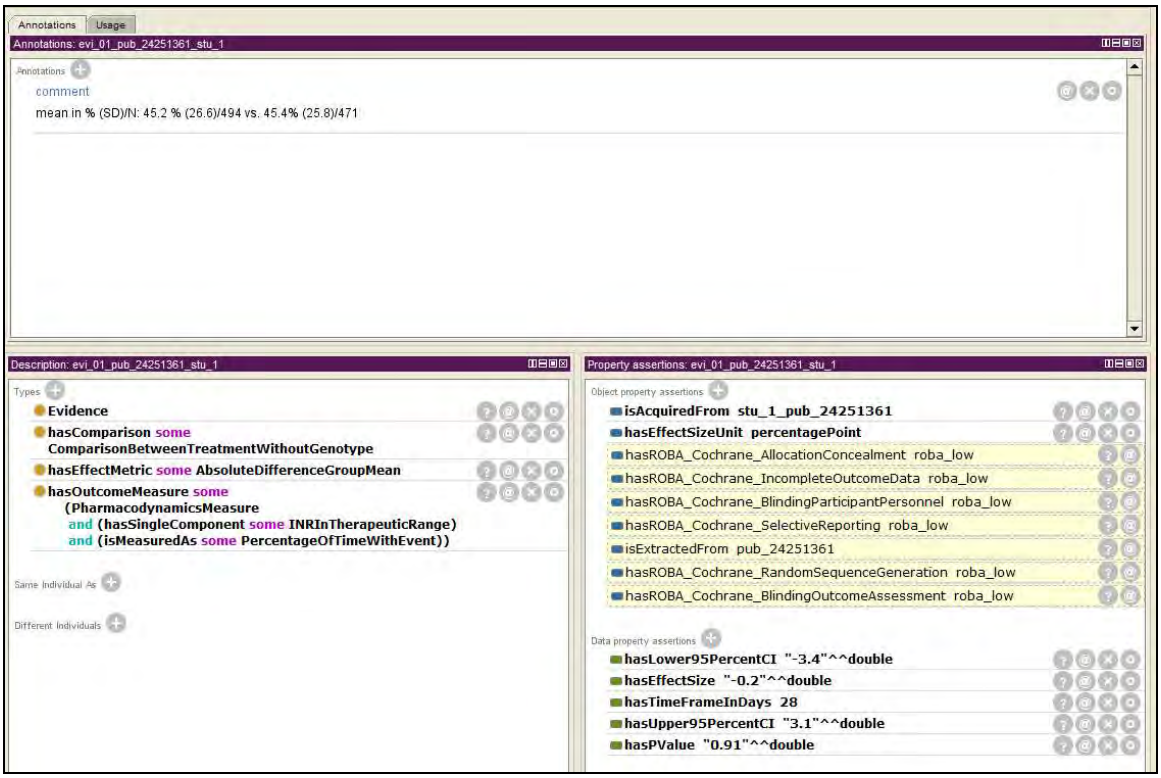

Figure 4.24: Example of assertion of individual piece of evidence.
`evi_01_pub_24251361_stu_1` refers to a piece of study result reported in the article [Kimmel et al., 2013].

- *Formal representation of genetic variation*

The genetic variations were represented by nested class expressions that involve existential restrictions with subproperties (see **Table 4.18**). All of the asserted 445 pieces of individual evidence could be divided into three categories in terms of genetic variation: evidence associated with genetic contrast (usually found in clinical validity research), evidence associated with genotype of interest (usually found in genetic modification research), and evidence not associated with genetic variation (usually found in comparative effectiveness research). A total of 27 sets of class expressions were created to describe the genetic contrasts of 243 pieces of clinical validity evidence which compared the drug effects between carriers versus noncarriers (see **Figure 4.25**). For example, 4 pieces of evidence which compared the drug effect between

(CYP2C19*1/*2 or CYP2C19*1/*3) and (CYP2C19*1/*1) were represented by the set of class expression `(hasGeneticContrast some (CarrierOf1VsNoncarrier and ((hasTwoGeneticVariant some CYP2C19star2) and (hasTwoGeneticVariant some CYP2C19*3))))` (See yellow highlighted area in **Figure 4.25**). The subproperties of `hasGeneticVariant` and their highly varied values of `GeneticVariant` class enabled the expression of the heterogeneity in genetic contrast.

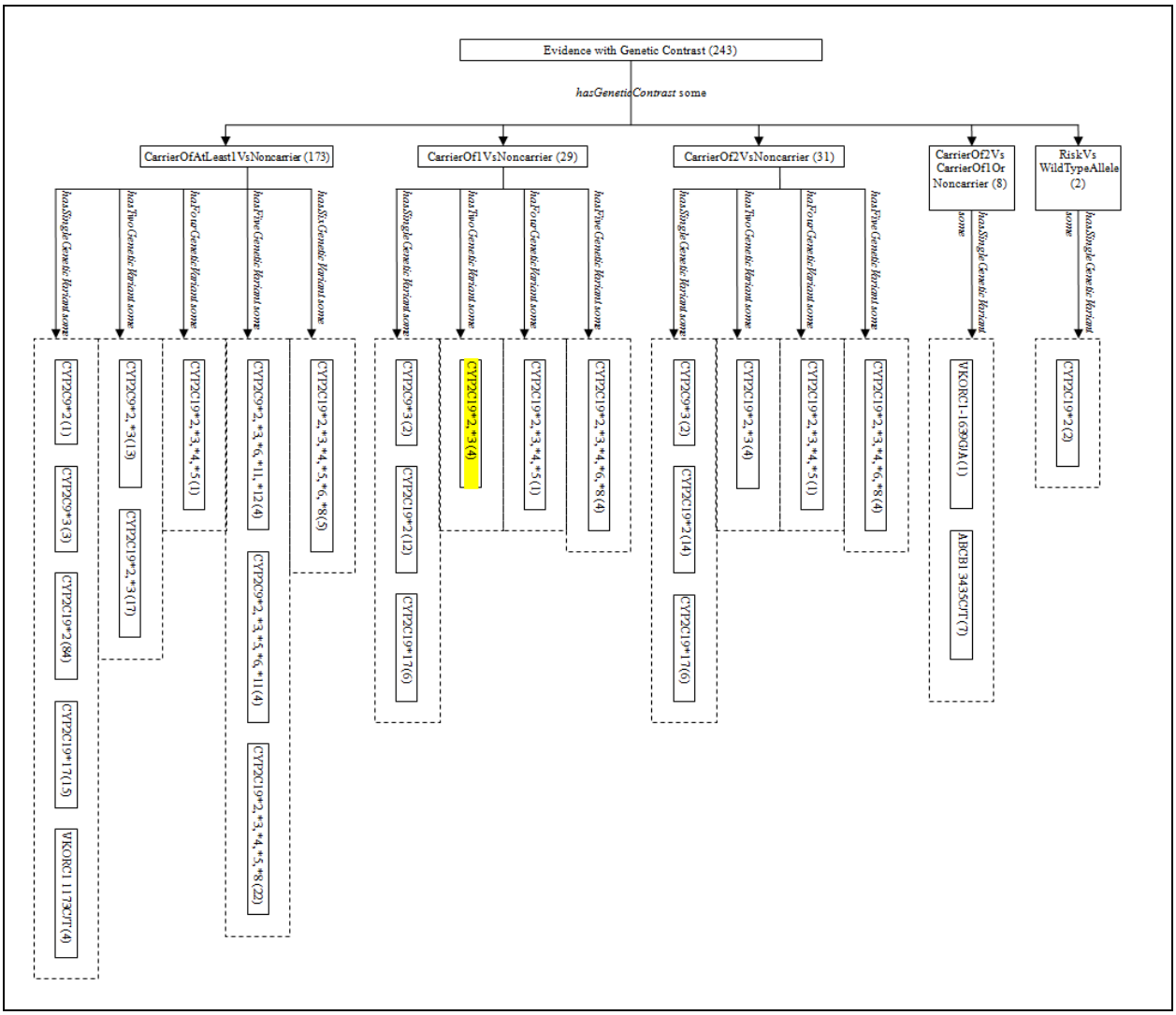

Figure 4.25: Class expressions that represent genetic contrasts in clinical validity evidence. The numbers in parentheses denote the numbers of pieces of evidence.

A total of 18 sets of class expressions were created to assert the genotypes of interest in 62

pieces of genetic modification evidence (see **Figure 4.26)**. Genetic modification evidence was a type of evidence that assessed whether or not alternative drug therapy was more effective than conventional drug therapy in patients carrying certain risk variants. For example, the genotype *CYP2C19*1/*2* involved in the comparison of (clopidogrelMD300mg vs. clopidogrelMD75mg) is represented using the set of class expression `(hasSingleGenotypeOI some (CarrierOf1 and (hasSingleGeneticVariant some CYP2C19star2)))`. The subproperties of `hasGenotypeOI` and `hasGeneticVariant` and their values contributed to the expression of heterogeneity in genotypes.

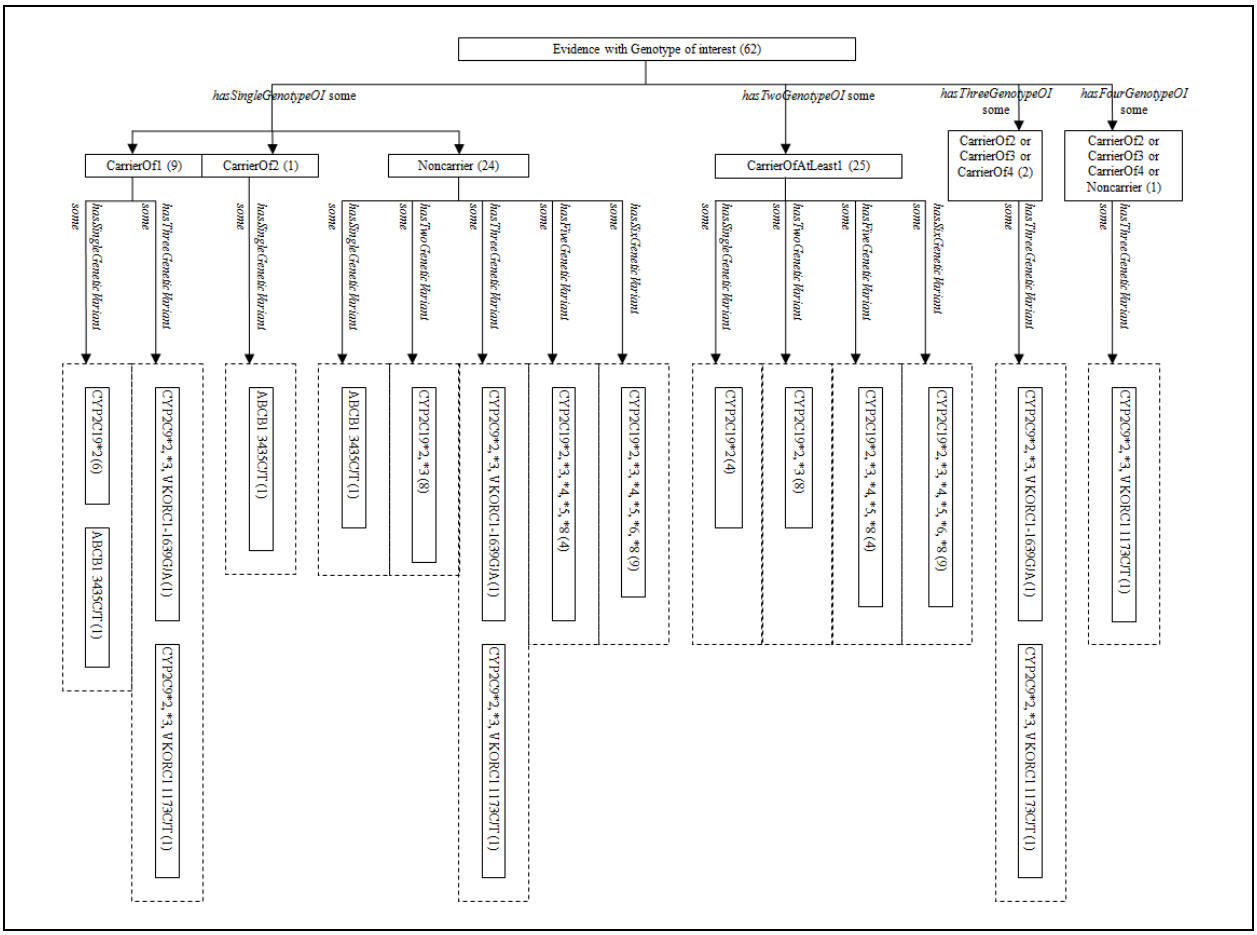

Figure 4.26: Class expressions that represent genotypes investigated in genetic modification evidence. The numbers in parentheses denote the numbers of pieces of evidence.

- *Formal representation of outcomes*

The outcomes were represented by nested class expressions that involve existential restrictions with subproperties (see **Table 4.18**). For example, this set of class expression (*hasOutcomeMeasure* some (**ClinicalEfficacyMeasure** and (*hasThreeComponent* some (**CVDeath** or **MyocardialInfarction** or **Stroke**)) and (*isMeasuredAs* some **IncidenceOfEvent**))) was created to describe evidence that measured the first incidence of any of the three categories of events (i.e., cardiovascular death or myocardial infarction or stroke). The heterogeneity in outcomes was too complicated to be illustrated in one figure because a total of 108 sets of class expressions were created to describe the diverse outcomes which were measured in 445 pieces of individual evidence. The subproperties of *hasComponent* and hierarchical classes declared in the ontology, i.e., **AdverseEvent**, **Disease**, **DrugDoseParameter**, **PharmacodynamicsParameter**, **PharmacokineticsParameters** and **Procedure** (See **Figure 4.27**) were used to describe the heterogeneity inherent in outcome.

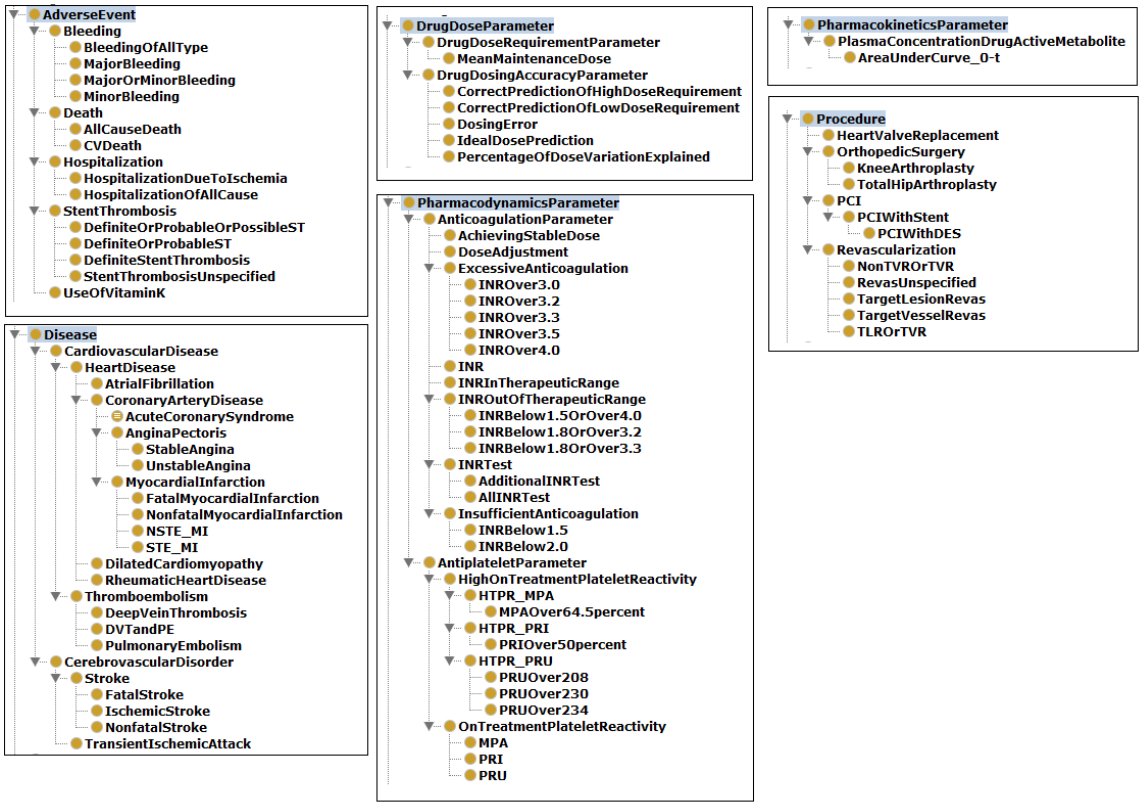

Figure 4.27: Classes that can be used to represent outcome measure components

4.6 VERIFICATION OF THE CONSTRUCTED ONTOLOGY AND THE ONTOLOGY-BASED KNOWLEDGE BASE

Since the core components of my envisioned knowledge-based system (i.e., an OWL 2 DL ontology and a ontology-based knowledge base) have been developed, they should be carefully tested to ensure the consistency and correctness of the developed knowledge-based system. In addition, it is necessary to verify whether the heavy use of set operators and constructors in the representation of individual information entities causes inefficiency in inference or even undecidability. To address the inference problem, developing verification mechanisms that evaluate whether or not the envisioned knowledge-based system is being developed correctly and effectively is necessary. And the implementation of verification mechanisms will largely rely on

a DL reasoner and its inference capability. This section provides the design of test cases to verify the consistency, correctness and efficiency of the developed knowledge-based system, and the results of verification.

4.6.1 Materials and method

The verification was conducted through the following 3 steps (see **Figure 4.28**) to ensure the consistency and correctness of the developed ontology and ontology-based knowledge base.

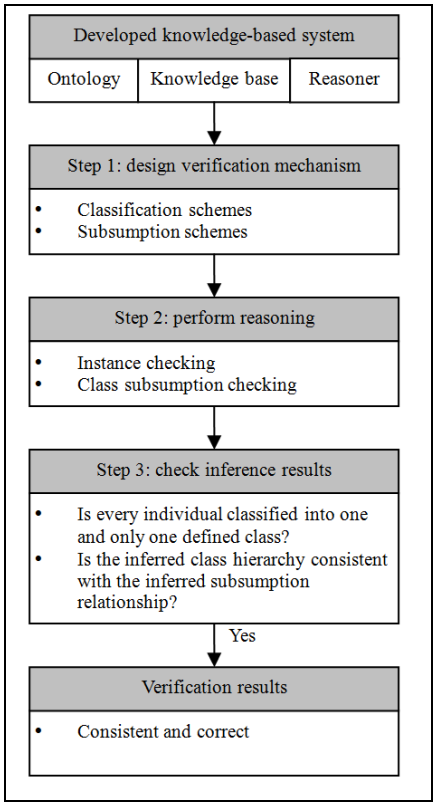

Figure 4.28: Verification of the developed knowledge-based system

- *Step 1: Design verification mechanisms*

Two types of schemes were designed as verification mechanisms to verify the developed knowledge-based system. Classification schemes comprise a set of mutually exclusive defined

classes and aim to exhaustively classify every asserted individual of a targeted group of evidence into one and only one defined class. Subsumption schemes comprise a set of defined classes with different levels of specificity and aim to infer a class hierarchy of all the defined class in the set.

- *Step 2: Perform reasoning*

The HermiT reasoner embedded in Protégé was triggered to perform two reasoning tasks. Task of instance checking retrieves all relevant individuals that satisfy various necessary and sufficient conditions described in defined classes, and task of class subsumption checking yields an inferred class hierarchy.

- *Step 3: Check inference results*

The inferred results of Step 2 were manually checked to see if they matched the expected results. If the expected class hierarchies and relevant individuals were correctly inferred, the developed ontology and knowledge base were verified as consistent and correct.

4.6.2 Design of test cases

Based on the above mentioned steps, four test cases were designed and summarized in **Table 4.20**. Briefly, test case 1 was to verify the logical consequence of using existential restriction to represent evidence type (i.e., clinical validity, clinical effectiveness, or genetic modification) with various outcome measure categories (efficacy, safety, composite of efficacy and safety, drug dose, pharmacodynamics, or pharmacokinetics). Test case 2 was to verify the logical consequence of using refined qualified cardinality restriction to form a conjunction of class expressions that describe the numbers and categories of genetic variants considered in genotype-guided warfarin therapies. Test case 3 was to verify the logical consequence of using existential restriction with subproperties to form a conjunction of class expressions that describe the

numbers and categories of genetic variants used to determine genotypes. Test case 4 was to verify the logical consequence of using the existential restriction with subproperties to form a union of class expressions that describe the numbers and categories of events measured in outcomes.

Table 4.20: Design of test cases to verify the developed ontology and knowledge base

Test case	Differentiating factors in classification schemes	Verified representation patterns
1	Evidence types and outcome measure categories	Conjunction of class expressions represented using existential restrictions
2	Number and categories of genetic variants considered in a genotype-guided drug therapy	Conjunction of class expressions represented using refined qualified cardinality restrictions
3	Number and categories of genetic variants used to determine genotypes	Conjunction of class expressions represented using existential restrictions with subproperties
4	Number and categories of events measured in an outcome measure	Union of class expressions represented using existential restrictions with subproperties

4.6.3 Results of verification

Each test case was composed of sets of defined classes that allowed a DL reasoner i.e., HermiT to perform automatic class subsumption checking and instance checking. All test cases were tested on a personal laptop (Intel Core i7-4700MQ 2.4GHz Processor, 16 GB DDR3 Ram and a 64-bit version of Windows 8.1). The results of verification are presented as follows.

4.6.3.1 Test case 1: verify logical consequences of using existential restriction to represent mutually exclusive evidence types

As mentioned in Chapter 3 **Table 3.5**, all the pharmacogenomics evidence could be divided into three categories: clinical validity evidence (**`Evi_CV`**), genetic modification evidence (**`Evi_GM`**) and comparative effectiveness evidence (**`Evi_CE`**). Therefore, test case 1 was designed firstly to exhaustively classify 445 individual pieces of evidence into 3 mutually exclusive basic evidence types. Next, each of the three basic evidence types was further classified by 6 categories of outcome measure. As illustrated in **Figure 4.29**, test case 1 created 19 defined classes that should

be inferred as a 2-level hierarchy of evidence types. Furthermore, each defined class should contain a specific number of inferred individual evidence as indicated in parentheses. **Table 4.21** presents the formal representation of 19 defined classes. Existential restrictions involving 5 object properties (*hasComparison*, *hasDrugTherapyOI*, *hasDrugTherapyObserved*, *hasDrugTherapyRef* and *hasOutcomeMeasure*) were used to classify different types of evidence.

Ontology_3 in **Table 4.3** is an extension of Ontology_2 with the addition of defined classes for implementation of Test case 1. Based on Ontology_3, the Hermit reasoner took around 3 seconds to infer the class hierarchy and retrieve the relevant individual evidence (see **Table 4.3**). The inferred class hierarchy (as shown in **Figure 4.30**) is consistent with the intended class hierarchy (as shown in **Figure 3.29**). It is worth noting that 2 non-pharmacogenomics individual evidence (i.e., `evi_01_pub_19717846_stu_1` and `evi_01_pub_17982182_stu_1`) were not inferred as members of any of the 19 defined classes.

In summary, this test case verified the representation patterns of existential restrictions on 5 object properties (i.e., *hasComparison*, *hasDrugTherapyOI*, *hasDrugTherapyRef*, *hasDrugTherapyObserved* and *hasOutcomeMeasure*) and the `isAcquiredFrom` relation that connected an individual piece of evidence to an individual study.

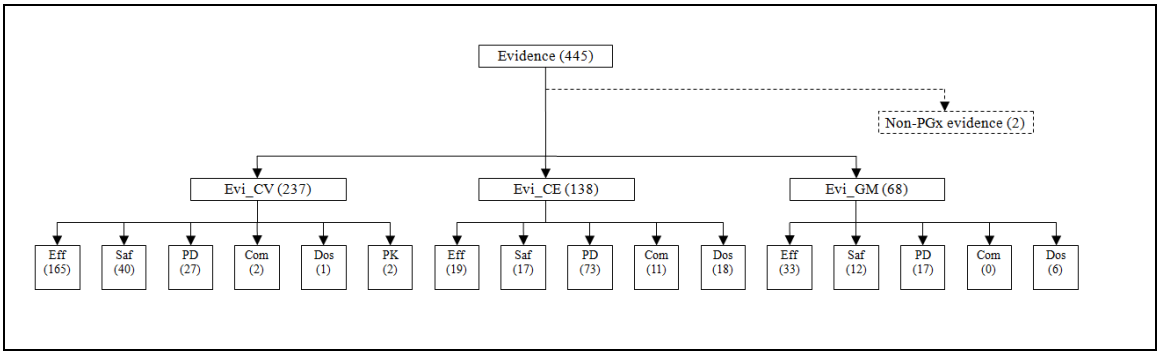

Figure 4.29: Design of classification schemes in test case 1. Evi_CV: clinical validity evidence, Evi_CE: comparative effectiveness evidence, Evi_GM: genetic modification evidence, Eff: efficacy, Saf: safety, PD: pharmacodynamics, Com: composite, Dos: drug dose, PK: pharmacokinetics.

Table 4.21: Formal representation of classification schemes in test case 1

Defined classes (number of class members)	Formal representation of defined classes
Evi_CV (237)	(Evidence and (hasComparison some ComparisonBetweenGenotypeWithinDrugTherapyOI) and (isAcquiredFrom some (Study and (hasDrugTherapyOI some DrugTherapy)))) or (Evidence and (hasComparison some ComparisonBetweenGenotypeWithinDrugTherapyObserved) and (isAcquiredFrom some (Study and (hasDrugTherapyObserved some DrugTherapy)))) or (Evidence and (hasComparison some ComparisonBetweenGenotypeWithinDrugTherapyRef) and (isAcquiredFrom some (Study and (hasDrugTherapyRef some DrugTherapy))))
Evi_CV_Eff (165)	Evi_CV and (hasOutcomeMeasure some ClinicalEfficacyMeasure)
Evi_CV_Saf (40)	Evi_CV and (hasOutcomeMeasure some ClinicalSafetyMeasure)
Evi_CV_PD (27)	Evi_CV and (hasOutcomeMeasure some PharmacodynamicsMeasure)
Evi_CV_Com (2)	Evi_CV and (hasOutcomeMeasure some (ClinicalEfficacySafetyMeasure or CompositeOutcomeMeasure))
Evi_CV_Dos (1)	Evi_CV and (hasOutcomeMeasure some DrugDoseRequirementMeasure)
Evi_CV_PK (2)	Evi_CV and (hasOutcomeMeasure some PharmacokineticsMeasure)
Evi_CE (138)	Evidence and (hasComparison some ComparisonBetweenTreatmentWithoutGenotype) and (isAcquiredFrom some (Study and (hasDrugTherapyOI some (DrugTherapy and (hasDrugTherapyStrategy some PGxDrugTherapy))) and (hasDrugTherapyRef some (DrugTherapy and (hasDrugTherapyStrategy some NonPGxDrugTherapy)))))
Evi_CE_Eff (19)	Evi_CE and (hasOutcomeMeasure some ClinicalEfficacyMeasure)
Evi_CE_Saf (17)	Evi_CE and (hasOutcomeMeasure some ClinicalSafetyMeasure)
Evi_CE_PD (73)	Evi_CE and (hasOutcomeMeasure some PharmacodynamicsMeasure)
Evi_CE_Com (11)	Evi_CE and (hasOutcomeMeasure some (ClinicalEfficacySafetyMeasure or CompositeOutcomeMeasure))
Evi_CE_Dos (18)	Evi_CE and (hasOutcomeMeasure some DrugDosingAccuracyMeasure)
Evi_GM (68)	(Evidence and (hasComparison some ComparisonBetweenTreatmentAndBetweenGenotype) and (isAcquiredFrom some (Study and (hasDrugTherapyOI some (DrugTherapy and (hasDrugTherapyStrategy some NonPGxDrugTherapy))) and (hasDrugTherapyRef some (DrugTherapy and (hasDrugTherapyStrategy some NonPGxDrugTherapy)))))) or (Evidence and (hasComparison some ComparisonBetweenTreatmentWithinGenotype) and (isAcquiredFrom some (Study and (hasDrugTherapyOI some (DrugTherapy and (hasDrugTherapyStrategy some NonPGxDrugTherapy))) and (hasDrugTherapyRef some Placebo)))) or (Evidence and (hasComparison some ComparisonBetweenTreatmentWithinGenotype) and (isAcquiredFrom some (Study and (hasDrugTherapyOI some (DrugTherapy and (hasDrugTherapyStrategy some NonPGxDrugTherapy))) and (hasDrugTherapyRef some (DrugTherapy and (hasDrugTherapyStrategy some NonPGxDrugTherapy)))))) or (Evidence and (hasComparison some ComparisonBetweenTreatmentWithinGenotype) and (isAcquiredFrom some (Study and (hasDrugTherapyOI some (DrugTherapy and (hasDrugTherapyStrategy some PGxDrugTherapy))) and (hasDrugTherapyRef some (DrugTherapy and (hasDrugTherapyStrategy some NonPGxDrugTherapy))))))
Evi_GM_Eff (33)	Evi_GM and (hasOutcomeMeasure some ClinicalEfficacyMeasure)
Evi_GM_Saf (12)	Evi_GM and (hasOutcomeMeasure some ClinicalSafetyMeasure)
Evi_GM_PD (17)	Evi_GM and (hasOutcomeMeasure some PharmacodynamicsMeasure)
Evi_GM_Com (0)	Evi_GM and (hasOutcomeMeasure some (ClinicalEfficacySafetyMeasure or CompositeOutcomeMeasure))
Evi_GM_Dos (6)	Evi_GM and (hasOutcomeMeasure some DrugDosingAccuracyMeasure)

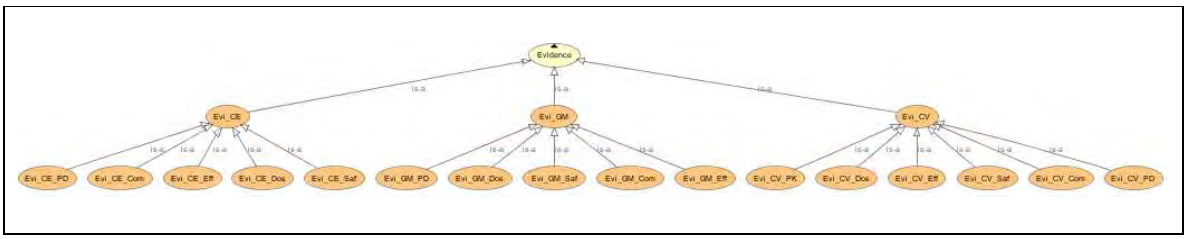

Figure 4.30: Inferred class hierarchy of test case 1. Visualization by OWLViz plugged in Protégé.

4.6.3.2 Test case 2: verify logical consequence of representation pattern of refined qualified cardinality restriction

The primary purpose of test case 2 was to verify the use of the representation pattern of refined qualified cardinality restrictions on describing and differentiating the heterogeneity of genetic variants considered in genotype-guided drug therapy. As illustrated in **Figure 4.31**, 111 pieces of comparative effective evidence of genotype-guided warfarin therapy (**`Evi_CE_Warfarin`**) were first selected from the class **`Evi_CE`** that includes 138 pieces of comparative effective evidence of any drug therapy. Next, **`Evi_CE_Warfarin`** was exhaustively classified into 5 mutually exclusive groups based on the exact numbers and types of genetic variants considered in deciding warfarin initial dose. Then, 3 groups with subsumption relation were created based on the minimal numbers and types of generic variants considered in deciding warfarin initial dose, i.e., at least 1 genetic variant (*CYP2C9*3*), at least 2 genetic variants (*CYP2C9*2* and *CYP2C9*3*) and at least 3 genetic variants (*CYP2C9*2* and *CYP2C9*3* and *VKORC1-1639G/A*), respectively. As shown in **Table 4.22**, the combination of the *`considersGeneticVariant`* property with constructor of qualified cardinality restriction (i.e., `exactly`) and different classes of genetic variants as property values is the key to differentiate the heterogeneity of genetic variants considered in genotype-guided drug therapies, whereas, the combination of the *`considersGeneticVariant`* property with constructor of existential restriction (i.e., `some`) is sufficient to infer subsumption relations between groups differing in minimal variants included in drug dose decision.

Ontology_4 in **Table 4.3** is an extension of Ontology_2 with the addition of defined classes for implementation of Test case 2. Based on Ontology_4, the Hermit reasoner took around 108 minutes to infer the class hierarchy and retrieve all the relevant individual evidence (see **Table 4.3**). The inferred class hierarchy is shown in **Figure 4.32**, which is consistent with the intended class hierarchy shown in **Figure 4.31**. The inferred members of 9 defined classes were manually checked as correct. This test case verified that the representation patterns of refined qualified cardinality restrictions on the object property `considersGeneticVariant` allowed retrieval of comparative effectiveness evidence of pharmacogenomics guided warfarin therapies that considered exactly or at least a set of enumerated genetic variant(s). The results indicated that the expressivity of the refined qualified cardinality restrictions was sufficient to describe and differentiate the heterogeneous genotype-guided drug therapies. However, its sophisticated expression may make the reasoning inefficient.

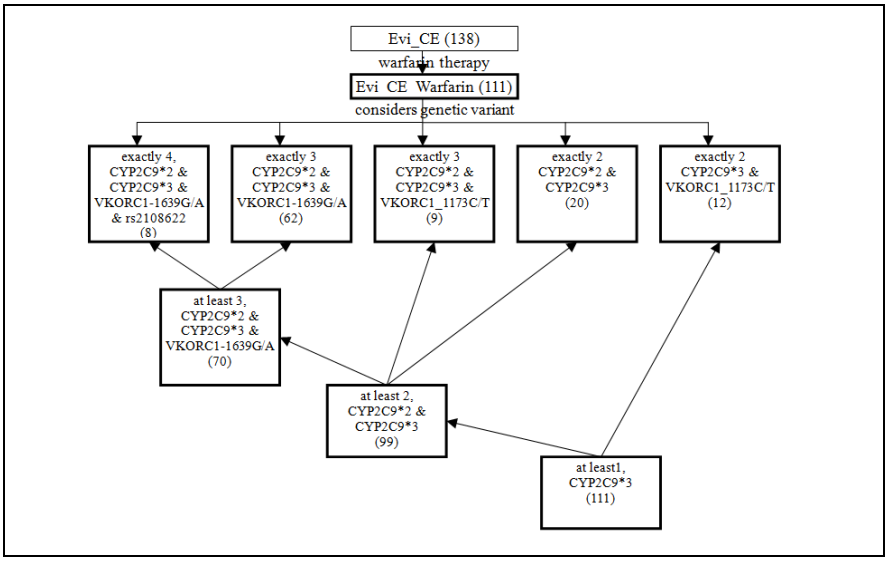

Figure 4.31: Design of classification schemes in test case 2

Table 4.22: Formal representation of classification schemes in test case 2

Defined classes (number of class members)	Formal representation of defined class
Evi_CE_Warfarin (111)	Evi_CE and (isAcquiredFrom some (Study and (hasDrugTherapyOI some (WarfarinTherapy and hasDrugTherapyStrategy some PGxDrugTherapy)) and (hasDrugTherapyRef some (WarfarinTherapy and hasDrugTherapyStrategy some NonPGxDrugTherapy))))
Evi_CE_Warfarin_2V _CYP2C9star2and3 (20)	Evi_CE_Warfarin and (isAcquiredFrom some (Study and (hasDrugTherapyOI some (WarfarinTherapy and hasDrugTherapyStrategy some (PGxDrugTherapy and ((considersGeneticVariant exactly 2 GeneticVariant) and (considersGeneticVariant exactly 1 CYP2C9star2) and (considersGeneticVariant exactly 1 CYP2C9star3)))))))
Evi_CE_Warfarin_2V _CYP2C9star3 andVKORC1_1173 (12)	Evi_CE_Warfarin and (isAcquiredFrom some (Study and (hasDrugTherapyOI some (WarfarinTherapy and hasDrugTherapyStrategy some (PGxDrugTherapy and ((considersGeneticVariant exactly 2 GeneticVariant) and (considersGeneticVariant exactly 1 CYP2C9star3) and (considersGeneticVariant exactly 1 VKORC1_C1173T)))))))
Evi_CE_Warfarin_3V _CYP2C9star2and3 andVKORC1_-1639 (62)	Evi_CE_Warfarin and (isAcquiredFrom some (Study and (hasDrugTherapyOI some (WarfarinTherapy and hasDrugTherapyStrategy some (PGxDrugTherapy and ((considersGeneticVariant exactly 3 GeneticVariant) and (considersGeneticVariant exactly 1 CYP2C9star2) and (considersGeneticVariant exactly 1 CYP2C9star3) and (considersGeneticVariant exactly 1 VKORC1_G-1639A)))))))
Evi_CE_Warfarin_3V _CYP2C9star2and3 andVKORC1_1173 (9)	Evi_CE_Warfarin and (isAcquiredFrom some (Study and (hasDrugTherapyOI some (WarfarinTherapy and hasDrugTherapyStrategy some (PGxDrugTherapy and ((considersGeneticVariant exactly 3 GeneticVariant) and (considersGeneticVariant exactly 1 CYP2C9star2) and (considersGeneticVariant exactly 1 CYP2C9star3) and (considersGeneticVariant exactly 1 VKORC1_C1173T)))))))
Evi_CE_Warfarin_4V _CYP2C9star2and3 andVKORC1_-1639 andrs2108622 (8)	Evi_CE_Warfarin and (isAcquiredFrom some (Study and (hasDrugTherapyOI some (WarfarinTherapy and hasDrugTherapyStrategy some (PGxDrugTherapy and ((considersGeneticVariant exactly 4 GeneticVariant) and (considersGeneticVariant exactly 1 CYP2C9star2) and (considersGeneticVariant exactly 1 CYP2C9star3) and (considersGeneticVariant exactly 1 VKORC1_G-1639A) and (considersGeneticVariant exactly 1 rs2108622)))))))
Evi_CE_Warfarin_min1V _CYP2C9star3 (111)	Evi_CE_Warfarin and (isAcquiredFrom some (Study and (hasDrugTherapyOI some (WarfarinTherapy and hasDrugTherapyStrategy some (PGxDrugTherapy and considersGeneticVariant some CYP2C9star3)))))
Evi_CE_Warfarin_min2V _CYP2C9star3and2 (99)	Evi_CE_Warfarin and (isAcquiredFrom some (Study and (hasDrugTherapyOI some (WarfarinTherapy and hasDrugTherapyStrategy some (PGxDrugTherapy and ((considersGeneticVariant some CYP2C9star3) and (considersGeneticVariant some CYP2C9star2)))))))
Evi_CE_Warfarin_min3V _CYP2C9star3and2 andVKORC1_1639 (70)	Evi_CE_Warfarin and (isAcquiredFrom some (Study and (hasDrugTherapyOI some (WarfarinTherapy and hasDrugTherapyStrategy some (PGxDrugTherapy and ((considersGeneticVariant some CYP2C9star2) and (considersGeneticVariant some CYP2C9star3) and (considersGeneticVariant some VKORC1_G-1639A)))))))

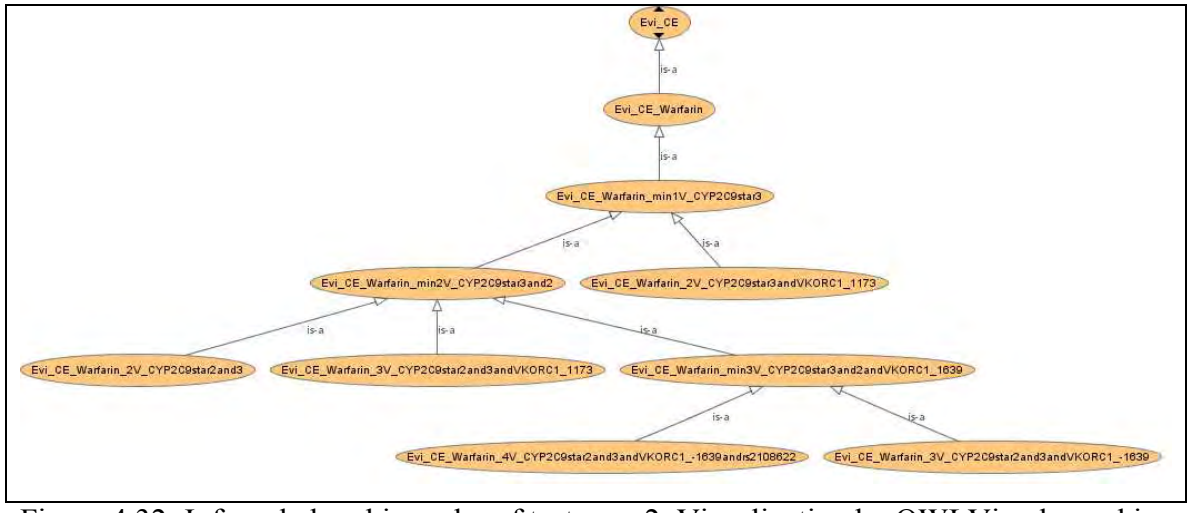

Figure 4.32: Inferred class hierarchy of test case 2. Visualization by OWLViz plugged in Protégé.

