PROVIDING PERSONALIZED MEDICATION INFORMATION TO PATIENTS WITH TYPE 2 DIABETES

by

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ABSTRACT

There is a gap between the amount of medication information desired by patients and information provided to them by health care providers at the point of care. To address unmet drug information needs for patients, this research takes a knowledge management approach to design and develop an ontology-driven knowledge-based system with the goal of providing patients with personalized medication information about their prescribed antidiabetic drugs. The evaluation results demonstrated the technical feasibility and application prospects of our solution to inform patients on elements of medication information in anti-diabetic drug regimens during their office visits.

LIST OF ABBREVIATIONS USED

ADM	Anti-Diabetic Medication
ADR	Adverse Drug Reactions
CCM	Chronic Care Model
CPS	Compendium of Pharmaceuticals and Specialties
DDIs	Drug-drug interactions
DPDⓘS	Diabetes Personalized Drug Information System
HCP	Health care provider
HISB	Health Information Seeking Behaviour
KBS	Knowledge-based system
OWL	Web ontology language
PCC	Patient-centered care
SWRL	Semantic web rule language
T2DM	Type 2 Diabetes Mellitus

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CHAPTER ONE: INTRODUCTION

1.1. *Introduction*

Patient-centered care (PCC) is widely accepted as a measure of the quality of care and is defined as "*providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions*" [1]. The definition of patient-centeredness can vary depending on the area to which it is applied, such as public policy perspective, economic perspective, clinical practice perspective, and patient perspective. In the context of clinical practice, PCC recognizes the patient as central to care provision. It requires a patient-provider relationship in which the patient's preferences and perspectives are taken into consideration when providing care [2]. Additionally, it requires the patient to be involved in their own care by empowering the patient with the requisite knowledge and skills [3]. Patient-centered practices include tailoring treatment plans according to the patient's needs, involving the patient in treatment decisions and enhancing communication between the patient and health care providers in an effort to achieve shared decision making [4].

Adherence to a long-term therapeutic plan is essential for the treatment of chronic conditions such as diabetes and hypertension. Poor adherence to long term therapies leads to poor health outcomes and increased health care costs. Patients who struggle with treatment adherence are reported to face a lower quality of life [5]. In addition, low adherence to the prescribed medical treatment is associated with higher hospitalization rates and higher medical costs [6]. Still, poor medication adherence remains a major challenge in the management of chronic conditions, causing a significant financial burden on the health care system [5], [7]. Patients with hypertension and diabetes, and those within the 18-29 age range are reported to have only a 50-55% medication adherence rate, with adherence improving as patients grow older [8]. In agreement with previous studies, a report from the World Health Organization highlights the poor adherence to treatment of chronic condition as a complex public health consideration across the globe

with 50% adherence rate in developed countries and a much lower rate in developing countries [9].

A wide range of factors can contribute to the low adherence to the therapeutic plan and includes both patient-related factors and therapy-related factors. Examples of patient-related factors are patient demographics (e.g., age, gender), patient beliefs and motivation, patient knowledge, patient diet, patient smoking and drinking habits, and the patient-provider relationship [10]. Research has found that when patients are informed and engaged about their care, they are more likely to play an active role in their own health and maintain healthier habits. This is essential in the management of chronic conditions. Patients with knowledge and confidence to take action are reported to demonstrate higher self-management behaviors, higher medication adherence, and a higher self-reported quality of life [11], [12]. Therefore, undertaking the patient-centered approach plays a major role in influencing treatment adherence in the management of chronic conditions.

The elements of patient-centeredness that affect adherence include *communication*, *shared decision making*, and *support for self-management* [2]. The association between patient-provider communication and medication adherence has been extensively confirmed in the literature. A meta-analysis about the association between physician communication and patient adherence to treatment has assessed studies published from 1949 through 2008 and reports that poor communication between the healthcare provider and the patient is described as the main contributing factor to poor adherence [13]. Health care providers have to explain the condition and the treatment plan to patients in a way that patients would have a clear understanding of benefits and risks associated with their treatment [7]. Taking the patient-centered approach to improve patient-provider relationship is reported to positively influence the level of adherence to a diabetes treatment plan [14]. Tailored information needs to be provided to patients about their treatment enabling them to make informed decisions and healthier choices regarding their own care. Research has shown that three main questions from a patient perspective may guide the discussion during the patient's visit:

1. What are my options?

2. What are the possible benefits and harms of those options?
3. How likely are the benefits and harms of each option to occur?

These questions can assist health care providers with organizing information to present to patients with the goal of promoting shared decision making [15]. In addition, literature shows that providing patient education will improve the understanding of medication treatment and instructions and may lead to higher medication adherence [7].

Literature shows that 34% of overall questions raised by health care providers (HCP) are associated with drug treatment; of which, questions concerning patient education on prescription drugs varies from 4% to 19% of the questions [16]–[18]. The chances of patients asking questions doubles when they are prescribed a new medication [19]. One of the core components of promoting rational use of drugs is patient education on medicines they receive [20]. This includes information on use instruction, side effects of the drugs, drug-drug interactions (DDIs) and potential adverse drug reactions. Therefore, informing patients on different aspects of their prescription drugs is central to promoting patient involvement [21].

1.2. *Problem Statement*

Many patients diagnosed with type 2 Diabetes (T2DM) take several medications perhaps due to the co-existence of other chronic conditions. Higher number of drug prescriptions increases the risk of adverse drug reactions (ADRs) and unwanted drug interactions [22]. Patients have indicated their desire to discuss basic information such as drug purpose and instruction in addition to detailed information about their medications including side effects, and ADRs for newly prescribed medication [23] [24]. Patients' satisfaction with the amount of information they receive about their medication has been associated with adherence to drug therapy [25].In practice, however, different aspects of prescribed medication including expected side effects and important ADRs are minimally described for patients mainly due to time constraint during office visits [22]–[24], [26]. This creates a gap between the amount of information desired by patients and the level of information they receive from their HCPs.

Diabetes Canada (formerly known as the Canadian Diabetes Association) offers comprehensive resources for patients on their website including educational content on pharmacologic therapy for T2DM such as summary information sheets for any anti-diabetic medications approved in Canada [27]. Despite tremendous effort, these education materials provide general information about medications without consideration of any patient characteristics. Appendix A presents a sample of metformin drug information sheet offered by Diabetes Canada.

In addition to government-funded websites, several consumer health information websites offer patient education on the web. WebMD [28] is a commercial website providing extensive drug information to patients including uses, side effects, precautions, interactions, and user reviews. The drug interaction checker on their website is a useful tool for patients to examine any potential interactions among their prescribed medications. However, information available on WebMD does not answer questions regarding patients' individual drug therapy and it is not customized to their individual needs. For instance, patients must manually enter the two drugs of their concern in order to get more information about possible interactions. Similar challenges apply to MedlinePlus [29], a US government-funded website aimed at providing consumer health information. Information on drug adverse effects on their website does not differentiate between various adverse effects within specific age ranges or any other patient factors that may influence adverse effects of medications.

Many factors affect the occurrence of ADRs for patients with T2DM. For instance, drugs that are intended to treat hypertension can impact the response of the body to anti-diabetic drugs for patients who have both T2DM and hypertension. Other than drug-related factors, patient-related factors such as age, sex, weight, dietary habits, smoking and drinking habits, and existing medical conditions can have a major impact on ADRs in patients with T2DM [30]. Therefore, to promote patient involvement in hopes of achieving higher drug adherence, a point-of-care health informatics solution is required to support HCPs in providing personalized drug-related educational materials to patients with T2DM that describes the risk of ADRs by taking all patient-related and drug-related factors into consideration.

1.3. *Research Objective*

The primary goal of this thesis is to design and develop a proof-of-concept web-based education system that could be used at the point-of-care by HCPs to provide personalized information about diabetes drug regimens for their patients with T2DM. We call this **D**iabetes **P**ersonalized **D**rug **I**nformation **S**ystem (**DPDⓘS)** for patients with T2DM. To achieve this goal, the objectives of this thesis are to:

1. Investigate and identify areas of medication information that are frequently sought by patients with T2DM;
2. Investigate and identify contextual factors that need to be considered to tailor medication information based on patients' individual needs;
3. Represent the obtained knowledge in a formal machine-readable format in an ontology-based knowledge model; and,
4. Provide tailored information to patients with T2DM about risk of potential ADRs considering their underlying risk factors including potential DDIs.

1.4. *Solution Approach*

The underlying principle that guided this thesis is employing the patient-centered approach and using knowledge management processes for the purpose of providing tailored educational information on prescribed medication for patients with T2DM. Fundamental principles of PCC can be broken into two main concepts: i) a patient-provider relationship that supports patient involvement, and, ii) individualized care according to the patient's own needs and preferences [2]. By taking the knowledge management approach, we are able to individualize medication information given to patients. This leads to patient empowerment where patients can make informed decisions and can participate in discussion about their therapeutic plan [31]. Figure 1-1 shows the vision behind our proposed system.

As presented in figure 1-1, on one hand, there is a gap between drug-related information sought by patients and information provided to them during interaction with their HCPs [22]–[24]. On the other hand, individualized medication information is a prerequisite for providing PCC and achieving higher medication adherence in patients with T2DM [32].

Our health informatics solution (DPDⓘS) is a proof-of-concept knowledge-based system (KBS) that uses the knowledge base developed in this research to provide appropriate educational drug-related information to patients with T2DM.

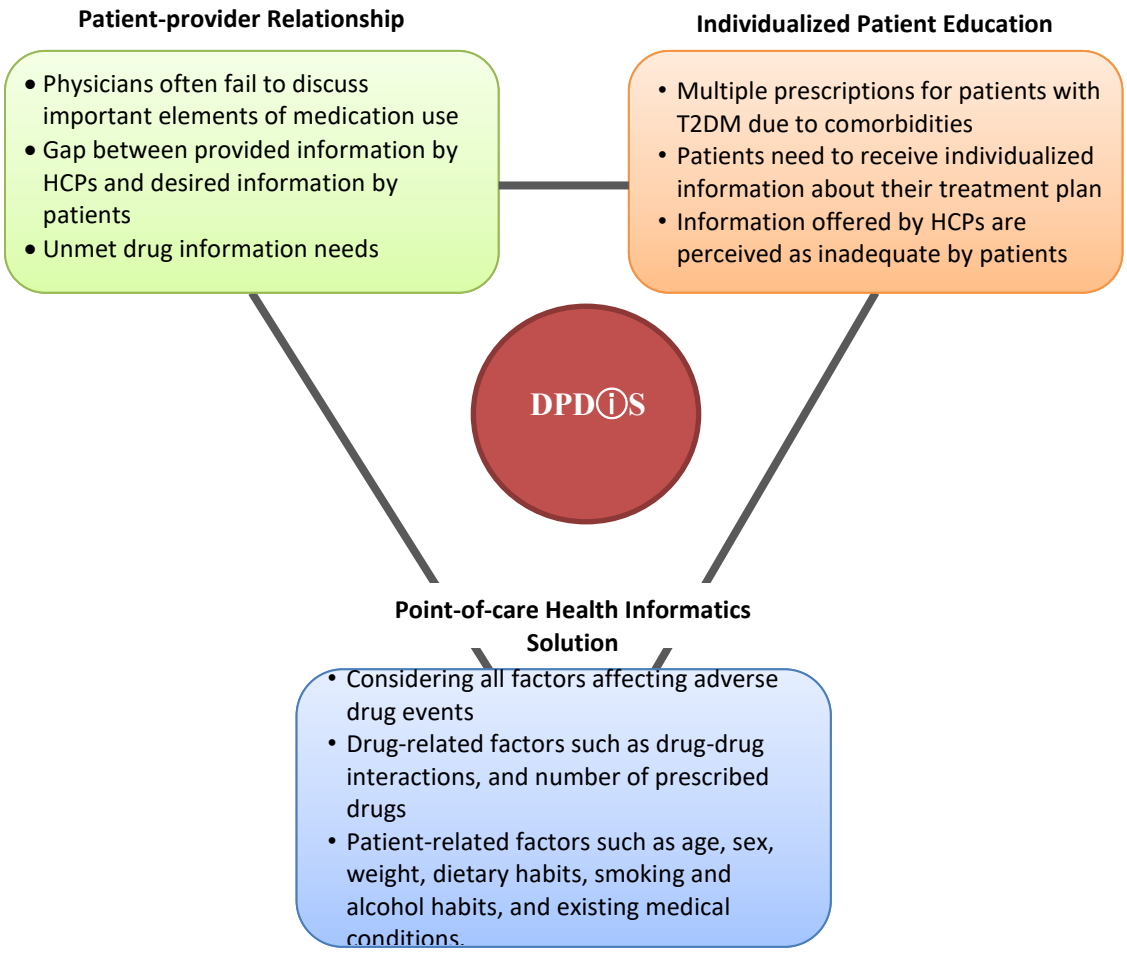


Figure 1-1 Vision behind the Diabetes Personalized Drug Information System

Taking the knowledge management approach, we will first identify the areas of unmet drug information needs. Second, there are contextual factors that need to be considered to enable delivery of individualized medication information. These can be related to patient-related factors (e.g., age, sex, weight, dietary habits, smoking and drinking habits, existing medical conditions) and/or drug-related factors (e.g., drug-drug interactions, type and number of current medications). We will obtain the required information by investigating various sources of evidence-based information about anti-diabetic drugs and elements of medication information. Using ontology-based knowledge modeling, we will

then explicitly represent the obtained information in an ontology model. To allow personalization of information, we will develop a set of rules in the semantic web rule language (SWRL) that will determine appropriate patient-specific educational information. Using an inference engine to reason with the knowledge base, DPDⓘS will identify risks and considerations related to a patient's prescription and highlight possible patient-specific ADRs that may occur based on the patient's clinical information. Subsequently, personalized educational content will be provided to patients.

To conduct this research, the following steps will be taken [33]. These steps will be discussed in greater detail in the Research Methodology chapter:

1. Knowledge Acquisition:
    a. Investigate drug information needs of patients with T2DM regarding their drug treatment regimen.
    b. Investigate type and other information related to anti-diabetic medications currently being prescribed for patients.
    c. Investigate and categorize risk factors associated with ADRs that may occur for anti-diabetic medications.
2. Development of the knowledge base:
    a. Represent the obtained knowledge using the ontology-based knowledge modeling approach.
    b. Develop a set of rules in SWRL to determine appropriate educational information based on the patient's profile.
3. Prototype Development: Using the inference engine, DPDⓘS will draw conclusions on patient-specific drug information and will subsequently present it to patients.
4. Prototype Evaluation

The decision to use ontological modeling to express the concepts and relations in the domain of anti-diabetic medication information was made due to the following reasons [34], [35]:

- Ontologies provide the means for defining explicitly the terms and relations behind the domain knowledge (i.e. anti-diabetic medication information)
- Using the formal logical language of OWL (Web Ontology Language) to specify the domain knowledge allows us to create machine-readable knowledge that can be processed by a computer while maintaining its semantic meaning.
- Additionally, using formal language for knowledge representation will allow us to infer new knowledge from existing concepts based on the explicitly described associations.
- Ontologies offer the possibility of sharing and reusing the existing knowledge across applications, that is, ontology engineers can integrate the existing ontology into the one they are designing.
- Ontologies enable interoperability between systems as the semantics in the domain knowledge is specified in a well-defined and unambiguous way.

1.5. *Thesis Contribution*

In this thesis, we adopted the knowledge management approach to present a novel solution for the provision of personalized patient education on medication information for patients diagnosed with T2DM. Our prototype DPDⓘS offers tailored information about the prescribed anti-diabetic medications based on several patient-related factors such as age, sex, smoking and alcohol habits, existing medical conditions as well as drug-related factors such as concomitant drugs prescribed for the patient.

A primary contribution of this research is the development of an ontology-based knowledge model that explicitly represents concepts and relations among those concepts related to anti-diabetic medication information. The advantages of building such a knowledge model include:

1. Providing common and standardized understanding for the domain knowledge of anti-diabetic medication-related information, thereby allowing the domain to be communicated to others without ambiguity.
2. Since the underlying conceptualization in the domain knowledge (i.e. anti-diabetic medication information) is formally described in the developed ontology,

the knowledge can be reused and shared for building future knowledge bases in similar domain areas. Our developed knowledge base can be extended to have finer granularity with the addition of sub concepts.

In addition, we offer a solution for personalization through the development of a set of SWRL rules that determine appropriate information to be communicated with the patient based on the patient's individual needs and underlying risk factors.

Furthermore, our proposed tool is another step in the direction of participatory decision making by informing patients about their drug-related concerns and questions. While patients can seek medication-related information from a variety of sources outside of their physicians' office including pharmacists and online resources, their HCPs remain the preferred source of information [24]. We demonstrate how our tool can be utilized at the point-of-care to provide tailored information for anti-diabetic medications that can guide conversations between HCPs and patients with T2DM to better achieve shared decision making.

1.6. *Thesis Organization*

The remainder of this thesis is organized as follows:

Chapter two presents the background information on T2DM and types of medications that are currently used for diabetes management and medication knowledge using semantic web technologies. Chapter three presents the research methodology employed. Chapter four outlines steps that were taken to design and develop the DPDⓘS. Chapter five demonstrates the scenario-based evaluation of the DPDⓘS system and chapter six covers discussion and conclusion of this research.

CHAPTER TWO: BACKGROUND AND RELATED WORK

2.1. *Type 2 Diabetes Mellitus*

2.1.1. Definition of Type 2 Diabetes Mellitus

T2DM is a chronic condition in which the body is not able to produce enough insulin or to use it properly. Insulin is an essential hormone that plays a central role in regulating blood sugar levels. As a result, T2DM is characterized by *hyperglycemia* which is a medical term referring to high levels of blood glucose (high blood sugar). T2DM makes up 90% to 95% of patients who are diagnosed with diabetes disease. The chronic hyperglycemia of diabetes is associated with long-term complications with eyes, kidneys, nerves, heart, and blood vessels [36]. Patients with T2DM have relative insulin deficiency. Thus, they are not completely dependent on insulin treatment to manage their condition. As hyperglycemia develops slowly, symptoms for T2DM may not be noticeable enough for a patient to investigate further. Therefore, T2DM can go undiagnosed for many years [36]. Obesity and weight gain are reported to be risk factors for T2DM as obesity can lead to some degree of insulin resistance. Other risk factors that are associated with an increased risk of T2DM include age and lack of physical activity [37]. Additionally, underlying medical conditions including gestational diabetes, hypertension, and dyslipidemia increase the risk of developing T2DM [36].

The main goal in diabetes management is to effectively control blood glucose levels. The medical term for this process is called *glycemic control*. The treatment regimens to achieve optimal glycemic control include a multifaceted long term approach including lifestyle changes, weight reduction and the use of medication. While glycemic control for some patients can be achieved with healthy nutritional habits and physical activity alone, most patients require antidiabetic (also known as *antihyperglycemic*) medications to prevent hyperglycemia and to reduce the risk of cardiovascular complications [38]. If healthy behavioral interventions are not successful in achieving target glucose levels within three months, the addition of prescription of antihyperglycemic medications is required [36]. In the next chapter, pharmacotherapy approaches and the selection of

medications used in the management of T2DM based on 2018 Canadian clinical practice guidelines will be described.

2.1.2. Pharmacotherapy in Type 2 Diabetes Mellitus

When prescribing medications for patients newly diagnosed with T2DM, health care providers must take into account a wide range of factors including the degree of hyperglycemia, medication efficacy for lowering blood glucose levels, medication impact on the risk of hypoglycemia (medical term referring to a condition in which blood sugar level is lower than normal), medication effect on body weight, the patient's coexistent medical conditions, affordability of the medication, the patient's ability to adhere to the drug regimen and the patient's preferences [38]. Given the increasing number of antidiabetic medications available on the market, Diabetes Canada has published a list of recommended medications to treat D2T in their 2018 Clinical Practice Guidelines. These recommendations are based on a detailed review of effectiveness and adverse effects of the medications. The following section of the thesis summarizes the information about medications that are currently prescribed for patients with D2T in Canada [38].

There are two types of antidiabetic medications: oral antihyperglycemic medication and insulin. Metformin is an oral antihyperglycemic drug that is recommended to be prescribed as an initial treatment for patients with T2DM, mainly due to effectiveness in lowering blood glucose level, mild side effects, minimal risk of hypoglycemia and lower weight gain compared to other antidiabetic medication classes including sulfonylureas, thiazolidinedione and DPP-4 inhibitors [38].

If target blood glucose levels are not achieved with metformin monotherapy, a second medication is required based on individual patient characteristics and drug interaction with other drug agents. The goal with adding a second antihyperglycemic agent is to improve the glycemic control, while considering the risk of hypoglycemia and weight gain in addition to affordability and the effect on cardiovascular disease outcomes. Diabetes Canada clinical guidelines recommend choosing a drug from medication classes of DPP-4 inhibitors, GLP-1 receptor agonists or SGLT2 inhibitors as a second-line therapy to metformin because hypoglycemia and weight gain effect in these classes are

less than other antihyperglycemic agents. Table 2-1 presents the list of medication classes, their respective drugs, and the effect on hypoglycemia and weight gain based on the 2018 Canadian clinical practice guidelines for pharmacotherapy in patients with T2DM [38].

Medication class	Drug	Hypoglycemia	Weight
Biguanide	Metformin	Minimal	Neutral
DPP-4 inhibitors	Alogliptin Linagliptin Saxagliptin Sitagliptin	Minimal	Neutral
GLP-1 receptor agonists	Exenatide Lixisenatide Dulaglutide Liraglutide	Minimal	Loss of weight
SGLT-2 inhibitors	Canagliflozin Dapagliflozin Empagliflozin	Minimal	Loss of weight
Alpha-glucosidase inhibitor	Acarbose	Minimal	Neutral
Insulin	Bolus (prandial) Insulins Basal Insulins Premixed Insulins	Significant risk	Weight gain
Sulfonylureas	Gliclazide Glimepiride Glyburide	Moderate risk	Weight gain
Meglitinides	Repaglinide	Moderate risk	Weight gain
Thiazolidinedione (TZD)	Pioglitazone Rosiglitazone	Minimal risk	Loss of weight

Table 2-1 Antihyperglycemic agents for use in T2DM [38]

Adherence to a strict treatment plan including medication, diet and exercise is crucial in controlling blood sugar levels, reducing risk of long-term complications such as kidney failure and lowering risk of hospitalizations in patients with T2DM [39]. Lack of adherence to T2DM therapeutic plan is associated with poor health outcomes, a high risk of complications and increased service utilization. To minimize long-term complications and to achieve optimal control of their blood glucose levels, patients with T2DM have to follow a strict treatment plan including medication, diet and exercise [39]. Adult patients

with T2DM who are non-adherent to oral antidiabetic medication are at higher risk of hospitalization [40] with research showing that higher medication adherence can decrease the hospitalization rate by 23% [41].

Despite empirical evidence for the relationship between non-adherence to oral antidiabetic medications and subsequent risk of complications and hospitalization [40], [42], [43], poor adherence to medication regimen persists in diabetes management [44]. Research has demonstrated the effectiveness of educational interventions on enhancing medication adherence for patients with T2DM. A wide range of patient education can include topics on the disease, complications, medication, side effects, lifestyle changes, and self-management skills [32], [45].

Additionally, patients' understanding of their drug treatment plan and patient-provider communication are reported to be main factors affecting adherence to medication in patients with T2DM [32]. Patients who view their provider's communication as good are reported to have significantly higher adherence to their oral antidiabetic medication [46]. Patient-centered interventions such as providing education materials for patients and encouraging them to ask questions have been shown to have a positive impact [47]. While there is overall agreement about the need of discussing medication information with patients, there are varying perceptions on the appropriate health care professional. Pharmacists are best equipped to address drug-related information needs of patients; however, patients prefer to receive information on medication during the visit with their physician [48]. Despite patient preference, pharmacists are reported to be the most convenient source of information when patients need information as they are more easily accessible [24].

2.2. *Theoretical Frameworks for Health Information Seeking Behaviour*

There are a number of frameworks in the literature related to Health Information Seeking Behaviour (HISB). In this section a number of these framworks will be discussed.

2.2.1. Health Information Search Model by Lenz et al [49]

Information seeking process is a part of the overall decision making process. Decisions are made based on the sequential steps of identifying a problem, obtaining information about various options, evaluating the options, choosing the best one among them and taking action to resolve the problem or to achieve a goal. The second step of this process which is obtaining information is commonly referred to as information seeking process. Lenz *et al.,* [49] propose six sequential steps related to health information search:

1- A Stimulus for health information search:

The first step in HISB is the presence of stimuli that would initiate the process of information search by recognizing the gap between the information that is needed and the information that is currently being held. Examples of such stimuli can be selection of a health care service for a patient planning a surgery or achieving the goal of optimal glycemic control and self-management for a patient with T2DMM.

2- Information goal setting:

This step involves deciding aspect of information search such as deadline for finding information, and type of information sources that can be used.

3- Decision point to determine if active information seeking is required

Once stimulus manifests itself, a decision has to be made to actively start the process of information seeking. The judgement about the sufficiency of prior information regarding the subject matter can impact this decision.

4- Search behaviour:

Once the decision is made to actively search for the information, HISB starts. The act of search behavior is influenced by two elements: the *extent* and *method* of search. In general, the obtained information increases as the extent of search is increased. One of the methods for information search is through impersonal information seeking which includes sources that are not personally known to the patient including referral services or printed patient education materials and online information sources. On the other hand, information can be sought through

personal methods in which the source of information is known to the patient such as the patient's HPC, friends, and family.

5- Information acquisition:

Following each search activity, the relevancy of the obtained information is evaluated to decide whether it enhances the information currently being held. Subsequently, new information will be captured into memory.

6- Decision point regarding the adequacy of the obtained information

In this step, the captured information is evaluated to assess its adequacy. If obtained information is considered inadequate, a decision has to be made to either start a new search effort or terminate the search with current status of inadequacy.

Lenz *et al.,*[49] identify two outcomes for HISB including cognitive and behavioral outcomes. Examples of cognitive outcomes are increased level of information, and change in opinion and beliefs as a result of HISB process. Behavioral outcomes refer to those that certain choices and decisions are ensued such as when patients use certain health care services, following drug treatment plans, or making an effort in self-management.

2.2.2. Comprehensive Model of Information Seeking by Johnson *et al.,* [50]

Combining three theoretical models of i) uses and gratifications, ii) the health belief model, and iii) a model of media exposure and appraisal, Johnson *et al.,*[50] have developed a comprehensive model of information seeking that has been widely adopted in the literature. In their model (shown in Figure 2-1), health-related factors are considered to affect health information seeking. *Demographic* factors, one of the components of health-related factors, include age, sex, education, and race. It is reported that demographic factors have minimal impact on health information seeking [49]. Another component of health-related factors is *direct experience* with the issue, meaning that if an individual has direct experience with a disease, either themselves or through personal network, this impacts the importance of health information regarding the issue. Perceived applicability of information to a problem (or *salience*) is another factor influencing an individual's motivation to seek information and it refers to how important health information is for them. Last factor in this group is *beliefs*; the idea that when an

individual believes there is an effective solution to solve a problem to achieve a goal, information seeking is more likely to be undertaken [50].

Another group of factors that impact the act of information seeking in the model proposed by Johnson *et al.,*[50] is information carrier factors, that is factors concerning information sources. One such factor is *characteristics* of the information carrier such as communication style or motives behind information that is offered. *Utility* refers to relevancy of the information provided by the information resource to an individual. If this information is perceived to be important and relevant to the needs of an individual, they are more likely to engage in active information seeking [50]

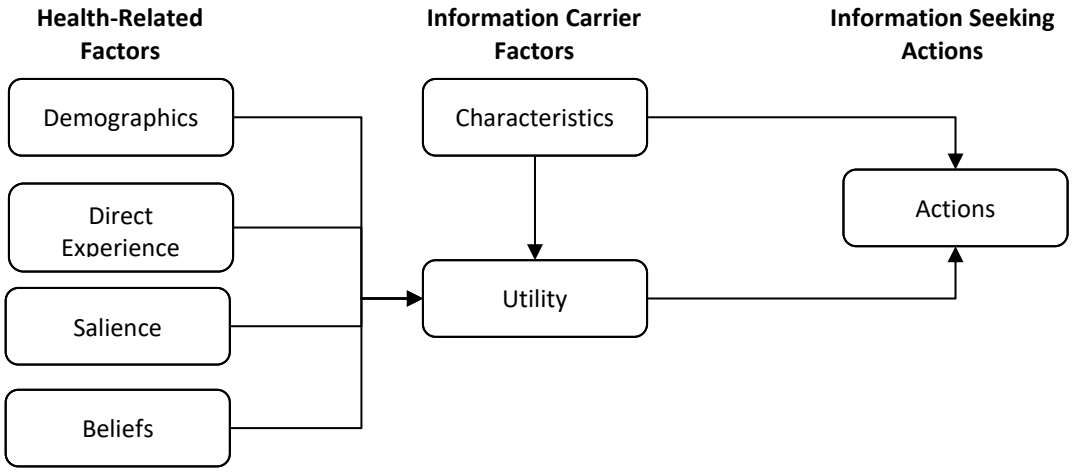


Figure 2-1 Comprehensive Model of Information Seeking, adapted from Johnson et al.,

2.2.3. Integrated Model for Health Information Seeking by Longo et al., [51]

In an attempt to improve the previous frameworks, Longo et al., propose an integrated conceptual model to capture interaction between health information, communication, and information seeking of patients. While the Lenz *et al.,* [49] describes two dimensions for HISB namely extent and methods, Longo *et al.,* focuses mainly on the method dimension. In their model, they recognize that health information is not always intentionally sought; still it can be acquired and may lead to significant health discovery. They take this into consideration and as part of HISB in their model, the existence and

importance of "passive receipt of information" is highlighted along with active information seeking that are conceptualized in previous models [51].

Furthermore, in their model, the role of traditional print media including magazines as health information source is emphasized in HISB of individuals despite new media such as Internet is often recognized as health information sources of patients. Figure 2-2 illustrates the integrated model by [51].

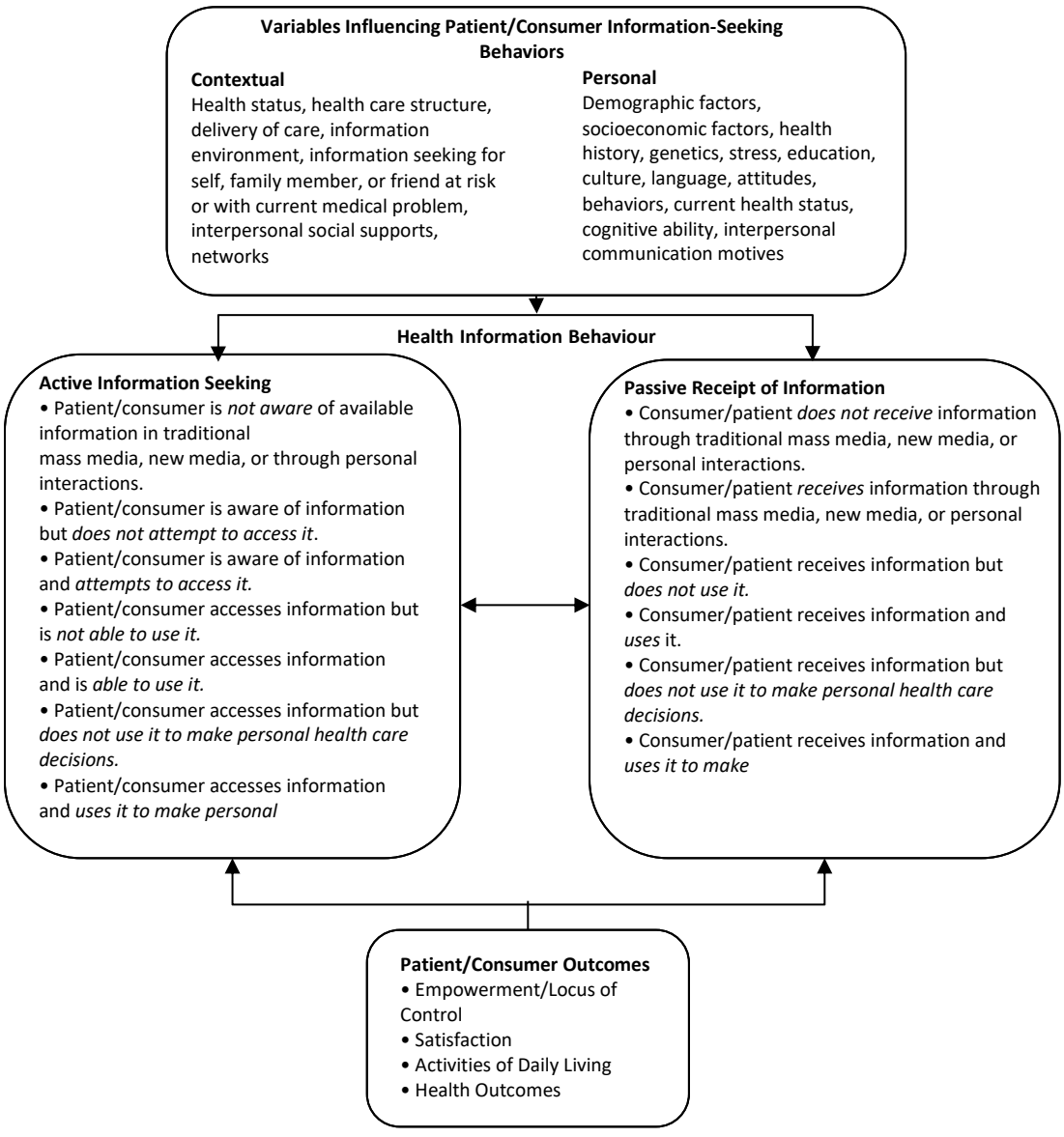


Figure 2-2 Expanded Conceptual Model of Health Information Seeking Behaviors, adapted from[51]

This model was utilized in a qualitative study to understand HISB of patients with diabetes in their attempt for diabetes self-management [52]. The findings of their research underscore the significance of receiving passive information about diabetes in patients' health information behaviour as one participant referred to television talk shows as information source where she casually come across health information about diabetes. Furthermore, the interaction between active information seeking and passive receipt of health information was analyzed. Patients with diabetes acquire information from many sources including websites such as WebMD, Mayo Clinic and government funded websites such as American Diabetes Association, but the vast amount of available information may lead to information overload. Therefore, patients with diabetes are reported to rely on their HCPs as creditable source of information. During officer visits, patients with diabetes tend to present information they acquired both passively and actively for their HCPs confirmation [52].

2.3. *Patient Medication Knowledge*

Patient medication knowledge is defined as "awareness of the drug name, purpose, administration schedule, adverse effects, or special administration instruction" [53]. Researchers have utilized different measures to evaluate patients' knowledge of their medication. Common measures used in the literature to assess medication knowledge include:

1. *Patient knowledge of the drug regimen* which includes understanding of the daily drug dosage schedule and administration of the drug.
2. *Patient knowledge of drug purpose* which refers to the patient's perception of how the drug can help with their condition.
3. *Patient knowledge of common drug side effects* which refers to the patient's understanding of potential side effects and adverse effects of the prescribed drug.
4. *Patient knowledge of appropriate course of action when a dose is missed* [53].

These knowledge measures collectively represent the overall state of a patient's understanding of their medication. There is wide variability among patients with respect to the level of knowledge for each measure mentioned above [54]. Although there is

varying level of knowledge, most patients tend to show higher levels of understanding for the knowledge of the drug regimen and the drug purpose (knowledge measure #1 and #2 in the list) [53]. Using focus groups to investigate what patients want to know about their medication, a qualitative study identified five areas of information topics desired by patients including side effects and risk, treatment options, length of the time required for taking medication, cost of medication, purpose and appropriateness of the medication based on their individual situation [24].

There is no standardized assessment tool to evaluate the level of patient medication knowledge. Several studies have defined and developed their own scoring system to evaluate patients' knowledge of medication. The Drug Regimen Unassisted Grading Scale (DRUGS) has been developed to examine the patient's ability to identify the medication, open the right medication container, know the right dosage amount and know the correct timing for taking the medication [55]. DRUGS, however, does not assess the patient's understanding of the purpose of the drug (i.e. the condition for which this drug is prescribed) or possible side effects. To improve upon this grading scale, Marks *et al.* propose the addition of two other knowledge areas leading to a four-point grading scale (0-4) called the Medication Knowledge Score (MKS) that evaluates the patient's knowledge of medication name, medication dosage, medication purpose and potential side effects [56].

The impact of patient medication knowledge on medication adherence is confirmed by several studies [54], [57]. Higher levels of medication knowledge increases the state of awareness of the condition for patients with T2DM and helps them understand the positive impact of their medication on the management of their condition and prevention of long-term complications [54]. In addition, patients who experience better communication from their health care provider in a way that thorough medication information is provided to them are reported to have higher rates of adherence [26].

While the association between general knowledge on chronic conditions and treatment outcomes is well examined in the literature [58], only a few studies have focused specifically on the link between knowledge about medication and treatment outcomes (i.e. excluding assessment of knowledge in other areas). McPherson

et al. investigate this relationship among patients with T2DM to determine whether patients who are more knowledgeable about their diabetes medication are more likely to have better blood sugar control. In their study, patient knowledge on diabetes medication was assessed based on the patient's understanding of medication name, reason for taking the medication, timing to take the medication, side effects and what to do if they forget to take a dose. Their findings show that patients with a knowledge score above average had much lower blood sugar level than those who were less knowledgeable about their medication, underlining the fact that a patient's knowledge of D2T medication directly impacts their glucose control [59].

2.4. *Factors Affecting Patient Medication Knowledge*

The level of patient knowledge on medication can be influenced by many factors including (1) the *medication requirement itself*, (2) *patient motivation and belief with respect to taking medications, (3) family support,* and (4) *patient-provider communication* [53]. Medication requirements refer to the complexity of the drug regimen including the type and number of medications, how and when to take them. Patients' beliefs refer to patients' perceptions on the meaning of disease and treatment options. Patients' beliefs can influence their motivation to learn more about medications prescribed for the treatment. For example, in some cultures taking Western medicines is perceived as damaging for the body if taken long term and traditional medicine is preferred. Family and social support is also shown to impact a patient's willingness and motivation to gain better understanding of the treatment plan [10]. The communication between the patient and the provider and its impact on patient medication knowledge will be discussed in more detail in the following section as it relates to the scope of this thesis.

2.4.1. Patient-Provider Communication as a Determinant of Patient Medication Knowledge

Of those factors mentioned above, the patient-provider communication has a noticeable and direct impact on all the knowledge measures discussed in section 2.2. The patient-provider communication encompasses various elements which are presented in Figure 2-3.

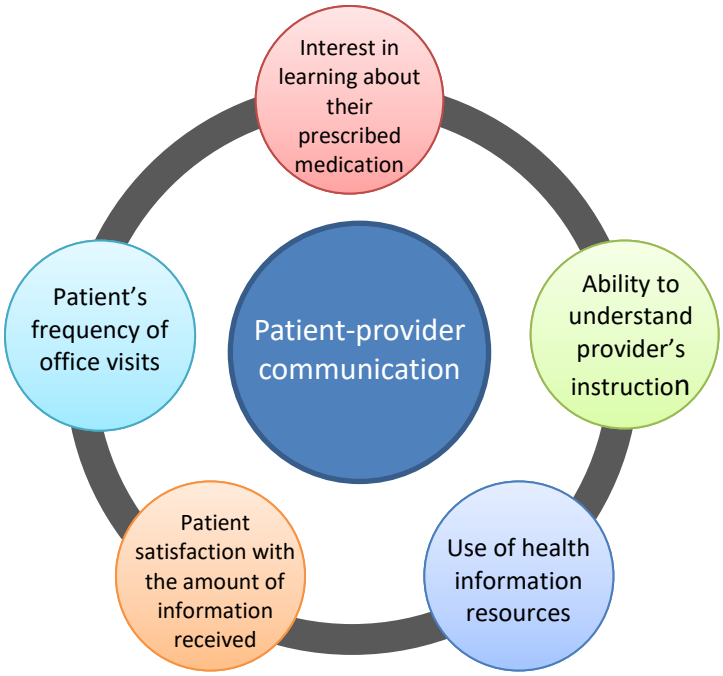


Figure 2-3 Components of the patient-provider communication process [53]

As shown in Figure 2-1, one of the components of patient-provider communication that affects the level of patient's knowledge of their medication is patient satisfaction with the extent of information they receive during office visits. Time limitations during visits are recognized as a common barrier to providing all aspects of information about newly prescribed medication [24]. As a result, some elements of medication information may be traded off against basic information in the limited time allocated for a patient encounter [26], [60]. When prescribing new medication, health care providers mostly discuss general medication information including drug instruction and regimen, and are less likely to talk about potential side effects during a patient's visit. Consequently, patients are mostly uninformed about drug sides effects and adverse drug effects [23], [24], [53], [54] with one study reporting that communication around adverse drug effects as low as 15% of the time [26].

There are conflicting perspectives on the extent to which conversations about side effects and adverse drug effects are beneficial for patients. From a patient perspective, they largely would like to receive all the information about possible adverse drug effects of the prescribed medication regardless of how mild or serious they are or how common or rare

they are in order to help the patient make informed decisions about their care [24], [61]. However, providers often find it challenging to determine how much detail regarding risks of adverse drug effects should be provided to patients, expressing concerns over unnecessarily alarming patients [53] and stating that too much information about risks of the newly prescribed medication can negatively impact the patients' adherence to the treatment [61].

Contrary to the fear on the part of health care providers, a randomized controlled study on over two hundreds patients found that providing a verbal description of the drug and potential side effects to the patients did not cause an increase in the reported incidents of side effects or in decreasing medication adherence [62]. Similarly, another study compared two patient leaflets about laparoscopy. The first leaflet was a generic one, and the second one included detailed information about potential side effects. Results of their study showed that the leaflet containing detailed risk information resulted in greater patient satisfaction with information and no increase in patient anxiety [63].

Patients who expect more information on side effects and potential adverse drug effects believe that understanding side effects of the drug will help them determine whether the medication is the right choice for them given their personal beliefs and preferences [64]. For instance, consideration of possible weight gain, which is a common side effect in many antihyperglycemic medications, is reported to affect patient's preference for treatment options and can contribute to poor medication adherence [65]. In addition, knowing what to expect prior to taking medication and ways to recognize adverse effects helps patients to be more prepared should adverse effects of the drug occur [64].

One in four patients visiting primary care clinics is reported to experience adverse drug events related to prescribed medication. A large portion of such events could be either completely avoided using computerized systems to prevent prescribing errors or their severity and duration significantly reduced with better communication between providers and patients. An example of such a case is when physicians fail to respond to symptoms and when patients fail to report symptoms to their physicians or are not aware that such symptoms are signs of adverse drug events related to their medications. Therefore, improvement in patient-provider communication including the development of

medication educational materials for patients is highlighted as a solution in the prevention of adverse drug events among primary care patients [66].

Similarly, a systematic review of hospital admissions due to ADRs shows that on average 45% of ADRs leading to hospitalization are considered preventable, with varying preventability rate from 16% in the pediatric population to 63% in elderly patients [67]. Patient education on drug information including dosage and administration, signs and symptoms of drug adverse effects, and drug interactions is reported to help prevent hospital admissions caused by ADRs [68].

In another study on ambulatory patients, patients' knowledge about their drug regimen and patients' perception of the communication with their provider were examined in relation to the occurrence of adverse drug events. The goal was to assess whether there is any correlation between these factors and adverse drug events reported by patients. The result of their regression analysis shows that patients with more drug knowledge are less likely to be hospitalized due to drug-related issues. Furthermore, a correlation between lack of patient knowledge of drug regimen and occurrence of adverse drug events was established [69].

This is of particular importance amongst the elderly population with multiple chronic conditions as they are more likely to be on a number of medications for a longer duration of time. A study of patients aged 60 years of age or older reported that 73% of patients were not provided any information on side-effects during their visits. As noted earlier, patients' understanding of possible adverse events is one of the components of medication knowledge. Their study found that having multiple prescribed medication was associated with a decrease of patients' medication knowledge, especially with respect to recalling possible side effects, putting patients at higher risk of experiencing adverse drug events [70]. Therefore, it is recommended that health care providers explain common side effects as well as serious adverse effects of the medication to patients during their visits. In addition, providing supplemental printed material that covers more rare adverse effects of the drug is suggested if the patient requests comprehensive information on the new medication [61].

To evaluate the quality of communication between patients and providers with respect to new medication, Derjung *et al.* proposed a scoring system called Medication Communication Index comprising of several topics that were recommended for discussed at the point of care based on the guidelines including medication name, purpose of taking the medication, duration of using the medication, adverse effects of the medication, number of tablets and frequency of timing for taking the medication [26]. Additionally, patients have expressed the need to receive education on their medication both verbally at the time of visit and in written format with a one-page summary in lay terms allowing them to easily recall helpful information without being overwhelmed with medical jargon [64]. Failure to cover these topics thoroughly may create a feeling of dissatisfaction for patients, prompting them to seek answers from alternative sources of information including pharmacists, medication package inserts and the internet.

2.5. *Patient-Centered Interventions on Medication Knowledge and its Impact on Medication Adherence*

Several studies have explored strategies to improve patients' knowledge of their medication and the related effect on medication adherence. A medication review led by a pharmacist that included a thirty-minute one-on-one counseling session has identified several knowledge deficits among patients at baseline prior to the intervention which included medication dosage, medication frequency, medication administration instruction and the reason for which medication was prescribed. An assessment of the patient's medication knowledge after the medication counselling was completed showed significant improvement in all areas of the knowledge deficits in addition to an increase in medication adherence rate among patients [71].

Similarly, in another study, standardized education covering the importance of adherence, purpose for each prescription and barriers to medication adherence was provided by the study pharmacist to the patients. In addition, a medication card, a list of tips on taking medications consistently, and a pillbox were also provided to patients. Their findings showed higher medication knowledge and prescription refill records among patients in the intervention group [72].

Researchers in another study employed a structured individualized information sheet generated via health technology solutions comprising of drug name, does and frequency, purpose of the drug, side effects and considerations. Based on the generated sheet, different knowledge areas for each prescribed medication was described verbally for patients in the intervention group and the printed information sheet was also provided as supplemental material. Their findings show that higher levels of medication knowledge, in particular knowledge on possible side effects reduces the likelihood that patients discontinue medication on their own [73].

There is wide agreement in the literature that provider communication with patients about medication information is positively correlated with medication adherence. Patient-provider relationship that is rooted in principles of patient-centeredness results in patients being informed about their drug regimen, being motivated and willing to gather information that will help them comply with their therapeutic plan [13].

2.6. *Related Work in the Area of Diabetes Care and Medication Information Using Semantic Web Technologies*

Various research efforts have been focused on ontology-based systems in the domain of diabetes care and medication knowledge. Chen *et al.* propose a rule-based system that will recommend an appropriate combination of antihyperglycemic drug therapies [74]. As discussed in section 2.1, if glycemic control is not achieved with monotherapy, a second antihyperglycemic drug is recommended as an add-on to metformin. When selecting the right combination of drug therapy, physicians have to take the patient's current risk factors into consideration [38].

With the help of domain experts and clinical practice guideline for T2DM, the proposed system by Chen *et al.* considers five underlying risk factors pertaining to an individual patient: the hypoglycemia effect of the drug, having heart failure, having a gastrointestinal dysfunction test, liver function test and renal function test. Based on the results of these risk factors and the blood glucose level, six (Semantic Web Rule Language) SWRL rules were developed in their system to recommend the most suitable antihyperglycemic drugs to be prescribed. For instance for patients with T2DM with

positive renal insufficiency test, only a subset of antihyperglycemic drugs available on the market would be recommended [74].

Chammas *et al.* offers an application on mobile devices that can be used on a daily basis to raise awareness for diabetes foot problems and to provide personalized support for patients in the prevention of developing diabetic foot [75]. One of the diabetes complications is limb amputation which is preventable if the patient is aware of the symptoms and the extent of risk for ignoring foot care and consequently developing diabetic feet. In their effort, an OWL ontology model was developed that stores the patient's supplied information as it relates to foot care such visual observation of the patient's feet, related symptoms for diabetic foot, lifestyle factors such as stress and diet that can impact the development of diabetic foot and any laboratory tests pertaining to diabetes foot care. In their application, SWRL rules have been used to enable reasoning on the ontology model. This in turn provides personalized reminders and advice to the patient for self-managing their foot care based on the information they provided [75].

Patients' poor understanding of their medication is a key issue in developing adverse drug events after being discharged from hospital. In an attempt to educate patients about their medication, Adnan *et al.* propose a prototype system in which personalized medication advice is provided to patients in their discharge summary that will assist them in self-care management post discharge [76]. An ontology-based approach was undertaken to model information related to a subset of high-risk discharge medication classes that are reported in the literature to have the highest rate of ADRs. In their ontology model, semantics of medication knowledge required for patients' discharge were defined including information about the side effects as well as appropriate patient advice. The semantic recommendation engine then executes forward IF-THEN decision rules to generate appropriate advice for the patient [76].

To prevent development of ADRs in patients taking non-steroidal anti-inflammatory drugs, a KBS was developed by Jara *et al.* in which the patients' intolerance to certain active ingredients is checked with their patient profile [77]. Their proposed system is based on an ontology knowledge base that represents the patients' profile including the semantics of patient information and allergic elements such as active ingredients that are

intolerable to the patient. Additionally, the system also utilizes the Jess rule engine to interact with the knowledge base to detect drug interactions and allergies for the anti-inflammatory drugs taken by the patient [77].

Quinn *et al.* propose an ontology-based system to provide tailored educational messages to patients with diabetes. Their ontology model represents knowledge around four concepts: patient, medical conditions, physical activities and the educational content. The latter covers patient characteristics, components of diabetes such as symptoms, complications and treatments, and aspects of physical activity. The system is personalized through decision rules that are developed in SWRL to choose certain educational components that will be presented to the patient based on patient characteristics and the elements of physical activities pertaining to the patient [78].

Table 2-2 summarizes related work in the literature regarding diabetes care management and medication information.

Paper	Personalization	Knowledge Model	Rules
Chen *et al*., 2012	The system uses the patients' test results and other medical information to recommend an appropriate prescription for anti-diabetes medication.	An OWL ontology model that represents patients' underlying conditions and medical tests as well as diabetes medication.	SWRL rules are used to identify appropriate antihyperglycemic medication to be prescribed.
Chammas *et al*., 2013	Based on observations, symptoms and medical tests related to foot care supplied by the patient. Reminder, advice or action will be issued for the patient according to severity level of the reported information.	An OWL ontology model is used to store patient provided information, reminder and advice messages.	SWRL rules are used to issue an appropriate level of reminder, advice or action for the patient's foot care.
Adnan *et al.,* 2010	The system uses knowledge about the patient and discharge medications to offer personalized recommendations in their electronic discharge summary.	An OWL ontology is used to represent knowledge about the patient, a set of high-risk discharge medications, and appropriate advice for patients.	Forward IF-THEN rules are used to determine medication information advice.
Jara *et al.,* 2010	The system uses the patient's allergic information to provide	An OWL ontology to define the patient's profile, including	The Jess rule engine is used to detect ADR, drugs interaction and

Paper	Personalization	Knowledge Model	Rules
	recommendation of its safety when taking non-steroidal anti-inflammatory drugs.	drugs concepts.	allergies.
Quinn ***et al.,*** 2017	The system presents personalized educational messages to patients with diabetes based on their preferences and needs.	An OWL ontology is constructed to represent characteristics of the patient, medical conditions (symptoms, complications, treatment), and aspects of physical activities.	SWRL rules are utilized to determine a selection of education materials based on patient characteristics and elements of the patient's physical activities.

Table 2-2 Characteristics of Related Work in Diabetes Care

CHAPTER THREE: RESEARCH METHODOLOGY

In this chapter, the problem statement and research objectives for this thesis will be revisited as well as the theoretical underpinning that was used to guide the research approach. Subsequently, research methodology for the design and development of the proposed proof-of-concept DPDⓘS that provides a patient-specific educational message on anti-diabetic drug regimen to patients with T2DM will be discussed.

3.1. *Problem Statement and Research Objectives*

Educational interventions with the goal of enhancing medication adherence have been proven to show positive results in health outcomes and adherence [71]. Therefore, it is recommended that when prescribing new medication, health care providers educate their patients on the medication name and its purpose, instruction on use (e.g., how and when to take the medication), side effects and possible ADRs [26]. Patients with greater understanding of medication-related topics can make more informed treatment decisions and achieve higher rates of medication adherence. Education on new prescriptions is even more imperative for patients with chronic conditions such as T2DM as they tend to have a complex drug regimen with multiple medications.

In practice, however, it is challenging for HCPs to describe all aspects of medication information to patients in part because of time constraints during the office visit. Consequently, only general information such as drug name and instruction on use is conveyed to patients, leaving most patients dissatisfied with the amount information they received about the side effects and adverse drug effects of their medication [24]. Despite communication efforts with patients having improved significantly in recent years, information topics around side effects and possible ADRs are still minimally discussed during the patient's visit [23], [24], [26], creating a gap between the amount of information desired by patients and the level of information provided by HCPs.