4.6.3.3 Test case 3: verify logical consequence of representation pattern of existential restriction with subproperties used in conjunction of class expressions

The primary purpose of test case 3 was to verify the use of the representation pattern of existential restrictions with subproperties on the *hasGeneticVariant* property to describe and differentiate the heterogeneity of genetic variants included in determining genotypes of study subjects. As illustrated in **Figure 4.33**, 158 pieces of evidence on the clinical efficacy of clopidogrel therapy (**Evi_CV_Eff_Clopidogrel**) were first selected from the class **Evi_CV_Eff** that includes 165 pieces of evidence on the clinical efficacy of any drug therapy. Though **Evi_CV_Eff_Clopidogrel** could be further classified by 5 different genetic contrasts, only 119 pieces of evidence that described the comparison between carriers of 1 or 2 alleles and noncarriers (**Evi_CV_Eff_Clopidogrel_1or2vs0**) were selected for verification. Then, **Evi_CV_Eff_Clopidogrel_1or2vs0** was exhaustively classified into 7 mutually exclusive defined classes based on the numbers and types of genetic variants included in determining genotypes that involved in genetic contrasts. Then, 4 defined classes were created for 2 purposes; first, to differentiate between single and multiple variants; second, to infer subsumption relations among multiple variants (see the grey highlighted definitions in **Table 4.23**). Based on the formal representation presented in **Table 4.23**, the combination of subproperties of *hasGeneticVariant* with the existential restriction constructor `some` and different classes of genetic variants as property values is the key to classify a group of evidence on the clinical efficacy of clopidogrel therapy that compared different carrier statuses to noncarriers.

Ontology_5 in Table 4.3 is an extension of Ontology_2 with the addition of defined classes for implementation of Test case 3. Based on Ontology_5, the Hermit reasoner took around 4 seconds to infer the class hierarchy and retrieve all the relevant individual evidence (see **Table**

4.3). The inferred class hierarchy is shown in **Figure 4.34**, which is consistent with the intended class hierarchy shown in **Figure 4.33**. The inferred members of all the 13 defined classes were manually checked as correct. The results indicate that the expressivity of existential restriction with subproperties of *hasGeneticVariant* property is sufficient to describe and differentiate the heterogeneous genotype comparisons among pharmacogenomics clinical efficacy evidence; moreover, it contributed to a very efficient retrieval of formally represented pharmacogenomics evidence.

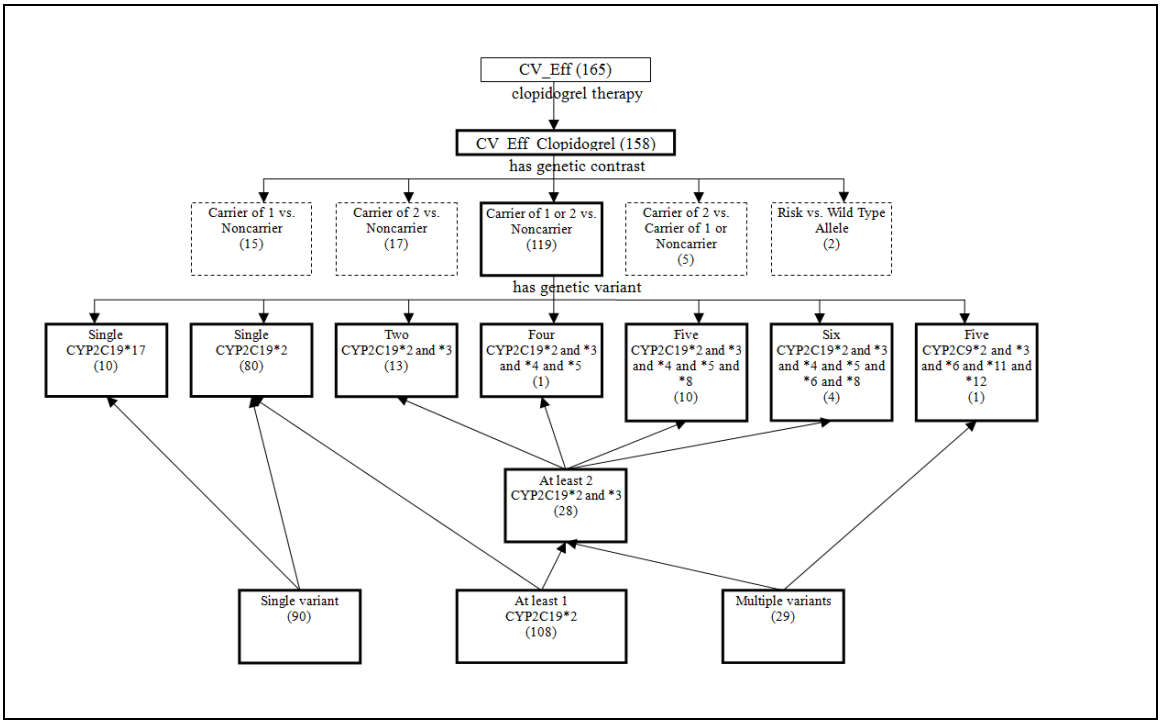

Figure 4.33: Design of classification schemes in test case 3

Table 4.23: Formal representation of classification schemes in test case 3

Defined classes (number of class members)	Formal representation of defined classes
Evi_CV_Eff_Clopidogrel (158)	Evi_CV_Eff and (isAcquiredFrom some (Study and ((hasDrugTherapyOI some (ClopidogrelTherapy and (hasDrugTherapyStrategy some FixedDrugDose))) or (hasDrugTherapyObserved some (ClopidogrelTherapy and (hasDrugTherapyStrategy some FixedDrugDose))) or (hasDrugTherapyRef some (ClopidogrelTherapy and (hasDrugTherapyStrategy some FixedDrugDose))))))
Evi_CV_Eff_Clopidogrel_1or2vs0 (119)	Evi_CV_Eff_Clopidogrel and (hasGeneticContrast some CarrierOfAtLeast1VsNoncarrier)
Evi_CV_Eff_Clopidogrel_1or2vs0_1V_CYP2C19star17 (10)	Evi_CV_Eff_Clopidogrel and (hasGeneticContrast some (CarrierOfAtLeast1VsNoncarrier and (hasSingleGeneticVariant some CYP2C19star17)))
Evi_CV_Eff_Clopidogrel_1or2vs0_1V_CYP2C19star2 (80)	Evi_CV_Eff_Clopidogrel and (hasGeneticContrast some (CarrierOfAtLeast1VsNoncarrier and (hasSingleGeneticVariant some CYP2C19star2)))
Evi_CV_Eff_Clopidogrel_1or2vs0_2V_CYP2C19star2and3 (13)	Evi_CV_Eff_Clopidogrel and (hasGeneticContrast some (CarrierOfAtLeast1VsNoncarrier and ((hasTwoGeneticVariant some CYP2C19star2) and (hasTwoGeneticVariant some CYP2C19star3))))
Evi_CV_Eff_Clopidogrel_1or2vs0_4V_CYP2C19star2and3and4and5 (1)	Evi_CV_Eff_Clopidogrel and (hasGeneticContrast some (CarrierOfAtLeast1VsNoncarrier and ((hasFourGeneticVariant some CYP2C19star2) and (hasFourGeneticVariant some CYP2C19star3) and (hasFourGeneticVariant some CYP2C19star4) and (hasFourGeneticVariant some CYP2C19star5))))
Evi_CV_Eff_Clopidogrel_1or2vs0_5V_CYP2C19star2and3and4and5and8 (10)	Evi_CV_Eff_Clopidogrel and (hasGeneticContrast some (CarrierOfAtLeast1VsNoncarrier and ((hasFiveGeneticVariant some CYP2C19star2) and (hasFiveGeneticVariant some CYP2C19star3) and (hasFiveGeneticVariant some CYP2C19star4) and (hasFiveGeneticVariant some CYP2C19star5) and (hasFiveGeneticVariant some CYP2C19star8))))
Evi_CV_Eff_Clopidogrel_1or2vs0_5V_CYP2C9star2and3and6and11and12 (1)	Evi_CV_Eff_Clopidogrel and (hasGeneticContrast some (CarrierOfAtLeast1VsNoncarrier and ((hasFiveGeneticVariant some CYP2C9star2) and (hasFiveGeneticVariant some CYP2C9star3) and (hasFiveGeneticVariant some CYP2C9star6) and (hasFiveGeneticVariant some CYP2C9star11) and (hasFiveGeneticVariant some CYP2C9star12))))
Evi_CV_Eff_Clopidogrel_1or2vs0_6V_CYP2C19star2and3and4and5and6and8 (4)	Evi_CV_Eff_Clopidogrel and (hasGeneticContrast some (CarrierOfAtLeast1VsNoncarrier and ((hasSixGeneticVariant some CYP2C19star2) and (hasSixGeneticVariant some CYP2C19star3) and (hasSixGeneticVariant some CYP2C19star4) and (hasSixGeneticVariant some CYP2C19star5) and (hasSixGeneticVariant some CYP2C19star6) and (hasSixGeneticVariant some CYP2C19star8))))
Evi_CV_Eff_Clopidogrel_SingleV (90)	Evi_CV_Eff_Clopidogrel and (hasGeneticContrast some (CarrierOfAtLeast1VsNoncarrier and (hasSingleGeneticVariant some GeneticVariant)))
Evi_CV_Eff_Clopidogrel_multipleV (29)	Evi_CV_Eff_Clopidogrel and (hasGeneticContrast some (CarrierOfAtLeast1VsNoncarrier and (hasMultipleGeneticVariant some GeneticVariant)))
Evi_CV_Eff_Clopidogrel_min1V_CYP2C19star2 (108)	Evi_CV_Eff_Clopidogrel and (hasGeneticContrast some (CarrierOfAtLeast1VsNoncarrier and (hasGeneticVariant some CYP2C19star2)))
Evi_CV_Eff_Clopidogrel_min2V_CYP2C19star2and3 (28)	Evi_CV_Eff_Clopidogrel and (hasGeneticContrast some (CarrierOfAtLeast1VsNoncarrier and ((hasMultipleGeneticVariant some CYP2C19star2) and (hasMultipleGeneticVariant some CYP2C19star3))))

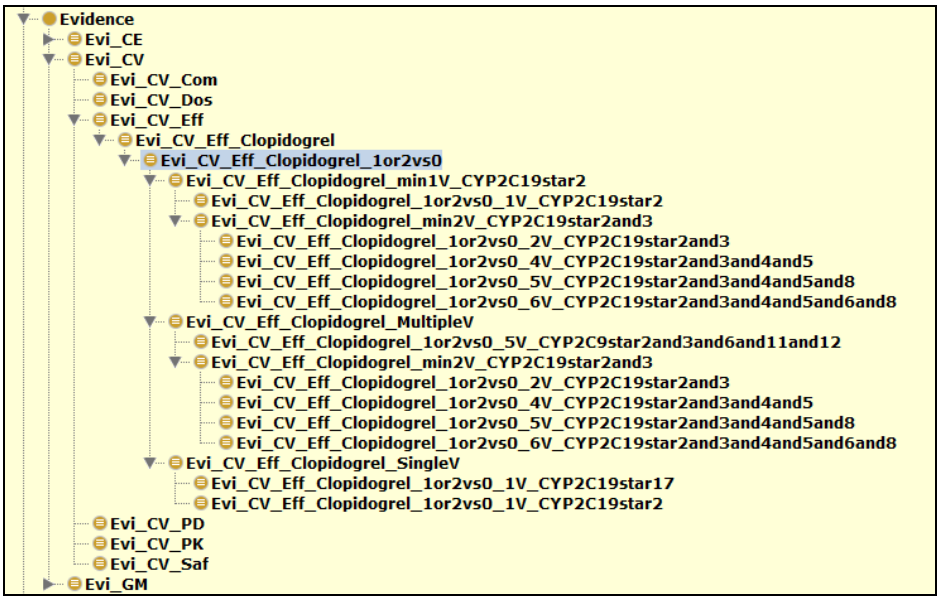

Figure 4.34: Inferred class hierarchy of test case 3. This is a screenshot extracted from Protégé.

4.6.3.4 Test case 4: verify logical consequence of representation pattern of existential restriction with subproperties used in union of class expressions

Test case 4 aimed to verify the use of the representation pattern of existential restrictions with subproperties of the *hasComponent* property to describe and differentiate the heterogeneity of outcome measure in pharmacogenomics clinical studies. As illustrated in **Figure 4.35**, 158 pieces of evidence on the clinical efficacy of clopidogrel therapy (**Evi_CV_Eff_Clopidogrel**) were exhaustively classified into 6 mutually exclusive defined classes based on the number of events included as the component of the outcome measure. Then, each of the 6 groups was further classified into mutually exclusive defined classes based on the categories of the events used as the restricted values of the subproperties of *hasComponent* property. In other words, the additionally created 27 mutually exclusive defined classes should be inferred into a 2-level class hierarchy (See grey highlighted areas in **Figure 4.35**). Next, 11 pieces of evidence with the outcome measure components of death or myocardial infarction (**Evi_CV_Eff_Clopidogrel_2E_CVDorMI**) were further classified into two mutually exclusive classes by the subcategories of death, i.e., cardiovascular death (**Evi_CV_Eff_Clopidogrel_2E_CVDorMI**) or death of all causes (**Evi_CV_Eff_Clopidogrel_2E_AllDorMI**). Then, 2 defined classes were created to retrieve all relevant evidence that measured at most 3 outcomes including (Death or Myocardial Infarction or Stroke) and at least 2 and at most 3 outcomes including (Death or Myocardial Infarction or Stroke) respectively. (See definitions listed in **Table 4.24**).

Ontology_6 in Table 4.3 is an extension of Ontology_2 with the addition of defined classes for implementation of Test case 4. Based on Ontology_6, the Hermit reasoner took around 2.5 minutes (see **Table 4.3**) to infer the class hierarchy and retrieve all the relevant individual

evidence (see **Figure 4.36**). The inferred results were manually checked and they were consistent with the intended class hierarchy shown in **Figure 4.35**. This test case verified the representation patterns of existential restriction with subproperties on the `hasComponent` property and a comprehensive retrieval of any efficacy evidence of clopidogrel that measured at most some events. The inference results indicated that the expressivity of existential restriction with subproperties was not only sufficient to infer subsumption relations between defined classes correctly but also efficient to retrieve relevant individual evidence that satisfied the defined necessary and sufficient conditions (see **Figure 4.36**).

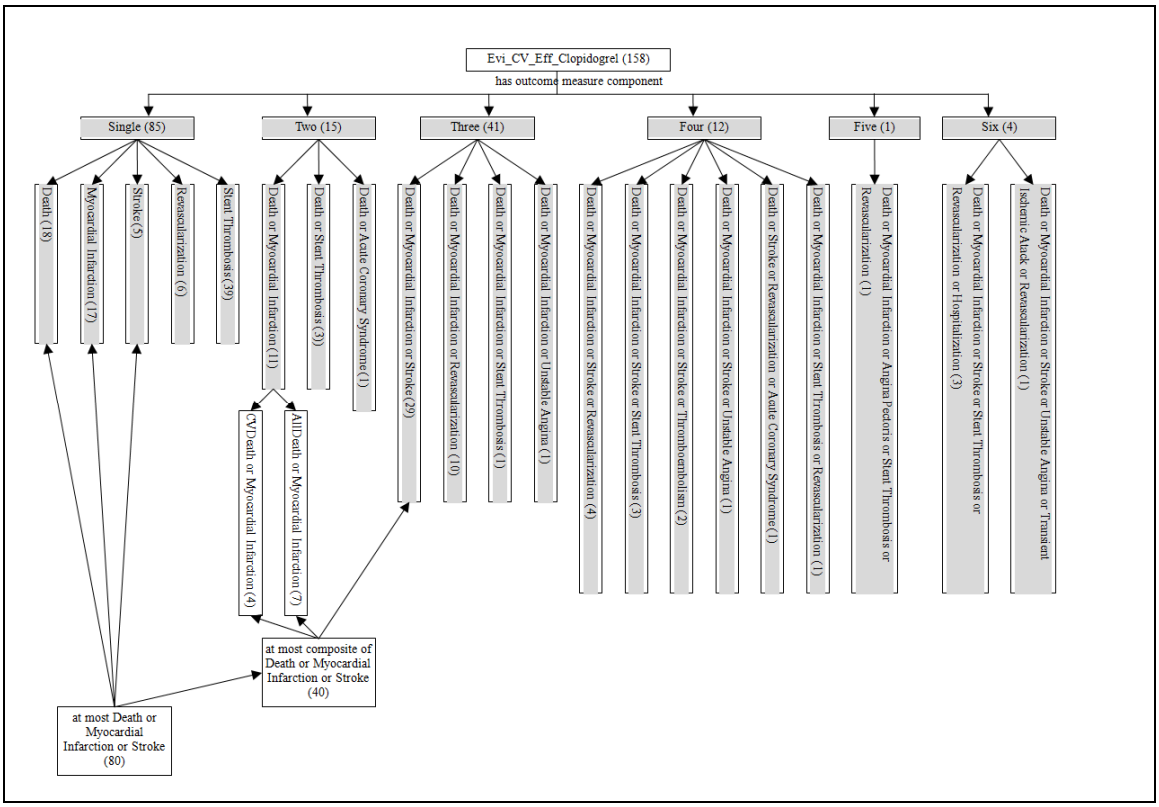

Figure 4.35: Design of classification schemes in test case 4

Table 4.24: Formal representation of classification schemes designed in test case 4

Defined class (number of class members)	Formal representation of defined classes*
Evi_CV_Eff_Clopidogrel_1E (85)	Evi_CV_Eff_Clopidogrel and (hasOutcomeMeasure some (ClinicalEfficacyMeasure and (hasSingleComponent some (AdverseEvent or Disease or Procedure))))
Evi_CV_Eff_Clopidogrel_2E (15)	Evi_CV_Eff_Clopidogrel and (hasOutcomeMeasure some (ClinicalEfficacyMeasure and (hasTwoComponent some (AdverseEvent or Disease or Procedure))))
Evi_CV_Eff_Clopidogrel_3E (41)	Evi_CV_Eff_Clopidogrel and (hasOutcomeMeasure some (ClinicalEfficacyMeasure and (hasThreeComponent some (AdverseEvent or Disease or Procedure))))
Evi_CV_Eff_Clopidogrel_4E (12)	Evi_CV_Eff_Clopidogrel and (hasOutcomeMeasure some (ClinicalEfficacyMeasure and (hasFourComponent some (AdverseEvent or Disease or Procedure))))
Evi_CV_Eff_Clopidogrel_5E (1)	Evi_CV_Eff_Clopidogrel and (hasOutcomeMeasure some (ClinicalEfficacyMeasure and (hasFiveComponent some (AdverseEvent or Disease or Procedure))))
Evi_CV_Eff_Clopidogrel_6E (4)	Evi_CV_Eff_Clopidogrel and (hasOutcomeMeasure some (ClinicalEfficacyMeasure and (hasSixComponent some (AdverseEvent or Disease or Procedure))))
Evi_CV_Eff_Clopidogrel_1E_D (18)	Evi_CV_Eff_Clopidogrel and (hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasSingleComponent some Death))
Evi_CV_Eff_Clopidogrel _1E_MI (17)	Evi_CV_Eff_Clopidogrel and (hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasSingleComponent some MyocardialInfarction))
Evi_CV_Eff_Clopidogrel _1E_Sk (5)	Evi_CV_Eff_Clopidogrel and (hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasSingleComponent some Stroke))
Evi_CV_Eff_Clopidogrel _1E_ST (39)	Evi_CV_Eff_Clopidogrel and (hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasSingleComponent some StentThrombosis))
Evi_CV_Eff_Clopidogrel _1E_RV (6)	Evi_CV_Eff_Clopidogrel and (hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasSingleComponent some Revascularization))
Evi_CV_Eff_Clopidogrel _2E_DorMI (11)	Evi_CV_Eff_Clopidogrel and (hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasTwoComponent some (Death or MyocardialInfarction)))
Evi_CV_Eff_Clopidogrel _2E_CVDorMI (4)	Evi_CV_Eff_Clopidogrel and (hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasTwoComponent some (CVDeath or MyocardialInfarction)))
Evi_CV_Eff_Clopidogrel _2E_AllDorMI (7)	Evi_CV_Eff_Clopidogrel and (hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasTwoComponent some (AllCauseDeath or MyocardialInfarction)))
Evi_CV_Eff_Clopidogrel _2E_DorST (3)	Evi_CV_Eff_Clopidogrel and (hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasTwoComponent some (Death or StentThrombosis)))
Evi_CV_Eff_Clopidogrel _2E_DorACS (1)	Evi_CV_Eff_Clopidogrel and (hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasTwoComponent some (Death or AcuteCoronarySyndrome)))
Evi_CV_Eff_Clopidogrel _3E_DorMIorSk (29)	Evi_CV_Eff_Clopidogrel and (hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasThreeComponent some (Death or MyocardialInfarction or Stroke)))
Evi_CV_Eff_Clopidogrel _3E_DorMIorRV (10)	Evi_CV_Eff_Clopidogrel and hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasThreeComponent some (Death or MyocardialInfarction or Revascularization))
Evi_CV_Eff_Clopidogrel _3E_DorMIorST (1)	Evi_CV_Eff_Clopidogrel and hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasThreeComponent some (Death or MyocardialInfarction or StentThrombosis))
Evi_CV_Eff_Clopidogrel _3E_DorMIorUA (1)	Evi_CV_Eff_Clopidogrel and hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasThreeComponent some (Death or MyocardialInfarction or UnstableAngina))
Evi_CV_Eff_Clopidogrel _4E_DorMIorSkorRV (4)	Evi_CV_Eff_Clopidogrel and hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasFourComponent some (Death or MyocardialInfarction or Stroke or Revascularization))
Evi_CV_Eff_Clopidogrel _4E_DorMIorSkorST (3)	Evi_CV_Eff_Clopidogrel and hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasFourComponent some (Death or MyocardialInfarction or Stroke or StentThrombosis))
Evi_CV_Eff_Clopidogrel _4E_DorMIorSkorTE (2)	Evi_CV_Eff_Clopidogrel and hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasFourComponent some (Death or MyocardialInfarction or Stroke or Thromboembolism))
Evi_CV_Eff_Clopidogrel _4E_DorMIorSkorUA (1)	Evi_CV_Eff_Clopidogrel and hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasFourComponent some (Death or MyocardialInfarction or Stroke or UnstableAngina))
Evi_CV_Eff_Clopidogrel _4E_DorSkorRVorACS (1)	Evi_CV_Eff_Clopidogrel and hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasFourComponent some (Death or Stroke or Revascularization or AcuteCoronarySyndrome))
Evi_CV_Eff_Clopidogrel _4E_DorMIorSTorRV (1)	Evi_CV_Eff_Clopidogrel and hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasFourComponent some (Death or MyocardialInfarction or StentThrombosis or Revascularization))
Evi_CV_Eff_Clopidogrel _5E_DorMIorSTorRVorAP (1)	Evi_CV_Eff_Clopidogrel and hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasFiveComponent some (Death or MyocardialInfarction or AnginaPectoris or StentThrombosis or Revascularization))
Evi_CV_Eff_Clopidogrel_6E _DorMIorSkorSTorRVorH (3)	Evi_CV_Eff_Clopidogrel and hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasSixComponent some (Death or MyocardialInfarction or Stroke or StentThrombosis or Revascularization or Hospitalization))
Evi_CV_Eff_Clopidogrel_6E_ DorMIorSkorUAorRVorTIA (1)	Evi_CV_Eff_Clopidogrel and hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasSixComponent some (Death or MyocardialInfarction or Stroke or UnstableAngina or TransientIschemicAttack or Revascularization))
Evi_CV_Eff_Clopidogrel_max 3EComposite_DorMIorSk (40)	Evi_CV_Eff_Clopidogrel and (hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasMultipleComponent some (Death or MyocardialInfarction or Stroke)))
Evi_CV_Eff_Clopidogrel _max3E_DorMIorSk (80)	Evi_CV_Eff_Clopidogrel and (hasOutcomeMeasure some (ClinicalEfficacyMeasure and hasComponent some (Death or MyocardialInfarction or Stroke)))

*See Table 4.23 for the formal representation of Evi_CV_Eff_Clopidogrel.

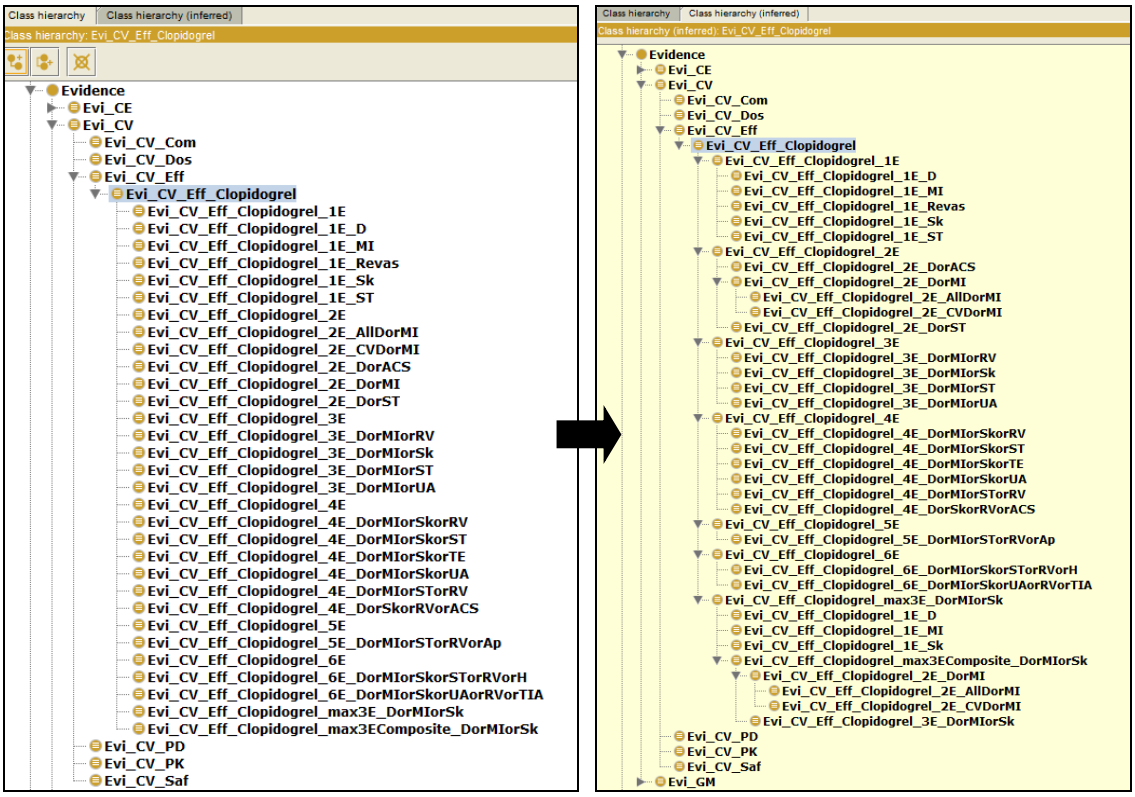

Figure 4.36: Asserted class hierarchy versus inferred class hierarchy in test case 4. This is a screenshot extracted from Protégé.

4.7 Discussion

This study aimed to develop a knowledge-based system that enables formal representation and automatic retrieval of pharmacogenomics evidence for systematic review with meta-analysis. OWL 2 DL is an appropriate choice as the formal language because of its language expressivity and reasoning capabilities. Therefore, OWL 2 DL was exploited to develop the envisioned knowledge-based system that includes an ontology, a knowledge base and an open source reasoner Hermit.

4.7.1 Major findings

The ontology was built with the primary aim to support the semantic annotation of heterogeneous pharmacogenomics evidence and the efficient reasoning over formally represented evidence. The constructed ontology is comprised of a collection of around 400 vocabulary words that commonly appeared in the domain of pharmacogenomics evidence assessment. Three-fourths of the vocabulary words were declared as classes for two reasons. First, the subsumption relations (i.e., the "is-a" relations) between classes stated in `SubClassOf` axioms provided a logical basis for organizing classes into a hierarchy. Second, pharmacogenomics knowledge was too complicated to describe in one simple word, the representation of complex pharmacogenomics knowledge regarding 73 individual publications, 82 individual studies and 445 individual evidence required using complex class expressions to describe the essential content including publication type, study population, study design, drug therapy, comparison, genetic variation, outcome and effect metric. Since a general form of the complex class expressions was an object property followed by a restriction constructor as property constraint and a class as property value, most of the vocabulary words were declared as classes to satisfy the representation requirement. Furthermore, multiple classes were also frequently used as property values to describe various drug therapies, genetic variations and outcomes of asserted individuals, therefore, two representation patterns i.e., existential restrictions with subproperties and refined qualified cardinality restrictions that were capable of differentiating and classifying heterogeneous content were adopted when asserting an individual study or evidence.

As a result, 3 sets of class expressions that involved existential restrictions were created to describe various publication types among 73 individual publications, 97 sets of class expressions

that involved existential restrictions and refined qualified cardinality restrictions were created to describe various study populations, study designs and drug therapies among 82 individual studies and 174 sets of class expressions that involved existential restrictions and existential restrictions with subproperties were created to describe various comparisons, genetic variations, outcomes and effect metrics among 445 individual evidence. The advantage of the formal representation of heterogeneous and complex pharmacogenomics knowledge based on class expressions was that the inherent heterogeneity of pharmacogenomics knowledge was explicitly revealed by the building blocks that made up the complex class expressions. In other words, object properties and classes that involved in assertions were capable of unambiguously revealing the heterogeneity of pharmacogenomics knowledge.

In addition to complex class expressions that were used to assert an individual evidence directly, `SubPropertyChainOf` axioms were used to allow indirect assertions such as that an individual evidence was extracted from a particular individual publication. Therefore, `SubPropertyChainOf` axioms were useful in reducing the burden of manual evidence annotation because they allowed a DL reasoner to automatically generate the *`isExtractedFrom`* relationship that connected an individual piece of evidence to a particular individual publication. It was also worth noting that the design of three types of asserted individuals (i.e., publication, study and evidence) instead of only one type of asserted individual (i.e., evidence) also improved the labor-intensive evidence annotation process. It meant that when asserting a group of individual evidence that were extracted from the same publication and study, rather than repeatedly stating the essential content such as publication year, PubMed identifier, study population, study design, results of risk of bias assessment, etc., those content stated only once when asserting a specific individual publication and a specific individual study.

Besides `SubPropertyChainOf` axioms, `EquivalentClasses` axioms allowed a DL reasoner not only to automatically infer the "is-a" relations between defined classes but also to retrieve all the relevant asserted individuals if they were satisfied the necessary and sufficient conditions described in the defined classes. Therefore, the verification of individual assertions was largely reliant on a DL reasoner and defined classes with specifically designed necessary and sufficient conditions.

Based on the results of 4 test cases, the class expressions that involved the representation pattern of existential restrictions were sufficient, efficient and suitable for representing some simple content such as publication types and study designs. Both representation patterns of existential restrictions with subproperties and refined qualified cardinality restrictions were sufficient to represent and differentiate heterogeneous asserted individuals with complex content such as drug therapies, genetic variations and outcomes. However, since it took almost 2 hours to retrieve the relevant comparative effective evidence of genotype-guided warfarin therapies which were represented using refined qualified cardinality restrictions, the long computing time suggests that the pattern of refined qualified cardinality restrictions was less efficient than the pattern of existential restrictions with subproperties.

4.7.2 Limitations

While the complex class expressions that involved all three above-mentioned representation patterns had been successfully applied to pharmacogenomics evidence annotation, there was a limitation to the three representation patterns when they were applied to perform a comprehensive retrieval of evidence that measured at least a single outcome or at least some outcomes. Such class expressions were not expressible by any representation patterns because the outcomes had been represented by a union of class expressions that comprised a subproperty

such as `hasThreeComponent` which explicitly denoted the total number of events that were measured in outcomes. Since the meaning of "at least something" implied something (specified) and something else (unspecified), it was unable to retrieve all the relevant evidence that satisfied the necessary and sufficient conditions unless the measured events and the total number of measured events were clearly specified in the defined classes.

4.7.3 Contributions

From the perspective of biomedical informatics, the research work in Aim 2 delivers an ontology and a number of representation patterns, which exploit the advanced constructors of OWL 2 DL with novel ideas. These representation patterns allow complex and heterogeneous pharmacogenomics evidence to be unambiguously represented and differentiated from each other. The ideas and methods that underlie the design of an OWL ontology and the implementation of an ontology-driven knowledge base in this study could be used by others who are interested in applying knowledge representation and reasoning to biomedical knowledge management. Furthermore, the limitations of OWL 2 DL constructors have been identified during designing representation patterns and test cases. The identified limitations of OWL 2 DL could motivate researchers to develop more constructors in order to satisfy the representation requirements for advanced applications.

4.8 CONCLUSIONS

My overall research goal was to build a knowledge-based system that fulfills three critical features including clinically relevant evidence, evidence-based approach, and semantically computable formalism to facilitate effective and efficient evidence assessment that supports decisions on adoption of pharmacogenomics in clinical practice. In Chapter 3, a conceptual

model has been developed to provide the conceptualization of the domain of pharmacogenomics evidence assessment. The model addressed the features of evidence-based approach by identifying 3 information entities (i.e., publication, study, and evidence) and 9 information components (i.e., bibliographical information, study design, study population, drug therapy, risk of bias assessment, comparison, outcome, genetic variation, and effect). The conceptual model addressed the feature of clinically relevant evidence by characterizing empirical evidence concerning the clinical validity and utility of clopidogrel and warfarin pharmacogenomics to derive essential building blocks (i.e., 30 concepts, 49 relations and around 250 terms) that could be used to substantiate the information content of the 3 information entities. Built on the conceptual model, the research in this chapter focused on realizing the feature of semantically computable formalism when implementing the envisioned knowledge-based system. This chapter has constructed, implemented and verified an OWL 2 DL ontology as well as a ontology-driven knowledge base that provides formally annotated pharmacogenomics publications, studies and evidence. OWL 2 DL demonstrates sufficient expressive power to represent heterogeneous pharmacogenomics evidence. Furthermore, the formally annotated evidence can be correctly and efficiently retrieved based on formally represented criteria. Since the goal of making pharmacogenomics evidence more accessible and computable has been achieved, in next chapter, some applications involved in the process of pharmacogenomics evidence assessment will be demonstrated using the implemented pharmacogenomics knowledge-based system. For example, inclusion criteria for a collection of existing meta-analyses will be transformed into sets of defined classes in order to evaluate the effectiveness (i.e., precision) and efficiency (i.e., computing time) of the implemented knowledge-based system as an informatics approach to support automatic evidence retrieval. Then, R, a language and environment for statistical

computing, will be incorporated with the system to demonstrate that a knowledge-based system is an effective and efficient informatics approach to provide evidence-based interpretation of the clinical significance of pharmacogenomics.

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Chapter 5. APPLICATIONS OF THE DEVELOPED PHARMACOGENOMICS KNOWLEDGE-BASED SYSTEM: ONTOLOGY-DRIVEN EVIDENCE RETRIEVAL, CLSSIFICATION AND INTERPRETATION IN SYSTEMAIC REVIEWS WITH META-ANALYSIS

5.1 INTRODUCTION

In the preceding chapter, the constructed OWL 2 DL ontology had proved its capability of formal representation of empirical pharmacogenomics evidence and the consistency of the formally asserted pharmacogenomics evidence had also been verified. The overarching goal of formal representation of pharmacogenomics evidence is to facilitate effective and efficient assessment of the clinical significance of genotype-guided drug therapy, hence, support more widespread adoption of pharmacogenomics into routine clinical care. Continuing with the results of Chapter 4, the aim of this chapter is to demonstrate that the developed pharmacogenomics knowledge-based system, with its core components of an OWL 2 DL ontology, a knowledge base instantiated with formally represented pharmacogenomics evidence and a DL reasoner, is capable of facilitating the following applications: (1) precise and efficient evidence retrieval for systematic review with meta-analysis, (2) effective and efficient assessment of the effects of *CYP2C19* loss-of-function variants on various outcomes among patients treated with clopidogrel, (3) effective and efficient assessment of the comparative effectiveness of genotype-guided versus non-genotype-guided dosing of warfarin, and (4) automatic inferences of the clinical significance of *CYP2C19* loss-of-function variants and genotype-guided dosing of warfarin. The step-wise implementation of the four applications will be presented in the following sections.

The first application is presented in Section 5.2. It focuses mainly on retrieving pharmacogenomics evidence from the developed knowledge base using test cases that are inclusion criteria applied in a collection of 33 existing meta-analyses. Precision and computing time taken by the HermiT reasoner to perform the instance checking are used to evaluate the effectiveness and efficiency of the evidence retrieval task enabled by the developed pharmacogenomics knowledge-based system.

The second and the third applications are presented in Section 5.3. These two applications involve a series of steps in conducting a systematic review with meta-analysis. First, predefined classification schemes are used to examine the current status of available evidence before embarking on a systematic review with meta-analysis. Thereafter, decisions about which meta-analyses to conduct and which individual evidence to include in meta-analysis are made. Then data for meta-analysis are acquired from the knowledge base and R and package 'meta', open sources for statistical computing, are incorporated with the system to provide a pooled, quantitative estimation of the effects of *CYP2C19* loss-of-function variants and genotype-guided warfarin therapy on patients' outcome respectively.

The fourth application is presented in Section 5.4. It attempts to formally represent the synthesized evidence that is yielded from meta-analyses so that clinical significance of pharmacogenomics evidence can be automatically inferred from the synthesized effect estimates once the results of meta-analyses have been accumulated in the knowledge base.

After demonstration of the four independent yet inter-related applications, the strengths and limitations of the developed knowledge-based system in supporting pharmacogenomics evidence assessment are discussed in Section 5.5.