Drug information leaflets created by the manufacturer are available for the purpose of patient education, but they contain lengthy and generic information and are not perceived as an effective strategy to inform patients of the benefits and risks of their medications

[79]. Educational content about anti-diabetic medications offered by Diabetes Canada have similar limitations in that their materials provide general information about medications without consideration of patients' individual needs [27]. In addition to manufacturer's leaflets and government-funded websites, several commercial websites such as WebMD [28] and MedlinePlus [29] offer drug-related information for consumers including uses, administration and side effects. However, information on drug adverse effects on their websites does not specify adverse effects within various age ranges or consider any other patient factors that may influence adverse effects. A patient's vulnerability to experience ADRs is dependent on multiple factors such a age, number of prescribed medications, underlying medical conditions, and drug-drug interactions [80].

In summary, the shortcomings of the provision of patient education on medication-related information at the point of care are:

1- Due to the limited time during office visits, when prescribing new medication, HCPs often fail to educate their patients on all aspects of medication information including potential ADRs and possible DDIs. As a result, patients may have a poor understanding of their drug regimen that could lead to poor medication adherence or increased risk of ADRs [26].
2- A significant portion of ADRs leading to hospitalization are preventable with better patient education [67]. Yet, current information produced for the purpose of patient education is not tailored to patients' characteristics including underlying medical conditions or medication history. As a result, they are not suitable to fully inform patients of the benefits and risks associated with their medication therapy plan and educate them on signs and symptoms of possible ADRs[79].
3- Furthermore, with the abundance of online health information resources providing consumer drug information, valid concerns have been raised by HCPs over the credibility and accuracy of the information found on the internet which can result in misinformation being provided to patients [81].

Considering this, it is ever more important to support HCPs with individualized and evidence-based information to educate patients with T2DM on their prescribed medication that is accessible at the point of care. Providing personalized information

tailored to patients' characteristics, risk factors, and medical history will better inform patients about managing medication side effects and early recognition of possible ADRs.

To address the abovementioned shortcomings, the goal of this research is to design and develop a proof-of-concept web-based personalized education system to improve understanding of diabetes medication regimen for patients with T2DM. We call this **D**iabetes **P**atient-specific **D**rug **I**nformation **S**ystem (**DPDⓘS)** for patients with T2DM. To achieve this goal, the objectives of this thesis are:

1. Investigate and identify areas of medication information that are frequently sought by patients with T2DM;
2. Investigate and identify contextual factors that need to be considered to tailor medication information based on patients' individual needs.
3. Describe the obtained knowledge in a formal machine-readable format in an ontology-based knowledge model; and,
4. Provide tailored information to patients with T2DM about risk of potential ADRs considering their individual underlying risk factors including potential DDIs.

3.2. *Knowledge Management Approach to Support Self-Management*

To accomplish the objectives for this thesis, concepts in knowledge management are utilized. Knowledge management involves the strategies and processes for identifying, collecting, structuring and sharing domain knowledge. The advantages of a health care system that is based on knowledge management are discussed in the literature. In particular, such systems facilitate efforts in self-care for patients by providing access to relevant information and enabling evidence-based patient education [82]. Knowledge management as opposed to information management involves understanding and identification of the end users' needs, and subsequently describing the types of information and classifying it in structured manner [82].

To help guide our research we refer to the model developed by DeLorme *et al.,*[83] in which they modified the Comprehensive Model of Information Seeking by Johnson *et al.,* [50] with the focus on drug information seeking and influencing factors on selection of information sources. In their model, use of specific source of information is considered to

be affected by perceived usefulness of that resource. Figure 3-1 presents the schematic view of the CCM developed by DeLorme *et al.,*[83].

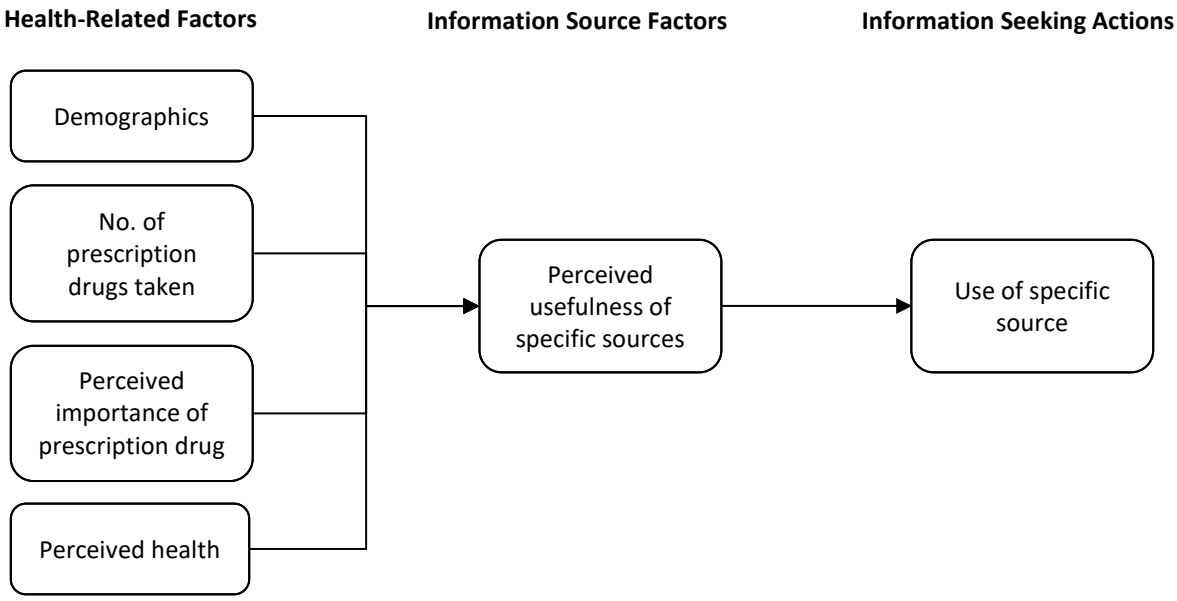


Figure 3-1 Comprehensive Model of Information Seeking with a Focus on Drugs

For management of chronic conditions, patients themselves play a central role by undertaking lifestyle changes such as a healthy diet and exercise, and adherence to medication therapy. Therefore, the self-management support is a key part of the diabetes management. It encompasses initiatives to encourage patient engagement in their care and involves providing patients with knowledge and education related to their chronic conditions and supporting them with appropriate tools to better manage their chronic condition [84]. To assist patients with self-management, patient education plays a key role. Examples of interventions to support patients' self-management are individual or group sessions for diabetes self-management education involving topics such as the importance of medication compliance, lifestyle goal setting and foot care [85].

The notion of self-management aligns well with research objectives for this thesis. Our proposed prototype, DPDⓘS, sits at the intersection of health technology and patients' self-management by providing tailored medication-related education for patients with D2T. A patient-centered approach in the process of care is characterized by a patient-

provider relationship that supports and encourages patient involvement and care that is customized for individual patients [2]. Taking a patient-centered approach and employing health technology, this research will demonstrate a solution to further support patient involvement in the process of care by offering patient-specific medication information and thereby facilitating self-management for patients with D2T.

3.3. *Research Approach*

To achieve the objectives listed in section 3.1, this research proposes the design and development of a Knowledge-Based System (KBS) for anti-diabetes medication information. The KBS is a form of artificial intelligence where the system can use knowledge to make decisions. In addition, KBSs can generate new knowledge based on data and information. The KBS consists of a Knowledge Base and an Inference Engine. The Knowledge Base is a repository holding the domain knowledge. These two components together support the main characteristics of a KBS which are decision reasoning and self-learning [86, p. 20]. Figure 3-2 shows the architecture of a KBS.

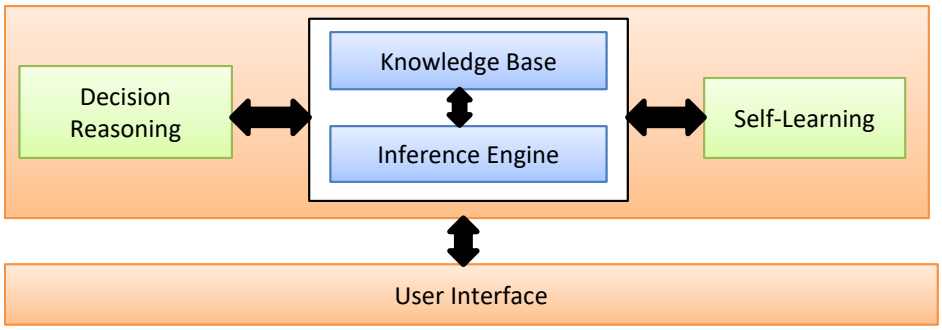


Figure 3-2 Architecture of a Knowledge Based System (KBS) [86, p. 20]

The provision of patient education on medication knowledge should be adaptable to the patient's circumstances including underlying medical conditions and other characteristics such as the patient's age. In addition, individualized patient education for prescription drugs should consider risk factors that are present for each patient. For instance, aging is associated with reduced renal function. This may put elderly patients with diabetes at higher risk of adverse drug events when taking the most common anti-diabetic drug, metformin, as prevalence of serious adverse reactions to metformin is higher in patients with impaired renal function [87].

The prototype KBS in this research, DPDⓘS, is aimed at patients, but will be provided to them or described to them at the point of care by their health care providers. DPDⓘS will help patients who would like to be informed about their diabetes medication to gain more knowledge regarding risks and considerations associated with their drug regimen including potential ADRs and DDI. It also assists health care providers with disseminating medication information in a way that covers aspects of medication knowledge about which patients are mostly uninformed. DPDⓘS will serve as a tool to guide conversation between patients and health care providers in a structured and more efficient way at the point of care. To develop the DPDⓘS, the following steps were taken:

1- Knowledge Acquisition: A literature review is conducted to examine drug information needs of patients. The initial challenge for determining appropriate medication information for patients with T2DM is to understand what patients want to know about their medication. The literature review identifies the areas of medication information about which patients are mostly uninformed. The proposed personalization will be undertaken based on the highlighted areas.
2- Knowledge Representation: An ontological modeling approach using Web Ontology Language (OWL) [88] is employed to define a knowledge model that represents concepts and relations in the domain of medication information for anti-diabetic drugs. “An ontology is a formal, explicit specification of a shared conceptualization [89]. Ontology-based approach has been recognized as a robust way for knowledge representation as it enables sharing and reuse of domain knowledge [90]. The anti-diabetic medication ontology describes different elements of medication information such as potential ADRs, possible DDIs, risk factors and considerations associated with anti-diabetic drugs. It provides semantic reasoning based on description logic (DL). The constructed ontology is part of the knowledge base used in DPDⓘS and plays a central role in its reasoning ability.
3- Subsequently, Semantic Web Rule Language (SWRL) [91] is used to formulate a rule base for the proposed DPDⓘS. OWL reasoning based on DL has some

expressiveness limitations. To overcome this, SWRL [91] has been introduced to allow for higher expressivity. With SWRL rules as an extension to OWL, a system can deduce high-level knowledge based on the If-Then rules. The anti-diabetic medication ontology together with the SWRL rule base will construct the knowledge base of the DPDⓘS. Using SWRL improves personalization ability in our proposed DPDⓘS and allows it to infer further knowledge based on the patient's individual context. The SWRL rule base for DPDⓘS includes a set of rules outlining the conditions for which personalization is considered. The reasoning component of the DPDⓘS will utilize the anti-diabetic medication ontology and rules to make inferences about new relations.

4- Prototype Development: The web-based prototype of the DPDⓘS will be developed to provide health care providers with necessary resources at the point of care to educate their diabetic patients on their drug regimens based on their individual characteristics and medication history.
5- Prototype Evaluation: A set of scenario-based cases will be utilized to evaluate DPDⓘS. The result of DPDⓘS outputs will be compared to evidence-based information sources to assess the correctness of the outcome.

Figure 3-3 represents the schematic representation of the research methodology steps utilized in this thesis.

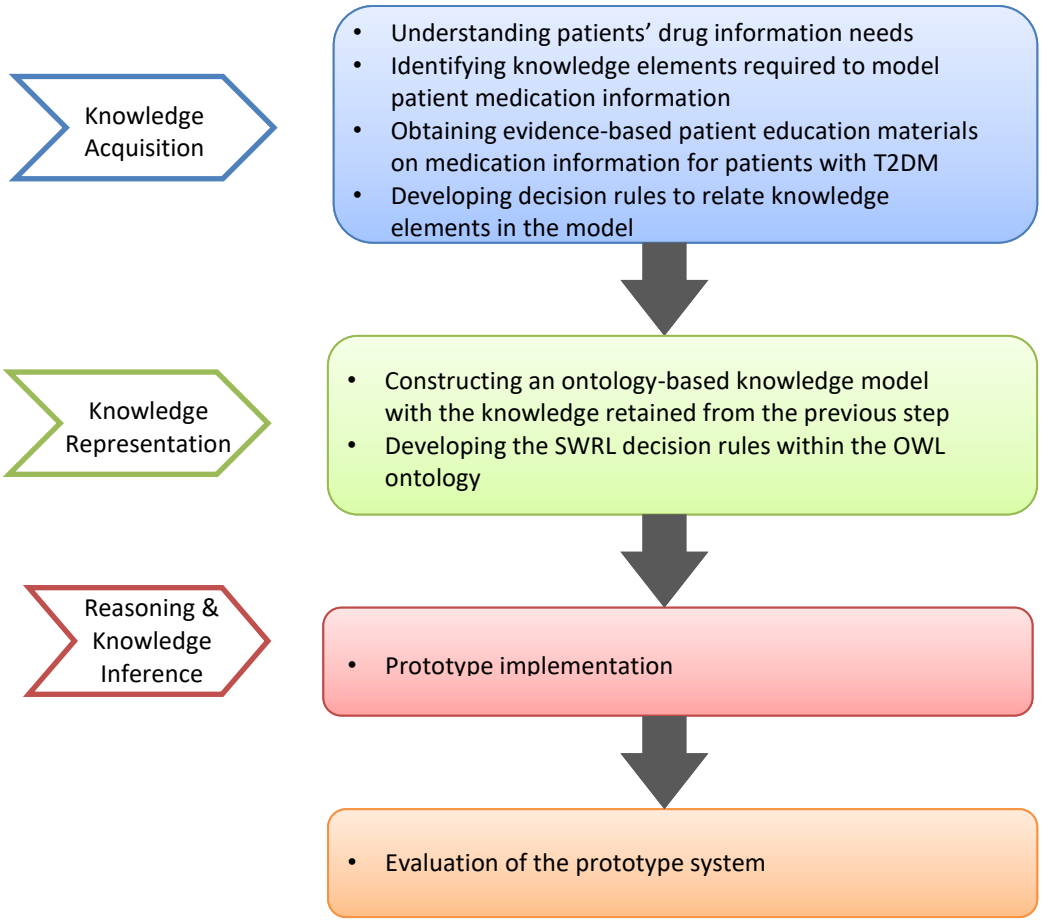


Figure 3-3 Schematic view of Research Methodology Steps

CHAPTER FOUR: METHODS

The DPDⓘS was developed as a proof-of-concept KBS to provide personalized medication-related information to patients with T2DM. The system combines domain-related knowledge about diabetes medication and inference logic to offer a patient-specific education message with respect to the patient's prescribed anti-diabetic drugs. It also serves as a support tool for health care providers to guide conversations with their patients about T2DM drug regimen at the point of care. The personalization of the DPD ⓘS is based on the patient's profile (e.g., age, drinking habits) and their specific underlying risk factors (e.g., concomitant prescription drugs, medical conditions).

4.1. *Conceptual Phase*

4.1.1. Patient Drug Information Needs

During the literature review phase of this research, different aspects of medication information that should be communicated with patients were investigated. As noted in section 2.2, a patient's medication knowledge involves understanding of drug purpose and instruction, understanding of drug side effects and potential ADRs, and knowledge of appropriate action if a dose of medication is missed [53]. Besides the basic information about administration of medication commonly referred to as "five rights" (i.e. right patient, right drug, right dose, right route, and right time) that has been practiced for many years, patients' growing involvement in their care and treatment process in recent years has led to their effort in learning more about different aspects of their prescribed medications in order to play an active role in their self-care [92].

Understanding what patients desire to know about their medications and common patients' medication-related questions is an essential step in representing that kind of knowledge in the knowledge base of our proposed system. As stated in the section 1.3, the first objective of this thesis is to identify and describe drug-related information sought by patients with T2DM. To accomplish this task, we explored the literature to identify patterns of drug information seeking among patients with T2DM. While there are studies investigating general information needs in patients with T2DM, little is known about

their specific medication-related information needs. Analysis of questions about T2DM raised by patients reveals that understanding what patients don't know and subsequently addressing their needs based on their questions provides better value than communicating the type of information that is perceived to be of importance by health care providers [93]. In their research, Crangle *et al.* reveal 23 diabetes-specific topics asked by patients; treatment was the most frequently discussed subject by patients which includes questions such as treatments for diabetes including medication and self-management behaviors that could be part of a treatment plan [93]. However, specifics on treatment-related questions that patients with T2DM asked were not addressed by their study.

In this context, we believe it is fair to assume that medication-related needs of patients with T2DM would be similar to that of patient populations in general irrespective of their chronic condition. Therefore, we reviewed available literature with the focus of identifying drug information needs raised by patients. Articles with one of the keywords "drug information", "patient information needs", "medication information questions", "patient drug questions", "patient drug information", and "Patient medication knowledge" in title/abstract in English language were searched using Medline (via PubMed).

Tarn *et al.,* [26] investigates physician communication when prescribing new medications through an observational study. For new prescribed medications, physicians described the specific medication name for 74% of new prescriptions and explained the purpose of the medication for 87%. Adverse effects were discussed for only 35% of medications [26]. In another study Ziegler et al., [61] examined the amount of information patient like to receive regarding adverse effect of drugs . Questionnaire was used to survey patients in an outpatient family practice. Some adverse effects are common and some are rare; similarly some are mild and some are severe. Patients were asked about the extent to which they desire to know about the adverse effects of their prescription medications. Their study reports that the majority of patients (76%) would like to hear any adverse effect, regardless of how rare they are. Similarly, 84% of patients expressed interests in knowing any serious adverse effect, no matter how rare [61].

In agreement with the previous research, Tarn et al., [23], conducted a study in which they compared patient preferences regarding adverse effect discussions with what physicians reported in their practice. More than 90 % of patients wanted a physician to discuss medication adverse effects; they wanted information about both dangerous (75 % of patients) and common (66 % of patients) adverse effects. Their study reports significant differences between the adverse effects physicians' report they describe to patients when prescribing new medications and the ones that older patients want to be communicated with them [23].

Another research group took a patient-centered approach to provide drug information via a drug information center. In their research Maywal et al., [94] analyzed patterns of patients' drug information needs calling drug and therapy information center over two years. Main information needs of patients regarding prescription drugs was reported as adverse drug reactions and drug interactions which accounted for 31.0%. Following that, questions around therapy information was around 27.2% of total questions asked [94].

An exploratory study was conducted to evaluate the engagement of individual consumers with the Facebook page of a non-profit organization offering services in the area of health technologies including medications and medical tests. On their Facebook page, a weekly Pharmacist Hour service is offered in which individuals can ask any medication-related questions. Subsequently, a pharmacist on the team would answer the questions, providing evidence-based medication information during the one hour period. Their study reports that most popular questions were related to adverse effects, following that treatment options for conditions, and drug interactions were among the most frequent question asked by the individual Facebook users [95].

To investigate what information about medication is desired by patients rather than health care providers' viewpoints, Borgsteede *et al.* [64] set out a qualitative analysis of patients' needs of information about their drug regimen. Most patients believe they are provided sufficient basic information about their medication which includes the name of the drugs, reason they were prescribed, and instruction for taking the drugs. However, patients highlighted the need for more information about side effects of the drugs and ways to recognize them by knowing signs and symptoms [64].

Patients' enquiries to a drug information service was examined by Huber *el al.,*[96] for the duration of 6 years with the goal of analysing the type of enquiries as well as answers provided by the drug information service. The group of cardiovascular medications was most often the subject of questions asked by patients. The most frequent enquiry adverse drug reactions (22.1%), the need for general information about the drug (19.9%), information about therapy (12.4%) and drug interactions (10.2%).

A recent scoping review by Kusch *et al.* [97] was of particular interest in which the researchers attempted to identify relevant drug information topics through analysis of patients' inquiries to various drug information sources along with a review of previous studies assessing patients' drug information seeking behaviour. Their review included 27 articles. Even though the authors acknowledge that they didn't apply full range of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, they included a number of criteria including eligibility criteria, information sources, data collection progress, synthesis of results, study characteristics, summary of evidence, limitations, conclusions, and funding. Their study concludes that the most frequent medication-related information sought by patients is about drug safety issues such as information on side effects, ADRs and DDIs. Following that information on dose and administration, treatment options and duration of treatment were among information topics requested by patients [97]. Figure 4-1 shows the frequency of drug information topics reported by scoping review of Kusch *et al.* [97].

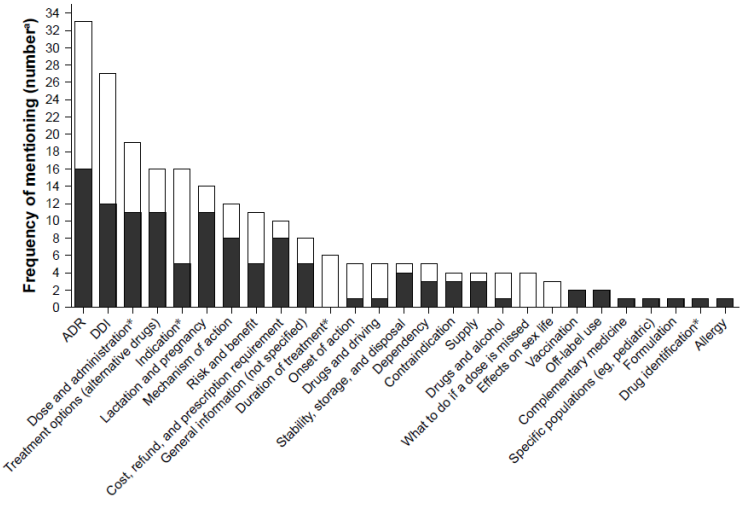


Figure 4-1 Frequency of Drug Information Topic Based on Scoping Review [97]

Based on our literature review the most frequent drug information needs raised by patients are about side effects, ADRs and DDIs which relates to our first object of this thesis. Table 4-1 provides summaries of articles that were reviewed to better understand patient drug information seeking behaviour.

Paper	Description
Tarn *et al.,* [26]	• Observational study to examine physicians' communication when prescribing new medications • Physicians described the specific medication name for 74% of new prescriptions and explained the purpose of the medication for 87%. • Adverse effects were addressed for 35% of medications.
Ziegler *et al.,* [61]	• To determine the amount of information patient would like to receive regarding adverse effect of drugs • Questionnaire was used to survey patients in an outpatient family practice to examine. • Majority of patients (76%) would like to hear any adverse effect, regardless of how rare they are.
Borgsteede *et al.* [64]	• To investigate what patients want to know about their medications. • A qualitative study • Most patients believe they are provided sufficient basic information about their medications but they highlighted the need for more information about side effects of the drugs.
Tarn et al., [23]	• To compare patient preferences for adverse effect discussions with reported physician practice. • A cross-sectional survey with convenience sample of 178 subjects recruited from 11 senior centers in the Los Angeles metropolitan area • 90 % of patients wanted a physician to discuss medication adverse effects; they wanted information about both dangerous (75 % of patients) and common (66 % of patients).
Maywald et al., [94]	• To explore patterns of patients' unmet drug information needs • Data obtained from callers of drug and therapy information center • During 24 months, 2049 telephone calls were recorded. Patients' unmet information needs were mainly related to adverse drug reactions/drug interactions (31.0%) and therapy information (27.2%).
Sleath et al**.** [19]	• To examine questions asking about medications during office visits • A dataset of 467 audiotapes and transcripts of outpatient • Approximately 20% of each encounter was spent discussing medication • Frequently asked questions were about what medications the patient was taking (80%), how the medication was influencing the patient's medical condition (56%), quantity or supply (51%), interval (41%), dosage (41%), and barriers or side effects.
Bentoli et al., [95]	• An exploratory research to described medication-related questions asked by individual consumers on a Facebook page during Pharmacist Hour • During this 12-month period, a total of 226 questions were posted • The most common topic was adverse effects of medicines followed by questions related to treatment options for conditions, drug interactions, and dose and administration.
Huber et al., [96]	• The group of drugs most often asked about were cardiovascular drugs

Paper	Description
	(33.4%), followed by drugs for the nervous system (16.2%) and for the alimentary tract and metabolism (12.4%). • Common reasons for contacting the service were adverse drug reactions (22.1%), the need for general information about the drug (19.9%), information about therapy (12.4%) and drug interactions (10.2%).
Kusch *et al.* **[97]**	• A scoping review examining drug information areas asked by patients in the literature. • Of 27 identified drug information topics in the literature search, patients most frequently requested information on ADRs and DDIs.

Table 4-1 Summary of Literature Review about Patient Drug Information Needs

4.1.2. Risk Factors for the development of Adverse Drug Reactions

The second objective of this thesis is to identify contextual factors that need to be considered to tailor medication information based on patients' individual needs. To achieve this, we need to better understand risk factors that affect the development of ADRs when taking anti-diabetic drugs.

Various factors affect the occurrence of adverse drug events including patient-related factors and drug-related factors [98]–[100]. An example of patient-related factor would be excessive alcohol consumption while taking metformin, a common medication for treating T2DM, which can increase the risk of lactic acidosis, a rare but serious adverse drug event. Similarly, diuretics drugs such as hydrochlorothiazide can interact with metformin and may increase the likelihood of hyperglycemia and lead to loss of blood sugar control. This can be considered drug-related factor.

The World Health Organization defines an adverse drug reaction as "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function" [101]. Based on the available data in the literature, the average rate of hospital admissions due to ADRs is 4.1% in young adults as opposed to 16.6% for the elderly population, with a significant portion of the hospitalisations (88%) considered to be preventable [102]. Some medication classes are reported to have the highest occurrences of ADRs including painkillers, anti-infectives, cardiovascular agents, and blood thinners.

A 10-year retrospective study found that painkillers resulted in the most ADRs overall and cardiovascular agents caused the largest number of severe ADRs [80].

There are many factors that contribute to the possibility of ADRs including age, gender, co-existence of medical conditions, multiple prescribed medications, dose and type of medications. Factors affecting the development of ADRs can be grouped into patient-related factors and drug-related factors. Each risk factor group will be discussed in more detail in the following sections.