5.2 Precise and Efficient Retrieval of Individual Evidence for Systematic Reviews with Meta-analysis

Systematic review with meta-analysis is a well-established methodology in evidence assessment. Generally, a systematic review with meta-analysis aims to pool all the available evidence across multiple studies that ask the same research question in order to assess the effect of an intervention. The review process usually involves the following steps: conducting a comprehensive literature search, screening articles to identify relevant studies, extracting quantitative data and other essential elements from included studies, synthesizing the extracted data when they are sufficiently similar in context, rating the quality and strength of evidence, and interpreting the results. The conventional manual approach in conducting a systematic review has often been criticized for being too time consuming and labor-intensive [Michelson, 2014; Tsertsvadze, Chen, Moher, Sutcliffe, & McCarthy, 2015]. In order to improve the efficiency of conducting a systematic review, many informatics approaches and techniques, such as natural language processing, machine learning, text mining, etc., have been adopted and mainly focused on reducing the burden of manual screening and data extraction for eligible studies to include in reviews [Kiritchenko, Bruijn, Carini, Martain, & Sim, 2010; Tsafnat et al., 2014; Jonnalagadda, Gitak, & Huffman, 2015]. However, there remains considerable room for improvement. From the perspective of knowledge representation, a knowledge-based system can make the evidence retrieval more precise and efficient because the essential evidence extracted from relevant articles is unambiguously represented in a logic-based formalism such as OWL DL and accumulated in a knowledge base which allows for automatic reasoning. Since a pharmacogenomics knowledge-based system, which provides 73 individual publications, 82 individual studies and 445 pieces of individual evidence, has been implemented in Chapter 4 (see

Section 4.5), its applicability to real-world evidence retrieval for systematic review with meta-analysis is demonstrated in this section.

5.2.1 Materials and methods

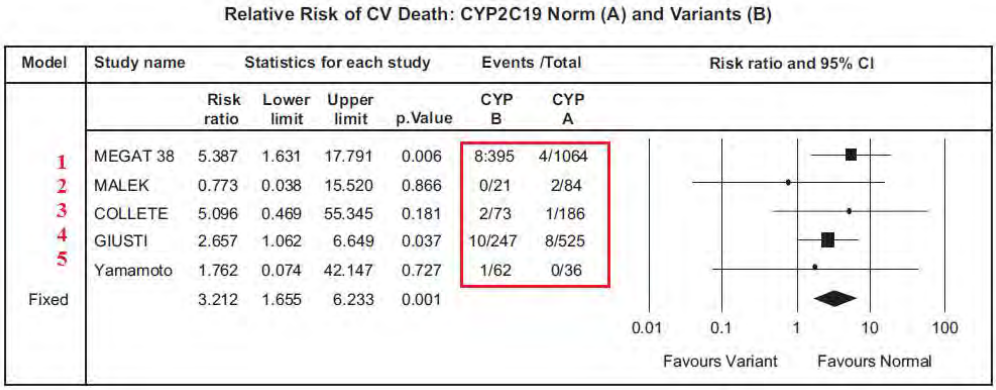
Step 1: Collect inclusion criteria and results of existing systematic reviews with meta-analyses

A convenience sample of 10 systematic reviews [Hulot et al., 2010; Mega et al., 2010; Sofi et al., 2011; Jin et al., 2011; Bauer et al., 2011; Holmes et al., 2011; Zabalza et al., 2012; Jang et al., 2012; Singh et al., 2012; Yamaguchi et al., 2012] that investigated the association between genetic variations and responses to clopidogrel was obtained from the CPIC guideline for *CYP2C19* genotype and clopidogrel therapy [Scott et al., 2013] because the existing systematic reviews were used as sources of relevant studies obtained through the conventional approach. A total of 60 meta-analyses were identified in 10 systematic reviews. From each meta-analysis, the criteria for inclusion of relevant studies and quantitative data (i.e., n/N in the experimental and control groups, where n is the numbers of participants with outcome and N is the total number of participants) about each relevant and included study provided in the forest plot were extracted. **Table 5.1** demonstrates the inclusion criteria and results of a meta-analysis which assessed the association between *CYP2C19*2* and the incidence of cardiovascular death in clopidogrel-treated patients with coronary artery disease and percutaneous coronary intervention [Singh et al., 2012]. Five studies (i.e., Mega et al., 2009; Malek et al., 2008; Collet et al., 2009; Giusti et al., 2009; and Yamamoto et al., 2011) were judged as relevant by [Singh et al., 2012], and the quantitative data about each relevant and included study were provided in the forest plot (See the red highlighted frame in **Table 5.1**). It makes this meta-analysis an appropriate test case because the necessary information to evaluate the retrieval effectiveness (i.e., precision) achieved by the conventional approach is available in this meta-analysis. After screening the inclusion criteria

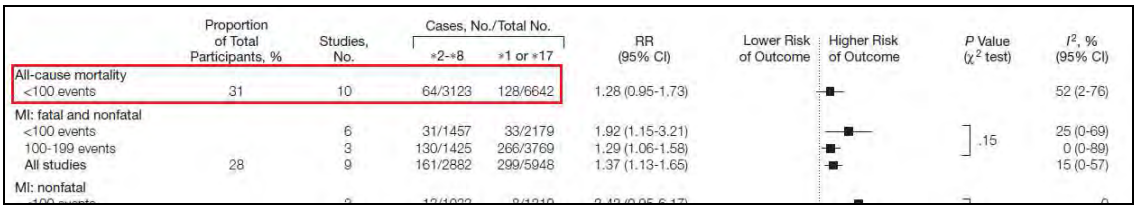
and forest plots of 60 meta-analyses, 27 of them were excluded from further evaluation because the quantitative data of each included study could not be verified. For example, **Figure 5.1** is the graphical representation of a meta-analysis on the association between *CYP2C19* polymorphisms and the risk of all-cause mortality [Holmes et al., 2011]. Instead of providing the quantitative data of each included study, this forest plot only provides the synthesized results obtained from pooling 10 studies (See the red highlighted frame in **Figure 5.1**). The source of relevant studies was undisclosed in this forest plot, therefore, this meta-analysis was excluded from further evaluation. As a result, only the results of 33 existing meta-analyses were selected to evaluate the retrieval effectiveness achieved by the conventional approach.

Table 5.1: Necessary information extracted from existing meta-analyses for evaluating the retrieval effectiveness by the conventional approach*

Inclusion criteria		
1	Publication year	Before 2011
2	Publication type	Refereed journal article or conference abstract
3	Study population	Patient with coronary artery disease and percutaneous coronary intervention
4	Study design	Randomized parallel-controlled trial or prospective cohort study
5	Drug therapy	Clopidogrel therapy with standard dose regimen
6	Genetic contrast	Carrier of at least one CYP2C19*2 allele versus noncarrier
7	Outcome	Incidence of cardiovascular death
Forest plot of meta-analysis results		



* Information extracted from [Singh et al., 2012]. Data in red highlighted frame are required for including a meta-analysis as a test case in evaluation of evidence retrieval.



	Proportion of Total Participants, %	Studies, No.	Cases, No./Total No. *2-*8	Cases, No./Total No. *1 or *17	RR (95% CI)	Lower Risk of Outcome	Higher Risk of Outcome	P Value (χ^2 test)	I^2, % (95% CI)
All-cause mortality									
<100 events	31	10	64/3123	128/6642	1.28 (0.95-1.73)				52 (2-76)
MI: fatal and nonfatal									
<100 events		6	31/1457	33/2179	1.92 (1.15-3.21)			.15	25 (0-69)
100-199 events		3	130/1425	266/3769	1.29 (1.06-1.58)				0 (0-89)
All studies	28	9	161/2882	299/5948	1.37 (1.13-1.65)				15 (0-57)
MI: nonfatal									

Figure 5.1: Example of an existing meta-analysis that was excluded from the evaluation of evidence retrieval. Information extracted from [Holmes et al., 2011]

Step 2: Represent the collected inclusion criteria using the OWL ontology and perform ontology-based instance checking over the pharmacogenomics knowledge base

The collected inclusion criteria of 33 meta-analyses were formally represented as 33 EquivalentClasses axioms (i.e., defined classes) using the constructed OWL ontology. **Figure 5.2** exemplifies how the inclusion criteria shown in **Table 5.1** were transformed into a defined class named **`CVDeath_CYP2C19star2_CADandPCI_Singh`**. Basically, inclusion criteria were expressed using a conjunction of class expressions, which represented the necessary and sufficient conditions that a piece of relevant individual evidence must satisfy to belong to the defined class (see the highlighted frame in **Figure 5.2**). After the formal representation of inclusion criteria for each meta-analysis, the HermiT reasoner embedded in Protégé was triggered to perform instance checking over the implemented pharmacogenomics knowledge base. As shown in **Figure 5.3**, five pieces of individual evidence that satisfied the necessary and sufficient conditions defined in the class of **`CVDeath_CYP2C19star2_CADandPCI_Singh`** were automatically retrieved. Detailed annotation of each piece of retrieved individual evidence could be found by clicking on the individual evidence itself. These five pieces of individual evidence, instances of the defined class of **`CVDeath_CYP2C19star2_CADandPCI_Singh`**, were the results of evidence retrieval obtained by ontology-based reasoning over the pharmacogenomics knowledge base. In other words, instances of the 33 defined classes were used to evaluate the retrieval

effectiveness achieved by the ontology-based approach. In addition, the computing time taken by the HermiT reasoner to perform the instance checking was monitored to evaluate the efficiency of the retrieval based on the ontology-based approach.

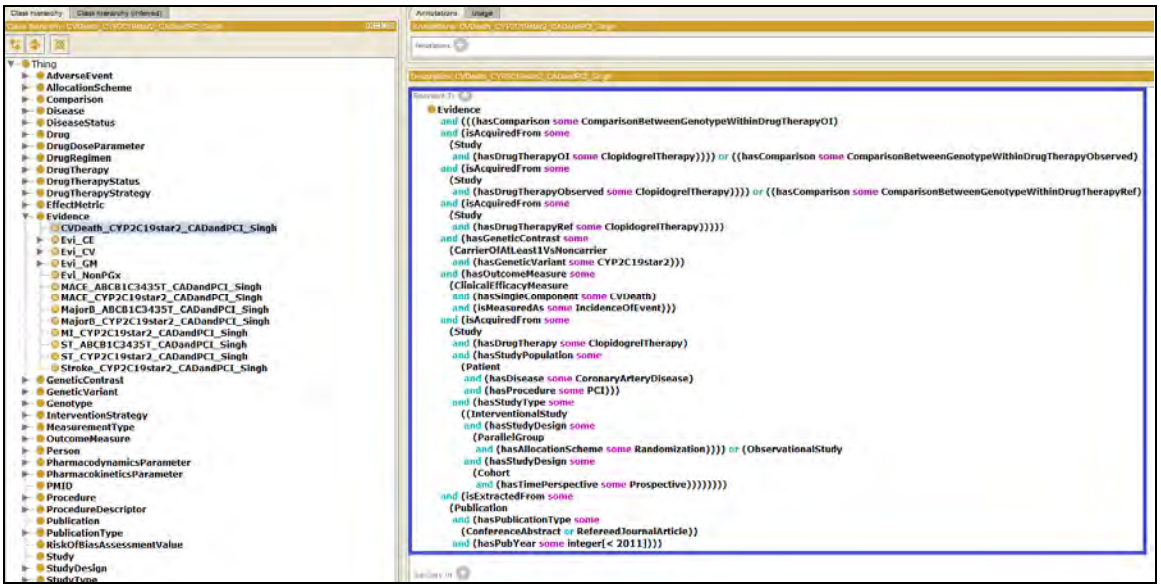


Figure 5.2: Example of formal representation of inclusion criteria as defined classes in OWL ontology. The description in the blue highlighted frame is inclusion criteria of `CVDeath_CYP2C19star2_CADandPCI_Singh`

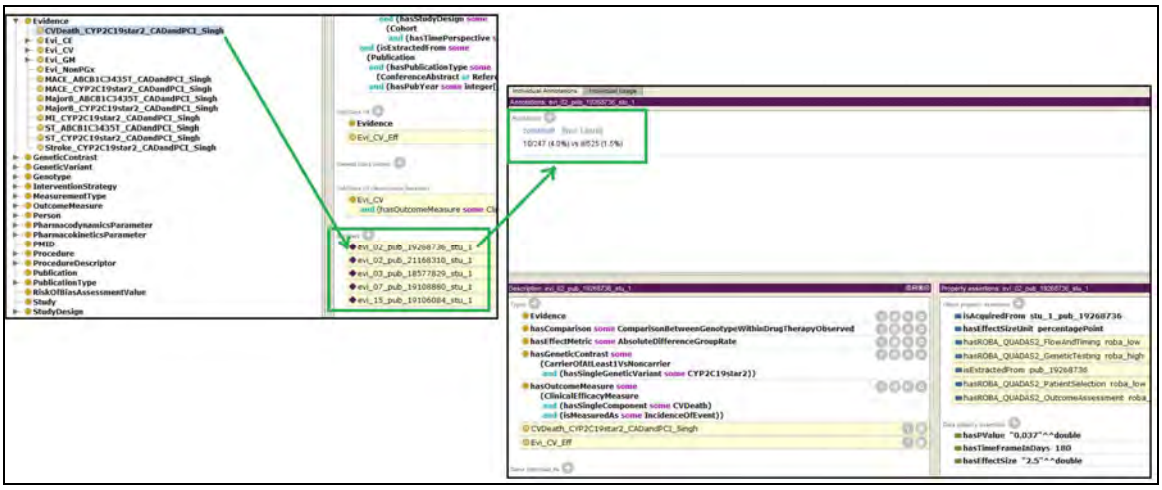


Figure 5.3: Example of ontology-based evidence retrieval. Five pieces of individual evidence which satisfied the necessary and sufficient conditions expressed in the defined class `CVDeath_CYP2C19star2_CADandPCI_Singh` (see Figure 5.2) were retrieved after triggering the Hermit reasoner. Clicking on a piece of retrieved individual evidence opens a window that shows the detailed annotations of this particular piece of individual evidence.

Step 3: Evaluate the retrieval effectiveness of two approaches and the efficiency of the ontology-based approach

Precision is one of the commonly used metrics for measuring the retrieval effectiveness and it is the percentage of retrieved studies and individual evidence that are relevant to the inclusion criteria and the necessary and sufficient conditions, respectively. The relevance of retrieved studies and individual evidence was judged by an expert (Beth Devine, Ph.D., Pharm.D., co-chair of my dissertation committee) who has domain knowledge about pharmacogenomics and rich experiences in conducting systematic review with meta-analysis. In order to facilitate the evaluation, the results obtained through conventional and ontology-based approaches respectively were organized and presented in a worksheet (see **Table 5.2**).

Table 5.2: Worksheet used to evaluate retrieval effectiveness by conventional and ontology-based approaches

Inclusion criteria		
1	Publication year (PY)	Before 2011
2	Publication type (PT)	Journal article or conference abstract
3	Study population (SP)	Patient with coronary artery disease and percutaneous coronary intervention
4	Study design (SD)	Randomized parallel-controlled trial or prospective cohort study
5	Drug therapy (DT)	Clopidogrel therapy with standard dose regimen
6	Genetic contrast (GC)	Carrier of at least one CYP2C19*2 allele versus noncarrier
7	Outcome (O)	Incidence of cardiovascular death

Results of evidence retrieval through the conventional approach and the ontology-based approach

R/NR	R_C	R_O	Individual evidence ID	Study shown in forest plot	n/N	PY	PT	SP	SD	DT	GC	GV	O
R	√	√	evi_02_pub_19268736_stu_1	GIUSTI	10/247 vs. 8/525	2009	Full article	ACS + PCI/DES	Prosp cohort	Clopidogrel LD 600mg, MD 75mg	Carrier of ≥1 vs. noncarrier	CYP2C19 *2	CV death
R	√	√	evi_02_pub_21168310_stu_1	Yamamoto	1/62 vs. 0/36	2010	Full article	CAD + PCI/Stent	Prosp cohort	Clopidogrel LD 300mg	Carrier of ≥1 vs. noncarrier	CYP2C19 *2, *3	CV death
R	√	√	evi_03_pub_18577829_stu_1	MALEK	0/21 vs. 2/84	2008	Full article	ACS + PCI/Stent	Prosp cohort	Clopidogrel LD 300mg or 600mg	Carrier of ≥1 vs. noncarrier	CYP2C19 *2	CV death
R	√	√	evi_07_pub_19108880_stu_1	COLLETE	2/73 vs. 1/186	2009	Full article	Acute MI + PCI/Stent	Prosp cohort	Clopidogrel MD 75mg	Carrier of ≥1 vs. noncarrier	CYP2C19 *2	CV death
R	√	√	evi_15_pub_19106084_stu_1	MEGAT 38	8/395 vs. 4/1064	2009	Full article	ACS + PCI	RCT	Clopidogrel LD 300mg	Carrier of ≥1 vs. noncarrier	CYP2C19 *2-*5, *8	CV death

R/NR: relevant/non-relevant judged by the expert, R_C: retrieval through the conventional approach, R_O: retrieval through the ontology-based approach, PY: publication year, PT: publication type, SP: study population, SD: study design, DT: drug therapy, GC: genetic contrast, O: outcome, ACS: acute coronary syndrome, CAD: coronary artery disease, MI: myocardial infarction, PCI: percutaneous coronary intervention, DES: drug eluting stent, Prosp: prospective, RCT: randomized control trial, LD: loading dose, MD: maintenance dose, CV death: cardiovascular death

Continuing with the previous example in step 2, **Table 5.2** shows that the conventional approach (i.e., an existing meta-analysis conducted by [Singh et al., 2012]) and the ontology-based approach (i.e., the defined class of **`CVDeath_CYP2C19star2_CADandPCI_Singh`** in the OWL ontology) retrieved 5 studies and 5 pieces of individual evidence to assess the association between *CYP2C19*2* and the incidence of cardiovascular death in clopidogrel-treated patients with clopidogrel for coronary artery disease and percutaneous coronary intervention, respectively. The retrieved results obtained through two approaches were identical because the retrieved quantitative data (i.e., n/N) matched. Moreover, the retrieved studies and individual evidence were considered relevant by the expert. That is to say, both approaches achieved a precision rate of 100% in this test case.

5.2.2 Results

A total of 33 test cases collected from 9 systematic reviews were summarized in **Table 5.3**. It is found that a systematic review often includes multiple meta-analyses because the effects of different genetic variants are often assessed on various outcomes among patients. **Table 5.3** presents the distribution of 33 test cases across different outcomes and genetic contrasts in comparisons. Briefly, the composite outcome of major adverse cardiac events and the single outcome of stent thrombosis are the most commonly compared outcomes, and the comparison between carriers of at least one *CYP2C19* loss-of-function alleles and noncarriers are the most commonly analyzed genetic contrast.

Table 5.3: Selected meta-analyses that were used as test cases for ontology-based evidence retrieval

Systematic review	MACE	ST	Death	MI	Stroke	Bleeding	Total MA included
Singh 2012	C>=1 vs. NC CYP2C19*2 C2 vs. C1 and NC ABCB1 C3435T	C>=1 vs. NC CYP2C19*2 C2 vs. C1 and NC ABCB1 C3435T	C>=1 vs. NC CYP2C19*2	C>=1 vs. NC CYP2C19*2	C>=1 vs. NC CYP2C19*2	C>=1 vs. NC CYP2C19*2 C2 vs. C1 and NC ABCB1 C3435T	9
Jang 2012	C>=1 vs. NC CYP2C19LOF C1 vs. NC CYP2C19LOF C2 vs. NC CYP2C19LOF	C>=1 vs. NC CYP2C19LOF	C>=1 vs. NC CYP2C19LOF	C>=1 vs. NC CYP2C19LOF	-	-	6
Bauer 2011	C>=1 vs. NC CYP2C19LOF C>=1 vs. NC CYP2C19GOF	C>=1 vs. NC CYP2C19LOF C>=1 vs. NC CYP2C19GOF	-	-	-	-	4
Zabalaza 2012	C>=1 vs. NC CYP2C19*2, *3, *4, *5 C>=1 vs. NC CYP2C19*17	C>=1 vs. NC CYP2C19*2, *3, *4, *5	-	-	-	C>=1 vs. NC CYP2C19*17	4
Jin 2011	C>=1 vs. NC CYP2C19*2	C>=1 vs. NC CYP2C19*2	C>=1 vs. NC CYP2C19*2	-	-	-	3
Hulot 2010	C>=1 vs. NC CYP2C19*2	C>=1 vs. NC CYP2C19*2	C>=1 vs. NC CYP2C19*2	-	-	-	3
Sofi 2011	C>=1 vs. NC CYP2C19*2	C>=1 vs. NC CYP2C19*2	-	-	-	-	2
Holmes 2011	C>=1 vs. NC CYP2C19LOF	-	-	-	-	-	1
Yamaguchi 2013	C>=1 vs. NC CYP2C19*2	-	-	-	-	-	1
Total MA included	14	9	4	2	1	3	33

MACE: Major adverse cardiac events, ST: stent thrombosis, MI: myocardial infarction, MA: meta-analysis, LOF: loss-of-function, GOF: gain-of-function, C>=1: carriers of at least one alleles, C1: carriers of one allele, C2: carriers of 2 alleles, NC: noncarriers

5.2.2.1 Retrieval effectiveness of conventional and ontology-based approaches

For each test case, the number of relevant/non-relevant studies and individual evidence retrieved through conventional and ontology-based approaches respectively were summarized in **Table 5.4**. The case-by-case precision of two approaches was illustrated in **Figure 5.4**. On average, the ontology-based approach achieved a precision rate of 100%, while the conventional approach achieved a precision rate of 97%. Among 33 test cases, non-relevant studies which were retrieved through the conventional approach were identified in 5 test cases. They were considered non-relevant because they did not satisfy the inclusion criteria specified in their corresponding systematic review protocols.

Table 5.4: Precision of evidence retrieval by conventional and ontology-based approaches

Test case		Conventional approach				Ontology-based approach			
		The number of studies retrieved			Precision =R/T	The number of individual evidence retrieved			Precision =R/T
		T	R	NR		T	R	NR	
1	Singh_MACE_CYP2C19*2	13	13	0	100%	22	22	0	100%
2	Singh_MACE_ABCB1/C3435T	3	3	0	100%	3	3	0	100%
3	Singh_ST_CYP2C19*2	5	5	0	100%	10	10	0	100%
4	Singh_ST_ABCB1/C3435T	2	2	0	100%	2	2	0	100%
5	Singh_D_CYP2C19*2	5	5	0	100%	5	5	0	100%
6	Singh_MI_CYP2C19*2	6	6	0	100%	8	8	0	100%
7	Singh_Sk_CYP2C19*2	3	3	0	100%	4	4	0	100%
8	Singh_B_CYP2C19*2	3	3	0	100%	2	2	0	100%
9	Singh_B_ABCB1/C3435T	2	2	0	100%	1	1	0	100%
10	Jang_MACE_CYP2C19LOF	13	13	0	100%	19	19	0	100%
11	Jang_MACE_CYP2C19LOF_C1/NC	4	4	0	100%	3	3	0	100%
12	Jang_MACE_CYP2C19LOF_C2/NC	4	4	0	100%	3	3	0	100%
13	Jang_ST_CYP2C19LOF	6	6	0	100%	12	12	0	100%
14	Jang_D_CYP2C19LOF	7	7	0	100%	12	12	0	100%
15	Jang_MI_CYP2C19LOF	5	5	0	100%	9	9	0	100%
16	Bauer_MACE_CYP2C19LOF	11	11	0	100%	26	26	0	100%
17	Bauer_MACE_CYP2C19GOF	4	4	0	100%	4	4	0	100%
18	Bauer_ST_CYP2C19LOF	9	9	0	100%	11	11	0	100%
19	Bauer_ST_CYP2C19GOF	3	3	0	100%	3	3	0	100%
20	Zabalza_MACE_CYP2C19*2to*5	11	11	0	100%	14	14	0	100%
21	Zabalza_MACE_CYP2C19*17	4	4	0	100%	3	3	0	100%
22	Zabalza_ST_CYP2C19*2to*5	6	6	0	100%	11	11	0	100%
23	Zabalza_B_CYP2C19*17	4	3	1*	75%	3	3	0	100%
24	Jin_MACE_CYP2C19*2	8	7	1*	88%	10	10	0	100%
25	Jin_ST_CYP2C19*2	5	4	1*	80%	5	5	0	100%
26	Jin_D_CYP2C19*2	5	4	1*	80%	4	4	0	100%
27	Hulot_MACE_CYP2C19*2	9	9	0	100%	11	11	0	100%
28	Hulot_ST_CYP2C19*2	4	4	0	100%	5	5	0	100%
29	Hulot_D_CYP2C19*2	5	5	0	100%	6	6	0	100%
30	Sofi_MACE_CYP2C19*2	7	6	1*	86%	13	13	0	100%
31	Sofi_ST_CYP2C19*2	3	3	0	100%	10	10	0	100%
32	Holmes_MACE_CYP2C19LOF	25	25	0	100%	31	31	0	100%
33	Yamaguchi_MACE_CYP2C19*2	6	6	0	100%	16	16	0	100%
		Average			97%	Average			100%

T: total number of study/individual evidence retrieved. R: total number of relevant study/ individual evidence. NR: total number of non-relevant study/ individual evidence. *Reasons for non-relevant are provided in Table 5.5.

The specific reasons for non-relevant retrievals occurred in 5 test cases are explained in **Table 5.5**. For example, Test case 23, a meta-analysis conducted in [Zabalza et al, 2012] that assessed the association between *CYP2C19*17* and the incidence of bleeding in clopidogrel-treated patients with coronary artery disease, included a primary study [Paré et al., 2010] which assessed the same association but in clopidogrel-treated patients with atrial fibrillation. This included study (i.e., [Paré et al., 2010]) was considered non-relevant by the expert because it did not meet the specified population of interest.

Table 5.5: Reasons for non-relevant studies retrieved by conventional approach

Systematic review	Test case*	Primary study	Information component	Specification of inclusion criteria in systematic review	Specification in primary study
Zabalza	23	Paré et al., 2010	Study population	patient with coronary artery disease	patient with atrial fibrillation
Jin	24, 25, 26	Mega et al., 2009	Study design	prospective cohort study	randomized control trial
Sofi	30	Sibbing et al., 2009	Outcome	composite outcome	single outcome (definite stent thrombosis)

*Test case numbering as shown in Table 5.4

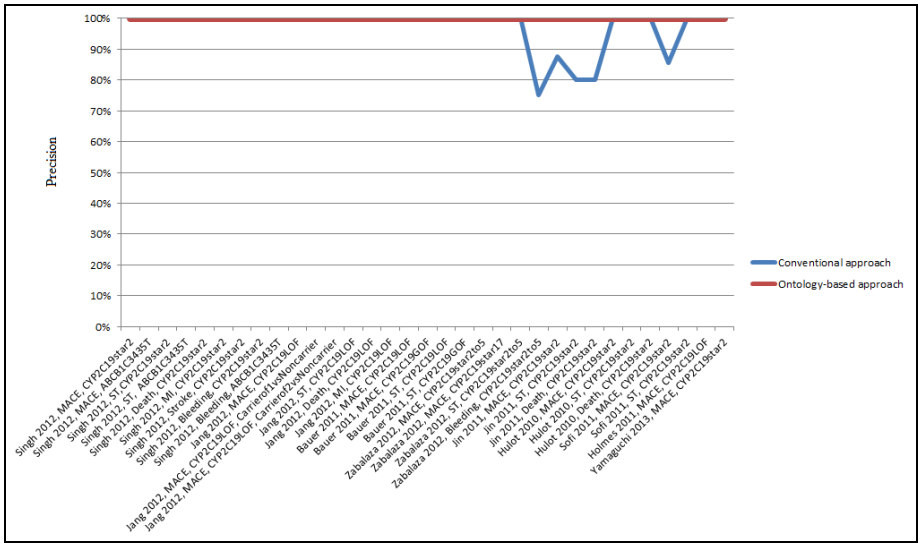


Figure 5.4: Precision of evidence retrieval by conventional and ontology-based approaches

5.2.2.2 Efficiency of the ontology-based retrieval

The computing time taken to perform instance checking for each systematic review ranged between 9 and 23 seconds (see **Table 5.6**).

Table 5.6: Computing time of ontology-based evidence retrieval

Systematic review	Singh 2012	Jang 2012	Bauer 2011	Zabalaza 2012	Jin 2011	Hulot 2010	Sofi 2011	Holmes 2011	Yamaguchi 2013
No. of test cases included	9	6	4	4	3	3	2	1	1
Computing time	22933ms (~23 seconds)	21163ms (~21 seconds)	20870ms (~21 seconds)	15927ms (~16 seconds)	17590ms (~18 seconds)	16707ms (~17 seconds)	18324ms (~18 seconds)	10543ms (~11 seconds)	8900ms (~ 9 seconds)

Note: The retrievals were tested on a personal laptop (Intel Corei7-4700MQ 2.4GHz Processor, 16 GB DDR3 Ram and a 64-bit version of Windows 8.1). ms: milliseconds

5.2.3 Discussion

A total of 33 meta-analyses were selected from 9 existing systematic reviews to investigate the applicability of the pharmacogenomics knowledge-based system to real-world evidence retrieval for systematic review with meta-analysis. The results show that the implemented pharmacogenomics knowledge-based system is an efficient approach to precisely retrieve relevant individual evidence for meta-analysis. This is accomplished by the formal representation of the inclusion criteria each meta-analysis as a defined class embedded in the OWL ontology. This approach allows unambiguous semantic annotation of inclusion criteria as the necessary and sufficient conditions of a defined class and thereby enables automatic reasoning to retrieve relevant individual evidence that is already formally represented in the knowledge base.

In addition to the short computing time, the pharmacogenomics knowledge-based system improves the efficiency of retrieval process by allowing users to create or refine necessary and sufficient conditions (i.e., inclusion criteria) very easily. For example, in **Table 5.7**, **`MACE_CYP2C19star2_CADandPCI_Singh`**, an existing defined class in the OWL ontology, aims to retrieve the relevant individual evidence so that the effects of *CYP2C19*2* on major adverse cardiac events among clopidogrel-treated patients with coronary artery disease and percutaneous coronary intervention can be assessed. Suppose that reviewers are also interested in assessing the effects of *CYP2C19*2* on the same outcome among patients with specific types of percutaneous coronary interventions such as percutaneous coronary intervention with drug eluting stents and elective percutaneous coronary intervention respectively. Two new defined classes, **`MACE_CYP2C19star2_CADandDES`** and **`MACE_CYP2C19star2_CADandElectivePCI`**, can be easily created from the necessary and sufficient conditions of **`MACE_CYP2C19star2_CADandPCI_Singh`**, by replacing the property value **`PCI`** with another class **`PCIWithDES`** in the former case, and by

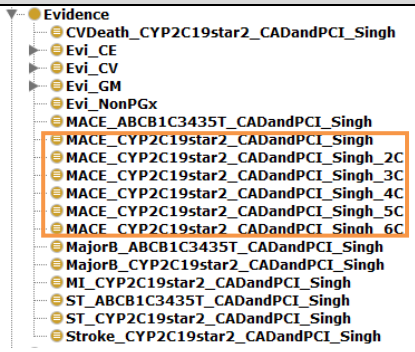
adding a class expression "(*hasProcedureDescriptor* some **Elective**)" to **PCI** in the latter case (See the yellow highlighted texts in **Table 5.7**).

Table 5.7: Examples of refining class expressions to describe various study populations

Defined class	Representation of necessary and sufficient conditions regarding to different but similar study populations
MACE_CYP2C19star2_CADandPCI_Singh	……**Study** and (*hasStudyPopulation* some (**Patient** and (*hasDisease* some **CoronaryArteryDisease**) and (*hasProcedure* some **PCI**)))……
MACE_CYP2C19star2_CADandDES	……**Study** and (*hasStudyPopulation* some (**Patient** and (*hasDisease* some **CoronaryArteryDisease**) and (*hasProcedure* some **PCIWithDES**))) ……
MACE_CYP2C19star2_CADandElectivePCI	……**Study** and (*hasStudyPopulation* some (**Patient** and (*hasDisease* some **CoronaryArteryDisease**) and (*hasProcedure* some (**PCI** and (*hasProcedureDescriptor* some **Elective**))))) ……

The easy creation of necessary and sufficient conditions for defined classes enables the knowledge-based system to retrieve and classify heterogeneous individual evidence into a hierarchical structure very quickly. For example, to further classify instances of the defined class **MACE_CYP2C19star2_CADandPCI_Singh** according to the number of components included in outcome measure, 5 new defined classes could be easily created by replacing the *hasMultipleComponent* property with its subproperties (see **Table 5.8**).

Table 5.8: Examples of refining class expressions to describe different outcome measures

Asserted class hierarchy	Representation of necessary and sufficient conditions regarding the number of components included in a composite outcome
	……*hasOutcomeMeasure* some (**ClinicalEfficacyMeasure** and (*hasMultipleComponent* some (**AdverseEvent** or **Disease** or **Procedure**)) and (*isMeasuredAs* some **IncidenceOfEvent**))……
	……*hasOutcomeMeasure* some (**ClinicalEfficacyMeasure** and (*hasTwoComponent* some (**AdverseEvent** or **Disease** or **Procedure**)) and (*isMeasuredAs* some **IncidenceOfEvent**))……
	……*hasOutcomeMeasure* some (**ClinicalEfficacyMeasure** and (*hasThreeComponent* some (**AdverseEvent** or **Disease** or **Procedure**)) and (*isMeasuredAs* some **IncidenceOfEvent**))……
	……*hasOutcomeMeasure* some (**ClinicalEfficacyMeasure** and (*hasFourComponent* some (**AdverseEvent** or **Disease** or **Procedure**)) and (*isMeasuredAs* some **IncidenceOfEvent**))……
	……*hasOutcomeMeasure* some (**ClinicalEfficacyMeasure** and (*hasFiveComponent* some (**AdverseEvent** or **Disease** or **Procedure**)) and (*isMeasuredAs* some **IncidenceOfEvent**))……
	……*hasOutcomeMeasure* some (**ClinicalEfficacyMeasure** and (*hasSixComponent* some (**AdverseEvent** or **Disease** or **Procedure**)) and (*isMeasuredAs* some **IncidenceOfEvent**))……

After these five defined classes are added to the OWL ontology, the HermiT reasoner automatically classifies instances of the defined class **`MACE_CYP2C19star2_CADandPCI_Singh`** into five subclasses according to the number of events being measured in the composite outcome (see **Table 5.9**).

Table 5.9: Examples of defining class hierarchy to classify heterogeneous individual evidence

Inferred class hierarchy	Classification of individual evidence	
Evidence Evi_CE Evi_CV Evi_CV_Com Evi_CV_Dos Evi_CV_Eff CVDeath_CYP2C19star2_CADandPCI_Singh MACE_ABCB1C3435T_CADandPCI_Singh MACE_CYP2C19star2_CADandPCI_Singh MACE_CYP2C19star2_CADandPCI_Singh_2C MACE_CYP2C19star2_CADandPCI_Singh_3C MACE_CYP2C19star2_CADandPCI_Singh_4C MACE_CYP2C19star2_CADandPCI_Singh_5C MACE_CYP2C19star2_CADandPCI_Singh_6C MI_CYP2C19star2_CADandPCI_Singh ST_ABCB1C3435T_CADandPCI_Singh ST_CYP2C19star2_CADandPCI_Singh Stroke_CYP2C19star2_CADandPCI_Singh Evi_CV_PD Evi_CV_PK Evi_CV_Saf Evi_GM Evi_NonPGx	**`MACE_CYP2C19star2_CADandPCI_Singh_2C`** Members evi_01_pub_18482659_stu_1 evi_01_pub_18577829_stu_1 evi_01_pub_Anderson_2009_stu_1 evi_03_pub_19268736_stu_1 evi_04_pub_20826260_stu_1 evi_07_pub_21099121_stu_1 evi_08_pub_19193675_stu_1 evi_10_pub_19108880_stu_1 evi_16_pub_20801498_stu_1	**`MACE_CYP2C19star2_CADandPCI_Singh_3C`** Members evi_01_pub_21099121_stu_1 evi_01_pub_21168310_stu_1 evi_03_pub_19106083_stu_1 evi_04_pub_19106083_stu_1 evi_06_pub_19108880_stu_1 evi_06_pub_20826260_stu_1 evi_11_pub_19193675_stu_1 evi_12_pub_20801498_stu_1 evi_13_pub_19106084_stu_1 evi_13_pub_20979470_stu_1
	`MACE_CYP2C19star2_CADandPCI_Singh_4C` Members evi_01_pub_Worrall_2009_stu_1 evi_08_pub_20826260_stu_1	**`MACE_CYP2C19star2_CADandPCI_Singh_6C`** Members evi_02_pub_19706858_stu_1

A collection of well-classified and formally represented evidence helps reviewers to better understand the current status of available evidence. For example, the retrieved results shown in **Table 5.9** are then organized into an evidence profile (see **Table 5.10**). This evidence profile presents an efficient way to understand the quantity and the heterogeneity inherent in the retrieved individual evidence. This is especially useful in assisting the reviewers in deciding which relevant evidence to include in a meta-analysis and whether or not there is enough evidence to carry out a meta-analysis. For example, based on the evidence profile shown in **Table 5.10**, there is enough evidence to assess the effects of *CYP2C19*2* on a composite of all-cause death or myocardial infarction because 3 pieces of individual evidence are available on assessing the outcome of interest. On the other hand, from a perspective on increasing the statistical power, individual evidence such as `evi_01_pub_18482659_stu_1`,

evi_04_pub_20826260_stu_1, evi_16_pub_20801498_stu_1, evi_01_pub_18577829_stu_1, and evi_10_pub_19108880_stu_1 (see cells highlighted in blue in **Table 5.10**) could be also included if reviewers think these pieces of individual evidence are sufficiently similar in outcomes. The advantage of using hierarchical classification of heterogeneous evidence to inform current availability of relevant evidence for conducting meta-analyses will be demonstrated in the following applications presented in Sections 5.3.

Table 5.10: Profile of evidence that informs the heterogeneity and quantity of a collection of individual evidence

A composite of 2 major adverse cardiac events (N=9)			
AllCauseDeath or MI	3	evi_01_pub_Anderson_2009_stu_1	48/350 vs. 89/900
		evi_07_pub_21099121_stu_1	2/42 vs. 2/58
		evi_08_pub_19193675_stu_1	52/680 vs. 121/1805
AllCauseDeath or NonfatalMI	2	evi_01_pub_18482659_stu_1	5/245 vs. 19/552
		evi_04_pub_20826260_stu_1	14/248 vs. 63/680
CVDeath or MI	1	evi_16_pub_20801498_stu_1	138/1388 vs. 306/3516
CVDeath or NonfatalMI	2	evi_01_pub_18577829_stu_1	1/21 vs. 5/84
		evi_10_pub_19108880_stu_1	12/73 vs. 7/186
CVDeath or DefiniteOrProbableST	1	evi_03_pub_19268736_stu_1	15/247 vs. 14/525
A composite of 3 major adverse cardiac events (N=10)			
AllCauseDeath or MI or TargetVesselRevas	1	evi_01_pub_21099121_stu_1	13/42 vs. 11/58
AllCauseDeath or NonfatalMI or TargetLesionRevas	1	evi_06_pub_20826260_stu_1	60/248 vs. 179/680
CVDeath or NonfatalMI or RevasUnspecified	1	evi_06_pub_19108880_stu_1	15/73 vs. 11/186
AllCauseDeath or NonfatalMI or Stroke	2	evi_03_pub_19106083_stu_1	76/635 vs. 218/1573
		evi_04_pub_19106083_stu_1	74/617 vs. 214/1561
AllCauseDeath or MI or IschemicStroke	1	evi_11_pub_19193675_stu_1	56/680 vs. 121/1805
CVDeath or MI or Stroke	1	evi_12_pub_20801498_stu_1	149/1388 vs. 332/3516
CVDeath or NonfatalMI or IschemicStroke	1	evi_01_pub_21168310_stu_1	5/62 vs. 0/36
CVDeath or NonfatalMI or NonfatalStroke	1	evi_13_pub_19106084_stu_1	46/395 vs. 83/1064
CVDeath or NonfatalMI or Stroke	1	evi_13_pub_20979470_stu_1	52/651 vs. 179/1886
A composite of 4 major adverse cardiac events (N=2)			
AllCauseDeath or MI or RevasUnspecified or Stroke	1	evi_01_pub_Worrall_2009_stu_1	4/24 vs. 6/80
AllCauseDeath or NonfatalMI or TargetLesionRevas or Stroke	1	evi_08_pub_20826260_stu_1	60/248 vs. 184/680
A composite of 6 major adverse cardiac events (N=1)			
CVDeath or DefiniteST or HospitalizationDueToIschemia or IschemicStroke or MI or NonTVROrTVR	1	evi_02_pub_19706858_stu_1	14/67 vs. 16/158

It is worth clarifying that the implemented pharmacogenomics knowledge-based system is an informatics approach to facilitate efficient retrieval and classification of relevant evidence for systematic review with meta-analysis, rather than to replace reviewers' judgments about which relevant evidence to include in a meta-analysis. Particularly, reviewers' judgments are necessary

for preventing substantially overlapping evidence from being included in a meta-analysis. For example, `evi_03_pub_19106083_stu_1` is a piece of individual evidence that compared the clopidogrel effects between the carriers of at least one *CYP2C19* loss-of-function alleles (**2*, **3*, **4*, **5*) and noncarriers on a composite of all-cause death, nonfatal myocardial infarction or stroke while `evi_04_pub_19106083_stu_1` is a piece of individual evidence that compared the clopidogrel effects between the carriers of at least one *CYP2C19*2* alleles and noncarriers on the same composite outcome. Both `evi_03_pub_19106083_stu_1` and `evi_04_pub_19106083_stu_1` are acquired form the same individual study (i.e., `stu_1_pub_19106083`), and therefore, there is a substantial overlap between these two pieces of evidence in the total number of participants (See texts highlighted in yellow in **Table 5.10**). Since the inclusion of substantially overlapping evidence leads to an overestimation of the intervention effects, it is critical to select only one of them when conducting a meta-analysis.

In summary, in the first application, the implemented pharmacogenomics knowledge-based system has proven to be an effective and efficient approach to retrieve relevant primary evidence for systematic review with meta-analysis. This approach exploits the pharmacogenomics knowledge-based system to perform three tasks involved in evidence assessment: (1) formal representation of inclusion criteria for meta-analyses into defined classes using the pharmacogenomics OWL ontology (2) a knowledge base serves as a repository of formalized primary pharmacogenomics evidence, and (3) a DL reasoner reasons over the ontology and the knowledge base to retrieve all the evidence that satisfies the defined necessary and sufficient conditions. Since evidence retrieval is the core task underlying process of a comprehensive evidence assessment, the first application will be scaled up and extended to two broader applications that encompass a set of consecutive tasks involved in the process of developing a

comprehensive evidence assessment. In Section 5.3, the application focuses on using the implemented pharmacogenomics knowledge-based system to assist evidence-based assessment that includes planning, implementation and interpretation. Two test cases are designed. The first test case assesses the association between *CYP2C19* loss-of-function variants and the efficacy of clopidogrel therapy, and the second test case assesses the comparative effectiveness of genotype-guided and non-genotype-guided dosing of warfarin.

5.3 Efficient Systematic Reviews on Clinical Validity of *CYP2C19* Loss-of-Function Variants on Efficacy of Clopidogrel Therapy and Clinical Utility of Genotype-Guided Warfarin Dosing

Pharmacogenomics holds promise as one of the approaches to precision medicine. Yet the adoption of pharmacogenomics in routine clinical care relies on the continuing accumulation and assessment of pharmacogenomics evidence that is relevant to the subject to be adopted. Pharmacogenomics evidence assessment usually adapts the general methods developed by the EGAPP (Evaluation of Genomic Applications in Practice and Prevention) Initiative [Teutsch et al., 2009]. Briefly, an analytic framework is developed before embarking on a full scale of assessment. The analytic framework uses a series of key questions to provide guidance on conducting an in-depth review. The key questions address three components that might be included in a process evaluation and the components are analytic validity, clinical validity and clinical utility. Each of the questions formulated in the analytic framework is answered by a comprehensive evidence assessment that follows the general steps of systematic reviews. Finally, the answers of the key questions form a chain of evidence and draw conclusions about the overall effect of the genomic application on health outcome, hence inform the decision on clinical adoption.

For example, a comparative effectiveness review entitled "*Testing of CYP2C19 Variants and Platelet Reactivity for Guiding Antiplatelet Treatment*" was conducted by the Tufts Medical Center Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ) [Dahabreh et al., 2013]. Four key questions that consist of 8 subquestions were formulated to guide the comprehensive assessment (see **Table 5.11)**.

Table 5.11: Key questions in a comparative effectiveness review of the testing for CYP2C19 variants and platelet reactivity in guiding antiplatelet treatment

Topic of assessment: **Testing for CYP2C19 variants and platelet reactivity for guiding antiplatelet treatment**
Key question 1: Does genetic testing for CYP2C19 variants predict intermediate and clinical outcomes in patients with clopidogrel therapy?
•Subquestion 1a: the analytic validity of CYP2C19 genetic testing
•Subquestion 1b: the clinical validity of CYP2C19 genetic testing
•Subquestion 1c: modifiers which are associated with the clinical validity of CYP2C19 genetic testing
Key question 2: Does phenotypic testing of platelet reactivity predict intermediate and clinical outcomes in patients with clopidogrel therapy?
•Subquestion 2a: the analytical validity of platelet reactivity test
•Subquestion 2b: the clinical validity of platelet reactivity test
•Subquestion 2c: modifier which are associated with the clinical validity of platelet reactivity test
Key question 3: What is the comparative effectiveness of testing of CYP2C19 or platelet reactivity on clopidogrel treatment outcome?
•Subquestion 3a: comparative effectiveness of different testing strategies
•Subquestion 3b: how modifiers affect the effectiveness of different testing strategies
Key question 4: What are the potential harms of different testing strategies?

* This table is abridged from [Dahabreh et al., 2013].

Key Question 1 is broken into three subquestions regarding: (1a) the analytic validity of CYP2C19 genetic testing: a testing will be positive when a particular variant is present and a test will be negative when a particular variant is absent, (1b) clinical validity of CYP2C19 genetic testing: the predictive value of CYP2C19 variants for outcomes, and (1c) possible modifiers (i.e., race or ethnicity, age, sex, disease severity etc.) that modify the effect of CYP2C19 variants on outcomes. Similarly, Key Question 2 is broken into three subquestions regarding: (2a) the analytic validity of phenotypic testing for platelet reactivity, (2b) clinical validity of phenotypic

testing for platelet reactivity, and (2c) possible modifiers that modify the association between phenotypic results and outcomes. Key Question 3 is broken into two subquestions regarding: (3a) the comparative effectiveness of different test-and-treat strategies including CYP2C19 genetic testing only, CYP2C19 genetic testing followed by phenotypic testing for platelet reactivity, phenotypic testing for platelet reactivity only or no testing, and (3b) how modifiers affect the effectiveness of different test-and-treat strategies. At last, Key Question 4 investigates the potential adverse effects or harms of different test-and-treat strategies.

Key findings for Key Question 1b (i.e. clinical validity) and 3a (i.e. clinical utility) are summarized in **Table 5.12** to explore the challenges that might have been encountered in conducting a comprehensive evidence assessment. First, classifying heterogeneous evidence to make it amenable to synthesis is tedious, time-consuming and requires substantial domain knowledge. For example, evidence that is relevant to Key Question 1b is pooled in meta-analyses when at least 3 pieces of evidence are available with sufficiently similar populations, genetic models of CYP2C19 alleles and outcome measures. In other words, a piece of evidence is iteratively judged on a given criterion as either satisfied or unsatisfied. The large number of key findings to subquestion 1b summarized in **Table 5.12** indicates that tremendous efforts have been devoted to iteratively retrieve and group relevant evidence for systematic review. Second, a priori research questions may lead to a situation that significant time and resources have been invested in full-scale reviews but there is not enough evidence to carry out a meta-analysis [Veenstra et al., 2013]. This paucity of evidence is frequently occurred when assessing the clinical utility of pharmacogenomics. For example, in the assessment of subquestion 3a, only a limited number of studies were identified regarding the use of CYP2C19 genotype testing to

guide antiplatelet drug selection. Moreover, it was unable to make the study results amenable to synthesis because the heterogeneity among study designs and treatment strategies was too high.

Table 5.12: Key findings of evidence assessment on two subquestions selected from Table 5.11

Key findings: Testing for CYP2C19 variants for guiding antiplatelet treatment				
•Subquestion 1b: the clinical validity of CYP2C19 genetic testing				
Study population	Genetic model	Genetic variant	Outcome	Evidence synthesis
ischemic heart disease	dominant model (carriers of at least one alleles versus noncarriers)	CYP2C19 LOF	all-cause death	N=7; RR=1.00 (0.64-1.55)
			cardiac death	N=7; RR=1.98 (1.13-3.46); significantly increased risk
			ACS	N=9; RR=1.35 (0.91-2.00)
			ST	N=17; RR=1.52 (1.17-1.97); significantly increased risk
			stroke	N=7; RR=2.07 (0.68-6.33)
			MACE	N=25; RR=1.20 (1.04-1.39); significantly increased risk
			bleeding	N=6; RR=1.02 (0.86-1.21)
			RV	N=6; not amenable to meta-analysis because of the extensive differences among studies; generally higher event rate among carriers.
			platelet reactivity	(N=61); not amenable to meta-analysis because of the extensive differences among studies; generally higher among carriers.
			high platelet reactivity	(N= 39); not amenable to meta-analysis because of the extensive differences among studies; generally higher event rate among carriers.
		*CYP2C19 *17*	all-cause death	N=3; RR=1.28 (0.81-2.02)
			cardiac death	N=0; not amenable to meta-analysis
			ACS	N=2; not amenable to meta-analysis
			ST	N=5; RR=0.83 (0.52-1.32)
			stroke	N=1; not amenable to meta-analysis
			MACE	N=7; RR=0.82 (0.74 to 0.92); significantly decreased risk
			bleeding	N=6; RR=1.51 (1.08-2.11); significantly increased risk
			RV	N=0; not amenable to meta-analysis
	recessive model (carriers of two alleles versus noncarriers)	CYP2C19 LOF	MACE	N=9; RR=1.85 (1.19-2.86); significantly increased risk
			ST	N=11; RR=2.40 (1.61-3.57); significantly increased risk
	additive model (carriers of one alleles versus noncarriers)	CYP2C19 LOF	MACE	N=6; RR=1.54 (1.11-2.14); significantly increased risk
			ST	N=9; RR=1.77 (1.44-2.18); significantly increased risk
non-ischemic heart disease	6 studies with heterogeneous study populations			not amenable to meta-analysis because of the extensive differences among study populations
•Subquestion 3a: comparative effectiveness of different testing strategies				
Test	Test-and-treat strategy	No. of study	Outcome	Evidence synthesis
testing of *CYP2C19* genotype	treatment guided by *CYP2C19* genotype vs. standard clopidogrel therapy	1	clinical outcome	not amenable to meta-analysis
			platelet reactivity	
	treatment effect modification by CYP2C19 variants on alternative antiplatelet vs. clopidogrel therapy	13	clinical outcome	not amenable to meta-analysis because of the extensive differences among studies
			platelet reactivity	
	patient selected based on *CYP2C19* genotype and then randomized to alternative antiplatelet treatment	1	clinical outcome	not amenable to meta-analysis
			platelet reactivity	

ACS: acute coronary syndrome, ST: stent thrombosis, MACE: major adverse cardiac events, RV: revascularization.

To improve the efficiency of evidence assessment, the EGAPP review is adjusted to a staged process that involves: (1) checking the quantity of evidence in early phase of the process, (2) making use of existing reviews, (3) evaluating clinical validity first, and (4) using decision modeling when absent of direct evidence [Veenstra et al., 2013]. To assist with the adjusted EGAPP review process, the developed knowledge-based system can be leveraged to provide up-to-date accounts of which primary evidence is currently available for systematic review and which synthesized evidence acquired from systematic review is available for reuse. How the developed pharmacogenomics knowledge-based system could be leveraged to conduct efficient systematic review is demonstrated in this section. Two test cases were designed for demonstration. Section 5.3.1 presents a stepwise implementation of systematic review that assesses the clinical validity of *CYP2C19* loss-of-function variants on efficacy of clopidogrel therapy (referred to as clopidogrel test case). Section 5.3.2 presents a step-wise implementation of systematic review that assesses the clinical utility of genotype-guided warfarin dosing (referred to as warfarin test case). Section 5.3.3 discusses major findings related to both test cases.

5.3.1 Implementation of clopidogrel test case

The clopidogrel test case aimed to assess the association between CYP2C19 loss-of-function variants and efficacy outcomes in patients treated with clopidogrel. The pharmacogenomics knowledge-based system developed in Chapter 4 was leveraged to implement the evidence-based assessment in clopidogrel test case through the following steps.

Step 1: Specify the assessment topic and inclusion criteria of relevant evidence

The collection of relevant evidence that addresses the assessment topic in clopidogrel test case is specified by 8 features, i.e., evidence type, publication type, study type, study population, drug therapy, genetic contrast, outcome and outcome measurement type. **Table 5.13** provides an overview of the 8 features. Specifically, the relevant evidence includes any evidence that is extracted from refereed journal full articles and acquired from randomized and paralleled trials or prospective cohort studies. The relevant evidence should compare clinical efficacy outcomes of a standard regimen of clopidogrel that include (1) death, (2) cardiovascular death, (3) myocardial infarction, (4) stroke, (5) stent thrombosis, (6) revascularization, (7) composite of death or myocardial infarction, (8) composite of death, myocardial infarction or stroke, (9) composite of death, myocardial infarction, stroke or stent thrombosis, or (10) composite of death, myocardial infarction, stroke, stent thrombosis or revascularization. The genetic contrasts in the comparison include: (1) carriers of one or two *CYP2C19* loss-of-functions (LOF) alleles versus noncarriers, (2) carriers of one *CYP2C19* LOF alleles versus noncarriers or (3) carriers of two *CYP2C19* LOF alleles versus noncarriers.

Table 5.13: Specification of inclusion criteria for retrieving relevant evidence in clopidogrel test case

Assessment topic	Effect of CYP2C19 LOF variants on efficacy outcomes among patients treated with clopidogrel
Inclusion criteria of relevant evidence	
Evidence type	Clinical validity
Publication Type	Full article of refereed journal
Study type	(1) randomized and paralleled clinical trial (2) prospective cohort study
Study population	Patients treated with clopidogrel
Drug therapy	Standard regimen of clopidogrel
Genetic contrast	(1) carriers of one or two CYP2C19 LOF alleles vs. noncarriers, (2) carriers of one CYP2C19 LOF alleles vs. noncarriers, and (3) carriers of two CYP2C19 LOF alleles vs. non-carriers
Outcome	Efficacy outcomes include: (1) death, (2) cardiovascular death, (3) myocardial infarction, (4) stroke, (5) stent thrombosis, (6) revascularization, (7) a composite of death or myocardial infarction, (8) a composite of death or myocardial infarction or stroke, (9) a composite of death or myocardial infarction or stroke or stent thrombosis, and (10) a composite of death or myocardial infarction or stroke or stent thrombosis or revascularization
Outcome measurement type	(1) incidence of event, and (2) time to event

LOF: loss of function

Step 2: Design and formal representation of evidence classification schemes to retrieve and classify relevant evidence

According to the specified inclusion criteria of relevant evidence listed in **Table 5.13**, a set of predefined classification schemes was planned as shown in **Table 5.14** to sequentially subdivide the collection of relevant evidence into a hierarchy of evidence groups which inform the availability of relevant evidence at different levels of specificity. Briefly, the relevant evidence is sequentially divided by 4 levels of classification. The first-level classification divided the relevant evidence into 3 categories by genetic contrasts, that were carriers of one or two *CYP2C19* LOF alleles versus noncarriers, carriers of one *CYP2C19* LOF alleles versus noncarriers and carriers of two *CYP2C19* LOF alleles versus noncarriers. The second-level classification divided the 3 categories further by the numbers of components included in outcome measure, i.e., from single to 5 components. The third-level classification was the 10 types of outcomes of interest (see **Table 5.13**) and the fourth-level classification was the 2 types of outcome measurement (i.e., incidence of event and time to event). As a result, a collection of relevant evidence was first retrieved from the developed knowledge base based on the inclusion criteria specified in **Table 5.13**, then, the collection of relevant evidence was classified into 109 groups of evidence based on the 4-level of classification schemes. In order to enable automatic evidence retrieval and classification, each classification scheme in **Table 5.14** was transformed into a defined class which had formally asserted inclusion criteria as the necessary and sufficient conditions. As a result, a total of 109 defined classes were added to the OWL ontology (see **Figure 5.5**).

Table 5.14: Evidence classification schemes designed in clopidogrel test case

ClopidogrelTestCase (relevant evidence according to inclusion criteria specified in Table 5.13)		
|- Carriers of 1 or 2 CYP2C19 loss-of-function alleles vs. Noncarriers	**|- Carrier of 1 CYP2C19 loss-of-function alleles vs. Noncarriers**	**|- Carrier of 2 CYP2C19 loss-of-function alleles vs. Noncarriers**
|- 1 component	|- 1 component	|- 1 component
|- 1 component, D	|- 1 component, D	|- 1 component, D
|- incidence of event	|- incidence of event	|- incidence of event
|- time to event	|- time to event	|- time to event
|- 1 component, CVD	|- 1 component, CVD	|- 1 component, CVD
|- incidence of event	|- incidence of event	|- incidence of event
|- time to event	|- time to event	|- time to event
|- 1 component, MI	|- 1 component, MI	|- 1 component, MI
|- incidence of event	|- incidence of event	|- incidence of event
|- time to event	|- time to event	|- time to event
|- 1 component, Sk	|- 1 component, Sk	|- 1 component, Sk
|- incidence of event	|- incidence of event	|- incidence of event
|- time to event	|- time to event	|- time to event
|- 1 component, ST	|- 1 component, ST	|- 1 component, ST
|- incidence of event	|- incidence of event	|- incidence of event
|- time to event	|- time to event	|- time to event
|- 1 component, RV	|- 1 component, RV	|- 1 component, RV
|- incidence of event	|- incidence of event	|- incidence of event
|- time to event	|- time to event	|- time to event
|- 2 component	|- 2 component	|- 2 component
|- 2 component, (D or MI)	|- 2 component, (D or MI)	|- 2 component, (D or MI)
|- incidence of event	|- incidence of event	|- incidence of event
|- time to event	|- time to event	|- time to event
|- 3 component	|- 3 component	|- 3 component
|- 3 component, (D or MI or Sk)	|- 3 component, (D or MI or Sk)	|- 3 component, (D or MI or Sk)
|- incidence of event	|- incidence of event	|- incidence of event
|- time to event	|- time to event	|- time to event
|- 4 component	|- 4 component	|- 4 component
|- 4 component, (D or MI or Sk or ST)	|- 4 component, (D or MI or Sk or ST)	|- 4 component, (D or MI or Sk or ST)
|- incidence of event	|- incidence of event	|- incidence of event
|- time to event	|- time to event	|- time to event
|- 5 component	|- 5 component	|- 5 component
|- 5 component, (D or MI or Sk or ST or RV)	|- 5 component, (D or MI or Sk or ST or RV)	|- 5 component, (D or MI or Sk or ST or RV)
|- incidence of event	|- incidence of event	|- incidence of event
|- time to event	|- time to event	|- time to event

D: death, CVD: cardiovascular death, MI: myocardial infarction, Sk: stroke, ST: stent thrombosis, RV: revascularization

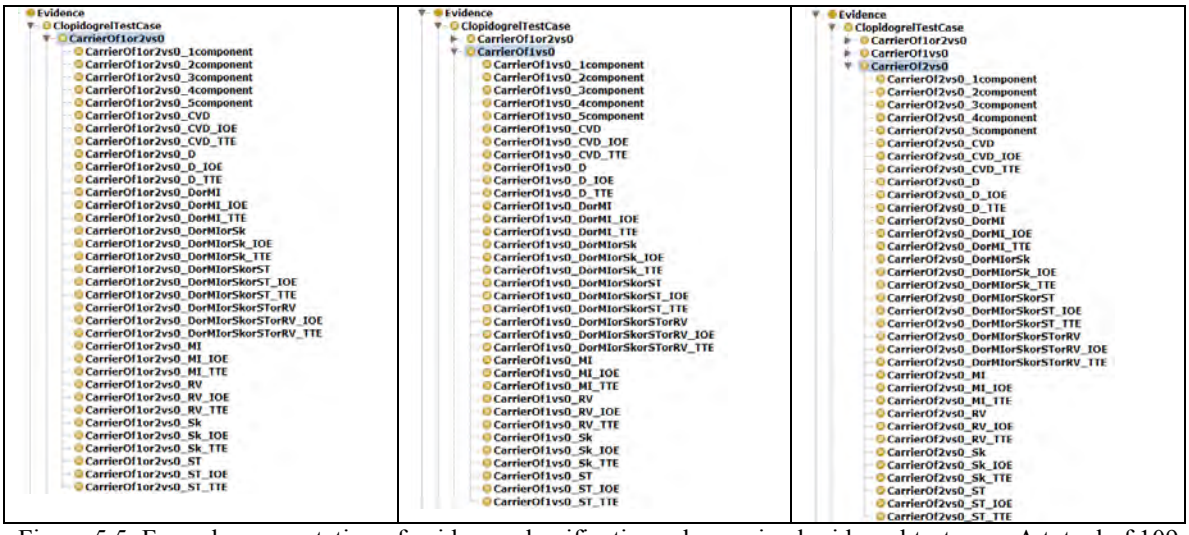


Figure 5.5: Formal representation of evidence classification schemes in clopidogrel test case. A totoal of 109 defined classes were asserted as class hierarchy

Step 3: Perform subsumption and instance checking over evidence classification schemes

The HermiT reasoner was triggered to perform instance checking and class subsumption checking (see **Figure** 5.**6**). The computing time taken by the HermiT reasoner to reason over the knowledge-based system was monitored (see **Figure** 5.**7**). The entire reasoning process took around 4 minutes (216,905 milliseconds). **Figure 5.8** and **Table 5.15** show the inferred class hierarchy and the results of instance checking respectively.

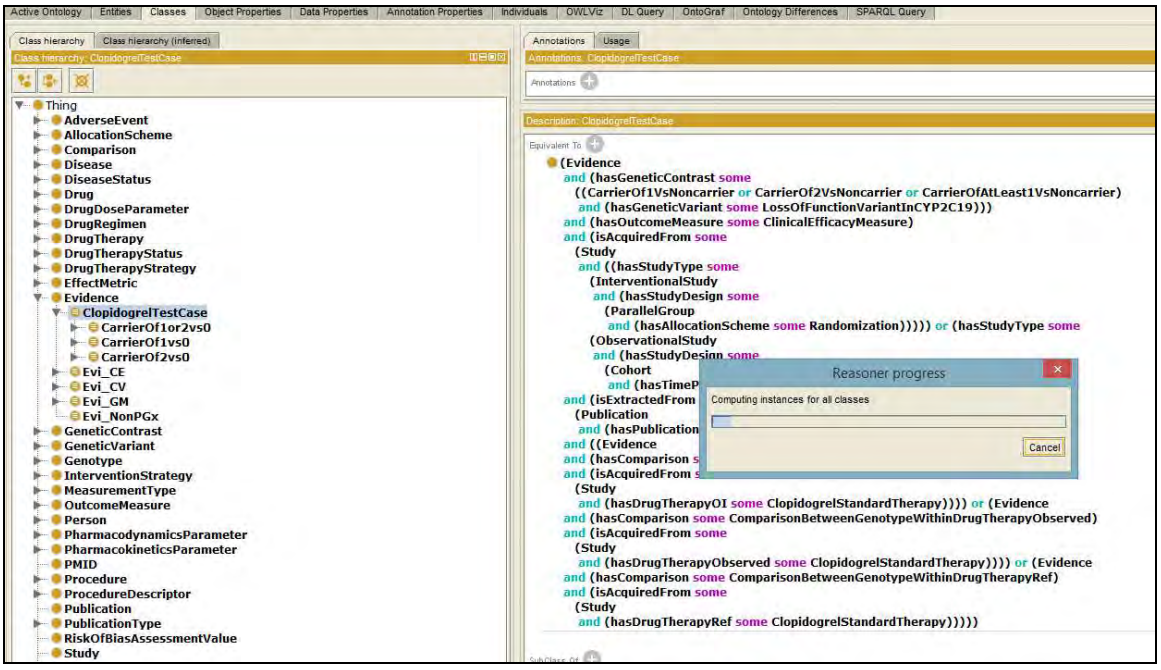


Figure 5.6: Trigger HermiT to conduct subsumption and instance checking

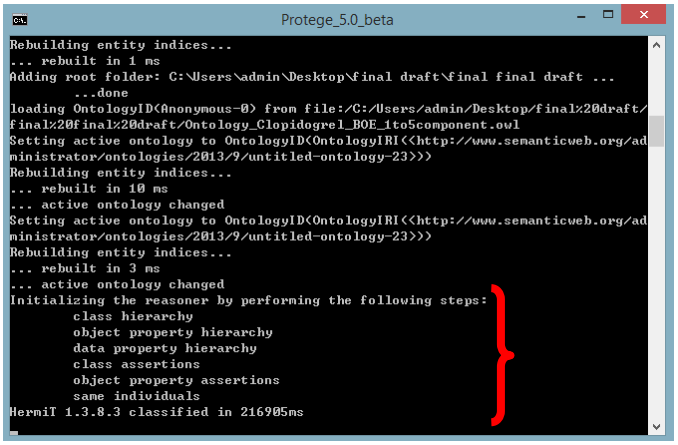


Figure 5.7: Monitor computing time after triggering HermiT

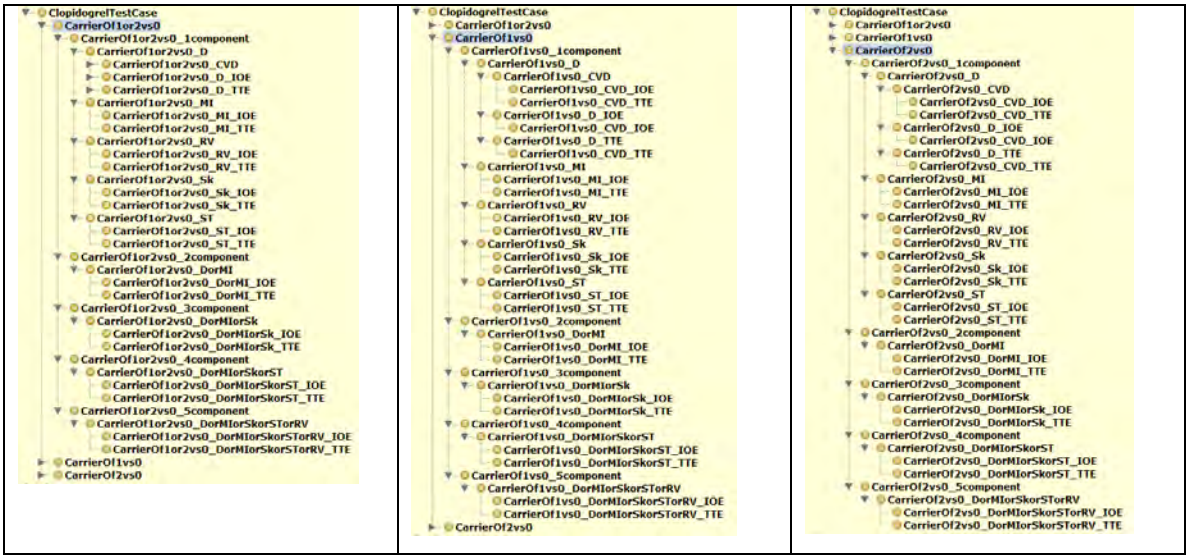


Figure 5.8: Inferred class hierarchy of evidence classification schemes designed in clopidogrel test case

Step 4: Create an evidence profile that informs the quantity of relevant evidence

Based on the inferred results of instance checking conducted in Step 3, the number of instances included in each of the 109 defined classes was provided in an evidence profile (see **Table 5.15**). The evidence profile table provides critical information necessary for deciding which meta-analysis to be conducted. According to the currently available evidence shown in **Table 5.15**, there was more evidence available for outcomes measured as incidence of event than those measured as time to event. Therefore, 12 defined classes that had outcomes measured as incidence of event and at least 2 instances were selected for further analysis (see texts and cells highlighted in green in **Table 5.15**).

Table 5.15: Profile of evidence that informs the quantity of relevant individual evidence in clopidogrel test case

Evidence profile					
ClopidogrelTestCase (N=115)					
|- Carriers of 1 or 2 CYP2C19 loss-of-function alleles vs. Noncarriers	96	**|- Carrier of 1 CYP2C19 loss-of-function alleles vs. Noncarriers**	9	**|- Carrier of 2 CYP2C19 loss-of-function alleles vs. Noncarriers**	10
|- 1 component	54	|- 1 component	2	|- 1 component	2
|- 1 component, D	14	|- 1 component, D	0	|- 1 component, D	0
|- **incidence of event**	11	|- incidence of event	0	|- incidence of event	0
|- time to event	3	|- time to event	0	|- time to event	0
|- 1 component, CVD	8	|- 1 component, CVD	0	|- 1 component, CVD	0
|- **incidence of event**	6	|- incidence of event	0	|- incidence of event	0
|- time to event	2	|- time to event	0	|- time to event	0
|- 1 component, MI	13	|- 1 component, MI	0	|- 1 component, MI	0
|- **incidence of event**	8	|- incidence of event	0	|- incidence of event	0
|- time to event	5	|- time to event	0	|- time to event	0
|- 1 component, Sk	5	|- 1 component, Sk	0	|- 1 component, Sk	0
|- **incidence of event**	4	|- incidence of event	0	|- incidence of event	0
|- time to event	1	|- time to event	0	|- time to event	0
|- 1 component, ST	17	|- 1 component, ST	2	|- 1 component, ST	2
|- **incidence of event**	13	|- **incidence of event**	2	|- **incidence of event**	2
|- time to event	4	|- time to event	0	|- time to event	0
|- 1 component, RV	5	|- 1 component, RV	0	|- 1 component, RV	0
|- **incidence of event**	4	|- incidence of event	0	|- incidence of event	0
|- time to event	1	|- time to event	0	|- time to event	0
|- 2 component	11	|- 2 component	1	|- 2 component	1
|- 2 component, (D or MI)	9	|- 2 component, (D or MI)	0	|- 2 component, (D or MI)	0
|- **incidence of event**	8	|- incidence of event	0	|- incidence of event	0
|- time to event	1	|- time to event	0	|- time to event	0
|- 3 component	21	|- 3 component	5	|- 3 component	6
|- 3 component, (D or MI or Sk)	14	|- 3 component, (D or MI or Sk)	4	|- 3 component, (D or MI or Sk)	5
|- **incidence of event**	10	|- **incidence of event**	2	|- **incidence of event**	2
|- time to event	4	|- time to event	2	|- time to event	3
|- 4 component	5	|- 4 component	1	|- 4 component	1
|- 4 component, (D or MI or Sk or ST)	1	|- 4 component, (D or MI or Sk or ST)	1	|- 4 component, (D or MI or Sk or ST)	1
|- incidence of event	0	|- incidence of event	0	|- incidence of event	0
|- time to event	1	|- time to event	1	|- time to event	1
|- 5 component	1	|- 5 component	0	|- 5 component	0
|- 5 component, (D or MI or Sk or ST or RV)	0	|- 5 component, (D or MI or Sk or ST or RV)	0	|- 5 component, (D or MI or Sk or ST or RV)	0
|- incidence of event	0	|- incidence of event	0	|- incidence of event	0
|- time to event	0	|- time to event	0	|- time to event	0

Step 5: Select relevant evidence, prepare data for meta-analysis, perform meta-analysis and cumulative meta-analysis, and summarize risk of bias assessment

Instances retrieved by each of the 12 defined classes were manually checked to decide which relevant evidence to include in each meta-analysis. Taking the defined class **`CarrierOf1or2vs0_ST_IOE`** as an example, 13 pieces of individual evidence were retrieved. Among them, there was a substantial overlap between `evi_04_pub_19268736_stu_1` and `evi_07_pub_19268736_stu_1` because both were acquired from the same study (see red arrows in

Figure 5.9). After excluding `evi_04_pub_19268736_stu_1`, a total of 12 pieces of evidence were selected to include in the meta-analysis. For each piece of included individual evidence, the essential quantitative data for meta-analysis and cumulative meta-analysis as well as the qualitative data for risk of bias summary were manually extracted from its assertions (See the green and blue highlighted frames in **Figure 5.9**). Once these data were saved in a CSV (comma separated value) file, it was then read into R so that the fixed and random-effects estimates were calculated using the R package 'meta' [Schwarzer, 2012] (see **Figure 5.10**). In addition, the risk-of-bias values provided in the CSV file were used to create the risk of bias graph using Microsoft Excel.

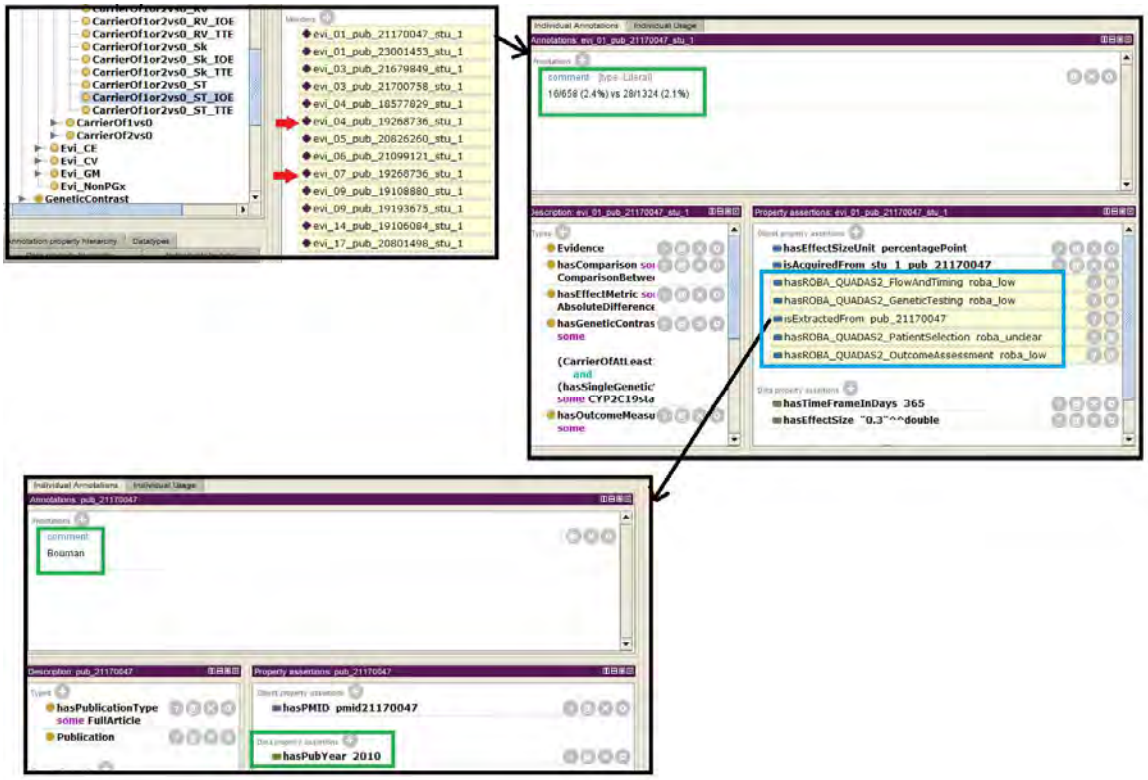


Figure 5.9: Selection of individual evidence to include in meta-analysis and acquisition of data to perform meta-analysis and make risk of bias summary graph.

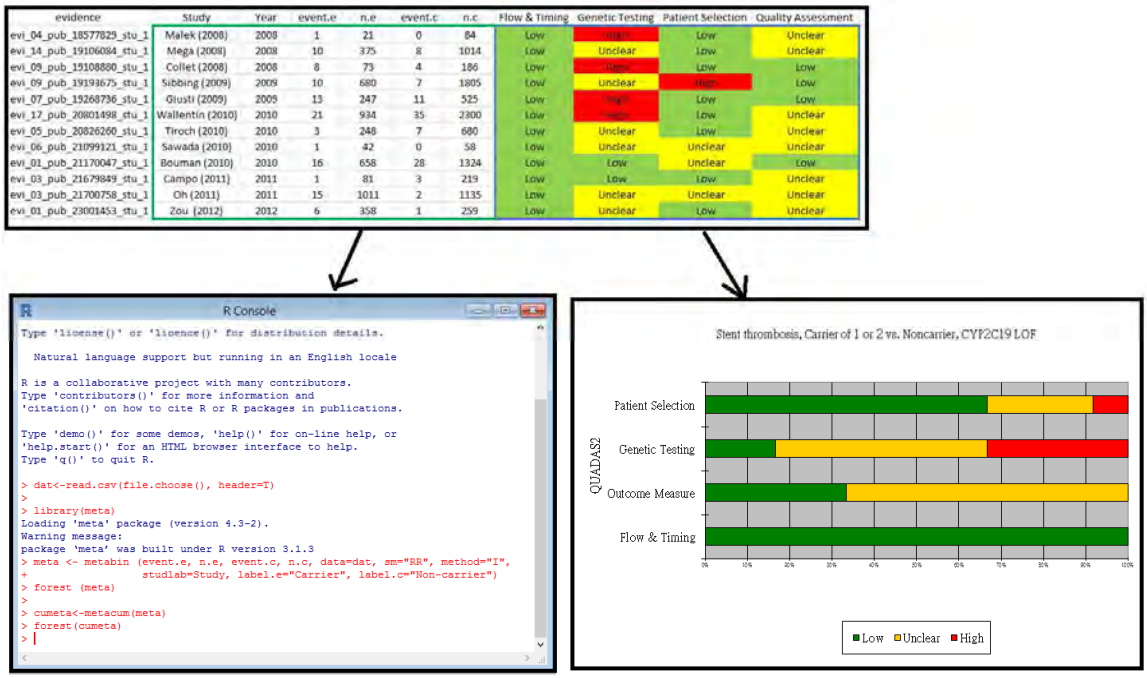


Figure 5.10: Compilation of essential data in CSV file for conducting meta-analysis and making risk of bias summary graph.

Step 6: Report results of meta-analysis, cumulative meta-analysis and risk of bias assessment summary

The Cochrane handbook for systematic reviews provides the formats to present results of a meta-analysis [Schünemann et al., 2011] as well as the summary of risk of bias assessment of included studies [Higgins et al., 2011]. For example, the 'summary of findings table' that provides key information concerning the magnitude of pooled effect by each outcome is presented in **Table 5.16**. Forest plots of meta-analysis and cumulative meta-analysis and risk-of-bias graphs were illustrated in **Table 5.17**. Among the 12 conducted meta-analyses, 6 of them reported statistically significant results (see cells highlighted in yellow in **Table 5.16**). In summary, the clinical validity of CYP2C19 LOF alleles for predicting efficacy outcomes in clopidogrel-treated patients is assessed as follows. Carriers of one or two CYP2C19 LOF alleles were statistically significantly associated with increased risk of death (RR=1.42; 95% confidence

interval, 1.02 to 1.97); cardiovascular death (RR=2.91; 95% confidence interval, 1.66 to 5.11); myocardial infarction (RR=1.33; 95% confidence interval, 1.07 to 1.66); stroke (RR=3.95; 95% confidence interval, 1.49 to 10.48); stent thrombosis (RR=2.07; 95% confidence interval, 1.56 to 2.75); composite of death or myocardial infarction (RR=1.17; 95% confidence interval, 1.02 to 1.35). Meanwhile, carriers of one or two CYP2C19 LOF alleles were also associated with increased risk of revascularization and composite of death, myocardial infarction or stroke; however, the results were not statistically significant. For both carriers of one CYP2C19 LOF alleles and carriers of two CYP2C19 LOF alleles, there were associations with increased risk of stent thrombosis and composite of death, myocardial infarction or stroke; however, the results were not statistically significant.