4.1.2.1 Patient-Related Factors

All drugs can potentially cause ADRs, but not all patients show symptoms of ADRs at the same level and type. Age is an important factor for developing ADRs. Ageing is associated with anatomical and physiological changes in human bodies. These age-related changes may lead to alterations in how the body absorbs the drug, distributes it, metabolizes it, and eventually eliminates the metabolic waste of the drug through lungs, kidneys, and skin. As a result of these processes, drug concentration may change, thereby impacting the clinical response and the effect of a drug on the body [103]. Elderly patients are at higher risk of experiencing adverse drug events. This is largely because elderly patients are more likely to have multiple chronic conditions. There is, however, disagreement in the literature on whether aging by itself is an independent factor or the combination of other issues that are prevalent among the elderly causes the increased risk of adverse drug reactions [104]. For instance, patients over 65 are more likely to be on combination of multiple medications to treat coexistent conditions with an average of 2 to 6 prescribed medications per patient [105] which in turn increases the risk of potential adverse drug-drug interaction, giving rise to possible adverse drug events. Furthermore, the rate of comorbid conditions is higher among the elderly population, ranging from 30% to 54%, and having three or more comorbidities increases the risk of possible occurrence of adverse drug events [106].

Sex is another risk factor for the development of ADRs. The anatomical differences between men and women including weight and body composition can influence drug metabolism [107]. In particular this is noticeable with cardiac and psychotropic medications. For example, women tend to achieve better therapeutic outcome with two

antipsychotic medications, chlorpromazine and fluspirilene [108]. A retrospective analysis on gender-related differences in ADRs concluded that cardiovascular ADRs are more frequent in men than women. On the other hand, the likelihood of experiencing ADRs as a result of neuropsychiatric medications is higher in women versus men [109].

Another contributing factor in developing ADRs is alcohol consumption. Alcohol can interact with many classes of prescription medications as well as over the counter medications. As a result, alcohol consumption both at heavy and moderate levels can impact the metabolism or activity of a drug, thereby potentially leading to an adverse drug event [110]. For instance, in patients with T2DM, chronic alcohol consumption can result in higher blood sugar levels (referred to as hyperglycemia) for those with good nutritional status. Whereas, for patients with T2DM with inadequate nutrition, chronic alcohol consumption can cause lower than normal blood sugar levels (referred to as hypoglycemia) [98].

4.1.2.2 Drug-Related Factors

Drug-Drug Interactions

Prescription drugs, over the counter medications such as nutritional supplements and food can affect the pharmacological impact of a medication. As a result, the effectiveness of a drug may be reduced or strengthened. Drug-drug interaction (DDIs) is a process in which one drug can possibly interfere with the pharmacological effect of another drug. The risk of potential DDIs increases as the total number of medications being taken increases. This translates to over 50% likelihood of having DDI occur when a patient is on five prescribed medications and the risk increases to 100% when seven or more drugs are taken [99].

Some DDIs are desirable and are utilized as part of a therapeutic drug regimen. Polypharmacy, defined as the use of multiple drugs (commonly more than 5 drugs) is prevalent in older population. For instance, combination therapy is employed in treating hypertension among elderly patients. The use of both chlorthalidone and atenolol, which belong to the diuretics and beta blocker medication class respectively, as combination antihypertensive therapy for hypertension has resulted in reduced number of strokes and

other cardiovascular complications [100]. However, DDIs resulted from concomitant drug therapy are also a common cause of adverse drug reactions. A retrospective analysis on ADRs data collected from community teaching hospital shows that DDIs are the second most frequent cause of preventable adverse drug reactions [111]. The rate of polypharmacy increases with advancing age. A national survey in United States reports that patients 65 years or older have the highest prevalence of prescription drugs with 23% of women and 19% of men in that population taking at least 5 drugs [112].

The number of prescription medications or polypharmacy is well acknowledged in the literature as a main contributing factor for drug-drug interactions. Certain classes of medications have been frequently cited to have high rates of drug-drug interactions. A recent study on older adults living in communities has reported that anti-inflammatory drugs are the most common medication class affecting other drugs, and cardiovascular medications are the most common class of medication being affected by other drugs [113]. In agreement with the previous study, Gurwitz *et al.* in their study on elderly patients in an ambulatory clinical setting found that cardiovascular drugs are the most frequent cause of adverse drug events, accounting for 26% of total reported incidents whereas anti-diabetic medication have resulted in 7% of the recorded adverse drug events [114].

Drug-Disease Interactions

In addition to drug-drug interactions, drugs can impact diseases as well. Although polypharmacy can be beneficial in treating chronic conditions and improving quality of life, its benefit is accompanied with potential harm. Drug-disease interactions refers to a process in which a medications have the potential to exacerbate an underlying condition, thereby posing more risk than benefit which leads to an increased risk of having an adverse drug event occur [115]. The prevalence of drug-disease interaction is higher among older adults. A study on community-based older adults found that at least one type of drug-drug interactions occurred for over one third of the participants, and 16% of them experienced drug-disease interaction with 3.7% of them having drug-disease interaction with non-prescription medication. The most frequent drug-disease interaction in their

study was reported for patients with peptic ulcer disease taking anti-inflammatory drugs including aspirin [113].

Different research groups have attempted to compile a list of drug-disease interactions that include a list of specific conditions and medications to be avoided in older adults. Their effort relied on group judgement and consensus panels [116]. There is however lack of overall agreement between their findings. For instance, Lindblad *et al.* [115] identified 28 drug-disease interactions that are considered harmful for the elderly. Only 11 of those drug-disease interactions overlapped with the previous list [116].

Various indicators are used to measure inappropriate medication use, among which are rates of using medications with clinically significant drug-drug interactions, and medications that are listed as drug-disease interactions in the literature, meaning their use is prohibited when certain conditions exist. In their prospective study, Chrischilles *et al.,* [117] examined the association between different measures of inappropriate medication use and self-reported adverse drug events Their study shows that use of drug-disease interactions is the most common aspect of inappropriate medication use and is reported to be significantly associated with the prevalence of self-reported adverse drug events [117]. Focusing only on the subcategory of ADRs that are preventable through dose adjustments or discontinuation of a drug, a retrospective analysis explored a similar relationship between drug–drug interactions and drug–disease interactions and the occurrence of ADRs among elderly patients. In alignment with the previous study, Hanlon *et al.* found that both drug-drug interactions and drug-disease interactions are linked with preventable ADRs [118].

In summary, there are several risk factors for the developing adverse drug reactions. Elderly patients are particularly at increased risk of experiencing ADRs, in part because they have often concurrent chronic conditions for which they take multiple prescription medications [114]. This polypharmacy is amplified by physiological age-related changes in the body composition that impacts the effects of the medication being taken [103]. One study reported that 35% of older patients with polypharmacy experienced at least one confirmed case of adverse drug reactions during a year; though 95% of these adverse drug reactions were preventable [119]. To reduce the risk of ADRs, it is recommended

that patients are educated by their prescribing physician regarding the presence of important risk factors for ADRs such as age, polypharmacy and comorbidities [105].

The summary of risk factors influencing occurrence of ADRs is presented in Table 4-2.

Patient-Related Risk Factors	Drug-Related Risk Factors
• Age • Sex • Allergy • Body weight • Alcohol drinking • Race and ethnicity • Smoking	• Polypharmacy (increase likelihood of DDIs) • Drug dose and frequency • Drug-disease interactions

Table 4-2 Summary of Factors Influencing the Risk of ADRs

With the obtained knowledge from literature review regarding ADRs and DDIs to be the most frequent drug information topics requested by patients and factors influencing development of ADRs (shown in Table 4-2), we developed the concept map for the proposed system. The diagram presented in Figure 4-2 is a simple graphical representation to convey the concepts and relationships between them that are considered relevant to the domain of anti-diabetic medication information as well as information elements that are considered desirable by patients based on the available literature. The concept map also serves as a basis for the ontology-based knowledge modeling approach carried out in the design phase.

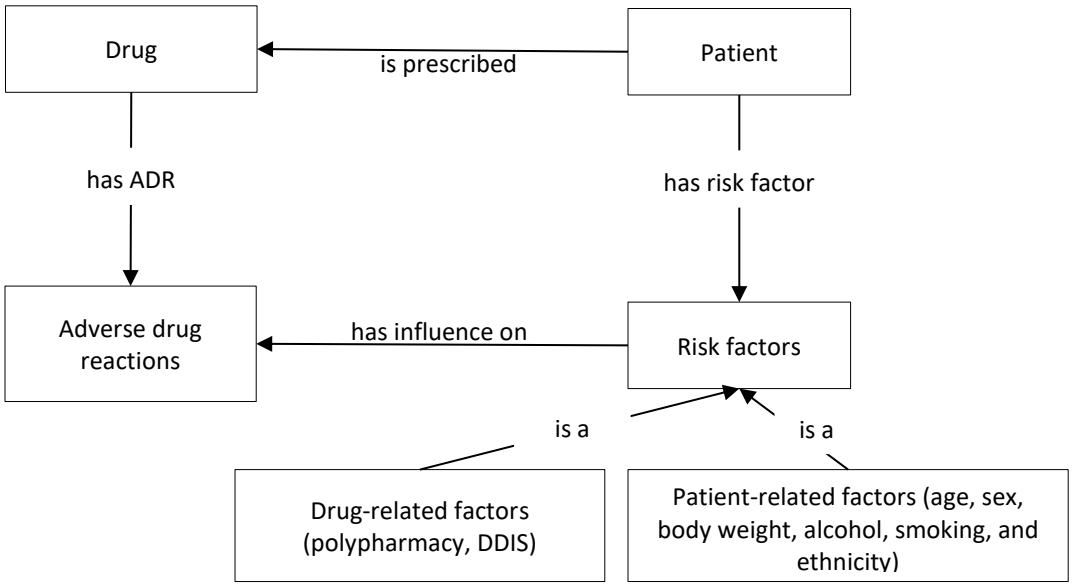


Figure 4-2 Concept Model for the Proposed KBS (DPDⓘS)

4.2. *Design Phase*

The concept model described in the section 4.1 guided our efforts in gathering and representing the knowledge related to ADRs and DDIs for anti-diabetic medications. In developing our proposed system, DPDⓘS, this section outlines the construction of the knowledge base for this system. As noted in the section 3.3, an ontology-based approach was employed to develop the knowledge model that formally describes concepts and relations among these concepts in the domain of ADRs and DDIs for anti-diabetic medications. Furthermore, to tailor medication information for patients, decision rules using SWRL were also developed in this phase. The addition of SWRL rules adds an extra layer of expressivity to the ontology model. The OWL ontology together with the set of SWRL rules constitutes the knowledge base of the DPDⓘS.

4.2.1. Development of the Anti-Diabetic Medication Ontology

To build the Anti-Diabetic Medication (ADM) ontology for our system, we followed the steps in the methodology for ontology development proposed by Noy and McGuinness [120]. The ADM ontology is constructed using OWL and Protégé 5.5 ontology editing environment [121]. It provides the semantic foundation for the domain of diabetes medications, targeting concepts and relations affecting elements of medication information that are sought by patients. Ontology-based knowledge modeling was adopted for representing the domain knowledge because it captures the knowledge in a formal way, thereby allowing sharing and reusing it in similar systems with the aim of educating patients on prescription medications that are used to treat other chronic conditions.

In a three-step process, we developed the ADM ontology: 1) the ontology requirement specification, 2) knowledge acquisition including selection of knowledge sources and knowledge abstraction, and 3) knowledge formalization using Protégé 5.5 ontology editor. In the subsequent sections, these steps will be discussed in detail.

4.2.1.1 Ontology Requirement Specification

Figure 4-3 illustrates the steps taken for the process of building the ADM ontology.

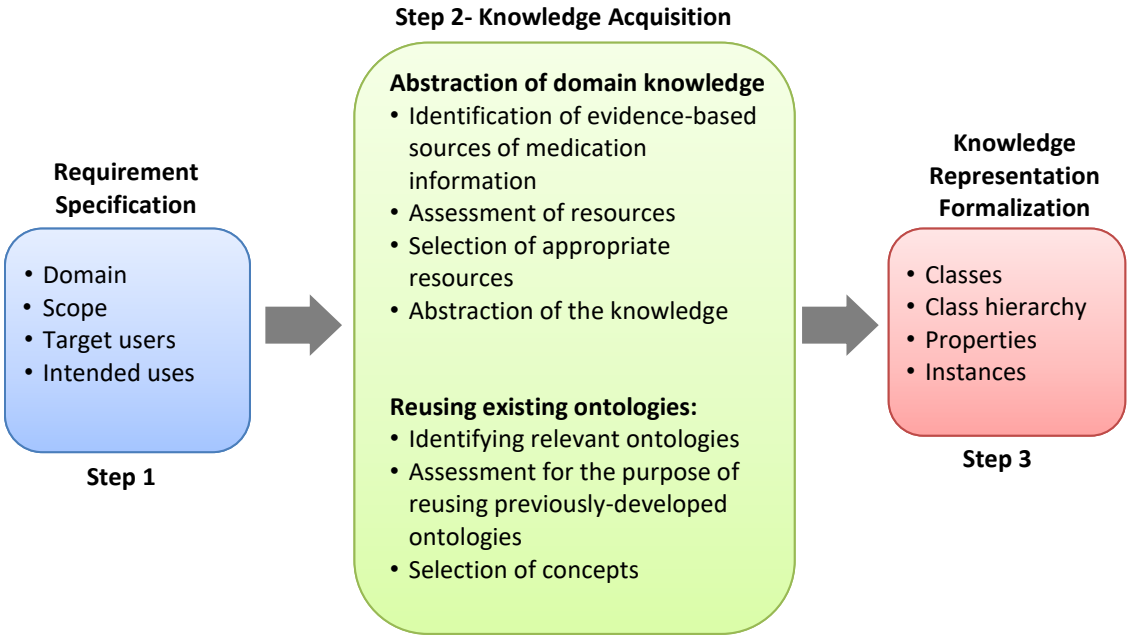


Figure 4-3 Steps for the ADM Ontology Development Process

As shown in figure 4-3, first, the ontology requirements were specified using the guideline proposed by Suárez-Figueroa *et al.* [33]. To prepare the ontology requirements specification, we sought to answer the following questions [33]:

1. Why build the ADM ontology?
2. What specific requirements will the ADM ontology fulfil?
3. Who are the users of the ADM ontology?
4. What is its intended use?

The *purpose* of the ADM ontology is to define the concepts and relationships between them in regards to side effects, ADRs and DDIs information of oral anti-diabetic medications. We narrowed the *scope* of the ADM ontology to classes of oral antihyperglycemic drugs that are used in pharmacotherapy of patients with T2DM diabetes. As this is Canadian research, we included antihyperglycemic agents that are approved by Health Canada and are listed in the latest edition of Diabetes Canada clinical practice guidelines [38]. A brief description of these drugs is covered in the background

section 2.1 and the list of drugs is also presented in table 2-1. The *end users* of the ADM ontology are both patients and health care providers. Patients seeking to enhance their medication knowledge beyond the basic information that includes the drug name, reason and use instruction can benefit from the ADM ontology by learning about side effects, ADRs, DDIs and risks and considerations associated with their anti-diabetic drug regimen. In addition, the ADM ontology can also assist health care providers in providing evidence-based patient education on prescription drugs for patients with T2DM. Furthermore, the ADM ontology can also be shared and reused by software developers to support the design and development of KBS in the domain of patient education on drug information. The *intended use* for the ADM ontology is to provide personalized solutions for educating patients with T2DM on medication information topics that are desired and frequently sought by patients including side effects, ADRs and DDIs in an anti-diabetic drug regimen.

Table 4-3 below outlines the ontology requirements specification including the scope, purpose, intended application and end users of the ADM ontology adapted from the guideline offered by Suárez-Figueroa *et al.* [33].

Ontology requirements	Description
Purpose	The purpose of the ontology is to describe concepts and relations among those concepts regarding specific aspects of medication information for patients with T2DM
Scope	The ontology focuses on knowledge about side effects, ADRs and DDIs for oral antihyperglycemic drugs
Target end users	• Patients - the ontology is aimed at patients wanting to enhance their knowledge on their prescription drugs for treating T2DM. • Health care providers - it can serve as a support tool for health care providers to guide them in providing medication information to their patients at the point of care. • Software developers - the ontology can be reused as a knowledge base to support computational applications in the domain of patient medication information.
Intended uses	Providing personalized medication information by considering patient-related factors and drug-related factors affecting the possibility of ADRs and DDIs in patients with an anti-diabetic drug regimen

Table 4-3 Ontology Requirement Specification

4.2.1.2 Knowledge Acquisition

The second step (Figure 4-3) in building our domain-specific ontology involved knowledge acquisition including the selection of knowledge resources and knowledge abstraction. As suggested in the methodology proposed by Noy and McGuinness [120], the possibility of re-using existing ontologies that were developed in the domain of adverse drug events and DDIs was explored. We examined the BioPortal Repository [122] which includes a comprehensive list of biomedical ontologies to search for existing ontologies in our domain knowledge. Multiple ontologies were of interest based on the relevance of their domain and purpose to our research topic. The related existing ontologies are listed in Table 4-4. While these ontologies assisted us in mapping key concepts in the domain of drug information, they lacked the required knowledge representation in certain aspects of our domain knowledge.

Ontology Name	Domain knowledge	Description
Ontology of Adverse Events (OAE) He *et al*. [123]	Adverse events	It represents various adverse events caused by medical interventions
Ontology of Drug Adverse Events (ODAE) Yu *et al.* [124]	Adverse drug events	It describes various adverse events that are caused by drug administration. It represents relations among drug and adverse events based on the patient's age and disease treated by the drug.
Drug Interaction Ontology (DIO) Yoshikawaa *et al.* [125]	Drug interaction	It represents drug–biomolecule interactions that result in certain types of DDIs. It captures pharmacological mechanisms of drugs to describe drug interactions.

Table 4-4 Existing Ontologies Related to the Domain Knolwedge

The Ontology of Adverse Events (OAE) represents information about adverse events caused by medical interventions such as the administration of a drug or vaccine, usage of a medical device, or surgery. It classifies different adverse events based on patient anatomic region affected by the adverse event, type of medical interventions preceding the adverse event, and signs and symptoms of the adverse event [123]. The classification of various adverse events in OAE, is performed at a high level, that is, OAE does not represent specific adverse events concerning individual drugs or vaccines. This is reflected in Figure 4-4 where a high-level association between *medical intervention* class and *adverse event* class is shown. In addition, factors affecting adverse events are not defined in OAE. While the authors recognize some of these factors including age, genetic

background, drug-drug interactions and drug-food interactions, they propose that ontological linkages can be carried out to incorporate the knowledge model that represents the relations between different factors and the occurrence of the adverse event with OAE [123].

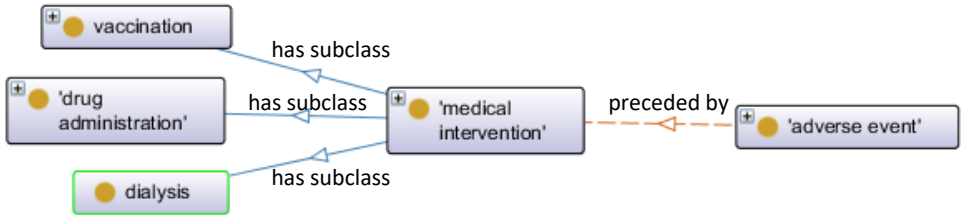


Figure 4-4 A Selection of Classes and Properties of OAE, adapted from [123]

Another ontology that was reviewed in relation to the domain of our interest was the Ontology of Drug Adverse Events (ODAE) developed by Yu *et al*. in 2019 [124]. ODAE is built upon existing OAE [123] and has incorporated some of its modules to specifically represent knowledge about adverse events caused by drug administration. Drugs may cause adverse events based on the age of the patient and the type of disease for which the drug is prescribed. Taken this into consideration, ODAE describes factors including age and disease that may affect the development of adverse events. In addition, ODAE offers finer granularity levels for drug products including information about drug chemical ingredients and mechanism of action [124]. Figure 4-5 illustrates a selection of classes and the associations that capture the relations between drugs, drug-treated diseases and adverse events.

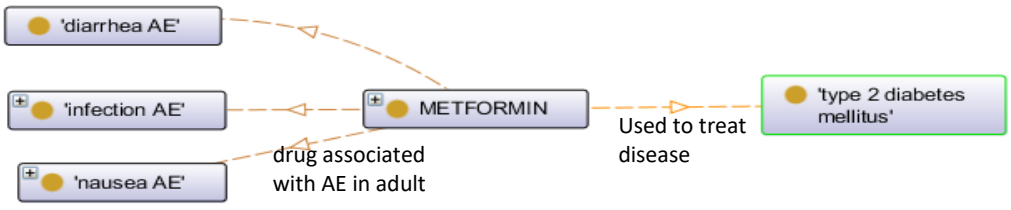


Figure 4-5 Selection of Classes and Properties of ODAE, adapted from [124]

Based on the representation in Figure 4-5, we can conclude that metformin is associated with adverse event of diarrhea and is used to treat T2DM [124]. While ODAE represents the relationship between age and disease with adverse events, it does not consider other

factors that may influence the development of adverse drug events such as alcohol consumption or drug-drug interactions. In addition, ODAE does not represent the likelihood of the occurrence of adverse events. For instance, diarrhea is a *common* side effect of metformin, whereas lactic acidosis is a *rare* adverse outcome of taking metformin. Classifying adverse events by frequency is important for the purpose of patient education as some patients would like to receive information about all possible ADRs irrespective of their likelihood [61].

Though the reviewed ontologies in Table 4-4 assisted us in understanding general concepts and relationship in the area of ADRs, none supported the type of knowledge representation that is required for the research topic of this thesis. Consequently, we explored non-ontological resources based on the guideline by Suárez-Figueroa *et al* [33]. The Canadian Pharmacist Association provides the electronic Compendium of Pharmaceuticals and Specialties (CPS) [126]. CPS drug information is the Canadian standard for drug monographs that covers a significant amount of information about drug products, including monographs for drugs and vaccines approved by Health Canada. CPS contains up-to-date, evidence-based therapeutic information and non-prescription therapy for many conditions. For each drug, CPS offers information in separate sections for health care professionals and for patients.

As part of the licence agreement with Dalhousie University, e-CPS database is freely accessible to Dalhousie University students. Figure 4-6 presents a snapshot of patient information for the drug metformin as it appears in the CPS. To create the ADM ontology we used CPS as the drug information resource. We adopted a bottom-up strategy by means of the "abstraction process" [34, p. 7]. Our knowledge abstraction process was based on by principles of grounded theory which involves using available information as a starting point to develop a model that would explain the investigated phenomenon [127], [128]. Woods *et al.,* [129] defines grounded theory as "a set of categories that are related to one another to form a framework that explains the main concern of the participants in relation to the research area". We undertook a reverse-engineering approach to deconstruct the CPS documents into identifiable elements related to our domain topic [130]. To this end, patient medication information documents on CPS

(Figure 4-6) were annotated for oral antihyperglycemic drugs, listed in Table 2-1, and are approved and recommended by the 2018 Canadian clinical practice guidelines for the treatment and management of T2DM [38].

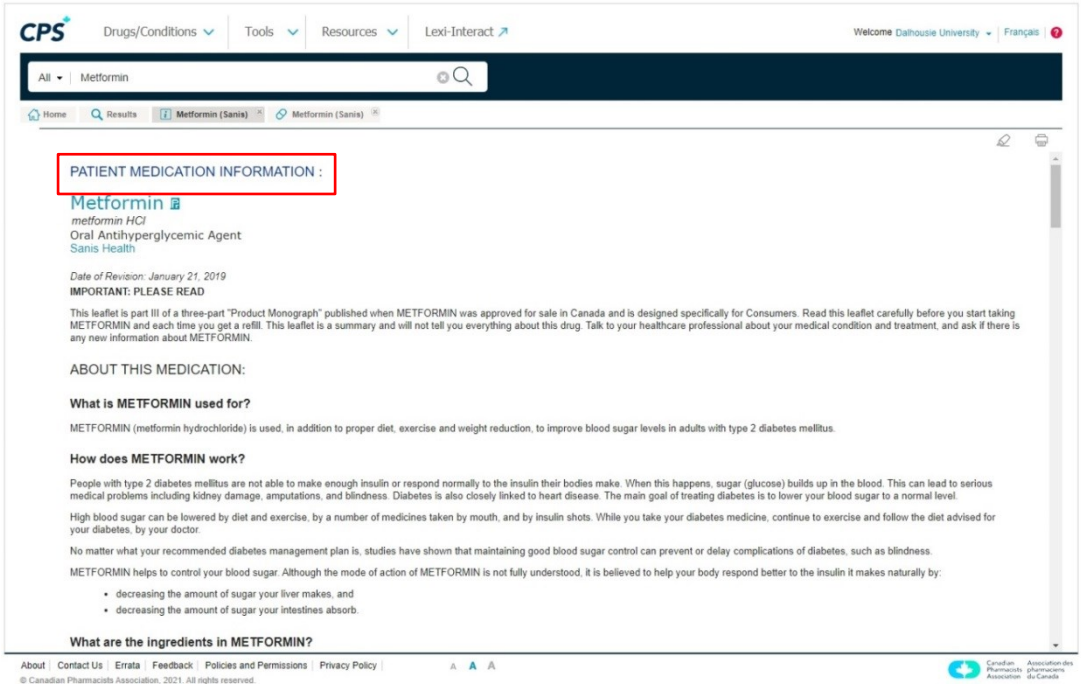


Figure 4-6 Patient Medication Information on CPS

The following concepts were emerged from manual abstraction of the CPS documents:

1- ADRs of oral antihyperglycemic medications: For this concept, the name and description of ADRs along with descriptive quality of ADR (e.g. common, rare) were abstracted. In total, 58 terms about ADRs were identified among antihyperglycemic drugs. Nausea and diarrhea were the most common ADRs associated with these drugs.

2- Prescription drugs: As noted earlier, the list of anti-diabetic drugs for the ADM ontology were taken from the 2018 Canadian clinical practice guidelines for the treatment and management of T2DM [38].

3- Drug-drug interactions: For this concept, the type of drug interacting with anti-diabetic drugs, and the outcome of the interaction were captured.

4- Risk factors: the risk factors influencing ADRs that were recognized through literature review (see Table 4-2) guided us in identifying these factors in the CPS

documents. For instance, the statement "*Diuretics (water pills), especially loop diuretics, may increase the risk of lactic acidosis (too much acid in the blood) due to their potential to decrease renal function"* were abstracted to the concepts ADR, DDI and a relation between them. Another example would be *"Avoid drinking alcoholic beverages and taking medicines containing alcohol while you are taking GLICLAZIDE as it can lead to drop in blood sugar (hypoglycemia)."* , which is abstracted to concepts alcohol risk factor, hypoglycemia ADR, gliclazide drug and a relationship between alcohol risk factor and hypoglycemia drug. Another example for elderly risk factor would be *"Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA, including hypotension"*

4.2.1.3 Formalization of Knowledge Representation

In step 3 of building the ADM ontology (Figure 4-3) we formally represented the concepts and relations from the concept map drawn in the conceptual phase (Figure 4-2) and abstracted knowledge from the CPS using OWL in Protégé 5.5 ontology editor. Figure 4-7 shows the top-level class design of the ADM ontology. The orange rectangle boxes represent *classes*, the blue boxes represent *object properties* and the green boxes represent data properties. Together, they indicate the association between a drug, ADRs and a patient, given patient risk factors. A property in OWL is defined as a binary relation. In the ADM ontology, we needed to represent a more complex relation between the drug and ADRs entities, called n-ary relations. Components of the ADM ontology including classes, object and data properties will be discussed in this section.