Table 5.16: Summary of findings of each meta-analysis conducted in clopidogrel test case

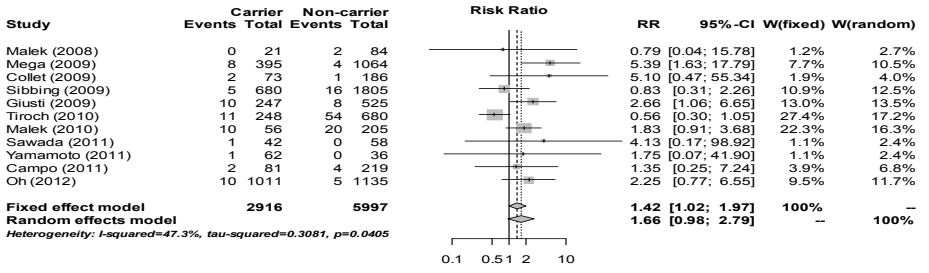
Assessment topic	The effects of CYP2C19 loss-of-function (LOF) variants on efficacy outcomes among patients treated with clopidogrel						
Meta-analysis method	Fixed effect model						
Defined class	Genetic contrast	Genetic variant	Outcome	Effect metric	Effect size	95% Confidence Interval	No. included evidence/ No. study subjects
CarrierOf1or2vs0_D_IOE	Carrier of 1 or 2 vs. Non-carrier	CYP2C19 LOF alleles	Death	Relative Risk	1.42	1.02, 1.97	11/ 2916 vs. 5997
CarrierOf1or2vs0_CVD_IOE	Carrier of 1 or 2 vs. Non-carrier	CYP2C19 LOF alleles	Cardiovascular death	Relative Risk	2.91	1.66, 5.11	6/ 1809 vs. 3030
CarrierOf1or2vs0_MI_IOE	Carrier of 1 or 2 vs. Non-carrier	CYP2C19 LOF alleles	Myocardial infarction	Relative Risk	1.33	1.07, 1.66	8/ 2532 vs. 5048
CarrierOf1or2vs0_Sk_IOE	Carrier of 1 or 2 vs. Non-carrier	CYP2C19 LOF alleles	Stroke	Relative Risk	3.95	1.49, 10.48	4/ 1385 vs. 3585
CarrierOf1or2vs0_ST_IOE	Carrier of 1 or 2 vs. Non-carrier	CYP2C19 LOF alleles	Stent thrombosis	Relative Risk	2.07	1.56, 2.75	12/ 4728 vs. 9589
CarrierOf1or2vs0_RV_IOE	Carrier of 1 or 2 vs. Non-carrier	CYP2C19 LOF alleles	Revascularization	Relative Risk	1.16	0.96, 1.41	3/ 1301 vs. 1873
CarrierOf1or2vs0_DorMI_IOE	Carrier of 1 or 2 vs. Non-carrier	CYP2C19 LOF alleles	Death or myocardial infarction	Relative Risk	1.17	1.02, 1.35	8/ 2992 vs. 7773
CarrierOf1or2vs0_DorMIorSk_IOE	Carrier of 1 or 2 vs. Non-carrier	CYP2C19 LOF alleles	Death or myocardial infarction or stroke	Relative Risk	1.11	1.00, 1.23	9/ 4719 vs. 11804
CarrierOf1vs0_ST_IOE	Carrier of 1 vs. Non-carrier	CYP2C19 LOF alleles	Stent thrombosis	Relative Risk	1.16	0.63, 2.14	2/ 867 vs. 1583
CarrierOf1vs0_DorMIorSk_IOE	Carrier of 1 vs. Non-carrier	CYP2C19 LOF alleles	Death or myocardial infarction or stroke	Relative Risk	0.83	0.68, 1.01	2/ 1166 vs. 3453
CarrierOf2vs0_ST_IOE	Carrier of 2 vs. Non-carrier	CYP2C19 LOF alleles	Stent Thrombosis	Relative Risk	3.59	0.41, 31.76	2/ 149 vs. 1583
CarrierOf2vs0_DorMIorSk_IOE	Carrier of 2 vs. Non-carrier	CYP2C19 LOF alleles	Death or myocardial infarction or stroke	Relative Risk	1.25	0.79, 1.98	2/ 119 vs. 3453

Note: Findings highlighted in yellow are statistically significant

Table 5.17: Graphical presentation of meta-analyses, cumulative meta-analyses and summary of risk of bias assessments conducted in clopidogrel test case

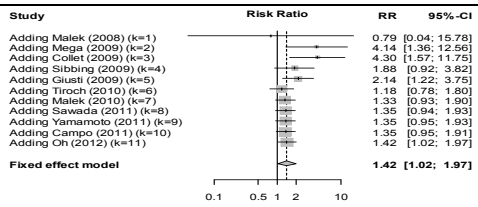
12 meta-analyses

Carriers of 1 or 2 CYP2C19 loss-of-function alleles vs. Noncarriers on death

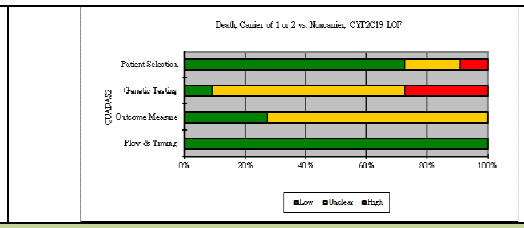


Study	Carrier Events	Carrier Total	Non-carrier Events	Non-carrier Total	RR	95%-CI	W(fixed)	W(random)
Malek (2008)	0	21	2	84	0.79	[0.04; 15.78]	1.2%	2.7%
Mega (2009)	8	395	4	1064	5.39	[1.63; 17.79]	7.7%	10.5%
Collet (2009)	2	73	1	186	5.10	[0.47; 55.34]	1.9%	4.0%
Sibbing (2009)	5	680	16	1805	0.83	[0.31; 2.26]	10.9%	12.5%
Giusti (2009)	10	247	8	525	2.66	[1.06; 6.65]	13.0%	13.5%
Tiroch (2010)	11	248	54	680	0.56	[0.30; 1.05]	27.4%	17.2%
Malek (2010)	10	56	20	205	1.83	[0.91; 3.68]	22.3%	16.3%
Sawada (2011)	1	42	0	58	4.13	[0.17; 98.92]	1.1%	2.4%
Yamamoto (2011)	1	62	0	36	1.75	[0.07; 41.90]	1.1%	2.4%
Campo (2011)	2	81	4	219	1.35	[0.25; 7.24]	3.9%	6.8%
Oh (2012)	10	1011	5	1135	2.25	[0.77; 6.55]	9.5%	11.7%
Fixed effect model		**2916**		**5997**	**1.42**	**[1.02; 1.97]**	**100%**	--
Random effects model					**1.66**	**[0.98; 2.79]**	--	**100%**

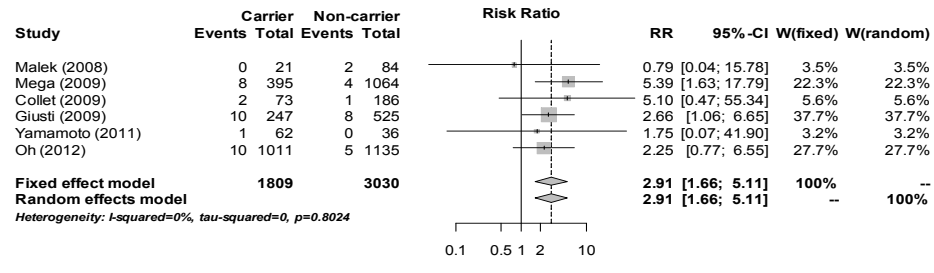
Heterogeneity: I-squared=47.3%, tau-squared=0.3081, p=0.0405



Study	RR	95%-CI
Adding Malek (2008) (k=1)	0.79	[0.04; 15.78]
Adding Mega (2009) (k=2)	4.14	[1.36; 12.56]
Adding Collet (2009) (k=3)	4.30	[1.57; 11.75]
Adding Sibbing (2009) (k=4)	1.88	[0.92; 3.82]
Adding Giusti (2009) (k=5)	2.14	[1.22; 3.75]
Adding Tiroch (2010) (k=6)	1.18	[0.78; 1.80]
Adding Malek (2010) (k=7)	1.33	[0.93; 1.90]
Adding Sawada (2011) (k=8)	1.35	[0.94; 1.93]
Adding Yamamoto (2011) (k=9)	1.35	[0.95; 1.93]
Adding Campo (2011) (k=10)	1.35	[0.95; 1.91]
Adding Oh (2012) (k=11)	1.42	[1.02; 1.97]
Fixed effect model	**1.42**	**[1.02; 1.97]**

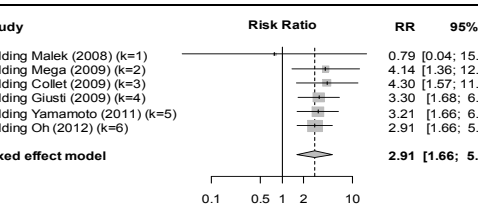


Carriers of 1 or 2 CYP2C19 loss-of-function alleles vs. Noncarriers on cardiovascular death



Study	Carrier Events	Carrier Total	Non-carrier Events	Non-carrier Total	RR	95%-CI	W(fixed)	W(random)
Malek (2008)	0	21	2	84	0.79	[0.04; 15.78]	3.5%	3.5%
Mega (2009)	8	395	4	1064	5.39	[1.63; 17.79]	22.3%	22.3%
Collet (2009)	2	73	1	186	5.10	[0.47; 55.34]	5.6%	5.6%
Giusti (2009)	10	247	8	525	2.66	[1.06; 6.65]	37.7%	37.7%
Yamamoto (2011)	1	62	0	36	1.75	[0.07; 41.90]	3.2%	3.2%
Oh (2012)	10	1011	5	1135	2.25	[0.77; 6.55]	27.7%	27.7%
Fixed effect model		**1809**		**3030**	**2.91**	**[1.66; 5.11]**	**100%**	--
Random effects model					**2.91**	**[1.66; 5.11]**	--	**100%**

Heterogeneity: I-squared=0%, tau-squared=0, p=0.8024



Study	RR	95%-CI
Adding Malek (2008) (k=1)	0.79	[0.04; 15.78]
Adding Mega (2009) (k=2)	4.14	[1.36; 12.56]
Adding Collet (2009) (k=3)	4.30	[1.57; 11.75]
Adding Giusti (2009) (k=4)	3.30	[1.68; 6.51]
Adding Yamamoto (2011) (k=5)	3.21	[1.66; 6.24]
Adding Oh (2012) (k=6)	2.91	[1.66; 5.11]
Fixed effect model	**2.91**	**[1.66; 5.11]**

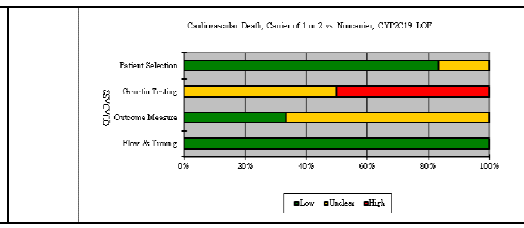
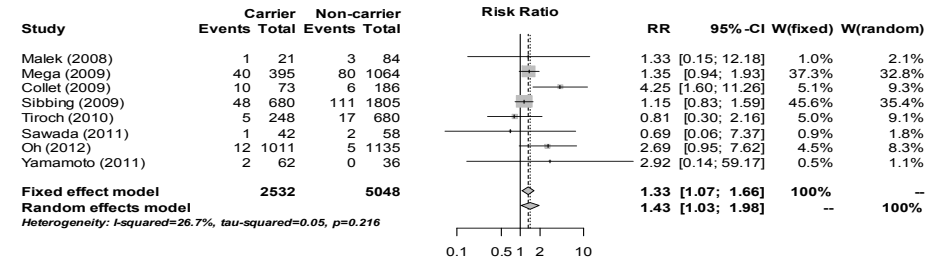
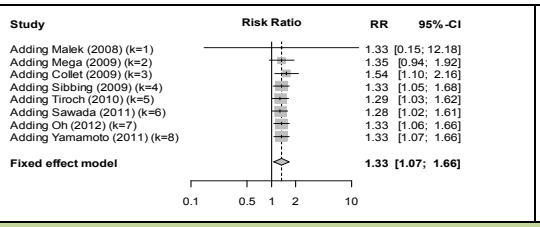
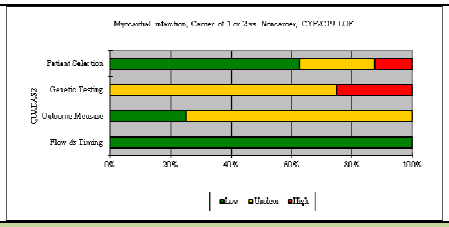


Table 5.17 (Continued): Graphical presentation of meta-analyses, cumulative meta-analyses and summary of risk of bias assessments conducted in clopidogrel test case

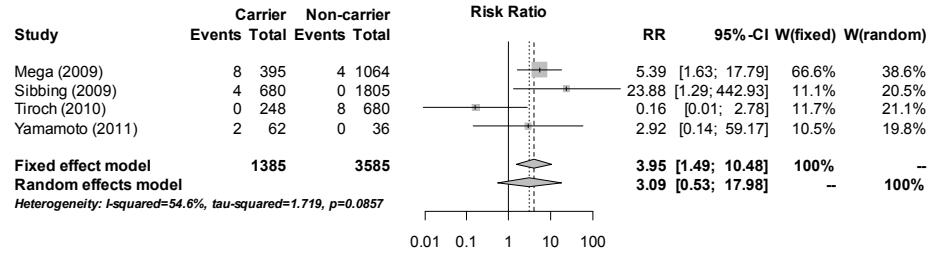
Carriers of 1 or 2 CYP2C19 loss-of-function alleles vs. Noncarriers on myocardial infarction

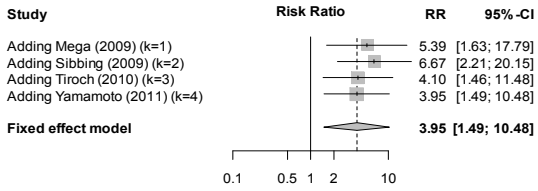


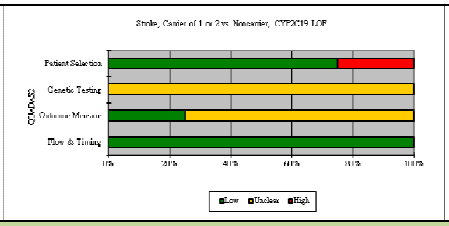




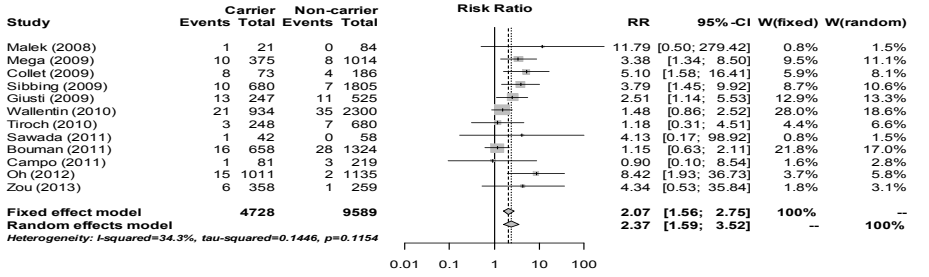
Carriers of 1 or 2 CYP2C19 loss-of-function alleles vs. Noncarriers on stroke

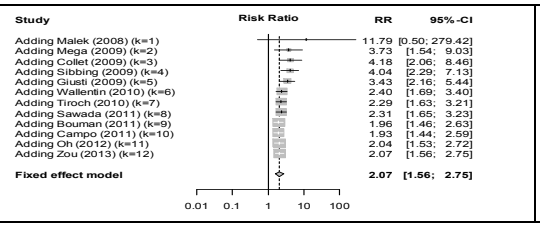






Carriers of 1 or 2 CYP2C19 loss-of-function alleles vs. Noncarriers on stent thrombosis





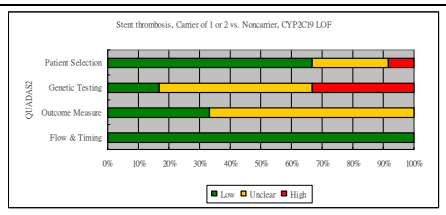
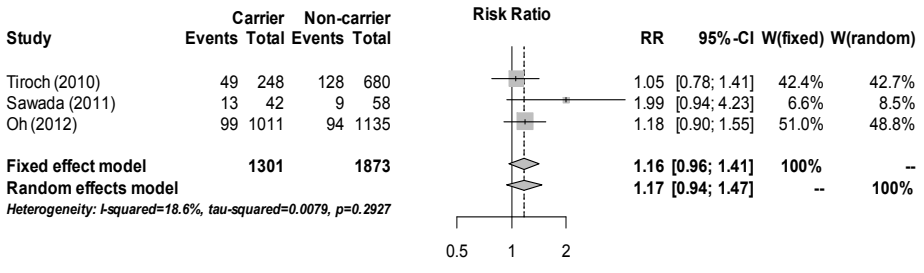
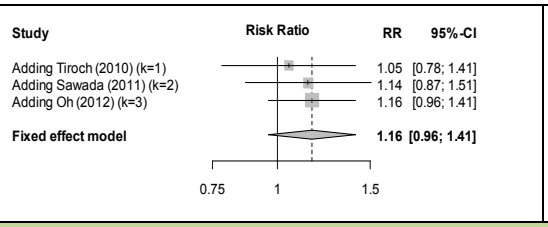
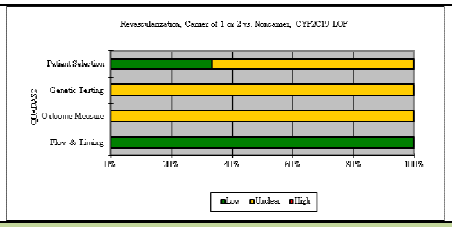


Table 5.17 (Continued): Graphical presentation of meta-analyses, cumulative meta-analyses and summary of risk of bias assessments conducted in clopidogrel test case

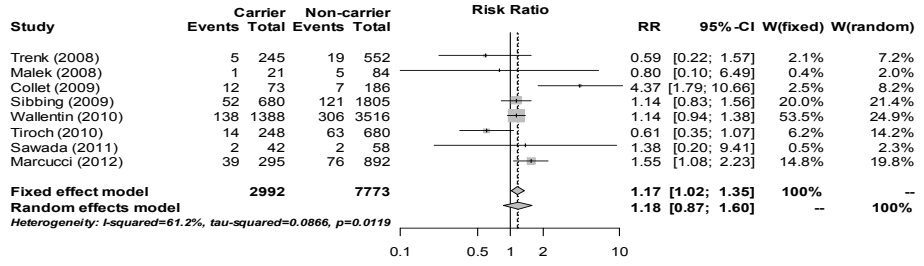
Carriers of 1 or 2 CYP2C19 loss-of-function alleles vs. Noncarriers on revascularization

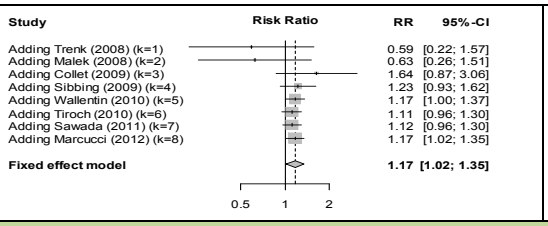


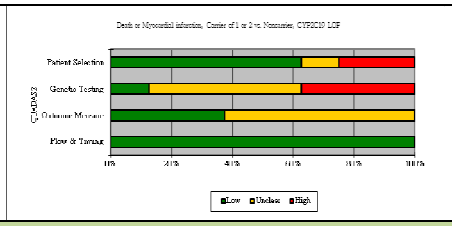




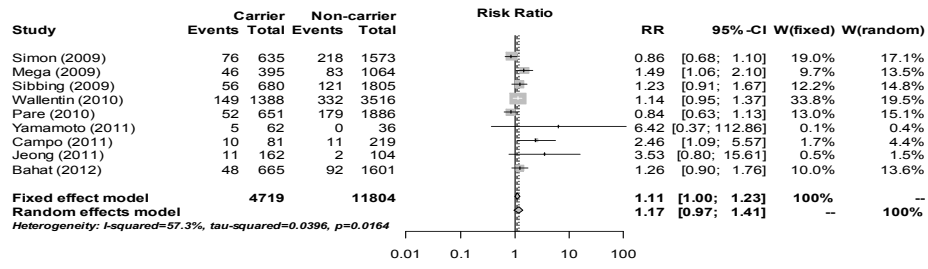
Carriers of 1 or 2 CYP2C19 loss-of-function alleles vs. Noncarriers on a composite of death and myocardial infarction

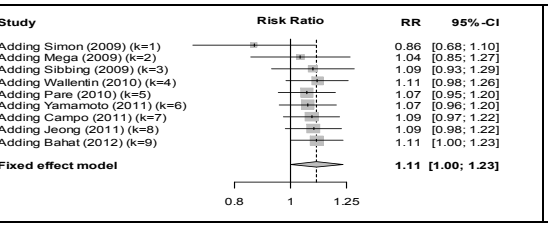






Carriers of 1 or 2 CYP2C19 loss-of-function alleles vs. Noncarriers on a composite of death or MI or stroke





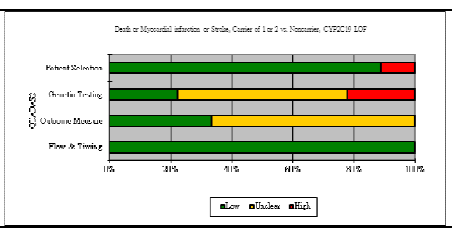
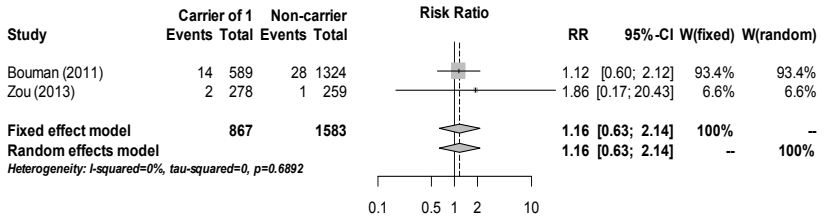
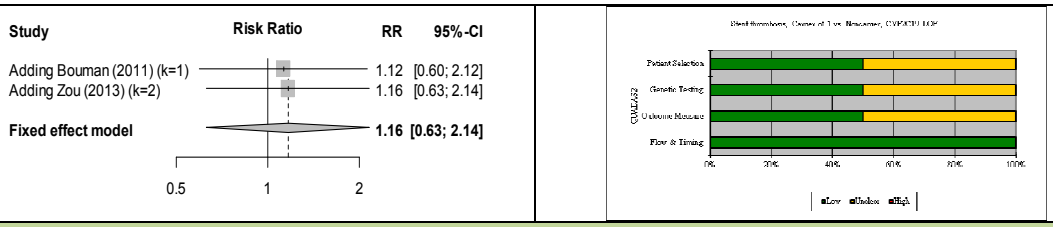


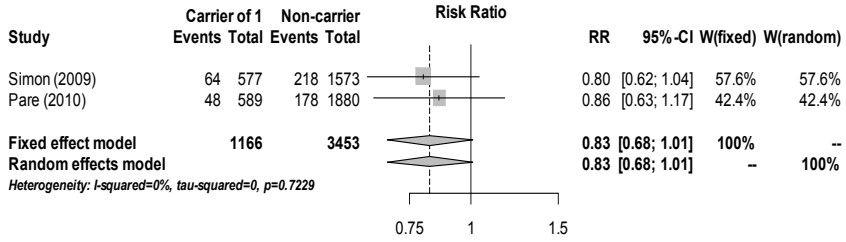
Table 5.17 (Continued): Graphical presentation of meta-analyses, cumulative meta-analyses and summary of risk of bias assessments conducted in clopidogrel test case

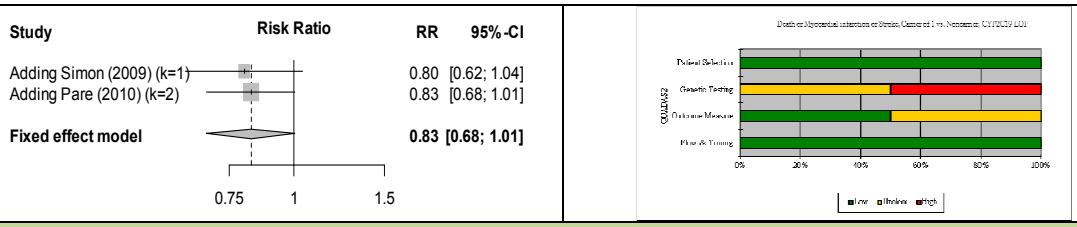
Carrier of 1 CYP2C19 loss-of-function alleles vs. Noncarriers on stent thrombosis



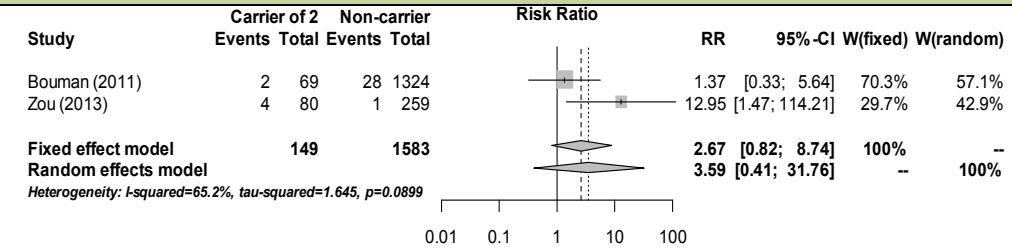


Carrier of 1 CYP2C19 loss-of-function alleles vs. Noncarriers on a composite of death or MI or stroke





Carrier of 2 CYP2C19 loss-of-function alleles vs. Noncarriers on stent thrombosis



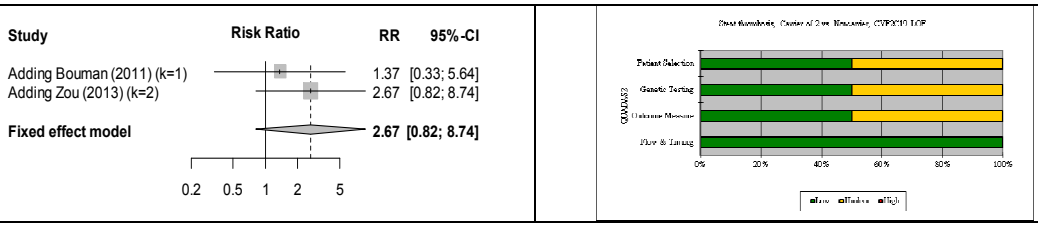
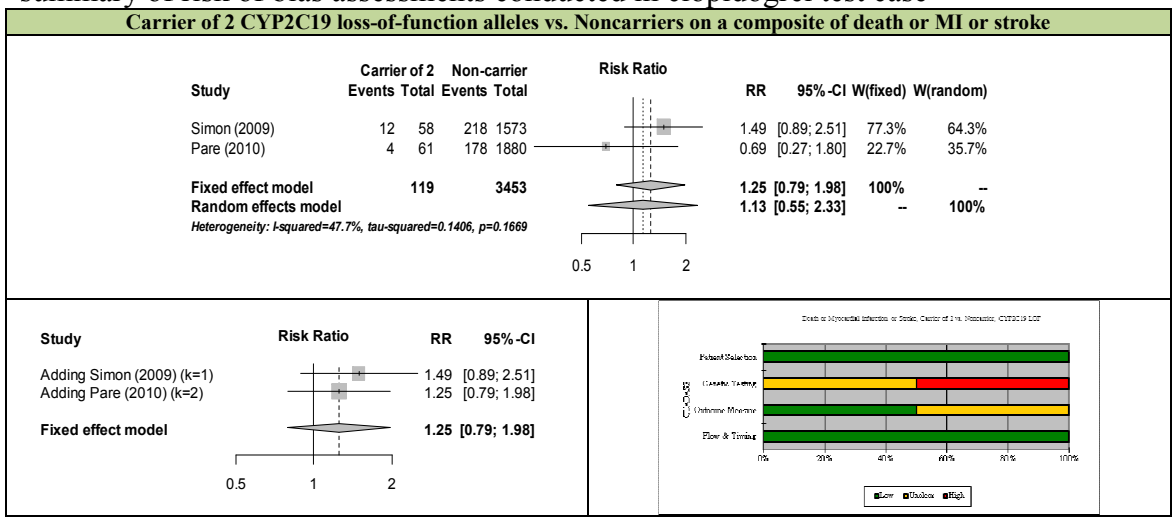


Table 5.17 (Continued): Graphical presentation of meta-analyses, cumulative meta-analyses and summary of risk of bias assessments conducted in clopidogrel test case



5.3.2 Implementation of warfarin test case

The warfarin test case aimed to assess the comparative effectiveness of genotype-guided and non-genotype-guided warfarin dosing on improving patients' clinical outcome, anticoagulation control, and warfarin dosing accuracy. The pharmacogenomics knowledge-based system developed in Chapter 4 was leveraged to implement the evidence-based assessment in warfarin test case through the following steps.

Step 1: Specify the assessment topic and inclusion criteria of relevant evidence

The collection of relevant evidence that address the assessment topic in warfarin test case is specified by 6 features, i.e., evidence type, study type, study population, compared drug therapy, outcome and outcome measurement type. **Table 5.18** provides an overview of the 6 features. Specifically, the relevant evidence includes any evidence acquired from an interventional study that compared the effectiveness of genotype-guided versus standard dosing of warfarin or genotype-guided versus clinically-guided dosing of warfarin on outcomes including (1)

thromboembolism, (2) death, (3) bleeding, (4) major bleeding, (5) minor bleeding, (6) major or minor bleeding, (7) INR in therapeutic range, (8) excessive anticoagulation, (9) dosing error, (10) composite of any disease or adverse event, or (11) composite of any disease or adverse event or excessive anticoagulation. All outcomes of interest were measured by the incidence of event or the time before an event was experienced, except that INR in therapeutic range was measured by the percentage of time spend in the therapeutic range and dosing error was measured by the absolute dose differences.

Table 5.18: Specification of inclusion criteria for retrieving relevant evidence in warfarin test case

Assessment topic	Comparative effectiveness of genotype-guided warfarin dosing in improving patients' clinical outcome, anticoagulation control and warfarin dosing accuracy
Inclusion criteria of relevant evidence	
Evidence type	Comparative effectiveness
Study type	Interventional study
Study population	Patients with indication for warfarin
Compared drug therapy	(1) genotype-guided vs. standard dosing of warfarin (2) genotype-guided vs. clinical guided dosing of warfarin
Outcome	(1) thromboembolism, (2) death, (3) bleeding, (4) major bleeding, (5) minor bleeding, (6) major or minor bleeding, (7) INR in therapeutic range, (8) excessive anticoagulation, (9) dosing error, (10) composite of any disease or any adverse event (11) composite of any disease or any adverse event or excessive anticoagulation
Outcome measurement type	(1) incidence of event (2) time to event (3) percentage of time with event (only for INR in therapeutic range) (4) absolute difference to final dose (only for dosing error)

INR: international normalized ratio

Step 2: Design and formal representation of evidence classification schemes to retrieve and classify relevant evidence

According to the specified inclusion criteria of relevant evidence in **Table 5.18**, a set of predefined classification schemes was designed and presented in **Table 5.19**. Briefly, a collection of relevant evidence was first retrieved from the developed knowledge base according to the inclusion criteria specified in **Table 5.18**, then the collection of relevant evidence was sequentially classified by 4 levels of classification. The first-level classification divided the relevant evidence into 2 categories by experimental and comparator drug therapies in

comparison, that were “genotype-guided versus standard dosing of warfarin” and “genotype-guided versus clinical guided dosing of warfarin” respectively. At the second level of classification, evidence within each of the two categories was further classified into 6 different outcome categories i.e., efficacy, safety, pharmacodynamics, dosing accuracy, composite of efficacy or safety, and composite of efficacy, safety or pharmacodynamics. At the third level of classification, evidence was further classified into 11 types of outcome of interest as specified in **Table 5.18**. Finally, evidence was classified based on the type of measurement (i.e., incidence of event or time to event).

Table 5.19: Evidence classification schemes designed in warfarin test case

Relevant evidence according to inclusion criteria specified in Table 5.18	
|- Genotype-guided versus standard dosing of warfarin	**|- Genotype-guided versus clinical guided dosing of warfarin**
|- Efficacy	|- Efficacy
|- 1 component, Thromboembolism	|- 1 component, Thromboembolism
|- incidence of event	|- incidence of event
|- time to event	|- time to event
|- 1 component, Death	|- 1 component, Death
|- incidence of event	|- incidence of event
|- time to event	|- time to event
|- Safety	|- Safety
|- 1 component, Bleeding	|- 1 component, Bleeding
|- 1 component, Major bleeding	|- 1 component, Major bleeding
|- incidence of event	|- incidence of event
|- time to event	|- time to event
|- 1 component, Minor bleeding	|- 1 component, Minor bleeding
|- incidence of event	|- incidence of event
|- time to event	|- time to event
|- 1 component, Major_or_Minor_bleeding	|- 1 component, Major_or_Minor_bleeding
|- incidence of event	|- incidence of event
|- time to event	|- time to event
|- Pharmacodynamics	|- Pharmacodynamics
|- 1 component, INR in therapeutic range	|- 1 component, INR in therapeutic range
|- percentage of time with event	|- percentage of time with event
|- 1 component, Excessive anticoagulation	|- 1 component, Excessive anticoagulation
|- incidence of event	|- incidence of event
|- time to event	|- time to event
|- Dosing accuracy	|- Dosing accuracy
|- 1 component, Dosing error	|- 1 component, Dosing error
|- absolute difference to final dose	|- absolute difference to final dose
|- A composite of efficacy or safety	|- A composite of efficacy or safety
|- Multiple components of any disease or any adverse event	|- Multiple components of any disease or any adverse event
|- incidence of event	|- incidence of event
|- time to event	|- time to event
|- A composite of efficacy or safety or pharmacodynamics	|- A composite of efficacy or safety or pharmacodynamics
|- Multiple components of any disease or any adverse event or excessive anticoagulation	|- Multiple components of any disease or any adverse event or excessive anticoagulation
|- incidence of event	|- incidence of event
|- time to event	|- time to event

Each cell in **Table 5.19** corresponds to a specific set of inclusion criteria, which was transformed into a defined class that had formally asserted necessary and sufficient conditions. As a result, a total of 73 defined classes were added to the OWL ontology (see **Figure 5.11**).

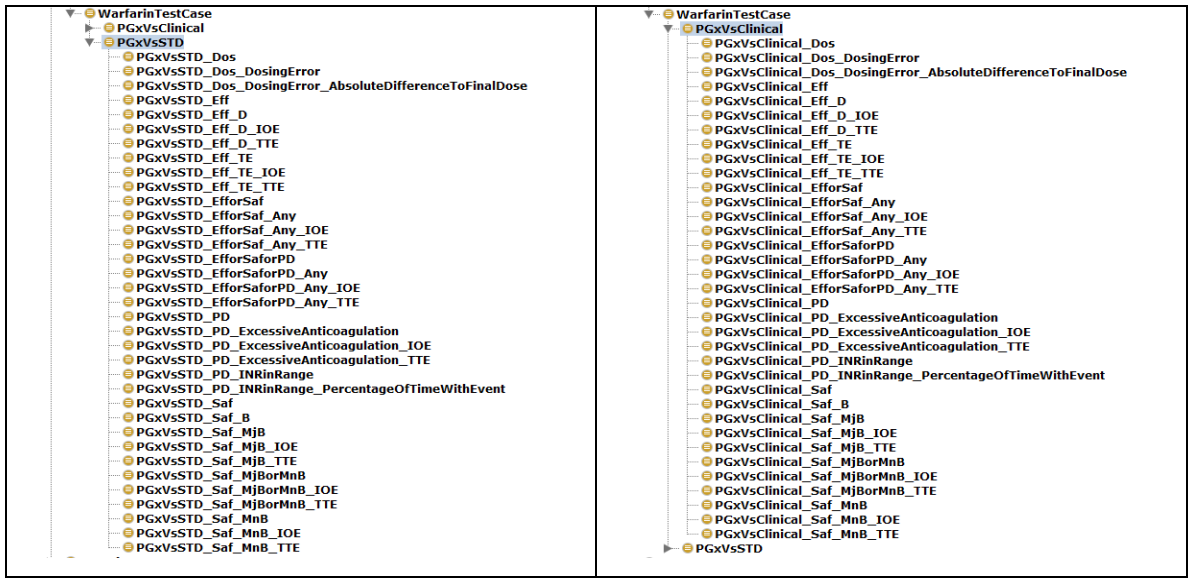


Figure 5.11: Formal representation of evidence classification schemes in warfarin test case. A total of 73 defined classes were asserted as class hierarchy

Step 3: Perform subsumption and instance checking over evidence classification schemes

The HermiT reasoner was triggered to perform instance checking and class subsumption checking for all of the 73 defined classes. The entire reasoning process took around 8 seconds (8,565 milliseconds). **Figure 5.12** shows the inferred class hierarchy and **Table 5.20** shows the results of instance checking of the evidence classification schemes designed in warfarin test case.

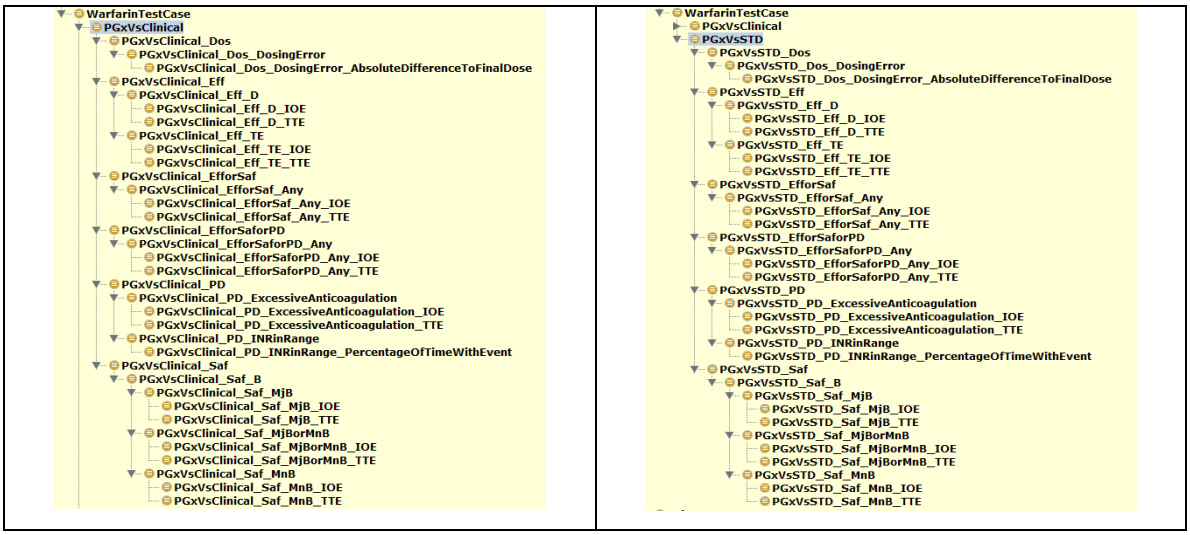


Figure 5.12: Inferred class hierarchy of evidence classification schemes designed in warfarin test case

Table 5.20: Evidence profile that informs the quantity of relevant evidence in warfarin test case

Evidence profile			
Warfarin Test Case (N=101)			
|- Genotype-guided versus clinical guided dosing of warfarin	33	**|- Genotype-guided versus standard dosing of warfarin**	68
|- Efficacy	5	|- Efficacy	5
|- 1 component, Thromboembolism	3	|- 1 component, Thromboembolism	3
|- **incidence of event**	3	|- **incidence of event**	3
|- time to event	0	|- time to event	0
|- 1 component, Death	2	|- 1 component, Death	0
|- **incidence of event**	2	|- incidence of event	0
|- time to event	0	|- time to event	0
|- Safety	6	|- Safety	6
|- 1 component, Bleeding	6	|- 1 component, Bleeding	6
|- 1 component, Major bleeding	3	|- 1 component, Major bleeding	3
|- **incidence of event**	3	|- **incidence of event**	3
|- time to event	0	|- time to event	0
|- 1 component, Minor bleeding	2	|- 1 component, Minor bleeding	2
|- **incidence of event**	2	|- **incidence of event**	2
|- time to event	0	|- time to event	0
|- 1 component, Major_or_Minor_bleeding	1	|- 1 component, Major_or_Minor_bleeding	1
|- incidence of event	1	|- incidence of event	1
|- time to event	0	|- time to event	0
|- Pharmacodynamics	17	|- Pharmacodynamics	44
|- 1 component, INR in therapeutic	7	|- 1 component, INR in therapeutic	14
|- **percentage of time with event**	4	|- **percentage of time with event**	7
|- 1 component, Excessive anticoagulation	4	|- 1 component, Excessive anticoagulation	8
|- **incidence of event**	2	|- **incidence of event**	5
|- time to event	1	|- time to event	1
|- Dosing accuracy	3	|- Dosing accuracy	4
|- 1 component, Dosing error	2	|- 1 component, Dosing error	3
|- **absolute difference to final dose**	2	|- **absolute difference to final dose**	3
|- Composite of efficacy or safety	1	|- Composite of efficacy or safety	5
|- Multiple components of any disease or adverse event	1	|- Multiple components of any disease or adverse event	5
|- incidence of event	1	|- **incidence of event**	4
|- time to event	0	|- time to event	1
|- Composite of efficacy or safety or pharmacodynamics	1	|- Composite of efficacy or safety or pharmacodynamics	4
|- Multiple components of any disease or adverse event or excessive anticoagulation	1	|- Multiple components of any disease or adverse event or excessive anticoagulation	4
|- incidence of event	0	|- **incidence of event**	3
|- time to event	1	|- time to event	0

Step 4: Generate an evidence profile that informs quantity of relevant evidence

Based on the inferred results conducted in the preceding step, the number of instances in each of the 73 defined classes designed in evidence classification schemes was provided in an evidence profile (see **Table 5.20**). According to the currently available evidence shown in the evidence profile, 15 defined classes that had at least 2 instances with sufficient similarity in drug therapies and outcome in comparison were selected for further analysis (See texts and cells highlighted in green in **Table 5.20**).

Step 5: Select relevant evidence, prepare data for meta-analysis, perform meta-analysis, cumulative meta-analysis and summarize risk of bias assessment

Instances retrieved by each of the 15 selected defined classes were manually checked for completeness of the data required for conducting meta-analysis and overlapping of individual evidence that is retrieved from the same study. Data incompleteness was found in 2 defined classes related to outcome of dosing error. Therefore, a total of 13 groups of evidence were selected to conduct meta-analysis for the warfarin test case. The data acquisition and analysis process was performed in the same way as that performed in clopidogrel test case (see Section 3.5.1, Step 5).

Step 6: Report results of meta-analysis, cumulative meta-analysis and summary of risk of bias assessment

Table 5.21 presents the summary of findings from 13 meta-analyses. Graphical representations of results of each meta-analysis, cumulative meta-analysis and risk of bias assessment were illustrated in **Table 5.22**. Among 13 meta-analyses, 3 meta-analyses reported statistically significant results (see cells highlighted in yellow in **Table 5.21**). The results shown that patients who received genotype-guided warfarin dosing had significantly decreased risk of

thromboembolic, increased time in INR therapeutic range, decreased risk of composite disease or adverse events than patients who received standard warfarin dosing. It was also found that patients who received genotype-guided warfarin dosing had decreased risk of major bleeding, minor bleeding, excessive anticoagulation, and composite disease, adverse events or excessive anticoagulation than patients who received standard warfarin dosing; however, the differences were not statistically significant. For comparison between genotype-guided and clinically guided warfarin dosing, the former had increased risk of thromboembolic and excessive anticoagulation; decreased risk of death, major bleeding, minor bleeding; increased time in INR therapeutic range than the latter. However, the differences were not statistically significant.

Table 5.21: Summary of findings of each meta-analysis conducted in warfarin test case

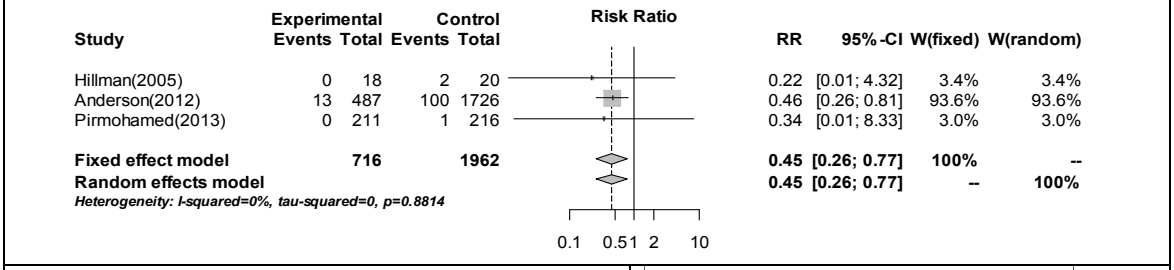
Assessment topic	The effectiveness of genotype-guided dosing of warfarin in patients who are eligible for warfarin						
Meta-analysis method	Random effect model						
Defined class	Drug therapy compared	Outcome category	Outcome component	Effect metric	Effect size	95% Confidence Interval	No. included evidence/ No. study subjects
PGxVsSTD_Eff_TE_IOE	PGx vs. Standard	Efficacy	Thromboembolism	Relative Risk	0.45	0.26, 0.77	3/ 716 vs. 1962
PGxVsSTD_Saf_MjB_IOE	PGx vs. Standard	Safety	Major Bleeding	Relative Risk	0.69	0.19, 2.49	3/ 716 vs. 1962
PGxVsSTD_Saf_MnB_IOE	PGx vs. Standard	Safety	Minor Bleeding	Relative Risk	0.46	0.10, 2.01	2/ 79 vs. 80
PGxVsSTD_PD_INRinRange_PercentageOfTimeWithEvent	PGx vs. Standard	Pharmaco-dynamics	INR in Therapeutic Range	Mean Difference	7.05%	2.05%, 12.04%	5/ 820 vs. 2214
PGxVsSTD_PD_Excessive Anticoagulation_IOE	PGx vs. Standard	Pharmaco-dynamics	Excessive Anticoagulation	Relative Risk	0.78	0.61, 1.01	4/ 303 vs. 308
PGxVsSTD_EfforSaf_Any_IOE	PGx vs. Standard	Efficacy or Safety	Any disease or adverse event	Relative Risk	0.64	0.51, 0.81	4/ 1492 vs. 4533
PGxVsSTD_EfforSaforPD_Any_IOE	PGx vs. Standard	Efficacy or Safety or Pharmaco-dynamics	Any disease or adverse event or excessive anticoagulation	Relative Risk	0.78	0.57, 1.08	3/ 212 vs. 210
PGxVsClinical_Eff_TE_IOE	PGx vs. Clinical	Efficacy	Thromboembolism	Relative Risk	1.53	0.49, 4.73	3/ 722 vs. 709
PGxVsClinical_Eff_D_IOE	PGx vs. Clinical	Efficacy	Death	Relative Risk	0.97	0.23, 4.02	2/ 627 vs. 613
PGxVsClinical_Saf_MjB_IOE	PGx vs. Clinical	Safety	Major Bleeding	Relative Risk	0.48	0.20, 1.16	3/ 722 vs. 708
PGxVsClinical_Saf_MnB_IOE	PGx vs. Clinical	Safety	Minor Bleeding	Relative Risk	0.49	0.23, 1.04	2/ 609 vs. 597
PGxVsClinical_PD_INRinRange_PercentageOfTimeWithEvent	PGx vs. Clinical	Pharmaco-dynamics	INR in Therapeutic Range	Mean Difference	4.74%	-4.92%, 14.41%	3/ 689 vs. 676
PGxVsClinical_PD_ExcessiveAnticoagulation_IOE	PGx vs. Clinical	Pharmaco-dynamics	Excessive Anticoagulation	Relative Risk	1.07	0.87, 1.32	2/ 627 vs. 613

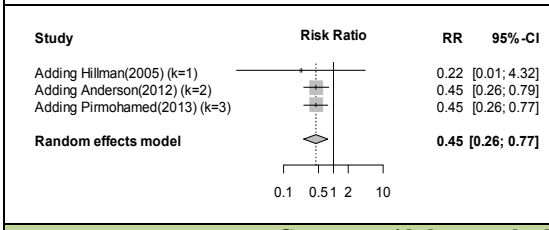
Note: Findings highlighted in yellow are statistically significant

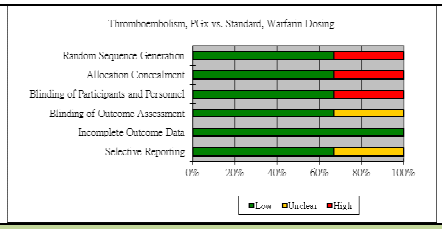
Table 5.22: Graphical representation of meta-analyses, cumulative meta-analyses and summary of risk of bias assessments in warfarin test case

13 meta-analyses

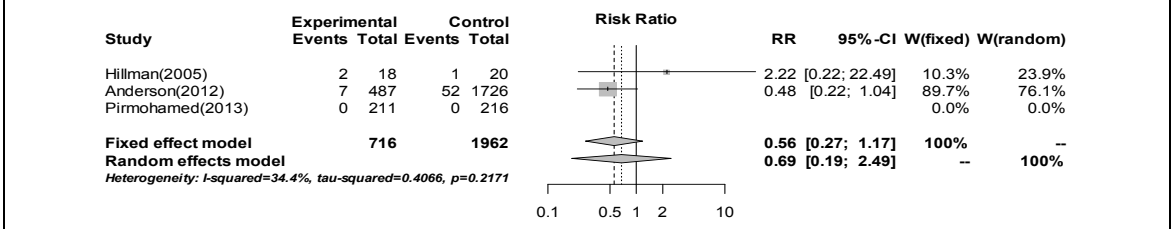
Genotype-guided vs. standard dosing of warfarin on thromboembolism

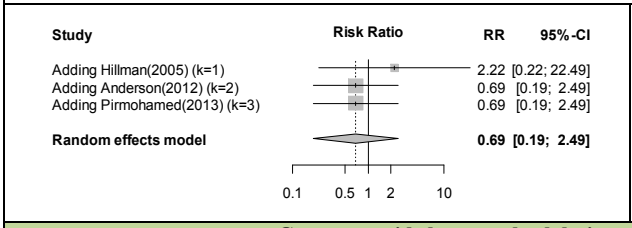


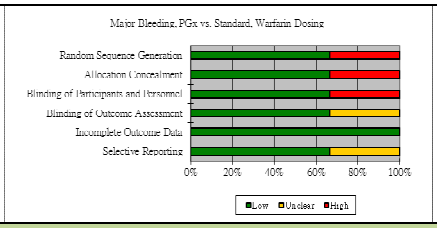




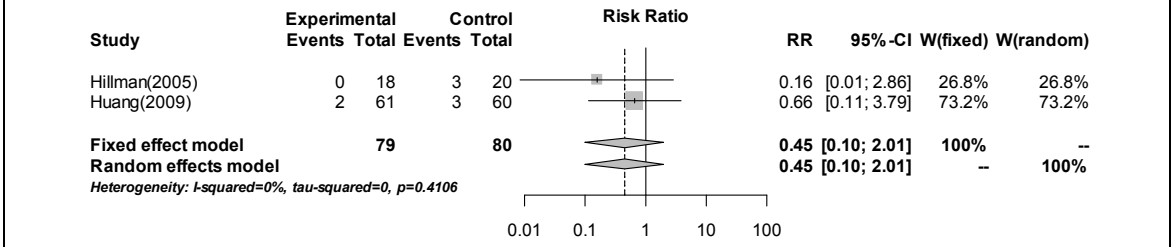
Genotype-guided vs. standard dosing of warfarin on major bleeding

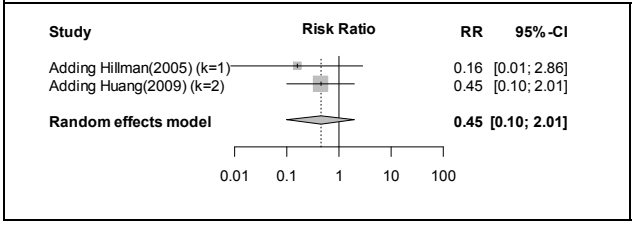






Genotype-guided vs. standard dosing of warfarin on minor bleeding





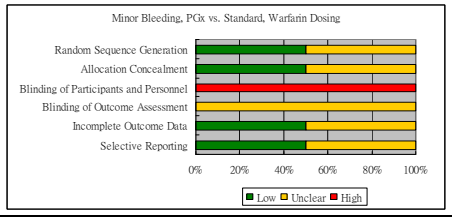
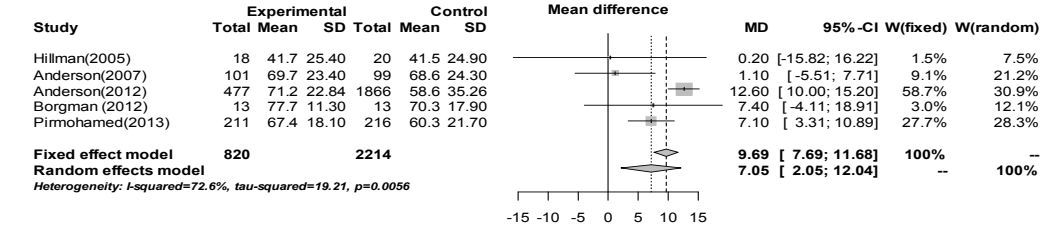
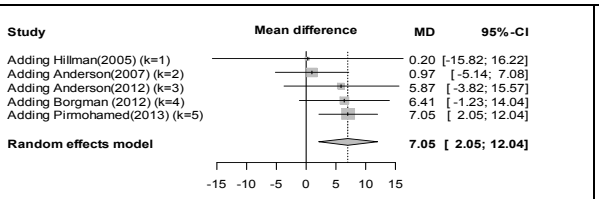
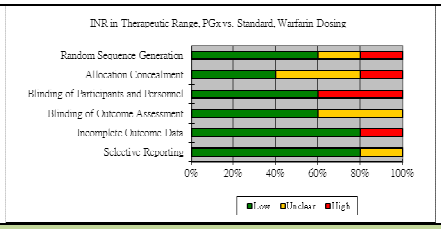


Table 5.22 (Continued): Graphical representations of meta-analyses, cumulative meta-analyses and summary of risk of bias assessments in warfarin test case

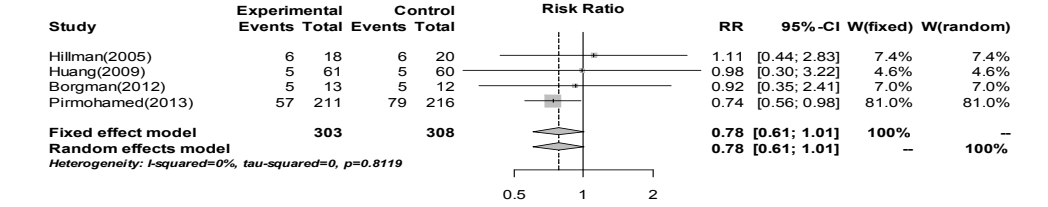
Genotype-guided vs. standard dosing of warfarin on INR in therapeutic range

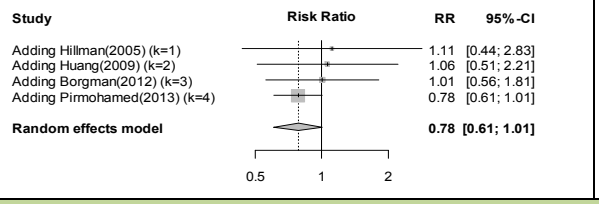


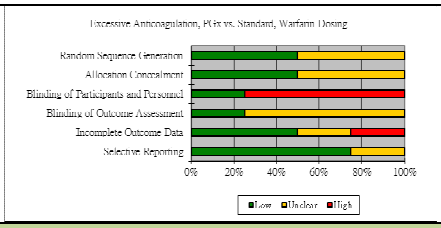




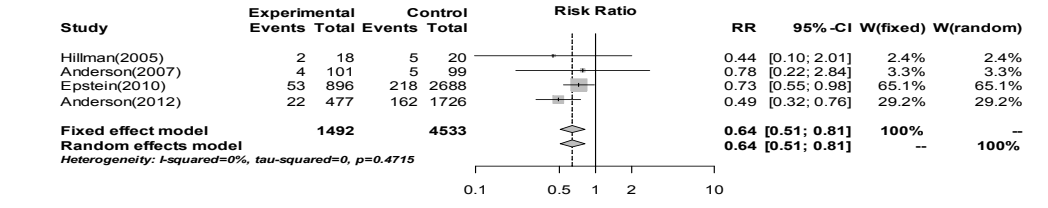
Genotype-guided vs. standard dosing of warfarin on excessive anticoagulation

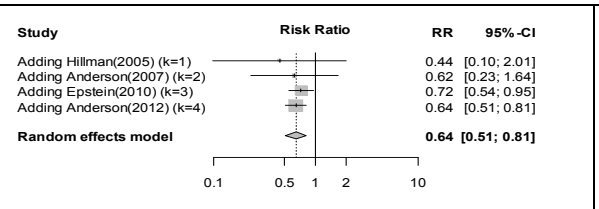






Genotype-guided vs. standard dosing of warfarin on a composite of any disease or any adverse event





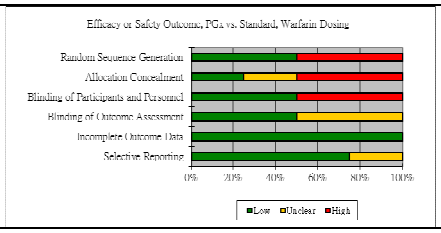
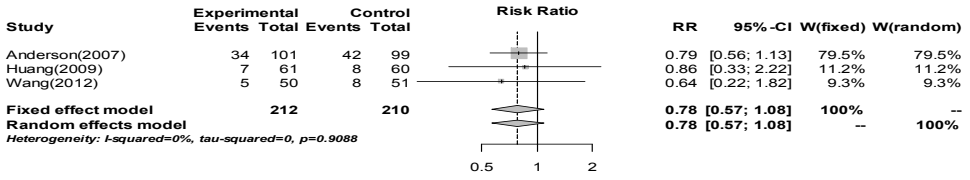
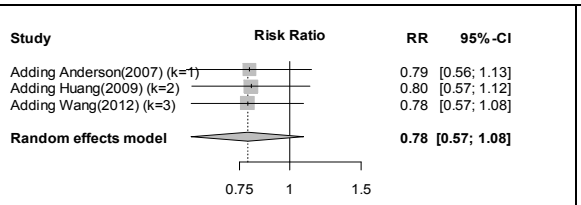
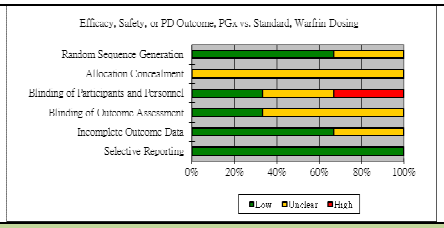


Table 5.22 (Continued): Graphical representations of meta-analyses, cumulative meta-analyses and summary of risk of bias assessments in warfarin test case

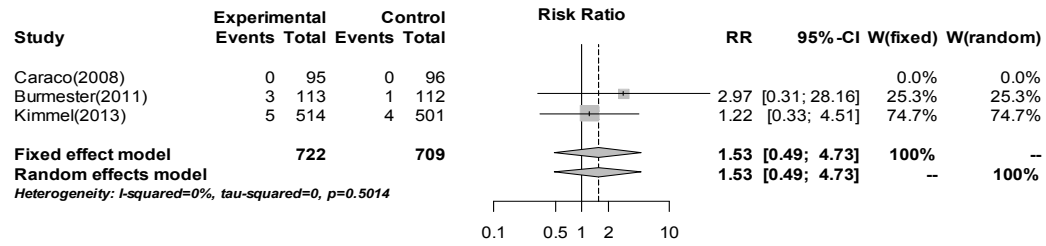
Genotype-guided vs. standard dosing of warfarin on a composite of any disease or any adverse event or excessive anticoagulation

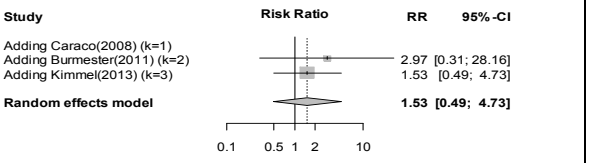


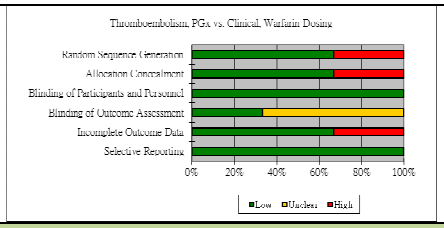




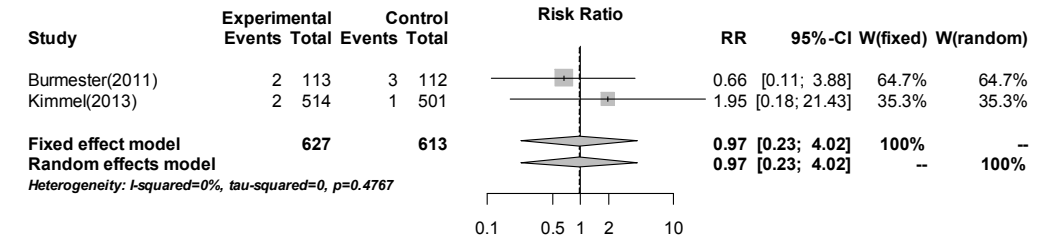
Genotype-guided vs. clinical guided dosing of warfarin on thromboembolism

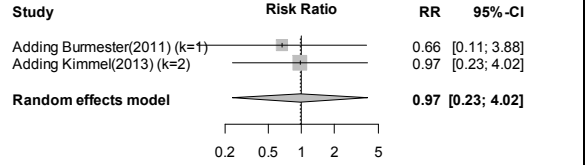






Genotype-guided vs. clinical guided dosing of warfarin on death





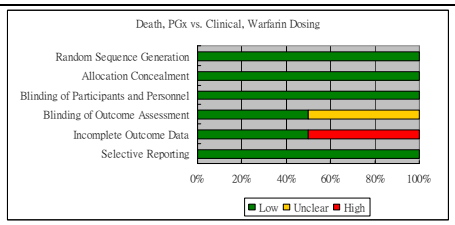
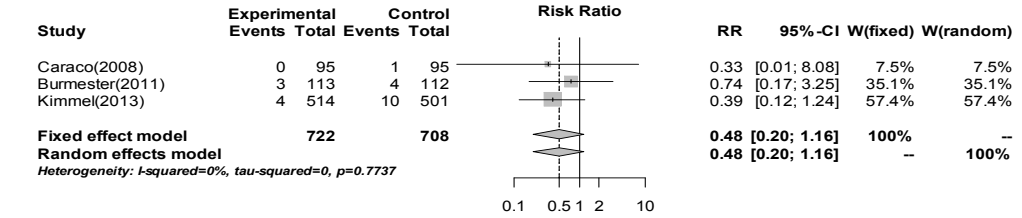
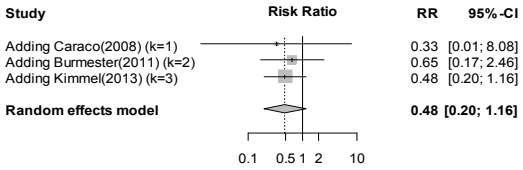
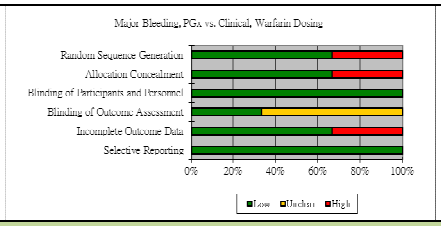


Table 5.22 (Continued): Graphical representations of meta-analyses, cumulative meta-analyses and summary of risk of bias assessments in warfarin test case

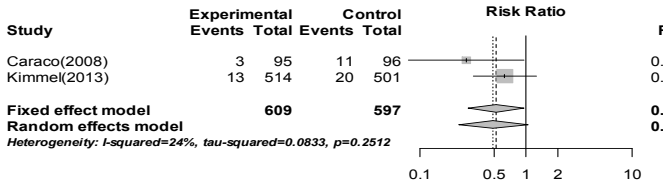
Genotype-guided vs. clinical guided dosing of warfarin on major bleeding

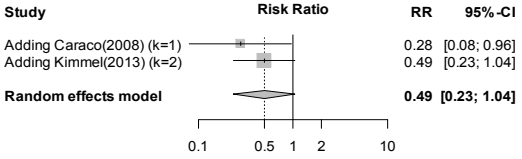


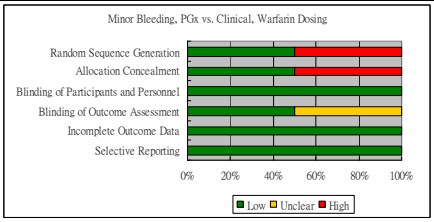




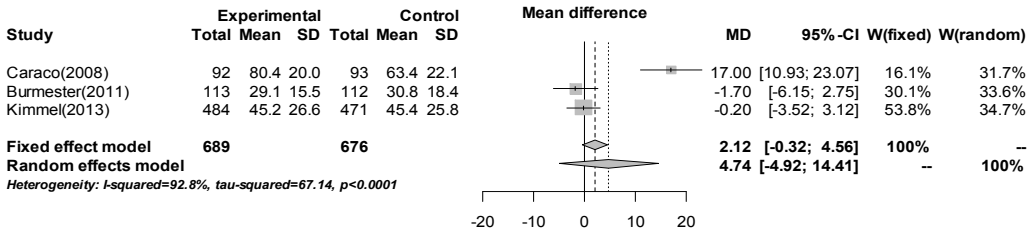
Genotype-guided vs. clinical guided dosing of warfarin on minor bleeding

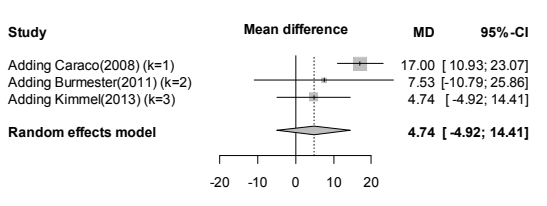






Genotype-guided vs. clinical guided dosing of warfarin on INR in therapeutic range





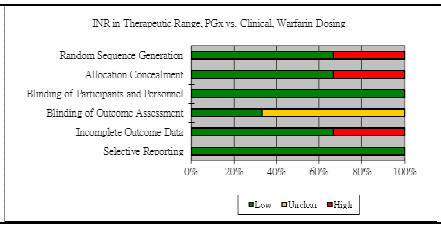
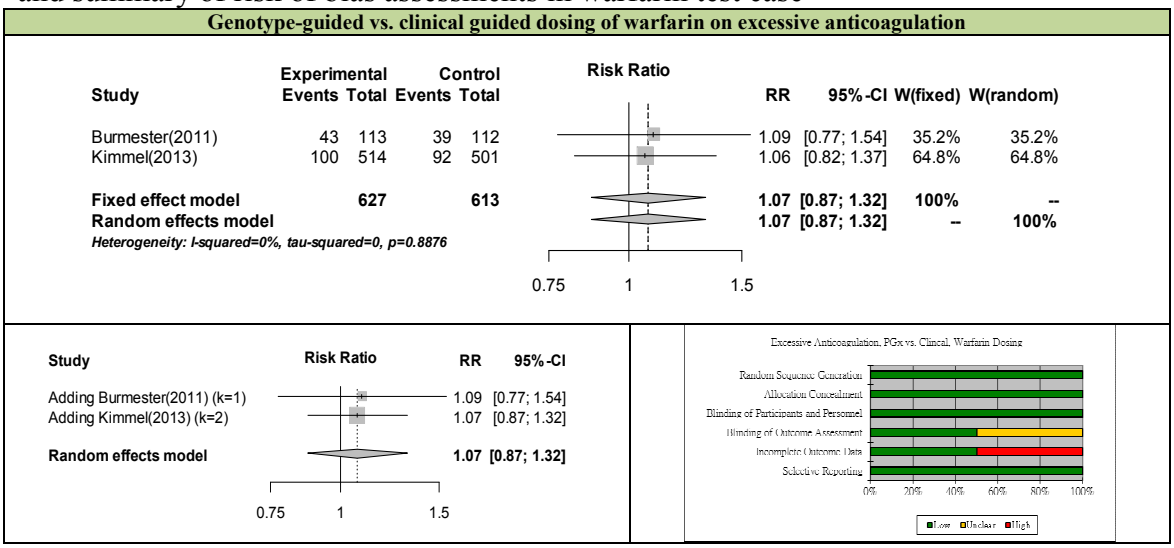


Table 5.22 (Continued): Graphical representations of meta-analyses, cumulative meta-analyses and summary of risk of bias assessments in warfarin test case



5.3.3 Discussion

In the preceding sub-sections 5.3.1 and 5.3.2, two systematic reviews were implemented by leveraging the developed knowledge-based system to provide essential information for effective and efficient meta-analysis. Although two systematic reviews assess different questions, one regards to the clinical validity of *CYP2C19* loss-of-function alleles in predicting efficacy outcome of clopidogrel therapy and the other regards to clinical utility of genotype-guided warfarin dosing in improving patients' outcome, the implementation process and methods are the same. Thus, the two use cases are discussed together in this sub-section.

I successfully implemented an innovative idea in both the clopidogrel test case and the warfarin test case to facilitate effective and efficient systematic review with meta-analysis. The idea was to design a large number of evidence classification schemes that subdivides a collection of relevant and retrieved evidence into groups were considered homogeneous in terms of study populations, interventions, comparisons, outcomes and etc. Then, the classification results were used to inform the availability of primary evidence before embarking on a comprehensive

systematic review. I exploited the developed pharmacogenomics knowledge-based system to implement this idea: (1) an OWL 2 DL ontology that models the domain of pharmacogenomics evidence assessment, (2) formal representation of pharmacogenomics publications, studies and evidence into asserted individuals composed of OWL 2 DL constructs and constructors, (3) a ontology-based knowledge base that provides formally represented pharmacogenomics knowledge, (4) formal representation of inclusion criteria into defined classes with unambiguously asserted necessary and sufficient conditions, (5) representation patterns that enable quick and easy editing of heterogeneous necessary and sufficient conditions when creating new defined classes, and (6) a highly efficient OWL 2 DL reasoner that enables iterative instance checking over a large number of defined classes. This design has several advantages. First of all, the current status of the availability of relevant evidence could be quickly examined using an evidence profile before actually embarking on time- and resource-consuming systematic reviews. That is to say, the implemented pharmacogenomics knowledge-based system helps to avoid undesirable circumstances that significant time and resources have been invested, but it turns out that there is insufficient evidence to undertake meta-analyses of interest [Veenstra et al., 2013]. Secondly, the evidence profile informs the decisions of whether there is enough evidence to carry out meta-analyses and which primary evidence to be included in meta-analyses. Thirdly, the knowledge base provides essential data of a meta-analysis so that statistical tools can be incorporated with the system to generate tables and graphs which report meta-analysis results. Finally, once the evidence classification schemes are regarded as the default and embedded in the OWL ontology, an automatic update of currently available evidence could be achieved whenever the HermiT reasoner is triggered. It means that the developed knowledge-based system improves the efficiency of review process not only by automatic

retrieval of relevant evidence but also by avoiding duplicate effort in developing the same systematic review protocol.

The implementation of the clopidogrel test case and the warfarin test case demonstrates the advantages of using a knowledge-based system for conducting an effective and efficient evidence assessment. Two evidence classification schemes were designed and formally represented into defined classes, one consisted of 109 defined classes for the clopidogrel test case and the other consisted of 73 defined classes for the warfarin test case. The HermiT reasoner completed instance checking for each of the evidence classification schemes in a very short computing time (i.e., 4 minutes for clopidogrel test case and 8 seconds for warfarin test case). Owing to the formalized necessary and sufficient conditions asserted in each defined class, instances (i.e., relevant and retrieved individual evidence) of each defined class are considered homogenous in terms of study populations, interventions, comparisons, outcomes and etc. Based on the principle that at least 2 pieces of individual evidence are required for a meta-analysis, 12 and 13 groups of individual evidence were amenable to meta-analyses for the systematic review of clopidogrel test case and warfarin test case respectively. The essential data of meta-analyses and cumulative meta-analyses were manually extracted from selected individual evidence and read by R to perform meta-analyses and cumulative meta-analyses and create forest plots.

While compiling the results of meta-analyses to form the "summary of findings" tables**,** it is found that when more meta-analyses results are available, interpreting the clinical significance of pharmacogenomics evidence from meta-analyses results becomes more complex. For example, when interpreting a multitude of synthesized evidence shown in **Table 5.16** and **Table 5.21**, many factors needs to be considered, including: the characteristics of outcomes (e.g., desirable or undesirable), methods used to measure the effect sizes (e.g. ratio or difference), directions and

magnitudes of effect sizes on outcomes and etc. In order to improve the efficiency in interpreting the results of a multitude of synthesized evidence, the developed knowledge-based system should be extended further to enable automatic inference of the clinical significance of pharmacogenomics based on the information contained in the synthesized evidence.

In summary, the developed pharmacogenomics knowledge-based system has been proven to provide an effective and efficient approach to conduct systematic reviews of clinical validity and clinical utility of pharmacogenomics applications. The need for automatic inferences of the clinical significance of synthesized evidence has been recognized. Therefore, methods that leverage the implemented pharmacogenomics knowledge-based system to address the need are provided in the next section.

5.4. Automatic Inference of Clinical Significance from Formally Represented Synthesized Evidence

In the two preceding sections 5.2 and 5.3, the developed pharmacogenomics knowledge-based system has proved its capability of facilitating effective and efficient systematic review with meta-analysis by ontology-driven retrieval and classification of the individual publications, studies and evidence that have been formally represented and accumulated in the knowledge base. Besides the primary purpose to assist in effective and efficient evidence assessment, I intend to extend the applicability of the system to make inference about clinical significance of pharmacogenomics drawn from synthesized evidence. Specifically, the idea is to formally represent the synthesized evidence so that ontology-driven methods could be developed to facilitate the interpretation of heterogeneous synthesized evidence generated from many pharmacogenomics evidence assessments that address the similar research questions, and ultimately assist in drawing an overall conclusion about clinical adoption of a specific

pharmacogenomics application. The idea conceived above is implemented in this section by continuing the clopidogrel test case and the warfarin test case presented in Section 5.3. The results of meta-analyses conducted in clopidogrel test case and warfarin test case respectively (see **Table 5.16** and **Table 5**.**21**), i.e., 25 pieces of synthesized evidence (12 from clopidogrel test case and 13 from warfarin test case), were used to demonstrate the implementation process. Four critical tasks, including modeling synthesized evidence as information entity, formal representation of individual synthesized evidence, formal representation of definitions of clinical significance, and generation of synthesized evidence profile, are presented in the following sub-sections to demonstrate my implementation approach.

5.4.1 Extend the constructed conceptual model to express synthesized evidence as an information entity

The concept of synthesized evidence is modeled as an information entity that is described by 4 types of information: (1) primary evidence included in the meta-analysis, (2) inclusion criteria used to select the eligible primary evidence to include in meta-analysis, (3) meta-analysis model used, and (4) estimate of the pooled effect.

In Chapter 3, I developed a conceptual model that contains 3 information entities, namely, publication, study and evidence. Three information entities are described by 9 information components: publication, study population, study design, drug therapy, risk of bias assessment, comparison, genetic variation, outcome and effect. Most of these building blocks were reused to describe the newly added information entity i.e., synthesized evidence. As the extended conceptual model shown in **Figure 5.13**, the modules of publication, study population, study design, drug therapy, genetic variation, and outcome were reused to specify the criteria for inclusion of relevant evidence in meta-analysis. The effect module was reused to specify the

pooled effect generated by meta-analysis**.** Only a few concepts and relations were added (see the yellow highlights in **Figure 5.13**). The concept of **`synthesized evidence`** is added to represent the set of individual synthesized evidence. The *`is_synthesized_from`* relation is added to link individuals in **`synthesized evidence`** to individuals in **`evidence`** to specify which individual primary evidence is included in a meta-analysis. The **`Meta-analysis Model`** concept and the *`has_meta-analysis_model`* relation are added to formed a meta-analysis module to specify the models (either fixed effect model or random effects model) used in conducting a meta-analysis.

5.4.2 Extend the constructed ontology to formally represent synthesized evidence

The ontology constructed in Chapter 4 was extended based on the extended conceptual model illustrated in **Figure 5.13**. Two root classes, i.e., **`SynthesizedEvidence`** and **`MetaAnalysisModel`**, and two object properties, i.e., *`isSynthesizedFrom`* and *`hasMetaAnalysisModel`*, were added to the ontology. The class of **`MetaAnalysisModel`** has two subclasses, i.e., **`RandomEffectModel`** and **`FixedEffectModel`**. Subsequently, the knowledge base constructed in Chapter 4 was expanded by instantiating 12 and 13 pieces of synthesized evidence for the clopidogrel and the warfarin test case respectively. Class expressions that are used to represent individual publications, studies and evidence can be reused to assert individual synthesized evidence. As shown in **Figure 5.14**, `s_evi_clopidogrel_01` is a piece of individual synthesized evidence in clopidogrel test case. It compares the risk of death between carriers of at least one *CYP2C19* loss-of-function allele and non-carriers among patients with standard clopidogrel therapy. The relative risk of death for the *CYP2C19* LOF carriers analyzed by a fixed effect model is 1.42, with 95% confidence interval of 1.02 to 1.97. The pooled relative risk is synthesized from 11 pieces of individual evidence. All the included individual evidence is extracted from refereed journal full articles and is acquired from randomized controlled trials or prospective cohort studies.