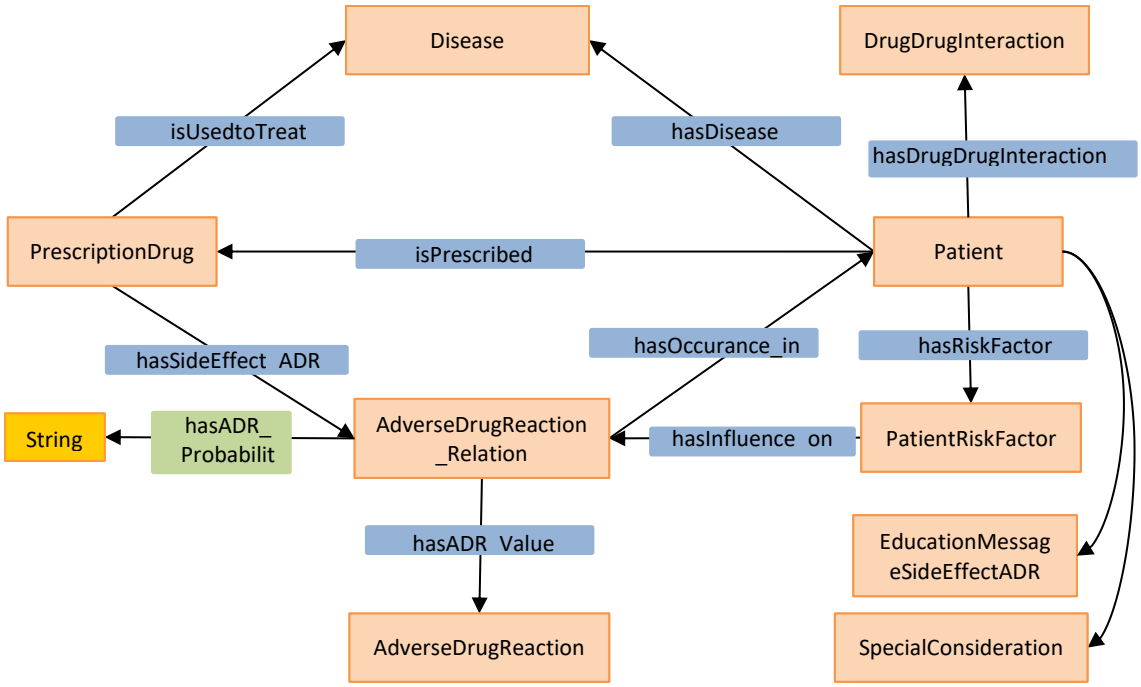


Figure 4-7 Top-Level Class Design of the ADM Ontology

Based on the concepts identified in the knowledge abstraction step, classes were defined within the Protégé 5.5 environment. Table 4-5 lists the classes in the ADM ontology. There are 135 classes and subclasses in the ontology.

Class Name	Definition
Disease	represents the type of chronic condition treated by the drugs
AdverseDrugReaction	represents the classification of ADRs based on CPS documents on patient medication information
DrugDrugInteraction	describes the various DDIS between antihyperglycemic drugs and other drugs
EducationMessageSideEffectADR	describes the generic side effects and ADRs pertaining to antihyperglycemic drugs
HealthCareProvider	classifies the type of health care provider treating the patient
Patient	describes patient concept
PatientRiskFactor	represents various patient risk factors related to ADRs
PrescriptionDrug	classifies antihyperglycemic drugs
SpecialConsideration	describes points of consideration for patients in regards to potential ADRs

Table 4-5 List of Classes for the ADM Ontology

Even though the ADM ontology represents only diabetes-specific medication knowledge, the class `Disease` is included to allow future extension to the ADM ontology with the

addition of medication knowledge related to other chronic conditions. The class `AdverseDrugReaction` has 57 subclasses to represent ADRs terms abstracted from CPS patient medication information documents. The class `PrescriptionDrug` describes anti-diabetic drugs based on Canadian clinical practice guideline for T2DM [38]. In addition, it represents other medication categories that are reported to have potential interactions with anti-diabetic drugs based on the evidence-based information from CPS [126]. Figure 4-8 shows an excerpt for the class hierarchy for `AdverseDrugReaction` and `PrescriptionDrug`.

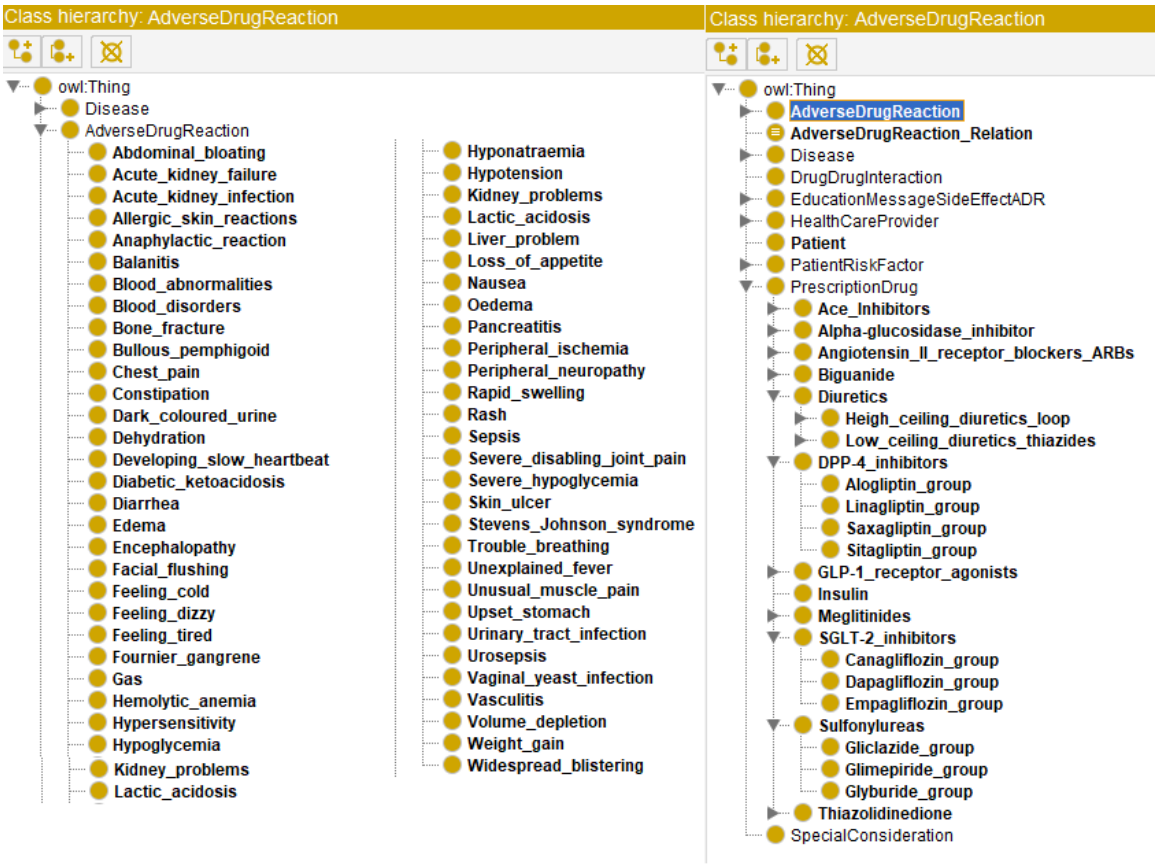


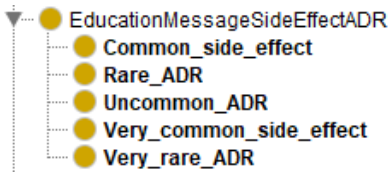
Figure 4-8 Class Hierarchy of AdverseDrugReaction and PrescriptionDrug

The class `PatientRiskFactor` defines various factors affecting the occurrence of ADRs. Similar to the `Disease` class, some of the concepts represented in this class are not necessarily for T2DM, rather they are general risk factors of ADRs that were gathered from the literature review phase. These factors are extensively covered in the background section 2.4. Modeling these factors in the ontology makes it expansive and

extendable. For instance, research indicates that gender may affect ADRs. This is because the anatomical difference between men and women can impact the metabolism of the drug [107]. During the knowledge abstraction phase, however, no evidence was found based on CPS documents concerning the role of sex for ADRs among antihyperglycemic drugs. Despite this, sex and other factors such as smoking are classified as subclasses for the class `PatientRiskFactor` so that the ADM ontology can be expanded to include any other ADRs that may be affected by the concepts represented in this class.

The three classes `EducationMessageSideEffectADR`, `DrugDrugInteraction` and `SpecialConsideration` capture characteristics of personalized medication information. Personalization SWRL rules are used to infer the values of the object properties of all three classes.

Class `EducationMessageSideEffectADR` includes five subclasses as shown below:



In addition, class `EducationMessageSideEffectADR` has an object property called `hasEducationMessageSideEffect` that indicates the components of side effects and ADRs based on the patient's prescribed medication. As mentioned above, the values for this property will be inferred when SWRL rules are invoked.

Class `DrugDrugInteraction` captures known DDIs based on the abstracted information from the CPS. Similar to the class `EducationMessageSideEffectADR`, values for the object property `hasDrugDrugInteraction` will be deduced by the inference engine.

Class `SpecialConsideration` represents considerations for patients based on the patient's risk factors and potential DDIs. Similar to the previous two classes, SWRL rules will identify the topics to be included. The full OntoGraf view of the ADM ontology is presented in Appendix C.

The ADM ontology has 14 object properties and 8 data properties. Table 4-6 outlines the list of object properties, and the corresponding domain and range for them in the ADM ontology.

Object Property Name	Domain	Range
hasOccurance_in	AdverseDrugReaction_Relation	Patient
isUsedtoTreat	PrescriptionDrug	Disease
hasInfluence_on	PatientRiskFactor	AdverseDrugReaction_Relation
hasDisease	Patient	Disease
hasADR_Value	AdverseDrugReaction_Relation	AdverseDrugReaction
hasDrugDrugInteraction	Patient	DrugDrugInteraction
hasEducationMessageSide Effect	Patient	EducationMessageSideEffectA DR
hasRiskFactor	Patient	PatientRiskFactor
hasSideEffect_ADR	PrescriptionDrug	AdverseDrugReaction_Relation
hasSpecialConsideration	Patient	SpecialConsideration
isCausedBy	AdverseDrugReaction_Relation	PrescriptionDrug
isConsisted_of	Common_side_effect or Rare_ADR or Uncommon_ADR or Very_rare_ADR or Very_common_side_effect	AdverseDrugReaction_Relation
isPrescribed	Patient	PrescriptionDrug
isTreatedBy	Patient	HealthCareProvider

Table 4-6 List of Object Properties in the ADM Ontology

Data Property Name	Domain	Range
has_DDI_Description	AdverseDrugReaction_Rel ation	Literal
hasADR_Description	AdverseDrugReaction_Rel ation	Literal
hasADR_Probability	AdverseDrugReaction_Rel ation	Literal
hasAge	Patient	Disease
hasATC_Code	PrescriptionDrug	integer
hasConsideration_Description	SpecialConsideration	Literal
hasICD9_Code	ComorbidityFactor	Decimal
hasTotalMedication	Patient	integer

Table 4-7 List of Object Properties in the ADM Ontology

A property in OWL is defined as a binary relation that associates two OWL individuals or an individual and data value. However, in the ADM ontology, we needed to represent

a more complex relation between drug and ADR concepts to capture the semantics of their association. For instance, drug *metformin* has the *rare* adverse reaction of *lactic acidosis*. In this statement, there is a binary relation between *metformin* and *lactic acidosis.* Moreover, there is a qualitative value (*rare)* describing this relation. In other words, the statement reads: drug *metformin* has adverse reaction of *lactic acidosis* with *rare* frequency. This type of relation is called an n-ary relation. To represent this ternary relationship, we followed the solution proposed by W3C Working Group Note [131], decomposing the n-ary relation to binary relations. We represented the relation between drug and ADRs as class rather than a property. We then specified additional properties to support binary relations to each component of the relation (i.e. value of the ADRs and frequency of the ADRs). Figure 4-8 further illustrates the two binary relations created to capture the semantics of the ternary relation between the class `PrescriptionDrug` and `AdverseDrugReaction`.

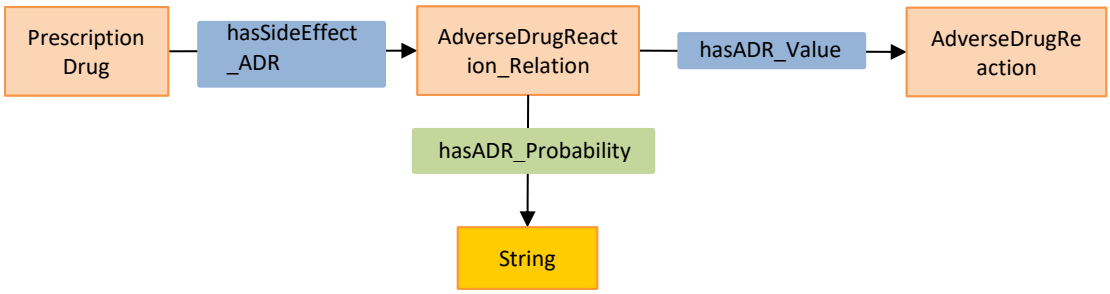


Figure 4-9 Ternary Relation in the ADM Ontology

As shown in Figure 4-9, class `PrescriptionDrug` is associated with class `AdverseDrugReaction_Relation` along with the property `hasSideEffect_ADR`. Class `AdverseDrugReaction_Relation` captures the relation itself. An individual from class `PrescriptionDrug` has a property `hasSideEffect_ADR`. The value of this property is an object (individual of class `AdverseDrugReaction_Relation`) that encapsulates both the value of the ADRs as well as its probability. Figure 4-9 illustrates this relation with the `metformin` drug (an individual from the class `PrescriptionDrug`). The individual `Metformin_lactic_acidosis` in Figure 4-10 describes `Lactic_acidosis` as the value for the ADR as well `rare` for its probability. Therefore, the original statement, drug *metformin* has adverse reaction of *lactic acidosis* with *rare* frequency, is well-defined.

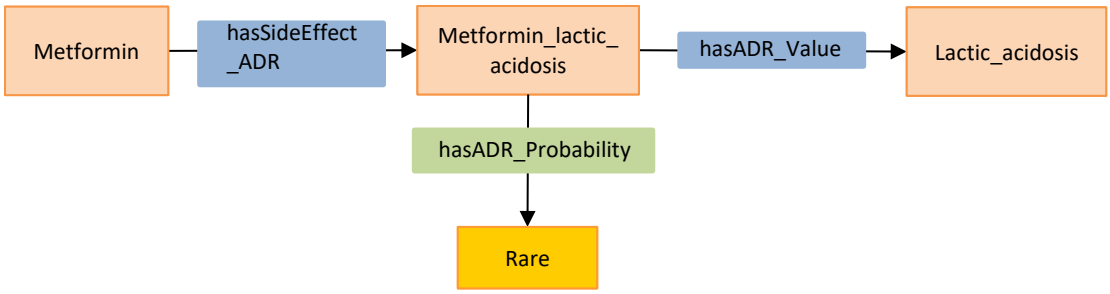


Figure 4-10 Ternary Relation for the Metformin Drug

Developing the n-ary relationship between class `AdverseDrugReaction` and `PrescriptionDrug` enabled us to link ADRs and drugs based on disease and frequency of the ADR. Take for instance `Bullous_pemphigoid`, a subclass of class `AdverseDrugReaction`. Properties for this subclass are presented in Figure 4-11. Frist, all subclasses of `AdverseDrugReaction` have data property of `hasADR_Description`. For class `Bullous_pemphigoid`, the data property `hasADR_Description` has the value of "*Bullous pemphigoid is severe skin reaction. Signs and symptoms include redness, peeling skin, and/or blistering of the skin, lips, eyes or mouth*".

Based on the object properties shown in Figure 4-11, we can describe that:

1- Bullous pemphigoid is participant of relationship that occurs in patients with T2DM who are prescribed alogliptin and the probability of this ADR happening for alogliptin is very rare.

However Bullous pemphigoid can also occur when taking linagliptin. This relationship is shown with the second object property that reads:

2- Bullous pemphigoid is participant of relationship that occurs in patients with T2DM who are prescribed linagliptin and the probability of this ADR happening for linagliptin is rare.

A full list of object properties pertaining class `AdverseDrugReaction` can be found in Appendix D

Figure 4-11 Properties of Subclass Bullous_pemphigoid

We can also represent the same relationship from the drug side. Take for instance the properties for the class `Alogliptin_group` that is shown below (Figure 4-12). The object describes that alogliptin has ADR value of Bullous pemphigoid with very rare probability among patients diagnosed with T2DM.

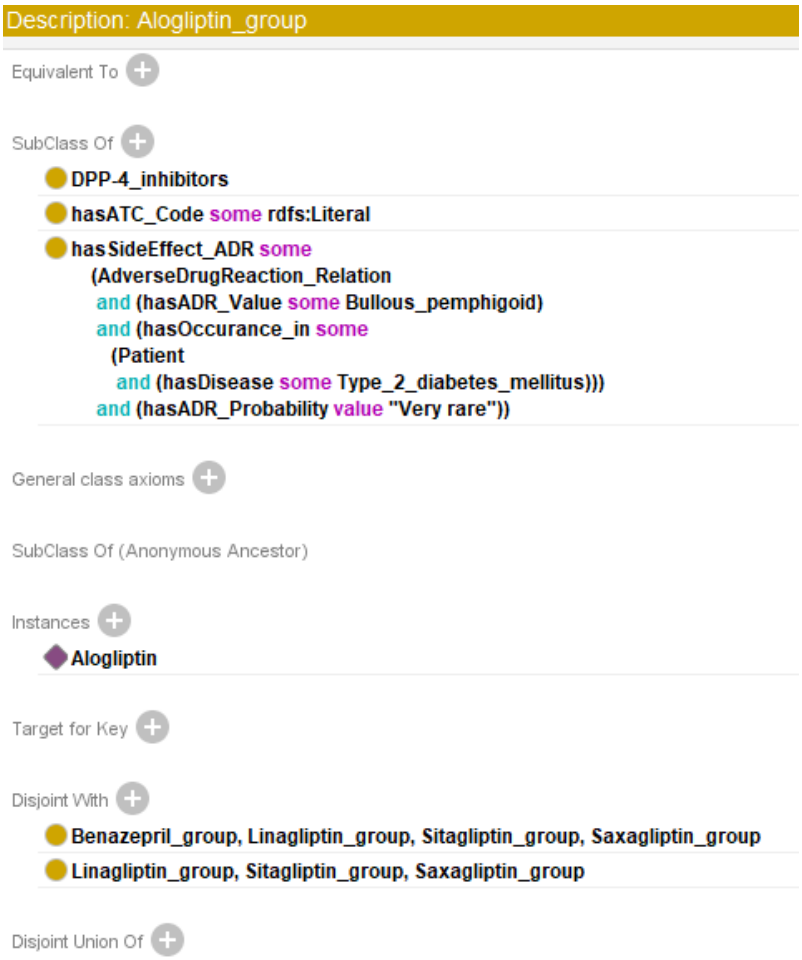


Figure 4-12 Properties of Class Alogliptin_group

Once the design of the ADM ontology was completed, we populated it with individuals to represent specific instances of represented classes. In total, 309 instances were created in the ADM ontology.

4.2.2. Development of the SWRL Rules

There are so many definitions for personalization in the literature. In this thesis, personalization is considered as the process of providing relevant content based on individual user needs. We followed the personalization framework offered by Fan and Poole [132]. Their proposed framework is consisted of three dimensions:

1- **Aspect of the information that is being personalized**

In this dimension, there are four elements in a system that can be personalized 1) *content* of the information, 2) *user interface* where the information is presented to the user, 3) *channel/information access* and 4) *functionality* of the system [132]. The personalization of our system occurs at the content level. The information that would be personalized involves around ADRs and DDIs information for oral antihyperglycemic drugs which is the most common patient drug information needs. Risk factors that were abstracted from the CPS (age, sex, alcohol, comorbidity) along with DDI are used for the basis of personalization. Based on patient profile and the presence of such risk factors, tailored messages regarding impact of risk factors on ADRs will be generated.

2- **Target of personalization**. For this dimension, the target of personalization in our system will be patients with T2DM.

3- **How personalization is done**. Personalization in which users provide information to the system, and the system subsequently customizes the information based on its input is called explicit personalization. In contrast, when personalization is done automatically by the system is called implicit personalization [132]. Our proposed system offers implicit personalization based on the clinical information stored for patients in the system.

Initial logic rules were developed in natural language format to convey the type of personalization required for the system.

If
Patient *isPrescribed* Gliclazide
and Patient *hasRiskFactor* Binge_drinking
then Patient *hasEducationMessageSideEffect* Consideration_gliclazide_alcohol

The preceding example shows the rule that considers the association between the patient and their prescription drugs and provides appropriate information about side effects and ADRs accordingly. To formulate the rules in the knowledge base, Semantic Web Ontology Language (SWRL) was employed. SWRL has been proposed in the Semantic Web area as an extension to OWL in order to solve its expressive restrictions. Currently,

SWRL is considered to be the standard rule language for the Semantic Web and it enables users to express Horn-like rules using OWL vocabulary [133].

SWRL rule of the previous example was developed as below:

```
Patient(?p) ^:isPrescribed(?p,Gliclazide) ^
hasRiskFactor(?p,Binge_drinking) ->
hasSpecialConsideration(?p,Consideration_gliclazide_alcohol)
```

The individual `Consideration_gliclazide_alcohol`, in turn has `hasConsideration_Description` data property with value of *"Risk of hypoglycemia. Drinking alcoholic beverages while you are taking gliclazide increases the hypoglycemic reaction and can lead to drop in blood sugar.*

Risk of facial flushing. The effect of alcohol in patients taking gliclazide includes facial flushing and sensation of warmth"

SWRL rules were developed in SWRLTab which is an interactive editor in the protégé environment that allows users to create and edit SWRL rules. In total, 112 SWRL rules were developed to express the conditions for personalization required for the system. Figure 4-13 shows an excerpt of the developed SWRL rules in the SWRLTab editor. The full list of SWRL rules can be found in the Appendix B.

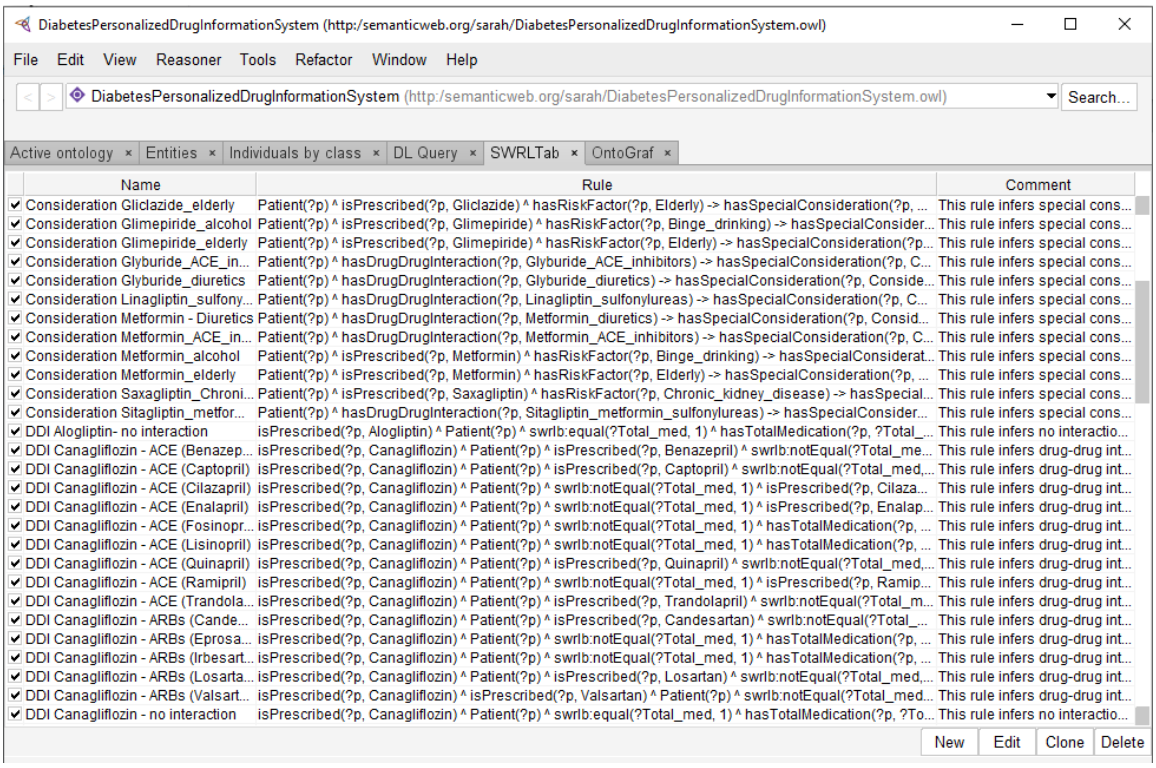


Figure 4-13 An Excerpt of SWRL Rules in SWRLTab Editor

A SWRL rule consists of the antecedent (body) and consequent (head) and can be presented with the syntax form of

`antecedent` ⟶ `consequent`

Each part comprises zero or more atoms in the form of $C(x), P(x, y)$, where C is an OWL class, P is an OWL property, and x, y are OWL individuals or OWL data values. Antecedent describes the conditions to be evaluated. If atoms are true in the antecedent part of the rule, then it is concluded that the atoms in the consequent part will be true as well [134].

For instance, the following SWRL rule uses class `Patient` and data property `hasAge`, built-in functions, and individuals to assign a patient's age risk factor:

```
Patient(?p) ^ hasAge(?p, ?age) ^ swrlb:greaterThan(?age, 65) ->
hasRiskFactor(?p,Elderly)
```

The first atom specifies that a patient is an individual of the class `Patient` and is represented by the variable `?p`. This individual has a data object property `hasAge`, which denotes the age of the patient. The built-in `greaterThan` determines if this age is over 65. If these three atoms are `TRUE` then the consequent will be true. Therefore, the object property of `hasRiskFactor` will be inferred (as opposed to asserted) for `?p` with the value `Elderly`.