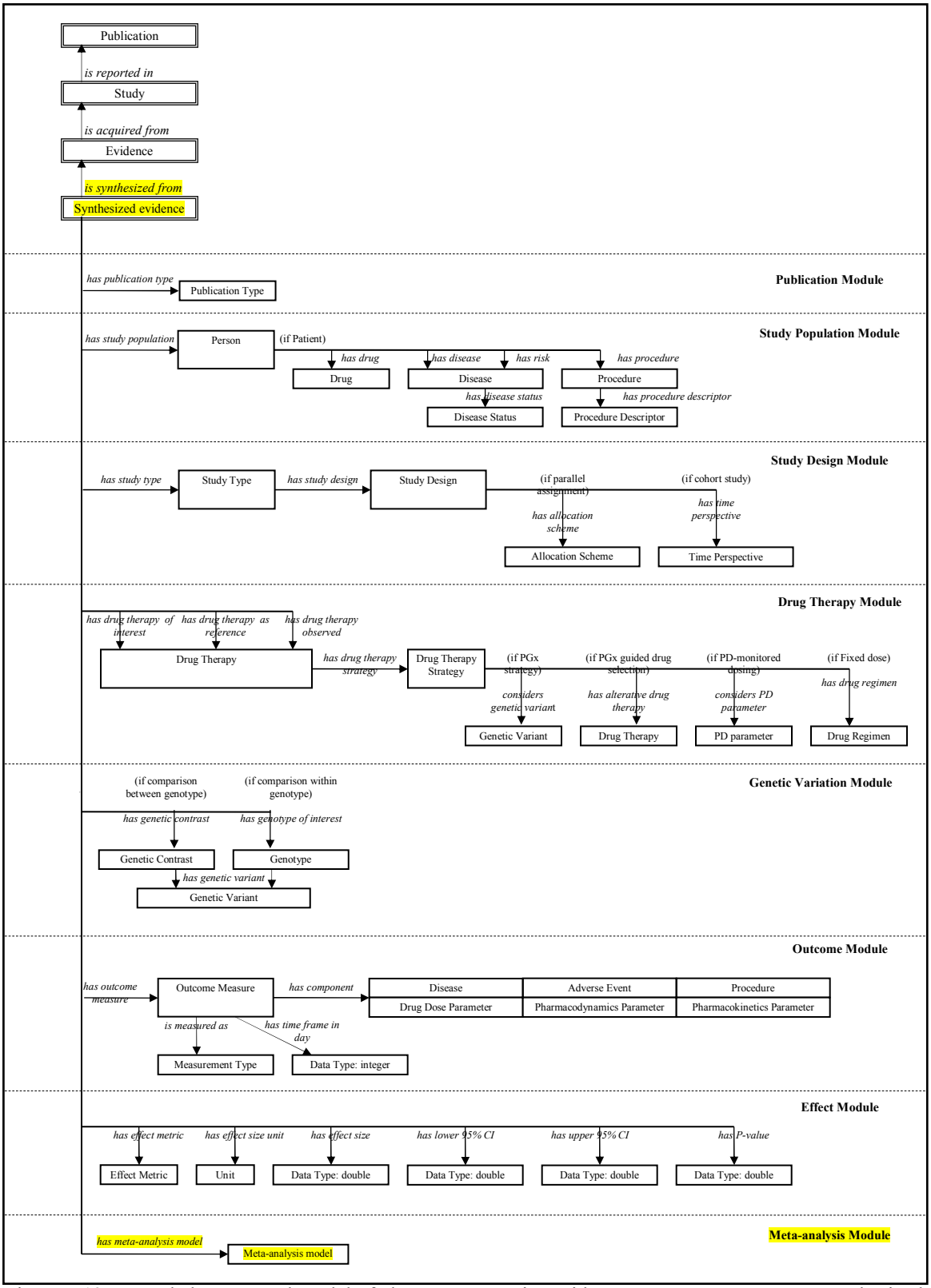


Figure 5.13: Extended conceptual model of pharmacogenomics evidence assessment to express synthesized evidence as information entity. Information entities are presented in double-lined squares. Concepts are presented in single-lined squares. Relations are presented in arrows. The dotted lines correspond to one information component. The yellow highlights indicate added concepts and relations.

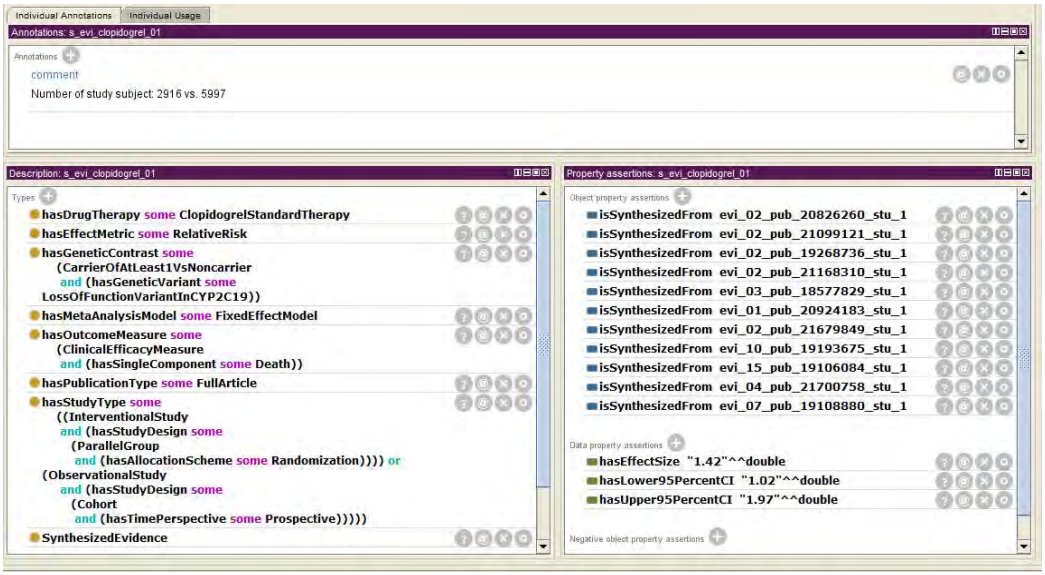


Figure 5.14: Formal representation of individual synthesized evidence. `s_evi_clopidogrel_01` is a piece of synthesized evidence selected from the clopidogrel test case.

5.4.3 Extend the constructed ontology to automatically infer clinical significance of synthesized evidence

Once the synthesized evidence is formally represented, the knowledge-based system can provide intelligent assistance in the interpretation of clinical significance of pharmacogenomics variants or genotype-guided interventions. The basic idea is to formally represent the concept of clinical significance to enable automatic classification of synthesized evidence into different types of clinical significance. The implementation of this idea is presented as follows

5.4.3.1 Modeling and formalizing the concept of clinical significance

Basically, I categorized clinical significance into 6 types, i.e., risk decrease, risk increase, risk no difference, benefit increase, benefit decrease, and benefit no difference. Each type of clinical significance is determined by 4 features including: (1) properties of outcome measures, (2) types of effect metrics, (3) value of effect sizes, and (4) statistical significance. Based on

these features, the definitions of 6 types and 12 sub-types of clinical significance are summarized in **Table 5.23**.

Table 5.23: Definition of types of clinical significance

Type of Clinical Significance	Subtype of Clinical Significance	Features Described in Definition			
		Property of Outcome Measure	Type of Effect Metric	Value of Effect Size	Statistical Significance
Risk Increase	Risk Increase _Ratio	Undesirable	Ratio	Effect Size >1	Significant: (lower 95% CI >1 and upper 95% CI >1) or (P-Value <=0.05)
	Risk Increase _Difference	Undesirable	Difference	Effect Size >0	Significant: (lower 95% CI >0 and upper 95% CI >0) or (P-Value <=0.05)
Risk Decrease	Risk Decrease _Ratio	Undesirable	Ratio	Effect Size <1	Significant: (lower 95% CI <1 and upper 95% CI <1) or (P-Value <=0.05)
	Risk Decrease _Difference	Undesirable	Difference	Effect Size <0	Significant: (lower 95% CI <0 and upper 95% CI <0) or (P-Value <=0.05)
Risk No Difference	Risk No Difference _Ratio	Undesirable	Ratio	Effect Size >=1 or <=1	Non-significant: (lower 95% CI <=1 and upper 95% CI >1) or (P-Value >0.05)
	Risk No Difference _Difference	Undesirable	Difference	Effect Size >=0 or <=0	Non-significant: (lower 95% CI <= 0 and upper 95% CI >0) or (P-Value >0.05)
Benefit Increase	Benefit Increase _Ratio	Desirable	Ratio	Effect Size >1	Significant: (lower 95% CI >1 and upper 95% CI >1) or (P-Value <=0.05)
	Benefit Increase _Difference	Desirable	Difference	Effect Size >0	Significant: (lower 95% CI >0 and upper 95% CI >0) or (P-Value <=0.05)
Benefit Decrease	Benefit Decrease _Ratio	Desirable	Ratio	Effect Size <1	Significant: (lower 95% CI <1 and upper 95% CI <1) or (P-Value <=0.05)
	Benefit Decrease _Difference	Desirable	Difference	Effect Size <0	Significant: (lower 95% CI <0 and upper 95% CI <0) or (P-Value <=0.05)
Benefit No Difference	Benefit No Difference _Ratio	Desirable	Ratio	Effect Size >=1 or <=1	Non-significant: (lower 95% CI <=1 and upper 95% CI >1) or (P-Value >0.05)
	Benefit No Difference _Difference	Desirable	Difference	Effect Size >=0 or <=0	Non-significant: (lower 95% CI <=0 and upper 95% CI >0) or (P-Value >0.05)

The definitions of types of clinical significance specified in **Table 5.23** can be formally represented as defined classes and embedded in the ontology for automatic reasoning. To enable this capability, a root class, i.e., **`OutcomeMeasureProperty`**, which has two subclasses, i.e., **`Desirable`** and **`Undesirable`** were added to the OWL ontology. Moreover, an object property i.e., *`hasOutcomeMeasureProperty`* was also added to the OWL ontology to describe the property of those classes that could be used as outcome measure component. For example, as shown in **Figure 5.15**, the class of **`AdverseEvent`** is described as a subclass of the class expression "*`hasOutcomeMeasureProperty`* some **`Undesirable`**", consequently, all the subclass of **`AdverseEvent`** such as **`death`** inherit the property as an undesirable outcome measure.

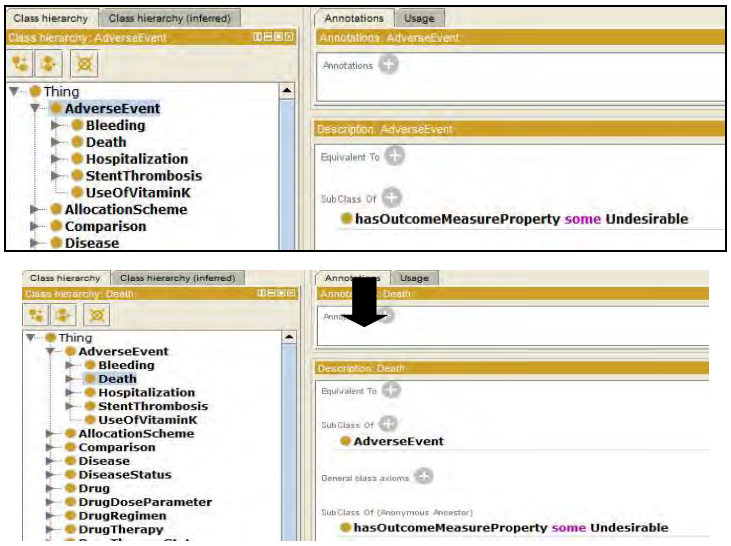


Figure 5.15: Description of outcome measure property by SubClassOf axiom. This example shows that adverse event and its subclasses are described as undesirable outcomes.

Next, 6 types and 12 subtypes of clinical significance were represented as defined classes using EquivalentClasses axioms (See the defined classes listed in **Table 5.24**) to enable inference of clinical significance of each individual synthesized evidence. Take the defined class **`RiskIncrease_Ratio`** as an example. It is interpreted as significant increase in risk because of the following assertions: first of all, "(*`hasOutcomeMeasure`* some (**`OutcomeMeasure`** and (*`hasComponent`* some ((**`AdverseEvent`** or **`Disease`** or **`DrugDosingAccuracyMeasure`** or **`PharmacodynamicsParameter`** or **`Procedure`**) and (*`hasOutcomeMeasureProperty`* some **`Undesirable`**))))) and (*`hasEffectMetric`* some **`Ratio`**)" indicates that the effect on an undesirable outcome is measured by ratio (e.g., hazard ratio, odds ratio and relative risk). Secondly, (*`hasEffectSize`* some double [>"1.0" ^^ double]) indicates a direction of increased risk because the effect size of ratio is greater than 1. Thirdly, "(*`hasLower95PercentCI`* some double [>"1.0" ^^ double]) and (*`hasUpper95PercentCI`* some double [>"1.0" ^^ double]) indicates a statistically significant effect because the 95% confidence interval does not include 1. Similarly, take the defined class **`BenefitIncrease_Difference`** as another example. "(*`hasOutcomeMeasureProperty`* some **`Desirable`**) and (*`hasEffectMetric`* some **`Difference`**)" indicates

that the effect on a desirable outcome is measured by difference, such as absolute difference between rates, etc. Then, (*hasEffectSize* some double [>"0.0" ^^ double]) indicates a direction of increased benefit because the effect size of difference is greater than 0. Finally, "(((*hasLower95PercentCI* some double [>"0.0" ^^ double]) and (*hasUpper95PercentCI* some double [>"0.0" ^^ double])) or (*hasPValue* some double [<"0.05" ^^ double]))" indicates a statistically significant effect because the 95% confidence interval does not include 0 or the P-value is less than 0.05.

Table 5.24: Formal representation of clinical significance as defined classes

Newly added EquivalentClasses axioms which define the clinical significance	Defined necessary and sufficient conditions
SynthesizedEvidence BenefitDecrease BenefitDecrease_Difference BenefitDecrease_Ratio BenefitIncrease BenefitIncrease_Difference BenefitIncrease_Ratio BenefitNoDifference BenefitNoDifference_Difference BenefitNoDifference_Ratio RiskDecrease RiskDecrease_Difference RiskDecrease_Ratio RiskIncrease RiskIncrease_Difference RiskIncrease_Ratio RiskNoDifference RiskNoDifference_Difference RiskNoDifference_Ratio	**RiskIncrease_Ratio** SynthesizedEvidence and ((hasLower95PercentCI some double[> "1.0"^^double]) and (hasUpper95PercentCI some double[> "1.0"^^double])) and (hasEffectMetric some Ratio) and (hasOutcomeMeasure some (OutcomeMeasure and (hasComponent some ((AdverseEvent or Disease or DrugDosingAccuracyMeasure or PharmacodynamicsParameter or Procedure) and (hasOutcomeMeasureProperty some Undesirable))))) and (hasEffectSize some double[> "1.0"^^double]) **BenefitIncrease_Difference** SynthesizedEvidence and (((hasLower95PercentCI some double[> "0.0"^^double]) and (hasUpper95PercentCI some double[> "0.0"^^double])) or (hasPValue some double[< "0.05"^^double])) and (hasEffectMetric some Difference) and (hasOutcomeMeasure some (OutcomeMeasure and (hasComponent some ((AdverseEvent or Disease or DrugDosingAccuracyMeasure or PharmacodynamicsParameter or Procedure) and (hasOutcomeMeasureProperty some Desirable))))) and (hasEffectSize some double[> "0.0"^^double])

Table 5.25 provides an overview of the evolution of ontology metrics from the originally constructed pharmacogenomics OWL ontology (presented in Chapter 4) to the extended ontologies in different applications (presented in Chapter 5). The initial OWL ontology comprised a collection of around 400 vocabulary words, 73 individual applications, 82 individual studies and 445 pieces of individual evidence. In the application of systematic review with meta-analysis, a largely increased number of classes and **`EquivalentClasses`** axioms resulted from the creation of evidence classification schemes in clopidogrel test case and warfarin test case (see Section 5.3.1 and 5.3.2). In the application of automatic inference of clinical significance for individual synthesized evidence, the number of individual counts was increased because of the

accumulation of individual synthesized evidence (see Section 5.4.2). **Table 5.26** provides an overview of the added ontology constructs in order to represent individual synthesized evidence and clinical significance.

Table 5.25: Ontology metrics of the constructed pharmacogenomics OWL ontology in different applications

Ontology metrics	**Initial OWL ontology + KB**	**OWL ontology_ Clopidogrel_SR**	**OWL ontology_ Clopidogrel_SR + Inference of clinical significance**	**OWL ontology_ Warfarin_SR**	**OWL ontology_ Warfarin_SR + Inference of clinical significance**
DL expressivity	*ALCRQ(D)*	*ALCRQ(D)*	*ALCRQ(D)*	*ALCRQ(D)*	*ALCRQ(D)*
Class count	326	436	461	399	424
Object property count	69	69	72	69	72
Datatype property count	12	12	12	12	12
Individual count	676	676	688	676	689
SubClassOf axioms count	307	309	333	309	333
EquivalentClasses axioms count	29	138	157	102	121
Computing time		216905 ms (~ 3.6 minutes)	308294 ms (~5.1 minutes)	8565 ms (~ 9 seconds)	14407 ms (~ 14 seconds)

Note: The retrievals were tested on a personal laptop (Intel Corei7-4700MQ 2.4GHz Processor, 16 GB DDR3 Ram and a 64-bit version of Windows 8.1). ms: milliseconds; KB: knowledge base; SR: systematic review

Table 5.26: Constructs of ontology additionally added to represent individual synthesized evidence and clinical significance

Additionally added classes (N=25)	Additionally added object properties (N=3)	Additionally added individual synthesized evidence (N=25)
OutcomeMeasureProperty |-**Desirable** |-**Undesirable** **MetaAnalysisModel** |-**FixedEffectModel** |-**RandomEffectModel** **SynthesizedEvidence** |-**BenefitDecrease*** |-**BenefitDecrease_Difference*** |-**BenefitDecrease_Ratio*** |-**BenefitIncrease*** |-**BenefitIncrease_Difference*** |-**BenefitIncrease_Ratio*** |-**BenefitNoDifference*** |-**BenefitNoDifference_Difference*** |-**BenefitNoDifference_Ratio*** |-**RiskDecrease*** |-**RiskDecrease_Difference*** |-**RiskDecrease_Ratio*** |-**RiskIncrease*** |-**RiskIncrease_Difference*** |-**RiskIncrease_Ratio*** |-**RiskNoDifference*** |-**RiskNoDifference_Difference*** |-**RiskNoDifference_Ratio***	*hasOutcomeMeasureProperty* *hasMetaAnalysisModel* *isSynthesizedFrom*	s_evi_clopidogrel_01 s_evi_clopidogrel_02 s_evi_clopidogrel_03 s_evi_clopidogrel_04 s_evi_clopidogrel_05 s_evi_clopidogrel_06 s_evi_clopidogrel_07 s_evi_clopidogrel_08 s_evi_clopidogrel_09 s_evi_clopidogrel_10 s_evi_clopidogrel_11 s_evi_clopidogrel_12 s_evi_warfarin_01 s_evi_warfarin_02 s_evi_warfarin_03 s_evi_warfarin_04 s_evi_warfarin_05 s_evi_warfarin_06 s_evi_warfarin_07 s_evi_warfarin_08 s_evi_warfarin_09 s_evi_warfarin_10 s_evi_warfarin_11 s_evi_warfarin_12 s_evi_warfarin_13

* denotes defined classes

5.4.3.2 Inference of clinical significance for individual synthesized evidence

Once the HermiT reasoner was triggered to reason over the extended pharmacogenomics OWL ontology and knowledge-base, the clinical significance of each individual piece of synthesized evidence was inferred automatically. For example, `s_evi_clopidogrel_01` was automatically inferred as a type of **`RiskIncrease_Ratio`** (see **Figure 5.16**), because its assertions satisfied the necessary and sufficient conditions described in the defined class of **`RiskIncrease_Ratio`**. In other words, `s_evi_clopidogrel_01` was automatically inferred by the HermiT reasoner as a piece of synthesized evidence that reported a statistically significant increased risk of death in clopidogrel-treated patients who carry at least one CYP2C19 loss-of-function allele.

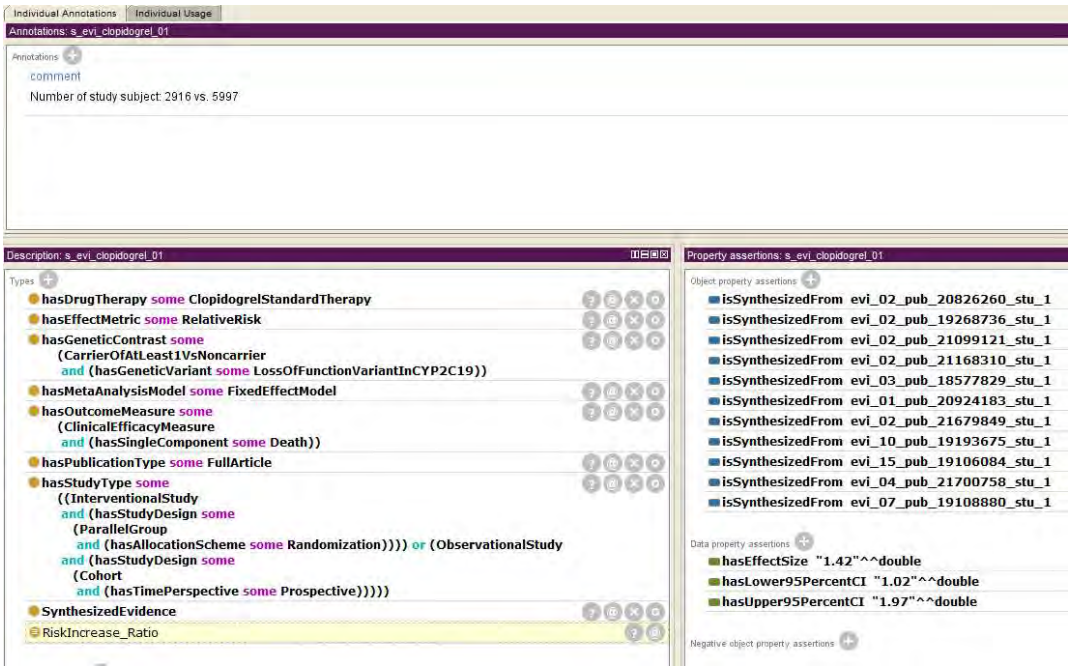


Figure 5.16: Inference of clinical significance of individual synthesized evidence. An individual synthesized evidence `s_evi_clopidogrel_01` was automatically inferred as a type of **`RiskIncrease_Ratio`**

The inferred clinical significance of individual piece of synthesized evidence is provided in the last column in **Table 5.27** and **Table 5.28**. The inferred results were manually checked and they were consistent with the definition of clinical significance listed in **Table 5.23**. According to the computing time taken by the HermiT reasoner (see **Table 5.25**), the task of inference of clinical significance of individual piece of synthesized evidence was completed in a very short computing time.

Based on the inferred clinical significance, individual piece of synthesized evidence was automatically classified into one of the six categories i.e., benefit decrease, benefit increase, benefit no difference, risk decrease, risk increase and risk no difference at the same time. As shown in **Table 5.29**, 12 pieces of synthesized evidence acquired from clopidogrel test case were classified into two categories of clinical significance, i.e., risk increase and risk no difference; 13 pieces of synthesized evidence acquired from warfarin test case were classified into 4 categories of clinical significance, i.e., risk decrease, risk no difference, benefit increase, and benefit no difference. Thus all of the individual pieces of synthesized evidence could be organized into a profile that informs the current status of available individual synthesized evidence set to assist reviewers to interpret the clinical implication. The implementation of the profile of individual synthesized evidence set is presented in the following subsection.

Table 5.27: Inferred clinical significance of individual piece of synthesized evidence regarding the clinical validity of CYP2C19 LOF variants on efficacy of clopidogrel therapy

Individual synthesized evidence obtained from the systematic review of clopidogrel test case						
Individual synthesized evidence	Comparison	Outcome	Effect metric	Effect size	95% CI	Inferred clinical significance
s_evi_clopidogrel_01	Carrier of 1 or 2 CYP2C19 LOF alleles vs. Non-carrier	Death	RR	1.42	1.02, 1.97	RiskIncrease_Ratio
s_evi_clopidogrel_02	Carrier of 1 or 2 CYP2C19 LOF alleles vs. Non-carrier	Cardiovascular death	RR	2.91	1.66, 5.11	RiskIncrease_Ratio
s_evi_clopidogrel_03	Carrier of 1 or 2 CYP2C19 LOF alleles vs. Non-carrier	Myocardial infarction	RR	1.33	1.07, 1.66	RiskIncrease_Ratio
s_evi_clopidogrel_04	Carrier of 1 or 2 CYP2C19 LOF alleles vs. Non-carrier	Stroke	RR	3.95	1.49, 10.48	RiskIncrease_Ratio
s_evi_clopidogrel_05	Carrier of 1 or 2 CYP2C19 LOF alleles vs. Non-carrier	Stent thrombosis	RR	2.07	1.56, 2.75	RiskIncrease_Ratio
s_evi_clopidogrel_06	Carrier of 1 CYP2C19 LOF alleles vs. Non-carrier	Stent thrombosis	RR	1.16	0.63, 2.14	RiskNoDifference_Ratio
s_evi_clopidogrel_07	Carrier of 2 CYP2C19 LOF alleles vs. Non-carrier	Stent Thrombosis	RR	3.59	0.41, 31.76	RiskNoDifference_Ratio
s_evi_clopidogrel_08	Carrier of 1 or 2 CYP2C19 LOF alleles vs. Non-carrier	Revascularization	RR	1.16	0.96, 1.41	RiskNoDifference_Ratio
s_evi_clopidogrel_09	Carrier of 1 or 2 CYP2C19 LOF alleles vs. Non-carrier	Composite of death or myocardial infarction	RR	1.17	1.02, 1.35	RiskIncrease_Ratio
s_evi_clopidogrel_10	Carrier of 1 or 2 CYP2C19 LOF alleles vs. Non-carrier	Composite of death or myocardial infarction or stroke	RR	1.11	1.00, 1.23	RiskNoDifference_Ratio
s_evi_clopidogrel_11	Carrier of 1 CYP2C19 LOF alleles vs. Non-carrier	Composite of death or myocardial infarction or stroke	RR	0.83	0.68, 1.01	RiskNoDifference_Ratio
s_evi_clopidogrel_12	Carrier of 2 CYP2C19 LOF alleles vs. Non-carrier	Composite of death or myocardial infarction or stroke	RR	1.25	0.79, 1.98	RiskNoDifference_Ratio

LOF: loss-of-function, RR: relative risk.

Table 5.28: Inferred clinical significance of individual piece of synthesized evidence regarding the clinical utility of genotype-guided warfarin dosing

Individual synthesized evidence obtained from the systematic review of warfarin test case						
Individual synthesized evidence	Comparison	Outcome	Effect metric	Effect size	95% CI	Inferred clinical significance
s_evi_warfarin_01	PGx vs. Standard	Thromboembolism	RR	0.45	0.26, 0.77	RiskDecrease_Ratio
s_evi_warfarin_02	PGx vs. Standard	Major Bleeding	RR	0.69	0.19, 2.49	RiskNoDifference_Ratio
s_evi_warfarin_03	PGx vs. Standard	Minor Bleeding	RR	0.46	0.10, 2.01	RiskNoDifference_Ratio
s_evi_warfarin_04	PGx vs. Standard	INR in Therapeutic Range	MD	7.05%	2.05%, 12.04%	BenefitIncrease_Difference
s_evi_warfarin_05	PGx vs. Standard	Excessive Anticoagulation	RR	0.78	0.61, 1.01	RiskNoDifference_Ratio
s_evi_warfarin_06	PGx vs. Standard	Any disease or adverse event	RR	0.64	0.51, 0.81	RiskDecrease_Ratio
s_evi_warfarin_07	PGx vs. Standard	Any disease or adverse event or excessive anticoagulation	RR	0.78	0.57, 1.08	RiskNoDifference_Ratio
s_evi_warfarin_08	PGx vs. Clinical	Thromboembolism	RR	1.53	0.49, 4.73	RiskNoDifference_Ratio
s_evi_warfarin_09	PGx vs. Clinical	Death	RR	0.97	0.23, 4.02	RiskNoDifference_Ratio
s_evi_warfarin_10	PGx vs. Clinical	Major Bleeding	RR	0.48	0.20, 1.16	RiskNoDifference_Ratio
s_evi_warfarin_11	PGx vs. Clinical	Minor Bleeding	RR	0.49	0.23, 1.04	RiskNoDifference_Ratio
s_evi_warfarin_12	PGx vs. Clinical	INR in Therapeutic Range	MD	4.74%	-4.92%, 14.41%	BenefitNoDifference_Difference
s_evi_warfarin_13	PGx vs. Clinical	Excessive Anticoagulation	RR	1.07	0.87, 1.32	RiskNoDifference_Ratio

PGx: pharmacogenomics, RR: relative risk, MD: mean difference, CI: confidence interval

Table 5.29: Classification of individual piece of synthesized evidence into categories of clinical significance

Defined class of clinical significance	Classification of individual piece of synthesized evidence	
	clopidogrel test case	warfarin test case
|- RiskIncrease		
|- RiskIncrease_Ratio	Members: s_evi_clopidogrel_01, s_evi_clopidogrel_02, s_evi_clopidogrel_03, s_evi_clopidogrel_04, s_evi_clopidogrel_05, s_evi_clopidogrel_09	
|- RiskIncrease_Difference		
|- RiskDecrease		
|- RiskDecrease_Ratio		Members: s_evi_warfarin_01, s_evi_warfarin_06
|- RiskDecrease_Difference		
|- RiskNoDifference		
|- RiskNoDiffernce_Ratio	Members: s_evi_clopidogrel_06, s_evi_clopidogrel_07, s_evi_clopidogrel_08, s_evi_clopidogrel_10, s_evi_clopidogrel_11, s_evi_clopidogrel_12	Members: s_evi_warfarin_02, s_evi_warfarin_03, s_evi_warfarin_05, s_evi_warfarin_07, s_evi_warfarin_08, s_evi_warfarin_09, s_evi_warfarin_10, s_evi_warfarin_11, s_evi_warfarin_13
|- RiskNoDifference_Difference		
|- BenefitIncrease		
|- BenefitIncrease_Ratio		
|- BenefitIncrease_Difference		Members: s_evi_warfarin_04
|- BenefitDecrease		
|- BenefitDecrease_Ratio		
|- BenefitDecrease_Difference		
|- BenefitNoDifference		
|- BenefitNoDiffernce_Ratio		
|- BenefitNoDifference_Difference		Members: s_evi_warfarin_12

5.4.4 Generate synthesized evidence profile to assist interpretation of overall findings from pharmacogenomics evidence assessment

The idea of a synthesized evidence profile was inspired by a goal of improving the efficiency in interpreting the results of a multitude of synthesized evidence generated from many comprehensive pharmacogenomics evidence assessments. The synthesized evidence profile provides systematic accounts of what the currently available synthesized evidence suggest. The

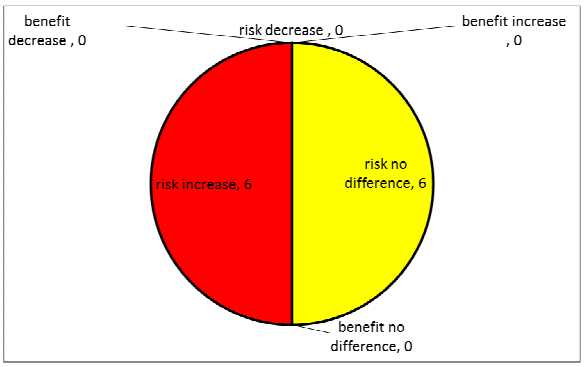
creation of synthesized evidence profile relies on formal representation of individual pieces of synthesized evidence and automatic inference of clinical significance that has been presented in sub-sections 5.4.2 and 5.4.3 respectively. This sub-section continues to present how the profile of individual pieces of synthesized evidence is generated and how it is used to interpret the overall findings regarding the clinical validity of *CYCP2C19* LOF alleles and the clinical utility of genotype-guided dosing of warfarin.

5.4.4.1 Interpretation of association between CYP2C19 LOF alleles and efficacy of clopidogrel therapy

Table 5.30 is a profile of 12 pieces of synthesized evidence generated from clopidogrel test case. It provides an overview of the availability of synthesized evidence in each category of clinical significance. Furthermore, each category of clinical significance is associated with one of three different types of associations, including: unfavorable association, favorable association or no association. In the case of assessing the association between a genetic variant and a drug response, if a piece of synthesized evidence is classified as the type of risk increase or the type of benefit decrease, then it provides supportive evidence of an unfavorable association. If a piece of synthesized evidence is classified as the type of risk decrease or type of benefit increase, then it provides supportive evidence of a favorable association. If a piece of synthesized evidence is classified as the type of risk no difference or the type of benefit no difference, then it does not provide any supportive evidence of an association.

Table 5.30: Profile of synthesized evidence regarding the association between *CYP2C19* LOF alleles and efficacy of clopidogrel therapy

Synthesized evidence profile: Clopidogrel and *CYP2C19* LOF alleles	
Availability and distribution of synthesized evidence by clinical significance	12



Interpretation of association		
Type of association	**Synthesized evidence classified by clinical significance**	
Unfavorable Association	|- Risk Increase	
	|- Carrier of at least one CYP2C19 LOF alleles vs. noncarriers	
	|- *Death*	1
	|- *Cardiovascular death*	1
	|- *Myocardial infarction*	1
	|- *Stroke*	1
	|- *Stent thrombosis*	1
	|- *A composite of death or myocardial infarction*	1
	|- Carrier of one CYP2C19 LOF alleles vs. noncarriers	
	|- Carrier of two CYP2C19 LOF alleles vs. noncarriers	
	|- Benefit Decrease	
	|- Carrier of at least one CYP2C19 LOF alleles vs. noncarriers	
	|- Carrier of one CYP2C19 LOF alleles vs. noncarriers	
	|- Carrier of two CYP2C19 LOF alleles vs. noncarriers	
Favorable Association	|- Risk Decrease	
	|- Carrier of at least one CYP2C19 LOF alleles vs. noncarriers	
	|- Carrier of one CYP2C19 LOF alleles vs. noncarriers	
	|- Carrier of two CYP2C19 LOF alleles vs. noncarriers	
	|- Benefit Increase	
	|- Carrier of at least one CYP2C19 LOF alleles vs. noncarriers	
	|- Carrier of one CYP2C19 LOF alleles vs. noncarriers	
	|- Carrier of two CYP2C19 LOF alleles vs. noncarriers	
No Difference	|- Risk No Difference	
	|- Carrier of at least one CYP2C19 LOF alleles vs. noncarriers	
	|- *Revascularization*	1
	|- *A composite of death or myocardial infarction or stroke*	1
	|- Carrier of one CYP2C19 LOF alleles vs. noncarriers	
	|- *Stent thrombosis*	1
	|- *A composite of death or myocardial infarction or stroke*	1
	|- Carrier of two CYP2C19 LOF alleles vs. noncarriers	
	|- *Stent thrombosis*	1
	|- *A composite of death or myocardial infarction or stroke*	1
	|- Benefit No Difference	
	|- Carrier of at least one CYP2C19 LOF alleles vs. noncarriers	
	|- Carrier of one CYP2C19 LOF alleles vs. noncarriers	
	|- Carrier of two CYP2C19 LOF alleles vs. noncarriers	

As shown in the pie chart of **Table 5.30**, the individual pieces of synthesized evidence regarding the association between *CYP2C19* LOF alleles and efficacy of clopidogrel therapy are

categorized into two types of clinical significance, i.e., risk increase and risk no difference. Thus, there is evidence that supports unfavorable association between *CYP2C19* LOF alleles and efficacy of clopidogrel therapy; meanwhile, there is also evidence that suggests no association between *CYP2C19* LOF alleles and efficacy of clopidogrel therapy. That is to say, the profile of synthesized evidence provides an account of the currently available synthesized evidence in a visualized and straightforward way that is more useful than a tabular view shown in **Table 5.27**.

Since this profile includes synthesized evidence of all relevant comparisons and outcomes of interests, it enables making interpretations on an overall picture. For example, under dominant genetic model (i.e., carriers of at least one alleles vs. non-carriers), there is sufficient evidence to support an unfavorable association between *CYP2C19* LOF alleles and the efficacy of clopidogrel therapy in terms of increased risks of death, cardiovascular death, myocardial infarction, stroke and composite of death or myocardial infarction. However, little evidence is provided to interpret the association under additive (i.e., carriers of one allele vs. noncarriers) and recessive (i.e., carriers of two alleles vs. noncarriers) model. Among different genetic models, inconsistent results were observed with regards to the association between *CYP2C19* LOF alleles and stent thrombosis. Under the dominant model, unfavorable association was observed, while under the additive and recessive models, no association was observed. In spite of the inconsistency, it make sense to draw a conclusion that *CYP2C19* LOF variants have the clinical validity in predicting efficacy of clopidogrel therapy, because there is sufficient evidence to support the association between *CYP2C19* LOF variants and most of the cardiovascular events, such as cardiovascular death, myocardial infarction and stroke.

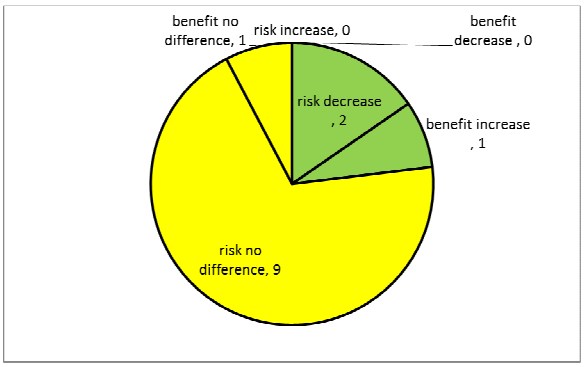
The findings presented in **Table 5.30** are largely consistent with the findings of AHRQ review [Dahabreh et al., 2013] (see sub-question 1b in **Table 5.12**) except that there is

inconsistent findings about the association between *CYP2C19* LOF variants and outcomes including death and stroke. The developed knowledge-based system addresses the inconsistency problem by allowing reviewers to backtrack the synthesized evidence to its included primary evidence via the `isSynthesizedFrom` property (see **Figure 5.14**). In other words, the formal representation of primary evidence, synthesized evidence and inclusion criteria makes the assessment process transparent so that it is clear to all users how the interpretations have been made.

5.4.4.2 Interpretation of comparative effectiveness of genotype-guided warfarin therapy

Table 5.31 is a profile of 13 pieces of synthesized evidence that have been generated from warfarin test case (see **Table 5.28**). In the case of assessing comparative effectiveness of a genotype-guided drug therapy, if a piece of synthesized evidence is classified as the type of risk decrease or the type of benefit increase, then it provides supportive evidence of benefit to patients. If a piece of synthesized evidence is classified as the type of risk increase or the type of benefit decrease, then it provides supportive evidence of harm to patients. If a piece of synthesized evidence is classified as the type of risk no difference or the type of benefit no difference, then it does not provide evidence that is recommend for or against the genotype-guided drug therapy.

Table 5.31: Profile of synthesized evidence regarding the comparative effectiveness of genotype-guided warfarin dosing

Profile of synthesized evidence: comparative effectiveness of genotype-guided warfarin dosin		
Availability and distribution of synthesized evidence by clinical significance		13
		
Interpretation of benefit/harm to patients		
Benefit/Harm to patient	**Synthesized evidence classified by clinical significance**	
Benefit to patients (synthesized evidence which supports the adoption of genotype-guided warfarin dosing)	|- Risk Decrease	
	|- Genotype guided vs. standard dosing of warfarin	
	|- *Thromboembolism*	1
	|- *Any disease or adverse event*	1
	|- Genotype guided vs. clinical guided dosing of warfarin	
	|- Benefit Increase	
	|- Genotype guided vs. standard dosing of warfarin	
	|- *INR in therapeutic range*	1
	|- Genotype guided vs. clinical guided dosing of warfarin	
No difference to patients (insufficient evidence to recommend for or against the genotype-guided warfarin dosing)	|- Risk No Difference	
	|- Genotype guided vs. standard dosing of warfarin	
	|- *Major bleeding*	1
	|- *Minor bleeding*	1
	|- *Excessive anticoagulation*	1
	|- *Any disease or adverse event or excessive anticoagulation*	1
	|- Genotype guided vs. clinical guided dosing of warfarin	
	|- *Major bleeding*	1
	|- *Minor bleeding*	1
	|- *Excessive anticoagulation*	1
	|- *Death*	1
	|- *Thromboembolism*	1
	|- Benefit No Difference	
	|- Genotype guided vs. standard dosing of warfarin	
	|- Genotype guided vs. clinical guided dosing of warfarin	
	|- *INR in therapeutic range*	1
Harm to patients (synthesized evidence which DOES NOT support the adoption of genotype-guided warfarin dosing)	|- Risk Increase	
	|- Genotype guided vs. standard dosing of warfarin	
	|- Genotype guided vs. clinical guided dosing of warfarin	
	|- Benefit Decrease	
	|- Genotype guided vs. standard dosing of warfarin	
	|- Genotype guided vs. clinical guided dosing of warfarin	

Given the synthesized evidence profile shown in **Table 5.31**, the comparative effectiveness of genotype-guided versus non-genotype-guided dosing of warfarin is interpreted as follows. Majority of synthesized evidence were classified into the category of no difference to patients,

which indicates that genotype-guided warfarin dosing has no benefit or harm to patients as compared with either standard or clinically-guided dosing. There are 3 pieces of evidence indicating that genotype-guided dosing has some benefits to patients when compared with the standard dosing, i.e., decreased risk of thromboembolism, increased time of INR within therapeutic range and decreased risk of composite of disease or adverse events. Given that there is insufficient evidence to demonstrate that patients who receive genotype-guided dosing of warfarin have lower risk of bleeding than patients who receive non-genotype-guided dosing of warfarin, the clinical utility of genotype-guided dosing of warfarin remains unclear. Since existing systematic reviews that examined clinical utility of genotype-guided warfarin dosing showed no consistent finding to the clinical utility of genotype-guided warfarin dosing [Pirmohamed et al., 2015], I did not compare the findings between **Table 5.31** and those reported by previous systematic reviews.

5.4.5 Discussion

In Section 5.4, I present the implementation of an innovative idea in both the clopidogrel test case and the warfarin test case to facilitate interpretation of a multitude of synthesized evidence acquired from comprehensive systematic reviews with meta-analyses. The idea was to formally represent individual synthesized evidence and definitions of clinical significance so that clinical significance implied in individual synthesized evidence could be inferred automatically via HermiT reasoner. Subsequently, a synthesized evidence profile that systematically organizes currently available synthesized evidence into 6 categories of clinical significance was generated to facilitate the interpretation of the overall findings from systematic reviews. Implementation of this idea involves: (1) formal representation of synthesized evidence, (2) design and formal representation of a typology of clinical significance (i.e., risk/benefit, increase/decrease/no

difference), (3) derive a typology of interpretation in the context of assessing clinical validity of genetic variants (i.e., unfavorable/favorable/no different association) and assessing clinical utility of genotype-guided drug therapy (i.e., benefit/harm/no difference to patients), and (4) mapping the typology of clinical significance to the typology of interpretation.

In order to formally represent synthesized evidence, most of the classes and properties declared in the ontology were successfully reused (see **Figure 5.13**). In order to formally represent the concept of clinical significance, I designed a typology of clinical significance that includes definitions of 6 types and 12 subtypes of clinical significance (see **Table 5.23**). The formal representation of types of clinical significance also relied on the reuse of existing classes and properties declared in the ontology. As a result, the pharmacogenomics OWL ontology developed in Chapter 4 was extended by adding 25 new classes and 3 new properties to allow for semantic representation of 25 pieces of synthesized evidence acquired from the clopidogrel and the warfarin test cases and 18 types of clinical significance derived from the typology of clinical significance (see **Table 5.25** and **Table 5.26**).

The extended ontology and knowledge base enables automatic inference of the clinical significance of individual pieces of synthesized evidence (see **Table 5.27** and **Table 5.28**) and automatic classification of individual pieces of synthesized evidence into different types of clinical significance (see **Table 5.29**). The automatic classification of individual pieces of synthesized evidence into different types of clinical significance is the key to effectively and efficiently interpret the association between genetic variant and drug response as well as the comparative effectiveness of genotype-guided drug therapy versus non-genotype-guided drug therapy, because types of clinical significance can be mapped straightforward to the types of association, i.e., unfavorable, favorable or no association (see **Table 5.30**), and to the types of

effectiveness, i.e., benefit, harm, or no difference to patients (see **Table 5.31**). Thus, a synthesized evidence profile could provide an account of what the currently available synthesized evidence suggests in a visualized and straightforward way that is more useful than the commonly used "summary of findings" table (see **Table 5.16** and **Table 5.21**).

The interpretation of the association between *CYP2C19* LOF variants and efficacy of clopidogrel therapy derived from the clopidogrel test case (see **Table 5.30**) was verified by referencing to an AHRQ review report [Dahabreh et al., 2013] that assessed the same topic (see **Table 5.12**). The interpretations drawn from the clopidogrel test case are largely consistent with the interpretations made in the AHRQ report. While inconsistency was found, the formal representation of primary evidence, synthesized evidence and inclusion criteria curated in the knowledge-based system makes the assessment process transparent so that it is clear to all users how the interpretations have been made.

In summary, the application presented in Section 5.4 addresses the information need in the final phase of pharmacogenomics evidence assessment, that is, interpretation of overall findings from a number of systematic reviews to draw an overall conclusion on clinical validity and clinical utility of pharmacogenomics. The implementation in both the clopidogrel test case and the warfarin test case demonstrates that the developed knowledge-based system is capable of providing intelligent support in pharmacogenomics evidence assessment by exploiting ontology-driven representation, classification and interpretation.

5.5 Synthesis of Findings from Four Applications

This section provides a synthesis of the implementation of four applications demonstrated in Chapter 5. The first application focused on the ontology-driven evidence retrieval for meta-analysis. The second and the third application focused on the ontology-driven evidence

classification that supports the planning and execution a multitude of meta-analyses. The fourth application focused on the ontology-driven interpretation that supports the interpretation of overall finding acquired from a number of comprehensive pharmacogenomics evidence assessments. The applications addressed consecutive tasks involved in the process of comprehensive evidence assessment for adoption of pharmacogenomics in routine clinical care. Each succeeding application built on the methods and results that have been implemented and verified in its preceding application. The major findings from each of the application are summarized as follows.

5.5.1 Major findings

In the first application, a total of 33 meta-analyses were selected from 9 existing systematic reviews and used as test cases to evaluate the precision and efficiency of the ontology-driven evidence retrieval for meta-analysis. The ontology-based retrieval was accomplished by formal representation of inclusion criteria of each meta-analysis into a defined class embedded in the OWL ontology. This approach allows unambiguous semantic annotation of inclusion criteria and thereafter enables automatic and precise retrieval of relevant individual evidence. The results showed that the ontology-based retrieval achieved a precision rate of 100%, which is better than the 97% precision rate achieved by the conventional manual approach. The ontology-based approach had completed the evidence retrieval tasks very quickly, ranging from 9 to 23 seconds, depending on the number of meta-analyses conducted in a specific systematic review.

In the second and the third applications, the developed knowledge-based system was leveraged to provide useful information to assist in the planning, execution and reporting of a multitude of meta-analyses. The second application was implemented in the context of a clopidogrel test case that assessed clinical validity of *CYP2C19* loss-of-function variants in

predicting efficacy of clopidogrel therapy. The third application was implemented in the context of a warfarin test case that assessed the comparative effectiveness of genotype-guided warfarin dosing versus non-genotype-guided dosing of warfarin. The key to implement these two applications is the design of evidence classification schemes that subdivide a collection of relevant and retrieved evidence into groups of which the included individual pieces of evidence were considered homogeneous and amenable to meta-analyses. Two sets of evidence classification schemes were designed and formally represented into defined classes, one consisted of 109 defined classes for the clopidogrel test case and the other consisted of 73 defined classes for the warfarin test case. The Hermit reasoner completed instance checking for each test case in a very short time. The ontology-driven evidence classification took advantage of two features of the developed knowledge-based system: (1) well-designed representation patterns that enable quick and easy creation of a large number of inclusion criteria, and (2) highly efficient OWL 2 DL reasoner that enables iterative instance checking over a large number of defined classes. Subsequently, based on the evidence profiles that inform the availability of relevant individual evidence curated in the system, 12 and 13 groups of individual evidence were regarded as amenable for meta-analyses to assess the clinical validity of *CYP2C19* LOF variants and the clinical utility of genotype-guided dosing of warfarin, respectively. The essential data for meta-analyses and cumulative meta-analyses were manually extracted from selected individual evidence and read into the "meta" package in R to perform meta-analyses and cumulative meta-analyses. The forest plots that present results of meta-analyses and cumulative meta-analyses were also generated by "meta" in R. Furthermore, the risk of bias assessment values were also manually acquired and inputted into Microsoft Excel to generate risk of bias summary graphs.

In the fourth application, the developed knowledge-based system was leveraged to facilitate interpretation of overall findings acquired from a number of comprehensive pharmacogenomics evidence assessments. The key to implement this application is the design of a typology of clinical significance that is formalized to enable automatic classification of a multitude of individual pieces of synthesized evidence based on different types of clinical significance. Specifically, implementation of this application involved four key tasks: (1) extend initially developed ontology to enable formal representation of synthesized evidence, (2) design and formal representation of a typology of clinical significance to enable automatic inference of clinical significance of individual pieces of synthesized evidence, (3) derive a typology of interpretation in the context of assessing clinical validity of genetic variant and assessing clinical utility of genotype-guided drug therapy, and (4) mapping the typology of clinical significance to the typology of interpretation. The initial ontology developed in Chapter 4 was extended by adding 25 new classes and 3 new object properties to allow for semantic representation of 25 pieces of synthesized evidence acquired from both the clopidogrel and the warfarin test cases and 18 types of clinical significance derived from the typology of clinical significance. The extended ontology and knowledge base together enable automatic inference of the clinical significance of individual pieces of synthesized evidence and automatic classification of individual pieces of synthesized evidence into types of clinical significance. By mapping each type of clinical significance to its corresponding type of interpretation, two synthesized evidence profiles were generated, one assisted in interpretations of the clinical validity and the other assisted in interpretations of the clinical utility of pharmacogenomics based on the overall findings acquired from a multitude of meta-analyses.

5.5.2 Limitations

The limitations of applicability are discussed as follows. First, no potential users of the developed pharmacogenomics knowledge-based system were included in the implementation process. Therefore, it is unclear whether the proposed four applications of the pharmacogenomics knowledge-based system are useful for them. Second, the research works of this chapter focused on providing a proof of concept implementation that was designed to realize key ideas underlying ontology-driven retrieval, classification and interpretation of evidence. No efforts have been undertaken to develop software tools to seamlessly streamline the whole process. For examples, the essential data of meta-analyses were manually extracted from individual evidence curated in Protégé and then saved in a CSV file rather than automatically exported to EXCEL. Thus, lots of research works remain to be done to improve the usability of the developed knowledge-based system.

5.5.3 Contributions

In spite of the limitations, the research works in Aim 3 provide a proof-of-concept that ontology-driven retrieval, classification and interpretation of evidence can contribute to effective and efficient evidence assessment. Furthermore, the ontology-driven representation makes it possible to formally represent different types of knowledge (i.e., primary evidence, clinical validity evidence, clinical utility evidence, and synthesized evidence) in a unified model, therefore, form a pharmacogenomics knowledge resource that provides different kinds of semantically computable knowledge, and ultimately lead to automatic systematic reviews. Thus, from the perspective of evidence-based medicine, the research findings in Chapter 5 suggest that innovative informatics approaches expediting or radically changing conventional systematic

review approach are essential and critical in order to address the growing needs for evidence-based practice in genomic medicine.

In summary, the step-wise implementation of four applications demonstrates that the developed knowledge-bases system is capable of providing intelligent support in pharmacogenomics evidence assessment by ontology-driven retrieval, classification and interpretation of evidence. The capabilities are built on the conceptual model of pharmacogenomics evidence assessment presented in Chapter 3, the OWL 2 DL ontology and knowledge base constructed in Chapter 4, and the highly efficient reasoning enabled by OWL 2 DL reasoner. In the final chapter of this dissertation, I will present an overview of the major findings under three research aims, discuss the overall contributions, address the limitations of this research, and propose some future works to enhance the capability and applicability of the prototypic knowledge-based system developed so far.

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Chapter 6. CONCLUSIONS

My overarching research goal was to build a knowledge-based system that fulfills three critical features including clinically relevant evidence, an evidence-based approach, and a semantically computable formalism to facilitate effective and efficient evidence assessment, and therefore to assist timely decisions on the adoption of pharmacogenomics in clinical practice. To achieve the overarching research goal, three aims were formulated. Aim 1 was to develop a concept model to address the information needs and heterogeneity problem encountered in the domain of pharmacogenomics evidence assessment (see Chapter 3). Aim 2 was to exploit OWL 2 DL to build a knowledge-based system that enables formal representation and automatic retrieval of pharmacogenomics evidence for systematic review with meta-analysis (see Chapter 4). Aim 3 was to provide a proof-of-concept that a pharmacogenomics knowledge-based system as an informatics approach is capable of providing intelligent support in pharmacogenomics evidence assessment by ontology-driven retrieval, classification and interpretation of evidence (see Chapter 5). In this concluding chapter, I summarize the major findings from each aim to see if they address the research questions concerned in this research (Section 6.1). I discuss the limitation of the generalizability of these research findings and the weakness of this research because of the lack of participation of stakeholders who are involved in pharmacogenomics evidence assessment (Section 6.2). I discuss the contributions of my dissertation to biomedical informatics and evidence-based medicine (Section 6.3). Finally, directions for further research are provided, including enhancing the system's applicability in the domain of cancer pharmacogenomics and expanding the system's capability to provide evidence-based interpretation of drug responses based on individuals' genomic profiles (Section 6.4).

6.1 MAJOR RESEARCH FINDINGS

6.1.1 Aim 1: Conceptual modeling of pharmacogenomics evidence assessment (Chapter 3)

Chapter 3 presents the development of a conceptual model for modeling the domain of pharmacogenomics evidence assessment. The research work focused on addressing (1) the issue of heterogeneity encountered in pharmacogenomics evidence assessment, and (2) two features i.e., clinically relevant evidence and evidence-based approach, that have been pre-specified as critical features of my envisioned knowledge-based system.

In order to explore the problem of heterogeneity inherent in pharmacogenomics evidence assessment, I reviewed 10 existing systematic reviews that investigated the association between *CYP2C19* loss-of-function variants and the efficacy of clopidogrel therapy. It was found that, text-heavy and heterogeneous primary evidence and inclusion criteria for systematic review collectively pose challenges in interpreting conclusions drawn from different systematic reviews, particularly when inconsistent conclusions occurred (see **Figure 3.2**).

Following the principles of faceted analysis as well as the information needs in conducting systematic reviews with meta-analysis, I proposed a basic information structure for the conceptual model. This structure is composed of 5 building blocks, namely, information entities (i.e., publication, study and evidence), information components (i.e., study population, drug therapy, comparison, outcome, genetic variant, study design, effect, risk of bias assessment and bibliographical information of publication), concepts, relations and terms (see **Figure 3.3**). Owing to the adoption of faceted analysis as the modeling method, the conceptual model is flexible enough to accommodate new information entities. Moreover, as opposed to exhaustively enumerate all the information components, concepts, relations and terms that fall under the information entities of interests, the conceptual model allows for on-demand addition of new

information components, concepts, relations and terms to accommodate the evolving field of pharmacogenomics.

A find-grained characterization of 73 publications, 82 studies and 445 pieces of evidence, that were extracted from empirical articles related to clinical validity and utility of pharmacogenomics in clopidogrel and warfarin therapies, yielded 30 concepts, 49 relations and approximately 250 terms to describe 3 information entities and 9 information components. Then, these building blocks were organized into a modular and layered structure (see **Figure 3.7**). Each information component is expressed as a module. The layered structure is composed of relation-concepts pairs where the concepts were directly substantiated by terms related to empirical and clinically relevant pharmacogenomics evidence. It was found that the layered structure allows developers to add incremental specifications to an information component by expanding the number of layers or increasing the number of relation-concepts pairs at the same layer, that is, adding depth or breadth to the information component being modeled. Furthermore, the terms filled in the concepts enable expressing the meaning of a concept at different levels of specialization. It was also found that the inter-related layered structure allows for modeling both the broad inclusion criteria that cover the likely diversity of evidence and the narrow inclusion criteria that ensure a meaningful answer to the research questions. Thus, the conceptual model relies on the sophisticated and flexible structure to accommodate heterogeneous information content in a unified conceptual model.

I validated the conceptual model through two selected primary studies. The validation results showed that the developed conceptual model was able to accommodate three types of pharmacogenomics evidence including clinical validity, comparative effectiveness, and genetic modification. Thus the feature of clinically relevant evidence is satisfied. Furthermore, I

validated the conceptual model using inclusion criteria extracted from two systematic reviews consisted of seven meta-analyses. The validation results showed that the developed conceptual model was able to accommodate heterogeneous inclusion criteria to retrieve primary evidence for conducting meta-analysis. Thus the feature of evidence-based approach is also satisfied.

The developed conceptual model was also validated against OCRe, which is a reference ontology that models human studies. It was found that the roles and modeling methods are different between OCRe and my developed conceptual model. OCRe is developed as a reference ontology that is independent of specific domain and application, while my developed conceptual model is served as an application ontology that supports the specific domain of pharmacogenomics evidence assessment. In addition, several gaps were identified by mapping OCRe to my developed conceptual model. First of all, OCRe does not model study results yet, which are critical information involved in evidence assessment (see **Figure 3.23**). Secondly, how to describe the domain-specific concepts of pharmacogenomics such as genetic variants and genotype-guided drug therapies in OCRe is unclear. Thirdly, the concepts and relations described in OCRe are too generic, and from my point of view, they are not straightforward enough. Finally, OCRe refers domain-specific concepts such as medical terms to external terminology systems, which might cause inefficiency in reasoning.

In summary, findings from Aim 1 have illustrated the development of a conceptual model that expresses the information needs in the context of pharmacogenomics evidence assessment and addresses the problems of heterogeneity encountered in the domain. These problems collectively make precise and meaningful evidence assessment more complex and challenging. These findings provide a compelling justification for the need of a knowledge-based system to assist in assessing pharmacogenomics evidence.

6.1.2 Aim 2: Adoption of OWL 2 DL to construct a knowledge-based system to enable formal representation and automatic retrieval of pharmacogenomics evidence for systematic review (Chapter 4)

Building on the conceptual model developed in Aim 1, Chapter 4 presents the construction of a knowledge-based system that enables formal representation and automatic retrieval of pharmacogenomics evidence for systematic review with meta-analysis. OWL 2 DL was adopted as the representation formalism because of its expressive power and reasoning capabilities. Therefore, both the basic constructs and the advanced features of OWL 2 DL were exploited to develop the envisioned knowledge-based system that includes an ontology, a knowledge base and an open source reasoner HermiT.

First of all, the ontology was built with the primary aim to support the semantic annotation of heterogeneous pharmacogenomics evidence and the efficient reasoning over formally represented evidence. Since the conceptual model that has been developed in Aim 1 served as the blueprint for constructing the ontology, I followed the W3C's guide for constructing OWL 2 ontologies to derive the principles of converting building blocks of the conceptual model into basic constructs of an OWL 2 DL ontology (see **Table 4.2**). Based on the principles, the conceptual model was encoded into an OWL 2 DL ontology that includes approximately 400 vocabulary words with the DL expressivity of $\mathcal{ALCRF}(\mathcal{D})$ (see **Table 4.3**). OWL 2 DL constructors (i.e., conjunction of classes, union of classes, existential restrictions on properties, datatype property restrictions and object property chains) were used to create 4 types of axioms (i.e., `SubClassOf`, `EquivalentClasses`, `SubPropertyOf`, and `SubPropertyChainOf` axioms) in the ontology. These axioms were created to enhance the efficiency of annotating individual information entities and to provide logical basis for automatic inference over the annotated individual information entities.

Since pharmacogenomics knowledge was too complicated to be described in one simple statement, the research work in Aim 2 focused on designing representation patterns for formalization of pharmacogenomics publications, studies and pieces of evidence that require using complex class expressions to describe the essential information contents including publication type, study population, study design, drug therapy, comparison, genetic variation, outcome and effect metric. The general form of a class expression is an object property followed by a restriction constructor as the property constraint and a class as the property value. While using a single class as the value of an object property was generally applicable to describe some less complicated information components (e.g., study design), it was found that the descriptions of some more complicated information components (e.g., study population, drug therapy, genetic variation and outcome) often involve using multiple classes as property values. To satisfy the need for the representation of heterogeneous components, 7 special representation patterns were designed, including (1) a conjunction of existential restrictions, (2) a conjunction of existential restrictions with subproperties, (3) a conjunction of qualified cardinality restrictions, (4) a conjunction of refined qualified cardinality restrictions, (5) a union of existential restrictions, (6) a union of existential restrictions with subproperties, and (7) a union of qualified cardinality restrictions (see Section 4.4.2.1 and Section 4.4.2.2). Considering that different representation patterns might result in different logical consequences and differentiating ability, 16 classification schemes composed of different qualifiers (e.g., *any*, *at least*, and *at most*) were designed to explore further the logical consequences of different representation patterns. It was found that although existential restriction and qualified cardinality restriction are limited in their ability to differentiate complex class expressions, they are easy to use and sufficient to infer subsumption relations among these class expressions. That is to say, they are suitable for

application scenarios that focus on inferring subsumption relations between classes defined in ontologies. On the other hand, the existential restriction with subproperty and the refined qualified cardinality restriction are capable of representing, differentiating and classifying heterogeneous information components (see **Table 4.11** and **Table 4.16**).

Then, the constructed OWL 2 DL ontology and the designed representation patterns were exploited to formalize the individual information entities contained in the envisioned pharmacogenomics knowledge base. To describe the heterogeneous information contents, 3 sets of class expressions that involved existential restrictions were created to describe various publication types among 73 individual publications, 97 sets of class expressions that involved existential restrictions and refined qualified cardinality restrictions were created to describe various study populations, study designs and drug therapies among 82 individual studies and 174 sets of class expressions that involved existential restrictions and existential restrictions with subproperties were created to describe various comparisons, genetic variations, outcomes and effect metrics among 445 individual pieces of evidence.

Finally, 4 test cases were designed to verify whether the heavy use of OWL 2 DL constructors and set operators in the representation of individual information entities causes inefficiency or even undecidability in inference. It was found that representation pattern of existential restriction was sufficient, efficient and suitable for representing simple components such as publication type and study design. Both the existential restriction with subproperty and refined cardinality restriction were sufficient to represent and differentiate heterogeneous asserted individual studies and pieces of evidence with complex components such as drug therapies, genetic variations and outcomes. However, the long computing time spent in test case

2 (see **Table 4.3**) suggests that the pattern of refined qualified cardinality restrictions was less efficient than the pattern of existential restriction with subproperty.

In summary, the research works in Aim 2 have explored the expressivity and logical consequences of using advanced features of OWL 2 DL in the context of representing pharmacogenomics evidence in semantically computable formalism. The overall findings provide justification and right directions to design, implement and verify an OWL ontology as well as an ontology-driven knowledge base that provides formally represented pharmacogenomics publications, studies and pieces of evidence.

6.1.3 Aim 3: Applications of the developed pharmacogenomics knowledge-based system: ontology-driven evidence retrieval, classification and interpretation in systematic reviews with meta-analysis (Chapter 5)

Based on the knowledge-based system developed in Aim 2, Chapter 5 demonstrates that the developed pharmacogenomics knowledge-based system, with its core components of an OWL 2 DL ontology, a knowledge base instantiated with formally represented individual publications, studies and pieces of evidence, and a powerful DL reasoner (i.e., HermiT), is capable of facilitating the following applications: (1) precise and efficient evidence retrieval for systematic reviews with meta-analysis, (2) effective and efficient evidence synthesis for assessment of the effects of *CYP2C19* loss-of-function variants on various outcomes among patients treated with clopidogrel, (3) effective and efficient evidence synthesis for assessment of the comparative effectiveness of genotype-guided versus non-genotype-guided dosing of warfarin, and (4) overall interpretation of the clinical significance of *CYP2C19* loss-of-function variants and genotype-guided dosing of warfarin.

In the first application, a total of 33 meta-analyses were selected from 9 existing systematic reviews and used as test cases to evaluate the precision and efficiency of the ontology-based retrieval of relevant evidence. The results showed that the developed knowledge-based system is an efficient approach to precisely retrieve relevant individual pieces of evidence for meta-analysis. The precise and efficient retrieval was accomplished by (1) formal representation of inclusion criteria for meta-analyses into defined classes using the OWL ontology, (2) a knowledge base that serves as a repository of formalized and semantically computable pharmacogenomics evidence, and (3) a DL reasoner that automatically reasons over the ontology and the knowledge base to retrieve all the satisfiable pieces of evidence.

In addition to the short computing time, the knowledge-based system improves the efficiency of retrieval process by allowing users to create or refine the criteria for including individual pieces of evidence very quickly (see **Table 5.7**). This advantage enables the developed knowledge-based system to retrieve and classify heterogeneous individual pieces of evidence into a hierarchical profile very quickly (see **Table 5.8** and **Table 5.9**). The evidence profile not only informs the quantity of relevant evidence but also explicitly reveals the heterogeneity inherent in the collection of relevant evidence. It is useful for reviewers to decide which individual pieces of relevant evidence to include in a meta-analysis and whether or not there is enough evidence to carry out an intended meta-analysis (see **Table 5.10**).

Building on the findings from the first application scenario, the ontology-based evidence retrieval was scaled up and extended to two broader applications that encompassed a set of consecutive tasks involved in the process of conducting a systematic review with meta-analysis. Specifically, the knowledge-based system was leveraged to provide useful information to assist in the planning, execution and reporting of a multitude of meta-analyses in the second

application scenario that assessed the clinical validity of *CYP2C19* loss-of-function variants in predicting efficacy of clopidogrel therapy, as well as in the third application scenario that assessed the clinical utility of genotype-guided warfarin dosing in improving patients' outcome. I implemented an innovative idea in both the clopidogrel and the warfarin application scenarios to facilitate effective and efficient systematic reviews with meta-analyses. The method was to design a multitude of evidence classification schemes that subdivide a collection of relevant and retrieved evidence into groups of which the included individual pieces of evidence were considered homogeneous and amenable to meta-analysis. This method has the following advantages. The current status of the availability of relevant evidence could be quickly examined using an evidence profile before actually embarking on time- and resource-consuming systematic reviews. That is to say, the evidence profile that informs whether there is enough evidence to carry out meta-analyses is helpful to avoid undesirable circumstances that significant time have been invested, but it turns out that there is insufficient evidence to undertake meta-analyses of interest. Moreover, once the evidence classification schemes are regarded as a default review protocol and embedded in the OWL ontology, an automatic update of currently available evidence could be achieved whenever the HermiT reasoner is triggered. It means that the knowledge-based system improves the efficiency of review process not only by automatic retrieval of relevant evidence but also by avoiding duplicate effort in developing the same systematic review protocol.

While compiling the results of 25 meta-analyses obtained from the second and the third applications, it was found that when more meta-analyses results were available, interpreting the clinical significance of pharmacogenomics from meta-analyses results became more complex. Many factors needed to be considered, including the properties of the measured outcomes (e.g.,

desirable or undesirable), metrics used to measure the effect sizes (e.g., ratio or difference), directions and magnitudes of effect on outcomes and statistical significance. In order to improve the efficiency in interpreting the results of a multitude of individual pieces of synthesized evidence, in the fourth application scenario, I presented the implementation of an innovative idea in both the clopidogrel test case and the warfarin test case to facilitate interpretation of a multitude of synthesized evidence acquired from comprehensive pharmacogenomics systematic reviews with meta-analyses. The methods include formal representation of individual pieces of synthesized evidence and typology of clinical significance so that clinical significance implied in individual pieces of synthesized evidence could be inferred automatically via HermiT reasoner. Subsequently, a synthesized evidence profile that systematically organized currently available synthesized evidence into categories of clinical significance could be generated to facilitate the interpretation of the overall findings from a number of systematic reviews. Specifically, the implementation of this innovative idea involved: (1) extending initially developed ontology to enable formal representation of individual pieces of synthesized evidence, (2) design and formal representation of a typology of clinical significance (i.e., risk/benefit in combination with increase/decrease/no difference) (see **Table 5.23** and **Table 5.24**), (3) deriving a topology of interpretation in the context of assessing the clinical validity of genetic variants (i.e., unfavorable/favorable/no different association) as well as in the context of assessing the clinical utility of genotype-guided drug therapies (i.e., benefit/harm/no difference to patients), (4) mapping the typology of clinical significance to the typology of interpretation, and finally presenting the mapping results in a synthesized evidence profile (see **Table 5.30** and **Table 5.31**). It is found that a synthesized evidence profile could provide an account of what the currently

available synthesized evidence suggests in a visualized way that is more straightforward than the commonly used "summary of findings" table (see **Table 5.16** and **Table 5.21**).

In summary, Aim 3 has presented 4 interrelated and ontology-driven applications and demonstrated that the developed knowledge-based system is capable of making effective uses of existing evidence to provide intelligent support in pharmacogenomics evidence assessment.

6.2 LIMITATIONS

The followings are the limitations of this research. First of all, when considering the generalizability of the conceptual model developed in Aim 1, its scope was limited to the pharmacogenomics evidence assessment that is related to clinical validity and utility of clopidogrel and warfarin therapy. Further investigation is needed to evaluate whether the developed conceptual model can be applied to other subdomains such as cancer pharmacogenomics. Secondly, the pharmacogenomics evidence instantiated and accumulated in the knowledge base is not exhaustive, but to serve as representative examples to provide proof-of-concept of the design, development, implementation, evaluation and application of the envisioned knowledge-based system. In order to enrich the contents of my developed knowledge base, further research is needed to evaluate the feasibility of automatic acquisition of the pharmacogenomics evidence from the existing comprehensive pharmacogenomics knowledge bases such as PharmGKB. Thirdly, due to the lack of participation of stakeholders involved in pharmacogenomics evidence assessment, it is unclear whether the proposed four ontology-driven applications of the pharmacogenomics knowledge-based system are useful to them. Thus usability studies are needed to address whether intended users could actually carry out the intended functions of the developed knowledge-based system. Finally, given time and resources constraints no effort has been undertaken in this dissertation to develop software, plug-ins or

user-friendly interfaces to seamlessly streamline the whole process. For example, the essential data of meta-analyses were manually extracted rather than automatically exported from the knowledge base represented in Protégé. Thus lots of informatics tools remain to be developed to improve the usability of the developed knowledge-based system.

6.3 CONTRIBUTIONS

This dissertation contributes to the field of biomedical informatics and evidence-based medicine. The contributions are summarized as follows.

From the perspective of biomedical informatics, Aim 1 delivers an extensible and easy-to-understand conceptual model that is able to express heterogeneous information contents in the domain of pharmacogenomics evidence assessment. To my knowledge, the developed conceptual model is the first one that considers different dimensions of information needs in a unified model, including (1) annotation of primary evidence and inclusion criteria to address the need for evidence retrieval, (2) annotation of clinical validity and utility evidence to address the need for integration of pharmacogenomics into clinical practice, and (3) annotation of three information entities (i.e., publication, study and evidence) to address the need for systematic review with meta-analysis. This model fills the gap identified from PharmGKB because PharmGKB provides a large amount of evidence obtained from genetic association studies but lacks evidence obtained from genetic sub-studies of clinical trials. Furthermore, the conceptual model also fills the gap identified from OCRe because neither the study results nor the pharmacogenomics-specific concepts such as genetic variants and genotype-guided drug therapy have been modeled using OCRe.

From the perspective of biomedical informatics, Aim 2 delivers an ontology and a number of representation patterns that exploit the advanced constructors of OWL 2 DL with novel ideas.

These representation patterns allow complex and heterogeneous pharmacogenomics evidence to be unambiguously represented and differentiated from each other. The idea and methods that underlie the design of the OWL ontology and the ontology-driven knowledge base in this study could be used by others who are interested in applying knowledge representation and reasoning to biomedical knowledge management. Furthermore, the limitations of OWL 2 DL constructors in describing some complex concepts and relations were identified during designing representation patterns and test cases. The identified limitations of OWL 2 DL could motivate researchers to develop more constructors in order to satisfy the representation requirements for advanced applications.

From the perspectives of evidence-based medicine and evidence synthesis (systematic review and meta-analysis), Aim 3 delivers 4 ontology-driven applications and ultimately provides a proof-of-concept that a knowledge-based system as an informatics approach is capable of facilitating effective and efficient evidence assessment. Therefore, innovative informatics approaches such as the developed pharmacogenomics knowledge-based system that expedite or radically change the conventional systematic review approach is essential to satisfy the growing needs for evidence-based practice in genomic medicine.

6.4 Future Research

Directions for future research are elaborated as follows. First, the modules of the 9 information components could be refined to express more critical information involved in pharmacogenomics evidence assessment. For example, the study population module could be refined by adding demographic characteristics of study subjects, such as age, body mass index and ethnicity. The effect module could be refined by adding other useful effect metrics that summarize the clinical

effectiveness of a treatment, such as the number needed to treat (NNT) and the number needed to harm (NNH).

Secondly, since cancer is one of the leading causes of death in the United States, the developed conceptual model could be expanded to model the domain of cancer pharmacogenomics so that pharmacogenomics biomarkers could be applied in improving efficacy or reducing toxicity in cancer therapies. Pharmacogenomics in cancer therapies, such as targeted therapy, is more complicated because it involves both the tumor's (somatic) genome and the patient's (germline) genome. The variability in tumor's genome dictates the selection of targeted drugs for personalized cancer therapy, while the variability in patient's genome affects drug exposure, efficacy and toxicity [Hertz & Rae, 2014]. Thus, integrating evidence from two types of genomic variations is essential to optimize treatment outcomes for cancer patients. Moreover, the complexity inherent in cancer pharmacogenomics provides an opportunity to further evaluate the robustness of the developed conceptual model that is the core of the developed knowledge-based system.

Thirdly, the application scenarios of the developed knowledge-based system could expand toward implementation of personalized medicine to provide evidence-based interpretation of drug responses for individuals based on their genomic profiles. The idea of expanding the existing knowledge-based system is illustrated in **Figure 6.1**. The OWL ontology has been constructed to enable formal representation of primary evidence and synthesized evidence (see the green highlighted components in **Figure 6.1**). It could be expanded to formalize associations between drugs (e.g., warfarin), variants (e.g., CYP2C9*2), and drug responses (e.g., bleeding) that are translated from synthesized evidence. It could also be expanded to formalize individual's genomics profile that specifies an individual's carrier status. With these expansions of the

developed knowledge-bases system (as shown in the red highlights in **Figure 6.1**), an example query such as "*find all drug response associated with CYP2C19*2 and CYP2C9*2*" is able to retrieve all the evidence-based associations related to the individual patient x's carrier status.

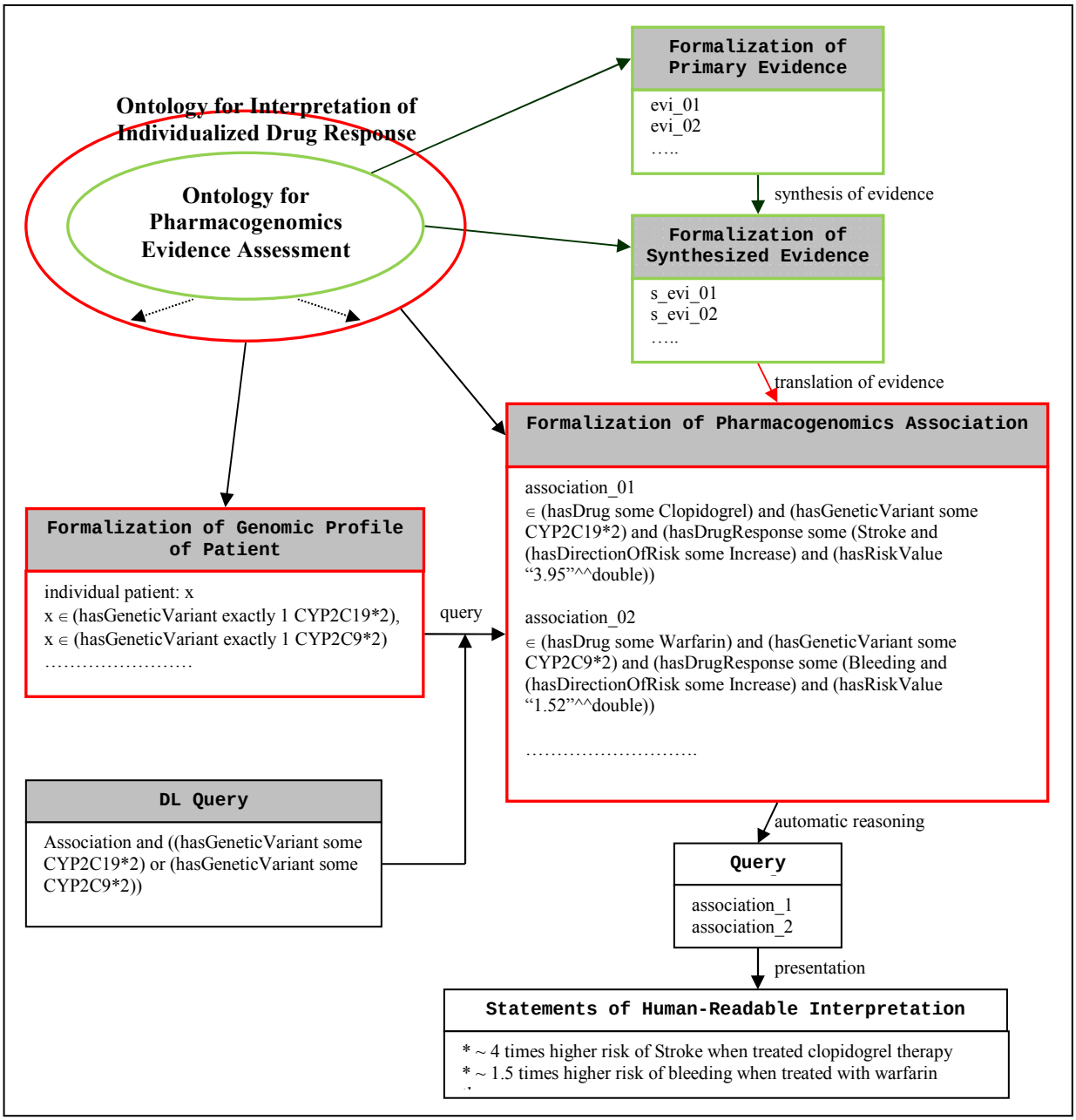

Figure 6.1: Expansion of application scenarios from pharmacogenomics evidence assessment to interpretation of individual patient's drug response based on individual patient's genomic profile. Green highlights denote components that have been developed in the knowledge-based system, red highlights denote components to be expanded in future research.

With the expanded scopes and enhanced applicability, the pharmacogenomics knowledge-based system might improve pharmacogenomics evidence assessment as well as evidence-based interpretation of pharmacogenomics at the point of care, and ultimately increase the adoption of pharmacogenomics in routine clinical care.

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