The SWRL rules enabled personalization by inferring elements of medication information based on a patient's characteristics such as age, sex, alcohol drinking, and comorbidity as well as DDI. These characteristics are abstracted from the CPS documents during the knowledge abstraction phase. Some SWRL rules determine object properties that will be evaluated in subsequent rules. For example, the above mentioned rule that infers `hasRiskFactor` property with the value `Elderly` for the variable `?p` will be evaluated as part of the antecedent for subsequent rules to personalize information based on the age risk factor. An example of this rule is the following:

```
Patient(?p) ^ isPrescribed(?p,Metformin) ^
hasRiskFactor(?p,Elderly) ->
hasSpecialConsideration(?p,Consideration_metformin_elderly)
```

The preceding rule infers points of consideration with regard to risk of ADRs based on the age risk factor. In particular, the object property `hasSpecialConsideration` will be assigned to `?p` with the value `Consideration_metformin_elderly` . The individual `Consideration_metformin_elderly`, in turn, has the data property `hasConsideration_Description` with the value "Risk of Lactic acidosis".

The SWRL rule-base contains three sets of rules to 1) determine the side effects and ADRs for the prescribed medication, 2) determine potential DDIs based on the patients' concomitant drugs, and 3) determine points of consideration for potential occurrences of ADRs. It is important to provide the patient with basic information about side effects and ADRs of their medication. Thus, the first subset of rules ensures all patients receive information on side effects and ADRs with the order of their frequency. This is possible due to the ternary relation represented in the ontology which was discussed earlier. Table

4-8 lists several SWRL rules pertaining to the first subset of rules and the list of all developed SWRL rules can be found in Appendix B.

Side Effects and ADRs Rules	
No	**SWRL Rule**
1	Patient(?p) ^ isPrescribed(?p, Metformin) -> hasEducationMessageSideEffect(?p,Metformin_uncommon_ADR) ^ hasEducationMessageSideEffect(?p,Metformin_common_side_effect) ^ hasEducationMessageSideEffect(?p,Metformin_rare_ADR)
2	Patient(?p) ^ isPrescribed(?p, Alogliptin) -> hasEducationMessageSideEffect (?p,Alogliptin_common_side_effect) ^ hasEducationMessageSideEffect (?p,Alogliptin_uncommon_ADR) ^ hasEducationMessageSideEffect (?p,Alogliptin_rare_ADR)
3	Patient(?p) ^ isPrescribed(?p, Canagliflozin) -> hasEducationMessageSideEffect (?p,Canagliflozin_very_common_side_effect) ^ hasEducationMessageSideEffect (?p,Canagliflozin_common_side_effect) ^ hasEducationMessageSideEffect (?p,Canagliflozin_uncommon_ADR) ^ hasEducationMessageSideEffect (?p,Canagliflozin_rare_ADR)
9	Patient(?p) ^ isPrescribed(?p, Gliclazide) -> hasEducationMessageSideEffect (?p,Gliclazide_very_common_side_effect) ^ hasEducationMessageSideEffect (?p,Gliclazide_uncommon_ADR) ^ hasEducationMessageSideEffect (?p,Gliclazide_very-rare_ADR)

Table 4-8 First Subset of SWRL Rules to Identify Side Effects and ADRs

The second subset of rules determines potential DDIs based on the patients' concomitant drugs. Table 4-9 lists some SWRL rules pertaining to this subset. SWRL only supports positive conjunctions of atoms. Therefore, to implement an *OR* condition in SWRL, the original rule has to be broken down into separate rules with positive conjunctions [135]. For instance, to establish the DDI association between metformin and drugs in the ACE inhibitors group, we could not directly use the following rule:

```
Patient(?p) ^ isPrescribed(?p, Metformin) ^
(isPrescribed(?p,Ramipril)or isPrescribed(?p, Captopril)) ^
hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) ->
hasDrugDrugInteraction(?p,Metformin_ACE_inhibitors)
```

Instead, we broke down the rule into multiple rules, with each rule including one drug belonging to the ACE inhibitors group. Thus, the correct way of presenting the preceding rule is:

1- Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p, **Ramipril**) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Metformin_ACE_inhibitors)

2- Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p, **Captopril**) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Metformin_ACE_inhibitors)

In total, ten SWRL rules (rule #13 to rule#22 in Appendix B) were developed to represent the DDI association between metformin and drugs in the ACE inhibitors medication category.

Drug-Drug Interactions Rules	
No	**SWRL Rule**
14	Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p,Ramipril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Metformin_ACE_inhibitors)
25	Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p,Hydrochlorothiazide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Metformin_diuretics)
31	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^ isPrescribed(?p,Furosemide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Canagliflozin_loop_diuretics)
42	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^ isPrescribed(?p,Candesartan) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Canagliflozin_ARBs)
54	Patient(?p) ^ isPrescribed(?p, Empagliflozin) ^ isPrescribed(?p,Glyburide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p, Empagliflozin_sulfonylureas)

Table 4-9 Second Subset of SWRL Rules to Identify DDIs

The third subset of SWRL rules evaluates the previously inferred properties and if they evaluate to true, property `hasSpecialConsideration` will be inferred with the value of specific consideration to be provided to the patient. Table 4-10 lists some SWRL rules for this subset. For example rule# 90 in table 4-7 indicates that if there is a DDI association is already inferred with the value of `Metformin_ACE_inhibitors`, points of consideration for potential occurrence of ADRs will be inferred by means of property

hasSpecialConsideration with the value of Consideration_metformin_ACE_inhibitors. The individual Consideration_metformin_ACE_inhibitors stores the description of the consideration through the data property of hasSpecialConsideration.

Special Consideration Rules	
No	**SWRL Rule**
87	Patient(?p) ^ isPrescribed(?p,Metformin) ^ hasRiskFactor(?p,Elderly) -> hasSpecialConsideration(?p,Consideration_metformin_elderly)
90	Patient(?p) ^hasDrugDrugInteraction(?p,Metformin_ACE_inhibitors) -> hasSpecialConsideration(?p,Consideration_metformin_ACE_inhibitors)
95	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^ hasRiskFactor(?p,Diabetes_kidney_disease) -> hasSpecialConsideration(?p,Consideration_canagliflozin_diabetic_kidney_disease)
100	Patient(?p) ^ isPrescribed(?p,Empagliflozin) ^ hasRiskFactor(?p,Binge_drinking) -> hasSpecialConsideration(?p,Consideration_empagliflozin_alcohol)
111	Patient(?p) ^ hasDrugDrugInteraction(?p,Glyburide_diuretics) -> hasSpecialConsideration(?p,Consideration_glyburide_diuretics)

Table 4-10 Third Subset of SWRL Rules for Patients' Consideration

4.2.3. Reasoning Process

Knowledge in an ontology is specified using a formal language. Thus, it allows the ontology to be processed by a computer program. This is referred to as the machine-readability characteristic of the Semantic Web which supports decision-making capabilities and allows for logical inferencing. As a result, we can perform reasoning upon OWL ontology concepts to infer new knowledge. Inference engines or reasoners are software applications that derive new facts from existing information. In Semantic Web, inference engines process the knowledge expressed in the ontology and draw logical conclusions based on the concepts and relationships that are already defined in the knowledge base, thereby extending the OWL knowledge base by means of adding the new inferred OWL concepts [35].

To perform reasoning on the OWL ontology combined with SWRL rules, one can either employ an ontology-based reasoning approach such as the Pellet reasoner or third party inference engines that support description logic reasoning such as Drools rule engine

[133]. Drools is an object-oriented Java-based rule engine that uses a forward chaining approach to invoke reasoning about ontologies [136]. Figure 4-14 presents the schematic view of how the Drools rule engine supports reasoning with OWL ontologies and SWRL rules.

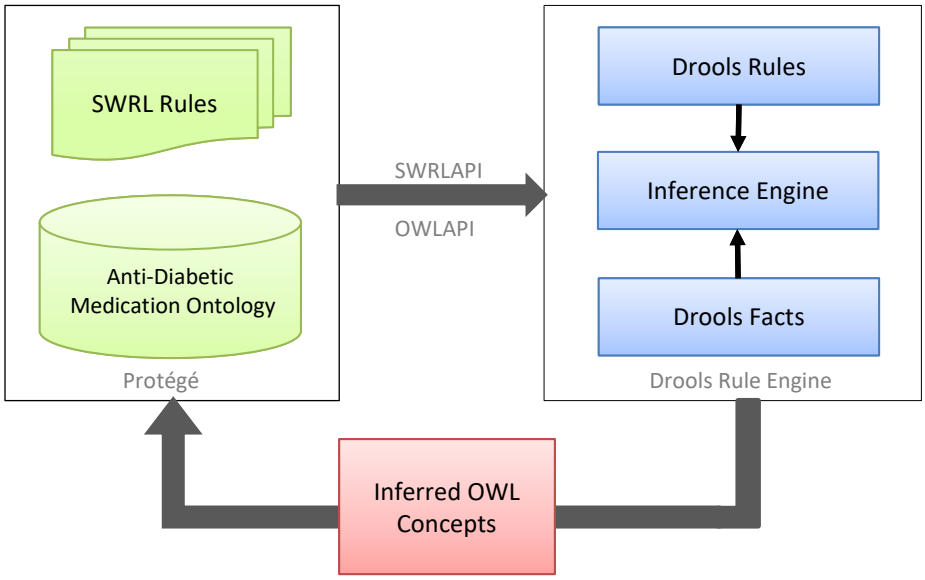


Figure 4-14 Drools Rule Engine Reasoning with OWL Ontologies with SWRL Rules

As shown in Figure 4-14, the Drools rule engine consists of a fact base, rule base and an inference engine. First, OWL concepts (classes, properties and individuals) along with SWRL rules are transformed to Drools facts and Drools rules respectively [136], [137]. This can be done in the protégé environment using the *OWL+SWRL → Drools* button of the SWRLTab editor (Figure 4-6). The underlying mechanism for this integration is SWRLAPI that provides a bridge between an OWL model with SWRL rules and a third-party rule engine or OWL reasoner [138]. Second, the Drools rule engine can be executed via the *Run Drools* button of the SWRLTab editor to do reasoning which entails matching Drools facts against Drools rules to infer new conclusions [137]. The reasoning results can be reviewed under Inferred Axioms of the SWRLTab editor (Figure 4-15). Lastly, inferred facts are inserted back to the OWL ontology using the *Drools → OWL* button. Through this process, SWRL rules along with the Drools rule engine support rule-based reasoning in the Semantic Web area.

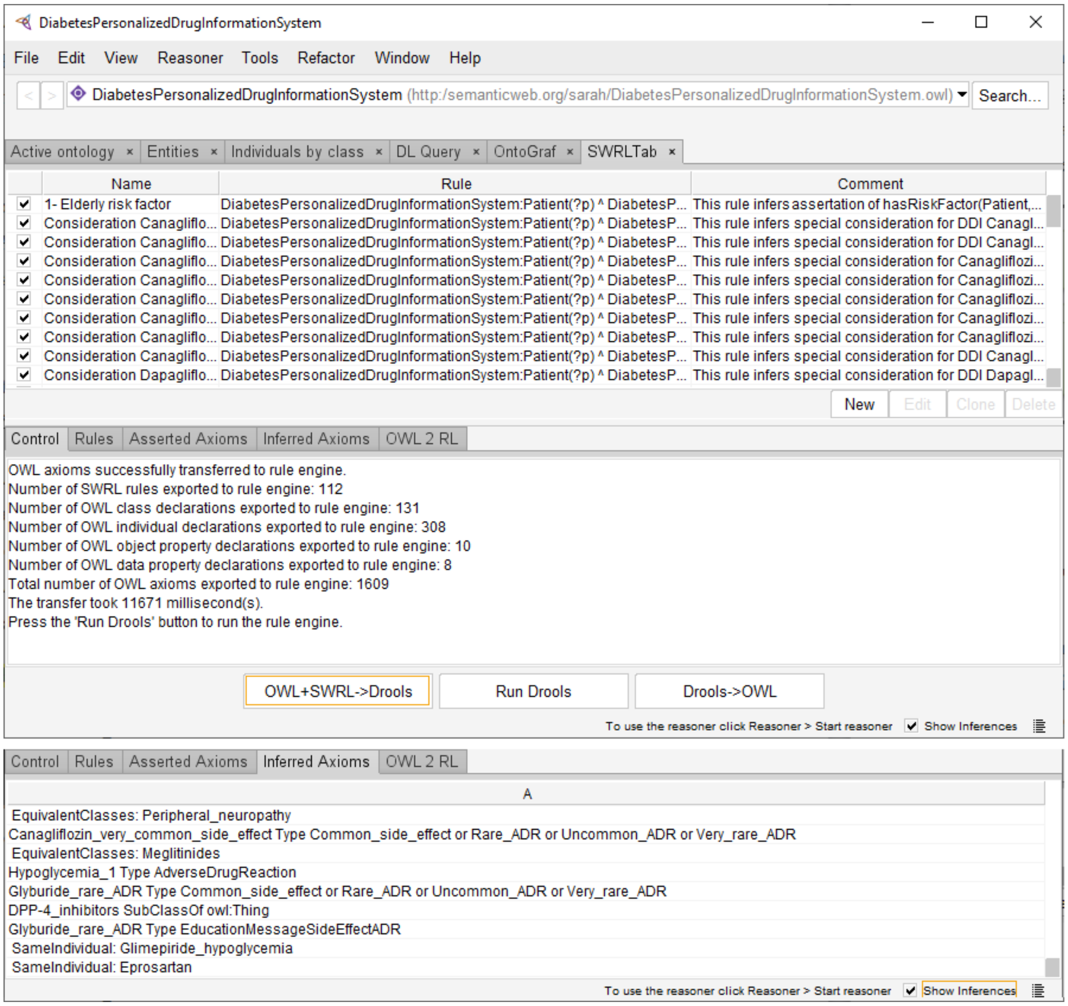


Figure 4-15 Integration of SWRLTab with Drools Rule Engine

Alternately, ontology-based reasoning is another method for reasoning with OWL and SWRL rules. The Pellet reasoner is an example of an OWL reasoner that is bundled with protégé 5.5. Pellet is a description logic reasoner, and since OWL is also constructed on the basis of description logic, Pellet is widely used to reason with OWL ontologies combined with SWRL rules [139].

We investigated the comparison between Drools-based reasoning and ontology-based reasoning in the literature to determine the appropriate approach for performing reasoning in our proposed system. For smaller numbers of rules, the Pellet reasoner is reported to execute the rules much faster than the Drools rule engine [140]. It is suggested that the Drools rule engine is better suited for large environments with complex domain knowledge because of its scalability and performance [140].

Similarly, Van Hille *et al.* compare these two reasoning approaches for the domain of cardiology taking into consideration different criteria. Similar to the previous study, Pellet-based reasoning ranks higher in terms of execution time [141].

One of the advantages of the Pellet reasoner is easy traceability of the executed rules with an explanation of how the new inferences are derived [139]; in contrast, a certain level of customization is required with Drools to provide a reasoning explanation. Since Pellet is a description logic reasoner, it can conveniently deduct subsumption relations in the ontology without having to require explicit rules. In contrast, formulation of subsumption relations will translate into multiple rules in Drools. Therefore, while Drools is a good solution for scaling up, maintaining the number of Drools rules may become challenging for ontologies with higher levels of granularity [141].

For those reasons, we chose to employ ontology-based reasoning and in particular the Pellet reasoner as the reasoning engine for our proposed KBS. Figure 4-16 shows the schematic view of how the Pellet performs the reasoning with the OWL ontology and SWRL rules. It combines the domain-related knowledge that is formally described in the ADM ontology along with the inference logic that is expressed in SWRL to draw conclusions on appropriate patient-specific medication information.

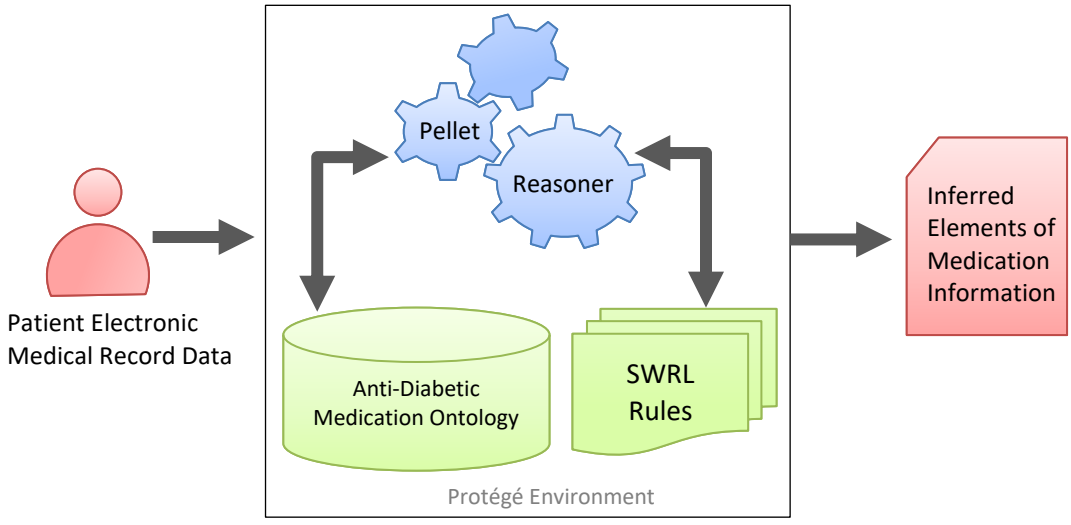


Figure 4-16 Ontology-Based Reasoning with OWL Ontologies and SWRL Rules

The reasoning process in DPDⓘS comprises execution of three sets of rules to derive the three personalized segments of medication information for patients including:

1- Inferring side effects and ADRs related to the patient's prescribed antihyperglycemic medication.
2- Inferring potential DDIs based on the patient's drug regimen.
3- Inferring appropriate risks and consideration based on the patient's risk factors.

To demonstrate the reasoning process in DPDⓘS, consider an elderly patient with T2DM and hypertension who is taking metformin for lowering blood sugar level and captopril for lowering blood pressure. Figure 4-17 shows the initial property assertions for `patient_02`, an individual of the class *patient*. Once reasoning is invoked in protégé, Pellet will infer new associations based on OWL and SWRL rules (Figure 4-15).

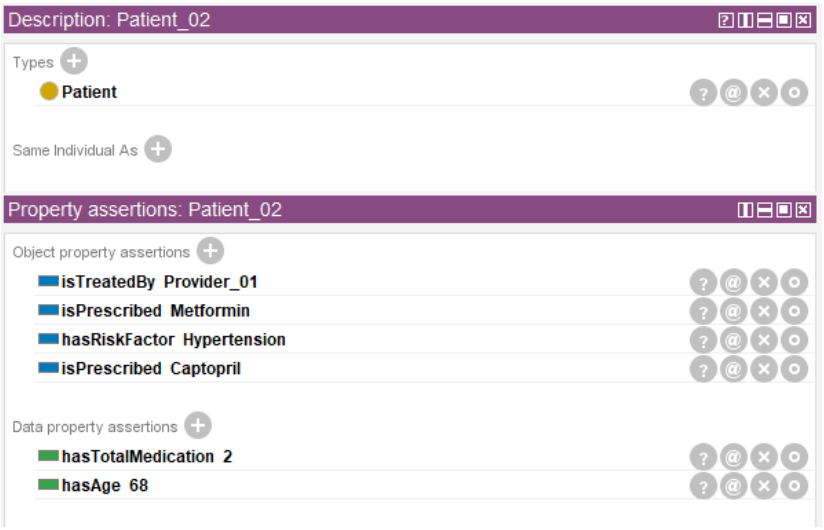


Figure 4-17 Asserted Object Properties (Before Reasoning)

As shown in the Figure 4-17, for the individual `patient_02`, four object properties and two data properties have been asserted in the ontology. When reasoning is completed, seven object properties are inferred and added into the list of object properties for the individual `patient_02` (Figure 4-18).

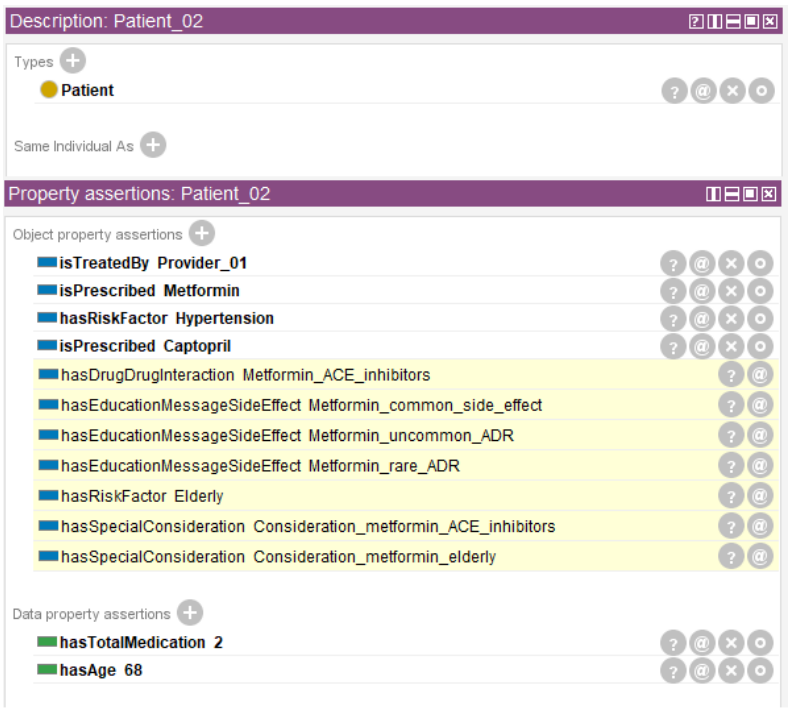


Figure 4-18 Inferred Object Properties (After Reasoning)

In this example, Pellet reasoner inferred the following information:

1- Elderly risk factor for ADRs due to the patient's age
2- The potential drug-drug interaction between metformin and captopril
3- Common sides effects and ADRs for metformin
4- Consideration for the patient concerning the age risk factor and possibility of ADRs
5- Consideration for the patient concerning potential DDIs

The Pellet reasoner derived the above inference by invoking five SWRL rules that are listed in the Table 4-11.

No	SWRL Rule
1	`Patient(?p) ^ hasAge(?p, ?age) ^ swrlb:greaterThan(?age, 65) -> hasRiskFactor(?p,Elderly)`
2	`Patient(?p) ^isPrescribed(?p,Metformin) -> hasEducationMessageSideEffect(?p,Metformin_common_side_effect) ^ hasEducationMessageSideEffect(?p,Metformin_uncommon_ADR) ^ hasEducationMessageSideEffect(?p,Metformin_rare_ADR)`
3	`Patient(?p) ^ isPrescribed(?p,Captopril) ^ swrlb:notEqual(?Total_med, 1) ^ isPrescribed(?p,Metformin) ^`

No	SWRL Rule
	`hasTotalMedication(?p, ?Total_med) -> hasDrugDrugInteraction(?p,Metformin_ACE_inhibitors)`
4	`Patient(?p)^ hasDrugDrugInteraction(?p,Metformin_ACE_inhibitors) -> hasSpecialConsideration(?p,Consideration_metformin_ACE_inhibitors)`
5	`Patient(?p) ^ isPrescribed(?p,Metformin) ^hasRiskFactor(?p,Elderly) -> hasSpecialConsideration(?p,Consideration_metformin_elderly)`

Table 4-11 Subset of SWRL Rules Used for Reasoning

Rule #1 will add the value of `Elderly` to the `hasRiskFactor` property for all those individuals of the class `Patient` who have the 65 and over for the value of the `hasAge` property. Rule #2 will derive generic side effects and ADRs for the drug metformin. Rule #3 will infer the potential DDIs between the metformin and captopril drugs. Rule #4 and #5 use the previously inferred associations as part of antecedent and if they are true, considerations for patients will be deduced given patient-specific risk factors.

The Pellet reasoner can show the logical steps it takes to reach a certain conclusion concerning each new inference. In other words, it provides proof of the reason an object property is inferred. For the above mentioned example, Pellet concluded seven object properties. Figure 4-19 shows the logic behind the inference of one of the object properties, the `hasDrugDrugInteraction` property to the individual `patient_02` with the value `Metformin_ACE_inhibitors`.

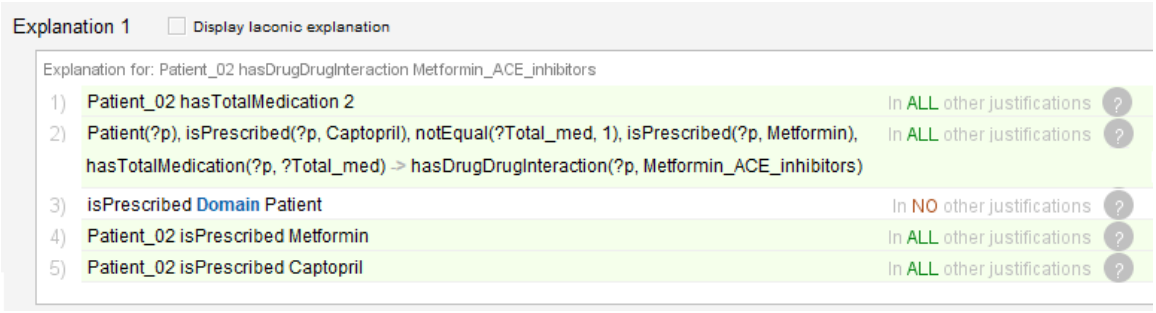


Figure 4-19 Logical Steps Taken to Infer Property Metformin_ACE_inhibitors

As shown in Figure 4-19, to make such an inference, Pellet has utilized:

- `hasTotalMedication` data property as shown in line #1 in the above figure
- One SWRL rule as shown in line #2 in the above picture
- `isPrescribed` object property as shown in line #4 and #5

- Two individuals from class `PrescriptionDrug`, namely `Metformin` and `Captopril`

4.2.4. Improvement to the Ontology of Drug Adverse Event

When reviewing existing ontologies, the ontology of drug adverse events [124] was analyzed. One of shortcomings about the way in which adverse events and drugs are represented in their ontology is the lack of representation for descriptive qualifiers about the adverse events. To better show the problem and the solution that is provided in the ADM ontology, Figure 4-20 presents each relation with top showing the object properties of `diarrhea AE` class from ODAE and the bottom one showing `Diarrhea` class from the ADM ontology. In ODAE, the severity of the adverse event is represented through separate object property `has participant quality` whereas in the ADM ontology, the descriptive quality of "common" is encapsulated within the relationship of metformin and diarrhea due to the n-ary design of the relation.

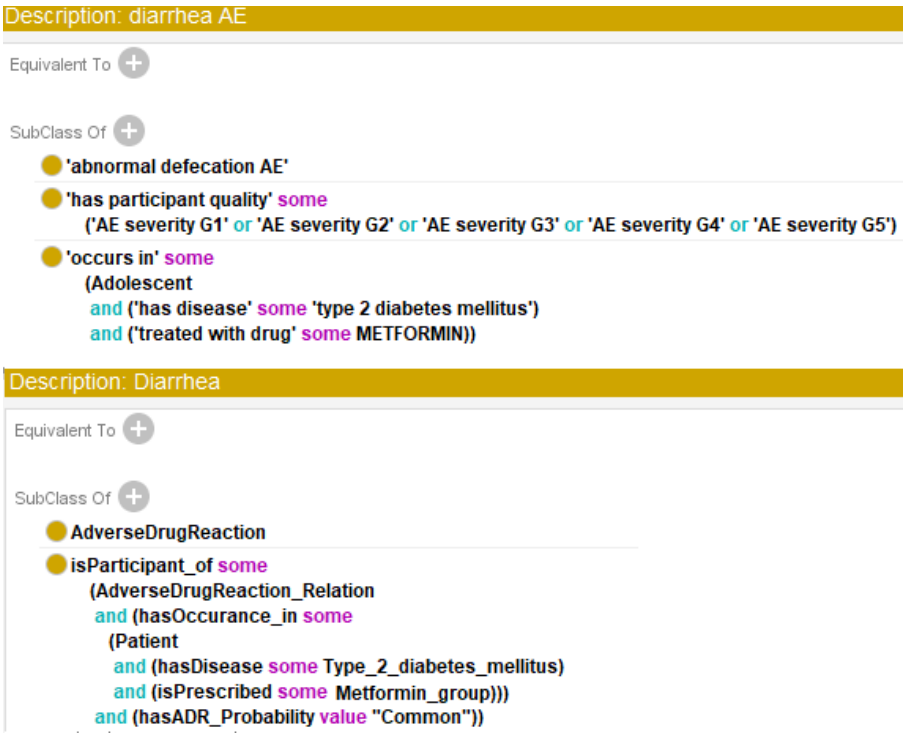


Figure 4-20 ADM Ontology versus Ontology of Drug Adverse Events

4.3. *Development of the Diabetes Personalized Drug Information System*

The final step in design and development of our proposed web-based KBS was to build the physical application of DPDⓘS. To build the physical application, the Python programming language along with Flask as a web framework was utilized. To handle the ADM ontology within Python, we used Python library Owlready2. Owlready2 is an updated module for ontology-oriented programming compared to the previous version, Owlready. It allows users to load OWL ontologies as Python objects, modify them and perform reasoning with Pellet reasoner in addition to HermiT, which was the only reasoner available in the Owlready version. Figure 4-21 shows the architecture of Owlready as presented in the original paper by Jean-Baptiste Lamy [142].

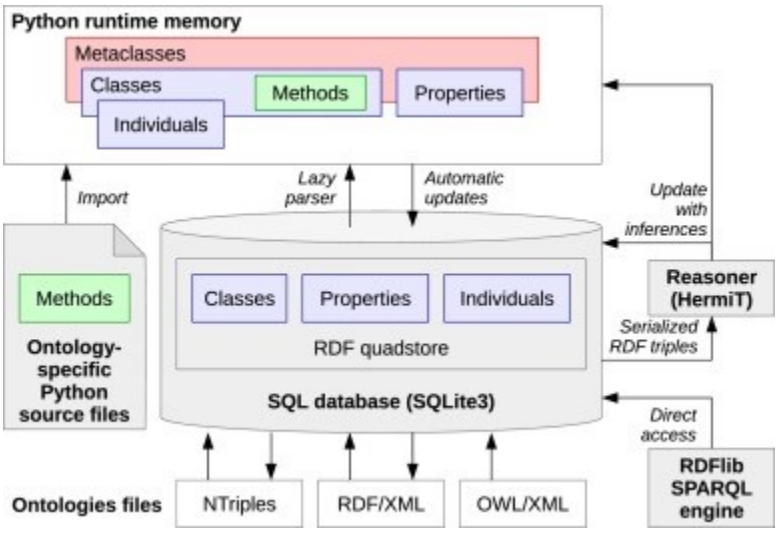


Figure 4-21 General Architecture of Owlready; Taken from [142]

As shown above, the Owlready module consists of five components: 1) resource description framework (RDF) database for storage and retrieval of triples, 2) metaclasses for OWL classes and constructs, 3) ontology-specific source files if they are needed, 4) the HermiT or Pellet reasoner, and 5) a query engine to access the RDF database. When an ontology is accessed in Python via Owlready, it is loaded to the memory from the RDF database and is wrapped in a Python object. If the Python object encapsulating the ontology is modified with changes in classes, properties or individuals, the underlying RDF database is updated by means of adding, removing or modifying the RDF triples [142].

The ADM ontology is created in OWL-DL in Protégé. To access the ADM ontology in Python, first we exported it as RDF format because Owlready2 supports the ontology file format of RDF/XML.

As explained, the imported ontology is wrapped in a Python object. Therefore, accessing classes, properties and individuals follows similar syntax as the object-oriented programming style via using dot notation [142]. For instance, once we imported the ADM ontology as RDF format and loaded it in `onto` object in Python, we were able to access the class `PrescriptionDrug` by using `onto.PrescriptionDrug`. Similarly, other constructs in the ADM ontology can be accessed the same way. The GitHub documentation on Owlready2 was reviewed for better understanding of features offered by Owlready2 module [143].

4.3.1. Presentation Layer

The presentation layer is responsible for presenting the result of personalization of medication information to patients. We used Python and Bootstrap templates to develop the interface and the forms for DPDⓘS. Bootstrap can be conveniently incorporated with the Flask web framework.

To better demonstrate the DPDⓘS interface, consider the following example adapted from case studies available on the Diabetes Canada website [144] (formerly known as Canadian Diabetes Association):

> *Johnathan is an 86-year-old obese man who has had type 2 diabetes for 3 years. His blood pressure is 132/83 mmHg and his physical exam is otherwise normal. He is currently on the following meds*:
>
> - *metformin 500mg* *2 tablets twice daily*
> - *alogliptin 5mg* *2 tablets twice daily*
> - *hydrochlorothiazide 10mg* *1 tablet daily*
> - *lisinopril 2.5mg* *1 capsule daily*

The first screen of DPDⓘS interface is the patient search screen as shown in the following figure. It searches through the list of patients that is prepopulated into a SQLite database.

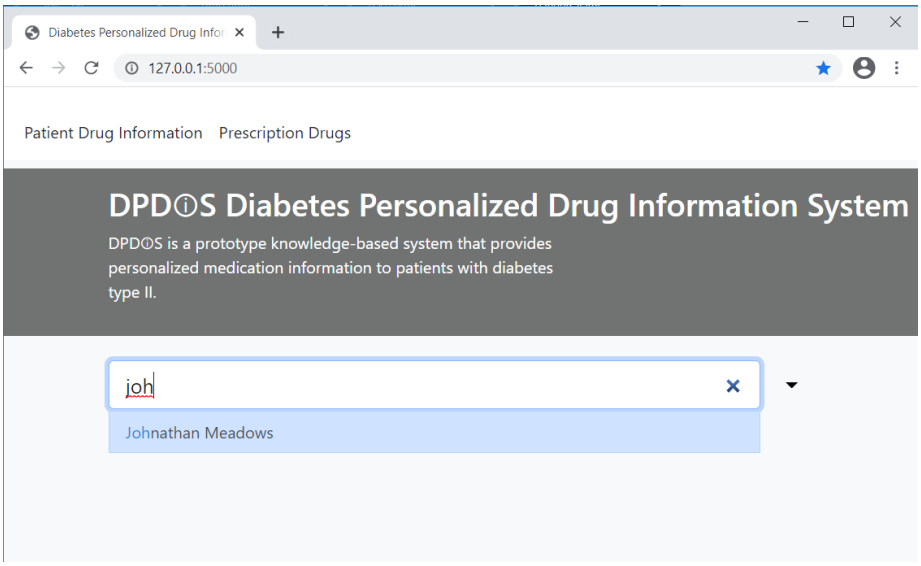


Figure 4-22 Patient Search Screen

Once the patient is selected from the drop down box, the next screen consists of four sections. The first part shows a summary of patient's characteristics that are relevant to providing medication information. The second section highlights points of consideration for patients regarding the possibility of ADRs given their individual situation. In this example, the patient is taking lisinopril and hydrochlorothiazide as diuretics for hypertension, and metformin and alogliptin to manage T2DM. Since the patient is over 65 years of age, DPDⓘS shows elderly as one of the risk factors for this patient. Given the patient's risk factors, medical conditions and other prescription drugs, DPDⓘS generates a list of potential ADRs with his drug regimen. The type of risk factor associated with each ADR is presented at the top along with a small description, explaining how the risk factor affects the occurrence of that specific ADR. For instance, the risk of lactic acidosis is higher among patients with impaired renal function and aging is associated with reduce renal function. Therefore, elderly patients are more susceptible to developing lactic acidosis. The description for each consideration is based on the

results of the knowledge abstraction phase that is discussed earlier. Figure 4-23 shows the patient's profile and the Consideration section of DPDⓘS.

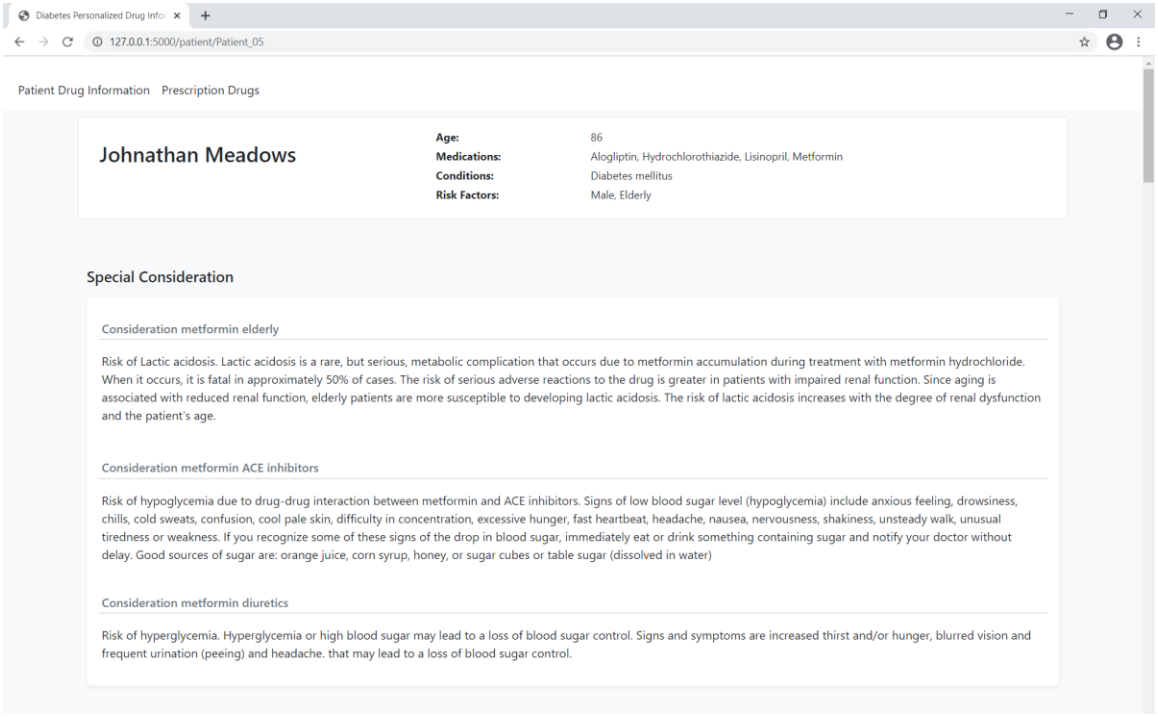


Figure 4-23 Summary of Patient's Profile and Special Consideration

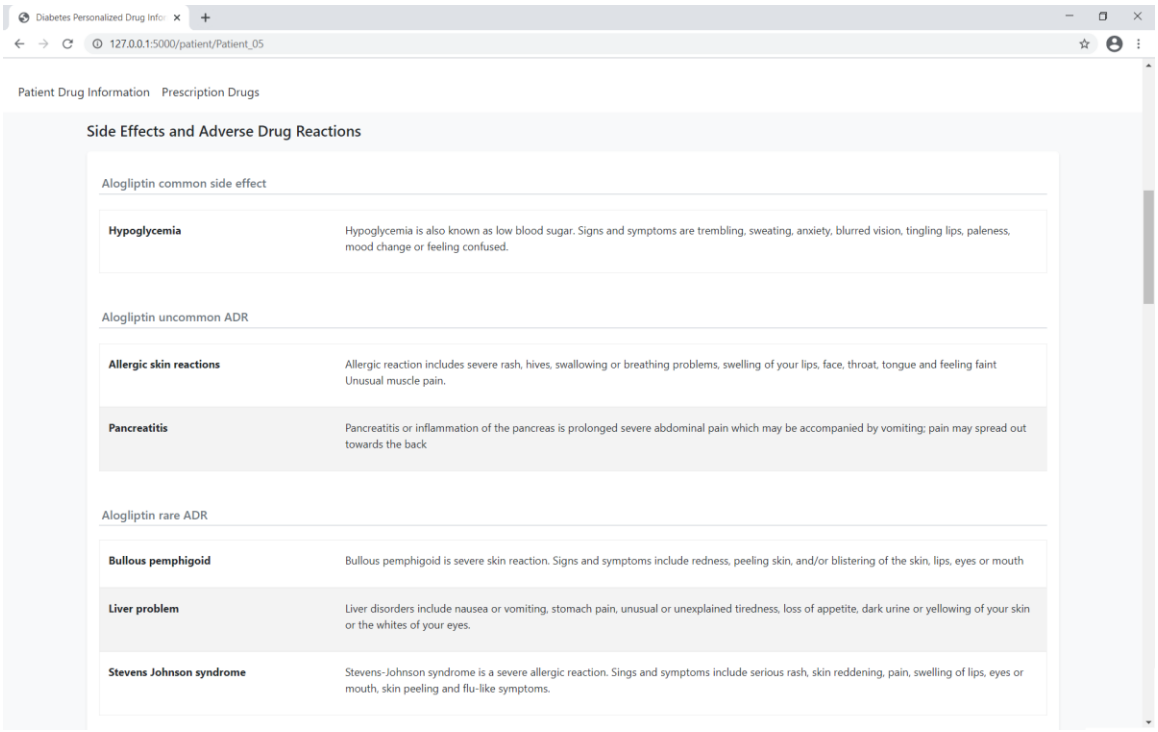


Figure 4-24 Generic Side Effects and ADRs for Alogliptin Drug

It is important to provide patients with basic side effects and ADRs for their medication in addition to personalized information for their drug regimen. Therefore, section two lists the side effects and ADRs with the order of their frequency for each antihyperglycemic drug prescribed for the patient. This is possible due to the ternary relation that is developed in the knowledge base of the system. Figure 4-24 presents the list of side effects and ADRs for the drug alogliptin in the patient's drug regimen. Similar to the previous section, the description for each ADR is an outcome of the knowledge abstraction phase.

The last section for presenting medication information is identification of potential DDIs among the prescribed medications shown in the following figure.

Figure 4-25 Potential DDIs among the Patient's Prescribed Medications

4.3.2. System Architecture

The general architecture of DPDⓘS is presented in Figure 4-26. It includes three layers:

1- Presentation Layer: DPDⓘS is aimed at both primary health care providers and patients. The presentation layer is responsible for the user-computer interaction for the purpose of data presentation. It presents personalized medication information based on the patient's profile and underlying risk factors.

2- Semantic Web Layer: This layer controls all the system operations by performing processes: i) to access to the knowledge model that was built in OWL-DL in the protégé editor; ii) to access patient data that is stored in a SQL database; and, iii) to connect to the interface for presenting medication information to health care providers at the point of care. These processes were explained in greater detail at the beginning of this chapter.

3- Data Layer: This layer serves as a repository for patient data in our prototype DPDⓘS. It contains 40 samples of patient records with information such as patient demographics, medical conditions, medications and other information that are required for the provision of patient medication information.

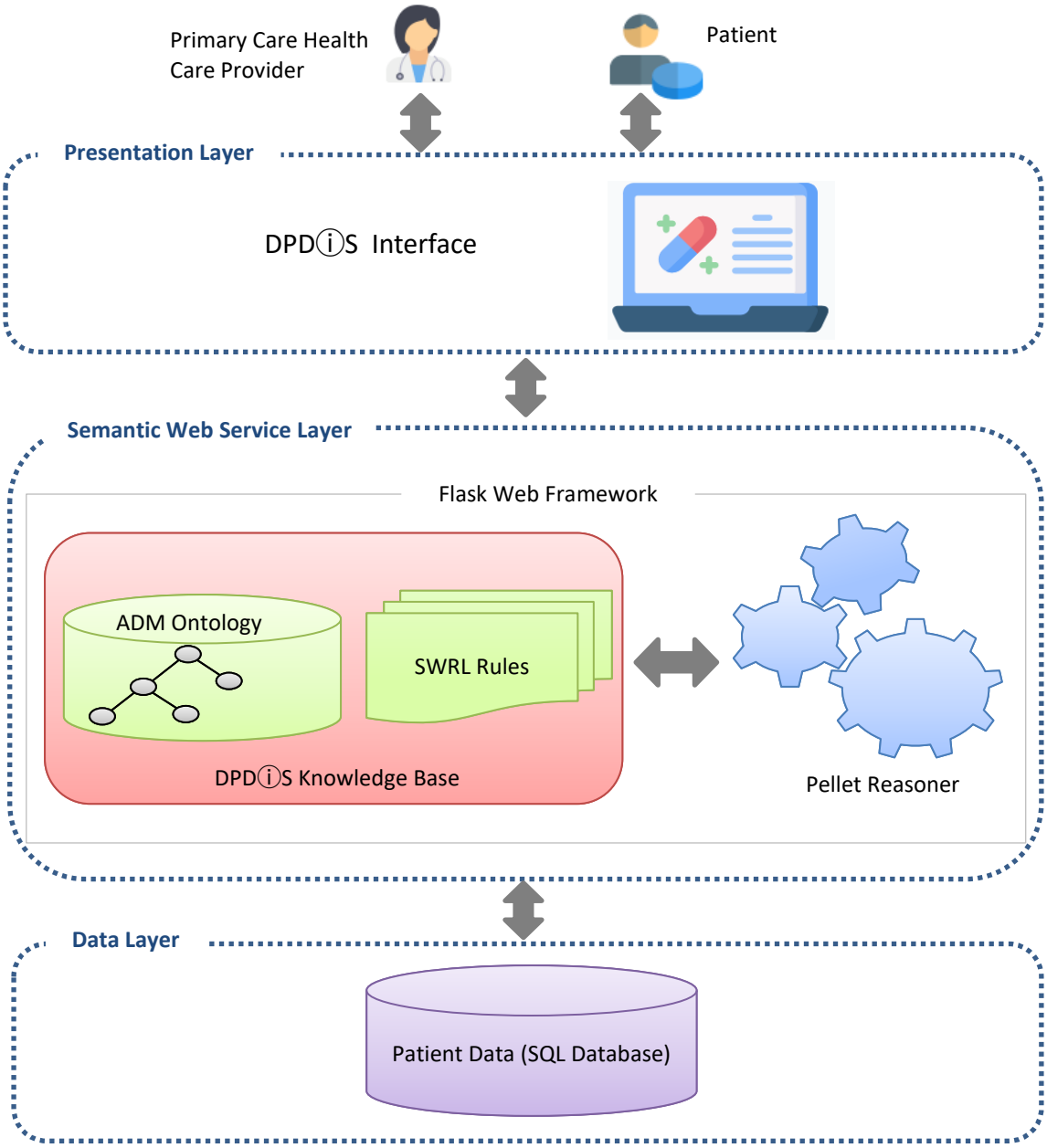


Figure 4-26 Schematic View of DPDⓘS Architecture

CHAPTER FIVE: EVALUATION

5.1. *Evaluation Approach*

DPDⓘS is a proof-of-concept KBS that uses an ontology-based knowledge model along with SWRL rule-based reasoning to provide tailored medication information to patients with T2DM with regard to their anti-diabetic drug regimen. As noted in the research methodology steps (Figure 3-3), the last step in this research is the evaluation of the proposed system. This chapter covers the processes undertaken to evaluate the DPDⓘS.

According to IEEE Standard Glossary of Software Engineering Terminology, verification and validation (V&V) processes are defined as [145]:

> Verification: *"(1) The process of evaluating a system or component to determine whether the products of a given development phase satisfy the conditions imposed at the start of that phase. (2) Formal proof of program correctness"*
>
> Validation: "*The process of evaluating a system or component during or at the end of the development process to determine whether it satisfies specified requirements*."

The verification process essentially investigates whether the product is being built correctly and the validation process addresses the question of whether the correct product is being built. These definitions, however, are for software programs. The architecture of KBS is different from conventional software programs in that they include concepts such as an inference engine, knowledge representation and reasoning. Therefore, the definition of verification and validation for these systems may differ [146].

In the context of KBS, the definition for verification can be adapted to describe the process of evaluating the system to investigate whether or not the requirements that are initially specified are fulfilled by the system. Similarly, validation of a KBS is defined as the process of evaluating the system to investigate whether or not it meets end-user requirements. In the verification process, we aim to determine whether the system is

built based on its formal design specifications and for the validation process, our effort is to determine if the KBS meets the actual needs of the user [147].

Knauf *et al.* characterize the validation process as something that "lies in the eye of the beholder". Figure 5-1 shows the difference between these two concepts and is adapted from the original illustration by Knauf *et al* [148].

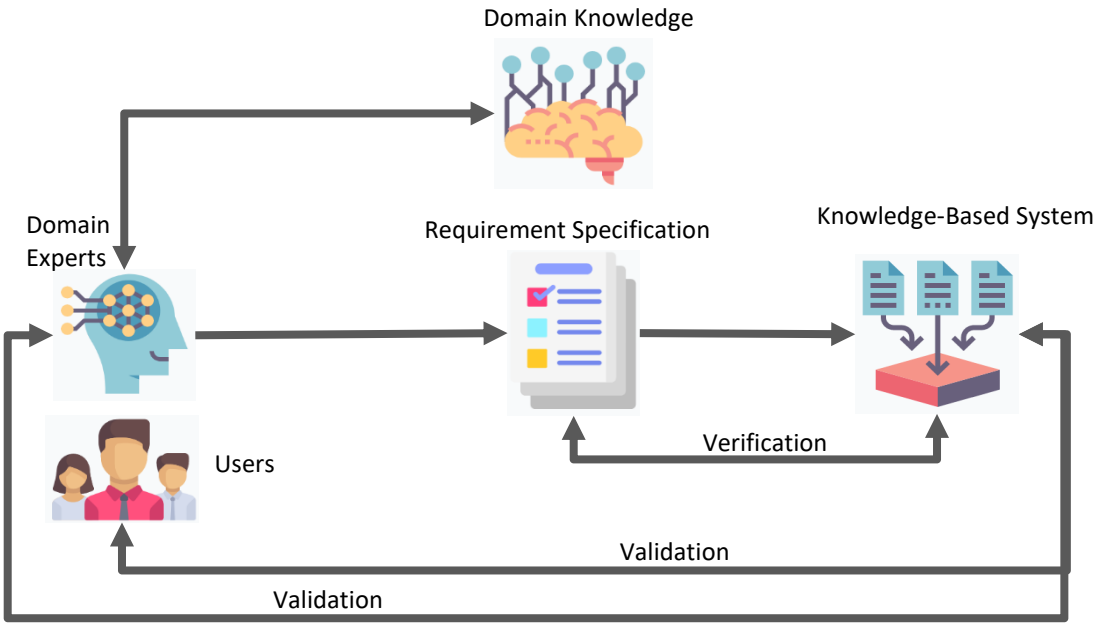


Figure 5-1 Verification and Validation of a KBS; adapted from [148]

To evaluate our proposed system, we focused on the validation process. To this end, we adopted the framework for validation of rule-based systems proposed by Knauf *et al*. [149] which includes the following steps:

1- *Test case generation*: Prepare and generate a set of test cases. In this step, two things need be taken into consideration that seemingly contradicts each other. On one hand, the number of test cases should be high enough to ensure the completeness in coverage for all scenarios. On the other hand, the number of case scenarios should be low enough to allow for efficiency and practical validation.

2- *Test case experimentation:* This step involves executing the prepared test cases by the KBS. Domain experts should then evaluate the correctness of the system's

outputs. Responses from KBS as well as domain experts should be documented for the next step.

3- *Evaluation:* In this step, disparities in results between KBS output and domain experts' opinion will be evaluated to determine errors associated with the KBS outputs.
4- *Validity assessment:* This step concludes the validity of the KBS by analyzing the results from the previous step.
5- *System refinement:* This step involves improving the KBS based on the errors found in the evaluation step.

We had to adapt the abovementioned methodology to fit the context of this research. Knowledge resources to be used for ontology development consists of ontological resources such as previously built ontologies, as well as non-ontological resources such as domain experts' knowledge or existing guidelines about domain knowledge [33]. For non-ontological resources, one can obtain knowledge directly from domain experts through various top-down knowledge elicitation techniques but this approach may not be practical as access to domain experts is often challenging. In this research, we selected the CPS as non-ontological knowledge resource to guide our ontology development efforts. For this reason, we modified the second step in the evaluation methodology described. The generated tests cases were not consulted with domain experts; rather the CPS was used to ensure the correctness of the outputs of the DPDⓘS.

5.2. *Test Case Generations*

A scenario-based approach was used to prepare test cases. The website for Diabetes Canada (formerly known as Canadian Diabetes Association) offers several case studies on drug therapy for T2DM as part of the clinical practice guidlines [144]. As noted in the background section 2.1, the majority of patients with T2DM are on metformin monotherapy. The addition of second antihyperglycemic agent is considered if the glycemic target is not achieved with monothepray of metformin [38]. We split the test cases into two groups. The first group consists of patients with T2DM who are prescribed only metformin medication. The second group comprises patients with T2DM who are on combination therapy, that is, metformin and one or two other antihyperglycemic agents

presented in Table 2-1. To achieve completeness for the test combinations in the first group (metformin monotherapy), several drug-related factors such as interactions between metformin and other drugs along with patient-related factors such as age, underlying medical conditions, and drinking habits were taken into consideration to generate the test cases. These factors will impact the occurrence of ADRs in patients taking metformin. Below is one of the examples for test scenarios used in group one, patients with T2DM who are on metformin monotherapy:

> *Willie is a 65-year-old white woman who was diagnosed with type 2 diabetes 11 years ago. She believes that her diabetes has been fairly well controlled during the past 11 years. Her multiple medical conditions include type 2 diabetes, hypertension, and asthma. Her routine medications include metformin 500mg twice day, the fluticasone metered dose inhaler, two puffs twice a day; captopril 80 mg every morning.*

All test cases were created in MS Excel format before being exported to SQLite database to be executed with DPDⓘS. Figure 5-2 shows a schematic view of different tables that construct the test case corresponding to this example.

(a)

Medication_ID	Patient_ID	Medication_start_date	Medication_end_date	Medication_name	Medication_code	Medication_strength	Measurement_unit	Medication_dose	Medication_frequency	Medication_duration_count	Medication_duration_unit	Medication_dispensed_count	Medication_dispensed_form
63	7	28-Oct-10	14-Feb-11	salmeterol and fluticasone	R03AC02	5	mg	1	QD	90	Day	90	Tablet
64	7	28-Oct-10	14-Feb-11	Captopril	C09AA01	80	mg	1	QD	90	Day	90	Capsule
65	7	01-May-19	01-May-20	Metformin	A10BA02	500	mg	2	BID	90	Day	360	Tablet

(b)

Disease_ID	Patient_ID	Disease_name	Disease_code
9	7	Diabetes mellitus	250
10	7	Essential hypertension	401.9
11	7	Asthma	493

Patient_ID	Birthyear	care_prov	First_name	Last_name	Gender
7	1955	1	Willie	Bennett	M

Figure 5-2 A Test Case (a) Medication Table, (b) Disease and Patient Table

To achieve completeness in test combinations of the second testing group(metformin drug plus second-line antihyperglycemic agents), we followed the recommendation by the diabetes clinical practice guidelines [38] as illustrated in Figure 5-3.

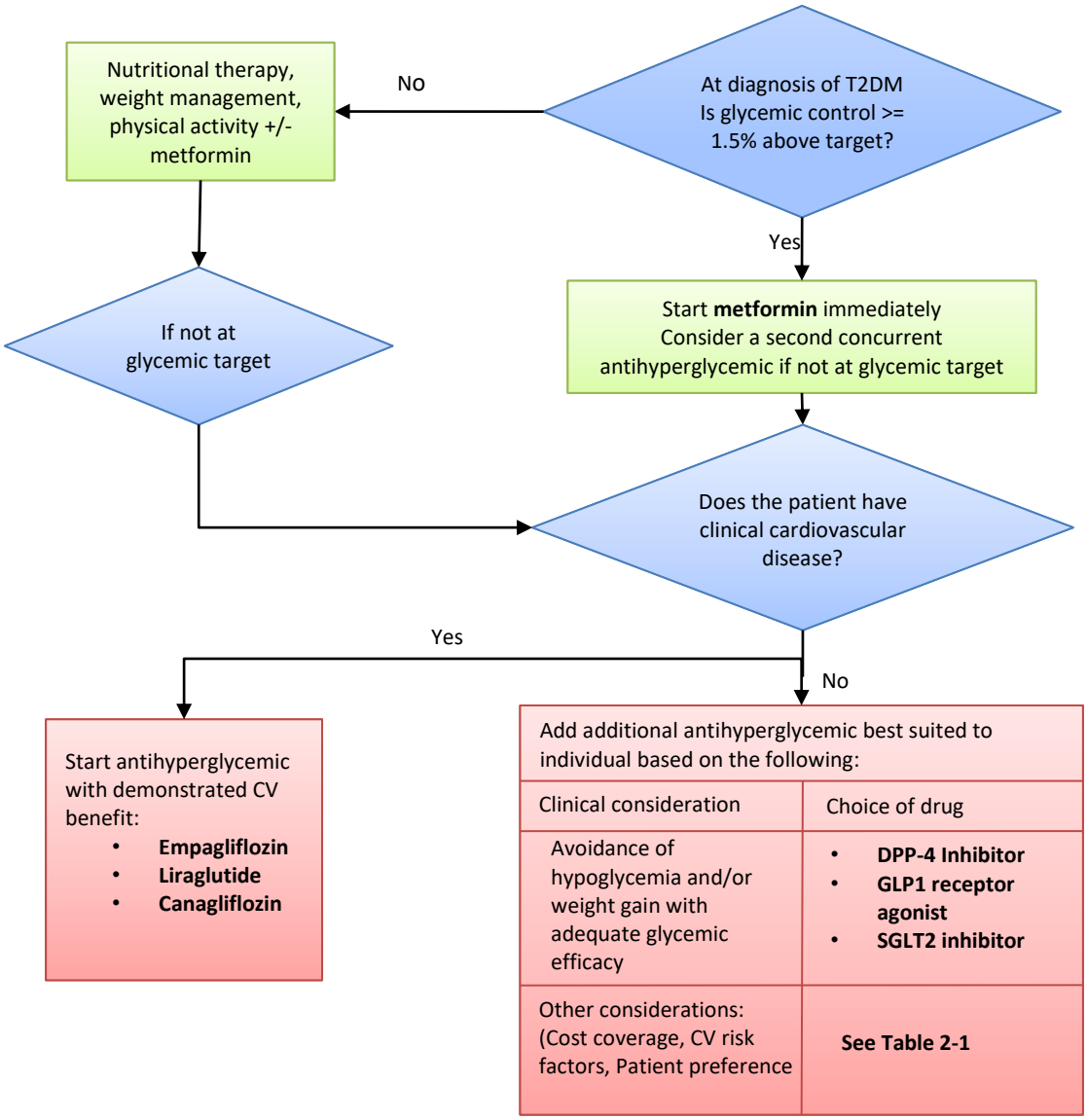


Figure 5-3 Pharmacotherapy in T2DM, adapted from [38]

Following the flowchart recommended by Diabetes Canada clinical practice guidelines [38] as shown in the preceding figure, we tried to generate combinations of metformin plus other antihyperglycemic agents that reflect the reality of the typical T2DM drug regimen as much as possible. For instance, if the patient does not have cardiovascular disease, any medication from drug classes of (DDP-4 inhibitor or GLP1 receptor agonist) and/or SGLT2 inhibitor was used for prescription. Below is an example of test cases used in the second group.

Evan is a 48 year old real estate executive who has had type 2 diabetes for the last 6 years. He has been treated with metformin for 2 years and is now taking 1000 mg bid. He is in for a visit and his A1C is 7.8%. He has no other co-morbidities and your goal A1C for him is < 7.0%. He has been successful at achieving this until now. He cannot think of any change in his lifestyle behaviour that could account for this increase in A1C. His health care provider determines that it is time to initiate a second pharmacologic agent. After considering drug cost, risk of hypoglycemia, effect on his weight, and expected A1C lowering, his health care provider chooses to add sitagliptin 40 mg bid for its low risk of hypoglycemia and weight gain, and long-term cardiovascular (CV) safety.

5.3. *Test Case Experimentation*

Tests cases developed in the MS Excel spreadsheet were exported to SQLite database that would be used as patient data in the data layer of DPDⓘS. To examine the correctness of the DPDⓘS outputs, test cases were evaluated with the evidence-based patient medication information documents offered by the CPS [126]. The results of both DPDⓘS and manual examination with the CPS were documented for evaluation.

5.4. *Evaluation*

Overall 35 cases were executed with DPDⓘS as well as manually evaluated with the CPS documents based on the patient's profile including demographics, medical conditions and concomitant drugs. The total number of tests cases for the metformin monotherapy group was 20 and the combination therapy group (metformin plus second-line antihyperglycemic agents) had 15 test cases.

For the first group, there were three DDIs for which part of the output for DPDⓘS was incorrect. According to the CPS information, thiazide diuretics (e.g., hydrochlorothiazide, indapamide) may interact and decrease antihyperglycemic effect of metformin, leading to hyperglycemia ADRs. However, furosemide drug is a loop diuretic. As a result of interaction between furosemide and metformin, plasma concentrations of metformin may be increased, leading to hypoglycemia ADR. In addition, loop diuretics may increase the

risk of lactic acidosis (too much acid in the blood) due to their potential of decreasing renal function. While DPDⓘS presents the correct risk of ADR for the metformin and thiazide diuretics interaction, it incorrectly categorized the furosemide and metformin interaction. It also missed the increased risk of lactic acidosis as a result of taking furosemide. The second DDI that was missed by DPDⓘS was the interaction between the corticosteroid medication class and metformin which may decrease antihyperglycemic effect of metformin and potentially lead to hyperglycemia ADR. These incorrect interactions occurred in 5 cases.

For the second group of test cases (metformin plus second-line antihyperglycemic agents), there was one scenario in which an increased risk of diabetic ketoacidosis, a rare but serious ADR that is seen with SGLT2 inhibitors, was missed by the DPDⓘS. According to the CPS, high alcohol consumption can precipitate diabetic ketoacidosis in patients taking dapagliflozin. The potential influence of high alcohol consumption on other medications in the SGLT2 inhibitors drug class had already been covered with SWRL rule #92 and SWRL rule #100 in Appendix B. The missing relationship between alcohol and dapagliflozin occurred in two cases. Altogether, there were 7 cases out of 35 for which DPDⓘS outputs did not match the information on CPS thoroughly.

Figure 5-4 shows the medication information elements in DPDⓘS in comparison with CPS evidence-based information. Color coding is utilized to illustrate the elements of information that DPDⓘS failed to identify. As shown in Figure 5-4, cells with green background color indicate a correct match between DPDⓘS outputs and CPS information. Cells with red background color reflect a failed outcome by DPDⓘS. This means that either the information was incorrectly shown to the patient, as in the case of the furosemide and metformin interaction, or there was lack of information in the areas where the system should have provided education to the patient, as in the case of increased risk of diabetic ketoacidosis ADR with alcohol consumption.

(a)

Patient_ID	DPDⓘS ouputs		
	Side effects/ADRs	DDIs	Considerations
15	metformin common side effects metformin uncommon ADR metformin rare ADR	metformin-diuretics	consideration-metformin-alchohol consideration-metformin-elderly
21	metformin common side effects metformin uncommon ADR metformin rare ADR	metformin-diuretics metformin-ACE interactions	consideration-metformin-elderly consideration-metformin-ACE
31	metformin common side effects metformin uncommon ADR metformin rare ADR glyburide common side effects glyburide uncommon ADR glyburide rare ADR glyburide very rare ADR dapagliflozin common side effects dapagliflozin uncommon ADR dapagliflozin rare ADR dapagliflozin very rare ADR	dapagliflozin-sulfonylureas	consideration-metformin-alchohol consideration-dapagliflozin-sulfonylureas

(b)

Patient_ID	CPS consultations		
	Side effects/ADRs	DDIs	Considerations
15	metformin common side effects metformin uncommon ADR metformin rare ADR	metformin-furosemide	consideration-metformin-alchohol consideration-metformin-elderly consideration-metformin-furosemide-hypoglycemia consideration-metformin-furosemide-lactic-acidosis
21	metformin common side effects metformin uncommon ADR metformin rare ADR	metformin-diuretics metformin-ACE interactions metofrmin-corticosteroids	consideration-metformin-elderly consideration-metformin-ACE consideration-metformin-corticosteroids
31	metformin common side effects metformin uncommon ADR metformin rare ADR glyburide common side effects glyburide uncommon ADR glyburide rare ADR glyburide very rare ADR dapagliflozin common side effects dapagliflozin uncommon ADR dapagliflozin rare ADR dapagliflozin very rare ADR	dapagliflozin-sulfonylureas	consideration-metformin-alchohol consideration-dapagliflozin-sulfonylureas consideration-dapagliflozin-alchohol

Figure 5-4 Evaluation between (a) DPDⓘS Results and (b) CPS Consultation

5.5. *Validity Assessment*

We calculated the accuracy of the DPDⓘS based on the following formula:

$$Accuracy = \frac{\text{Number of DPDⓘS decisions that matched the gold standard of CPS}}{\text{Total number of DPDⓘS decisions}} * 100\%$$

Overall, 27 cases out of 35 completely matched the result of manual evaluation with the CPS. Therefore, our prototype system reached an accuracy of 77%, that is, DPDⓘS was

able to correctly provide personalized medication information for 77% of anti-diabetic drug prescriptions.

5.6. *System Refinement*

Based on the results of the evaluation step, appropriate SWRL rules were developed and added to the ADM ontology to address the failed outputs by DPDⓘS. These rules determine the interaction between metformin and furosemide, between metformin and the corticosteroid medication class, and the influence of alcohol on dapagliflozin. Upon improvement of the SWRL rules, DPDⓘS was executed again and all test cases matched the results of the CPS information.

Drug-Drug Interactions Rules	
No	**SWRL Rule**
1	Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p, Furosemide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Metformin_loop _diuretics)
2	Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p, Hydrocortisone) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Metformin_corticosteroids)
3	Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p, Prednisolone) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Metformin_corticosteroids)
4	Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p, Dexamethasone) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Metformin_corticosteroids)
5	Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p, Betamethasone) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Metformin_corticosteroids)
6	Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p, Fluocinolone) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Metformin_corticosteroids)
Special Consideration Rules	
No	**SWRL Rule**
1	Patient(?p) ^hasDrugDrugInteraction(?p, Metformin_loop _diuretics) -> hasSpecialConsideration(?p,Consideration_metformin_loop _diuretics)
2	Patient(?p) ^hasDrugDrugInteraction(?p, Metformin_corticosteroids) -> hasSpecialConsideration(?p,Consideration_ metformin_corticosteroids)
3	Patient(?p) ^ isPrescribed(?p, dapagliflozin)

^hasRiskFactor(?p,Binge_drinking) -> hasSpecialConsideration(?p,Consideration_dapagliflozin_alcohol)

Table 5-1 Addition of the SWRL Rules for Improving the System

CHAPTER SIX: DISCUSSION AND CONCLUSION

6.1. *Discussion*

In this research, efforts were taken to improve representation and organization of elements of medication information that are sought by patients. There is an unmet information need related to patients' drug regimen. Patients are not being educated about all aspects of their prescription drugs by their HCPs at the point of care. This thesis helps fill this gap by proposing a novel solution to providing personalized medication information to patients diagnosed with T2DM by means of a proof-of-concept KBS called DPDⓘS.

To this end, a knowledge management approach was undertaken to formally specify the semantics of T2DM medication-related information through a high level knowledge model using an ontology-based modeling approach. As a result, we introduced the ADM ontology, a reusable ontology model focusing on diabetes medication and aspects of drug information topics that are requested by patients with T2DM. Through ADM ontology we explicitly represented the concepts and relations that would affect certain elements of medication information that are expected to be provided to patients.

Our contribution to the field of patient education on medication information includes the introduction of the DPDⓘS knowledge base that was developed as a result of a comprehensive knowledge management approach using information available in the literature, evidence-based resources such as the CPS, and a review of previously developed ontologies in the domain knowledge. The methods used in this research can be applicable across all prescription drugs and for other chronic conditions. The knowledge base of DPDⓘS provides a robust platform for semantic and logic representation of patient medication information that could accommodate additional classes of drugs prescribed for other chronic conditions. Thus, DPDⓘS knowledge base can be shared and reused by other KBSs aimed at providing individualized medication information to patients with other chronic conditions.

The main novelty in our research lies in personalization of content for patient medication information. To tailor information for patients, a set of personalization rules were developed in SWRL. These rules determine the appropriate information components to be presented to the patient by taking into consideration the concepts and relations specified in the ADM ontology including patients' demographics, underlying medical conditions, concomitant drugs and other risk factors. SWRL rules together with the ADM ontology provide the knowledge model and reasoning needed for the DPDⓘS. The reasoning of DPDⓘS is based on a description logic reasoner called Pellet.

The evaluation of DPDⓘS demonstrated an accuracy of 77% and identified areas of improvement in the system. Based on the results of the evaluation, nine additional SWRL rules were developed for the system to address the identified failed outputs. Further evaluation with domain experts as well as patients with T2DM would certainly strengthen the validity of our system. It is our hope that the health informatics solution proposed in this research can enable HCPs to increase patient involvement during clinical visits in which patients can ask questions regarding their prescribed medication. In addition, the patient-centered approach undertaken in our proof-of-concept system can possibly encourage patients' questions during their visits; thus enhancing patient-provider communication.

6.2. *Limitation*

One of the limitations in this research is the validation of the ADM ontology by the domain expert. Suarez-Figueroa *et al.* [150] defines the validation of ontologies as the process that compares the meaning of the ontology concepts and relations against what was originally intended to be conceptualized in the domain knowledge. In other words, ontology validation aims to answer the question of whether the right ontology is being built. Ontology verification, on the other hand, compares the ontology against the ontology requirement specification document to ensure that the ontology is being built correctly [150]. Our research is limited in that access to domain experts was not feasible to validate the developed ADM ontology.

Another limiting factor is the usage of case studies to assess the validity of our system. We found a number of case studies available on the Diabetes Canada website as part of the educational resources for HCPs and patients. We then followed recommendations offered by Diabetes Canada's clinical practice guidelines [38] for prescribing correct antihyperglycemic agents to generate several test cases of anti-diabetic drug regimens that are as close to reality as possible. Despite significant efforts, these test cases do not fully reflect the prescriptions that are prescribed by physicians for patients with T2DM in electronic medical records. Therefore, we were not able to validate the DPDⓘS with real prescription data as would have required research ethics approval.

6.3. *Future Work*

DPDⓘS provides personalized information regarding risks and considerations associated with individual drug regimens for patients with T2DM. Our hope is that by providing tailored information to patients' individual needs, we can enhance understanding and knowledge of diabetes medication. Therefore, future work needs to be done to evaluate the effectiveness of the tailored medication information provided to patients and how it affects the level of their medication knowledge concerning their anti-diabetic drug regimen. A patient-centered drug and therapy information center was designed by Maywald *et al.* where patients could use telephone services to inquire about their medications [94]. They evaluated the effect of their service by means of follow-up feedback questionnaires to patients. Based on their analysis, 68% of the callers indicated that they are more informed and have more self-confidence in dealing with their prescribed medication [94]. A similar study could be conducted with DPDⓘS.

Literature suggests that readability of materials designed for patient consumption should not be more than eighth grade [151]. However, patient educational materials available on government-funded websites such as MedlinePlus as well as on commercial websites such as WebMD and Mayo Clinic rank above the reading level recommended by the literature, with the former ranking slightly higher than the latter [152]. As noted in the methods section, the textual information provided in our system is abstracted from patient medication information documents offered by the CPS. Despite these documents having been designed for patient consumption, they often include medical vocabularies that

might be challenging to comprehend for patients with lower levels of health literacy. A usability study is required to examine the readability level of the information provided by DPDⓘS to ensure it is suitable for various levels of health literacy among patients with T2DM. Based on the results of the assessment, further efforts should be made to ensure that medication information communicated via DPDⓘS is easy for patients to comprehend.

Patients tend to be concerned about adverse effects of their newly prescribed medication. It is reported in the literature that good patient-provider communication can address patients' fears and assure them of the benefits of their therapeutic plan [26]. DPDⓘS supports HCPs with a point-of-care solution to guide the discussion on medication information with their patients. Future research can be done to evaluate patient-provider communication using DPDⓘS and assess whether the proposed solution improves communication at the time of visit for patients and provider with regard to diabetes medication information.

6.4. *Conclusion*

This research took a patient-centered approach and proposed an ontology-driven solution to provide patients with personalized medication information about their prescribed anti-diabetic drugs. In our study, we established the role that formal representation of patient medication information can play in a KBS with the purpose of providing patient-specific drug information. Our proposed KBS reached an accuracy of 77% in providing tailored medication information for anti-diabetic drug regimens.

The gap between the amount of medication information desired by patients and information provided to them by HCPs during office visits has resulted in unmet drug information needs for patients. Despite acknowledgement of the significance of patient medication knowledge and its relation to medication adherence [25], health informatics interventions providing personalized medication-related information are sparse. Current health technology solutions including Diabetes Canada's drug information sheets, as well as consumer health information websites such as WebMD and MedlinePlus offer general information about drugs including uses, instructions, side effects, and ADRs. They do

not, however, differentiate ADRs under specific patient-related factors including patient age, patient chronic conditions or drug-related factors including types of concomitant medications taken by patients.

To help fill this gap, our study undertook a knowledge management approach to formally represent the concepts and relationships between them with regard to specific elements of medication information including side effects, ADRs and DDIs for oral antihyperglycemic drugs that are used in pharmacotherapy of patients with T2DM diabetes. The result was the introduction of the ADM ontology. We demonstrated the usage of the ADM ontology by means of design and development of a proof-of-concept KBS called DPDⓘS with the goal of providing personalized medication information about ADRs and DDIs to patients with T2DM about their anti-diabetic drug regimen.

Given different patient-related and drug-related factors, the ADRs induced by the drug may vary. The architecture of the DPDⓘS uses the ADM ontology and SWRL rule-base to personalize medication information. Our system offers general information about potential side effects and ADRs caused by antihyperglycemic drugs based on the frequency of their occurrence. In addition, it tailors the information based on the patient's profile considering underlying chronic conditions, concomitant of drugs and other risk factors such as age and drinking habits. The reasoning engine of DPDⓘS employs the knowledge base to present patient-specific considerations related to the patient's anti-diabetic drug regimen.

The evaluation results demonstrated the technical feasibility and the application prospect of our solution to support HCPs with individualized and evidence-based information which in turn can be used to educate patients with T2DM on their prescribed medications at the point of care. While patients can seek medication-related information from a variety of sources outside of their HCPs office including pharmacists and online resources, HCPs remain patients' preferred source of information [24]. DPDⓘS can be utilized as a support tool to guide conversations between HCPs and patients concerning their diabetes drug regimen to better achieve shared decision making. Further study is

required to assess the usability of DPDⓘS by HCPs and to examine whether it improves patient-provider communication.

In addition, research has shown that prior knowledge about common ADRs, and their signs and symptoms especially in the elderly population will assist with early recognition of the ADRs. However, most elderly patients are not able to accurately identify ADRs in part due to lack of education on the subject matter [153]. Our research demonstrated that DPDⓘS is a proof-of-concept point-of-care solution to thoroughly inform patients about common and rare ADRs associated with their anti-diabetic medications. Furthermore, DPDⓘS provides tailored information about the risk of development of ADRs based on the patient's individual characteristics.

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APPENDIX A: METFORMIN INFORMATION SHEET OFFERED BY DIABETES CANADA

Biguanide

Type of drug	Biguanide
How does it work?	• Helps lower the amount of sugar (glucose) that your liver releases into the blood • Helps make it easier for your body to use insulin
Typical names	Metformin (Glucophage®), Long Acting Metformin (Glumetza®)
Usual doses	Metformin 500 to 2550 mg in single or divided doses
Dosing instructions	• The total daily dose is usually divided, and taken with food, for regular release metformin • Take once a day for long acting metformin, usually with evening meal
What if I forget a dose?	Ask your healthcare provider
A1C lowering (↓ = least, ↓↓↓ = most)	↓↓
Effect on weight	Neutral
Risk of low blood sugar (hypoglycemia)	Rare
Medication considerations and/or side effects	• Stomach upset such as, gas, diarrhea, and/or constipation (These side effects often improve over time and can be minimized by starting with a lower dose, then increasing it slowly to the desired dose)
When to call your doctor	• You are not tolerating the side effects, have developed kidney or liver complications or are being scheduled for tests involving radioactive dye (e.g. bone scans or kidney x-rays) • You develop any severe side effects and any negative changes in your overall health, talk to your health care provider
When you are sick	• You are sick, vomiting, have diarrhea, or cannot drink enough fluids, you should stop this medication until these symptoms go away • Check your blood sugar levels more often, and drink lots of fluids so you do not become dehydrated
Cost ($ = lowest, $$$$ = highest)	$

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APPENDIX B: LIST OF SWRL RULES USED IN DPDⓘS

No	SWRL Rule
	Side Effects Related Rules
1	Patient(?p) ^ isPrescribed(?p, Metformin) -> hasEducationMessageSideEffect(?p,Metformin_uncommon_ADR) ^ hasEducationMessageSideEffect(?p,Metformin_common_side_effect) ^ hasEducationMessageSideEffect(?p,Metformin_rare_ADR)
2	Patient(?p) ^ isPrescribed(?p, Alogliptin) -> hasEducationMessageSideEffect (?p,Alogliptin_common_side_effect) ^ hasEducationMessageSideEffect (?p,Alogliptin_uncommon_ADR) ^ hasEducationMessageSideEffect (?p,Alogliptin_rare_ADR)
3	Patient(?p) ^ isPrescribed(?p, Canagliflozin) -> hasEducationMessageSideEffect (?p,Canagliflozin_very_common_side_effect) ^ hasEducationMessageSideEffect (?p,Canagliflozin_common_side_effect) ^ hasEducationMessageSideEffect (?p,Canagliflozin_uncommon_ADR) ^ hasEducationMessageSideEffect (?p,Canagliflozin_rare_ADR)
4	Patient(?p) ^ isPrescribed(?p, Dapagliflozin) -> hasEducationMessageSideEffect (?p,Dapagliflozin_common_side_effect) ^ hasEducationMessageSideEffect (?p,Dapagliflozin_uncommon_ADR) ^ hasEducationMessageSideEffect (?p,Dapagliflozin_rare_ADR) ^ hasEducationMessageSideEffect (?p,Dapagliflozin_very_rare_ADR)
5	Patient(?p) ^ isPrescribed(?p, Empagliflozin) -> hasEducationMessageSideEffect (?p,Empagliflozin_very_common_side_effect) ^ hasEducationMessageSideEffect (?p,Empagliflozin_common_side_effect) ^ hasEducationMessageSideEffect (?p,Empagliflozin_uncommon_ADR) ^ hasEducationMessageSideEffect (?p,Empagliflozin_rare_ADR)
6	Patient(?p) ^ isPrescribed(?p, Linagliptin) -> hasEducationMessageSideEffect (?p,Linagliptin_very_common_side_effect) ^ hasEducationMessageSideEffect (?p,Linagliptin_uncommon_ADR) ^ hasEducationMessageSideEffect (?p,Linagliptin_rare_ADR)
7	Patient(?p) ^ isPrescribed(?p, Saxagliptin) -> hasEducationMessageSideEffect (?p,Saxagliptin_uncommon_ADR) ^ hasEducationMessageSideEffect (?p,Saxagliptin_very_rare_ADR)
8	Patient(?p) ^ isPrescribed(?p, Sitagliptin) -> hasEducationMessageSideEffect (?p,Sitagliptin_very_common_side_effect) ^ hasEducationMessageSideEffect (?p,Sitagliptin_rare_ADR)
9	Patient(?p) ^ isPrescribed(?p, Gliclazide) -> hasEducationMessageSideEffect (?p,Gliclazide_very_common_side_effect) ^ hasEducationMessageSideEffect (?p,Gliclazide_uncommon_ADR) ^ hasEducationMessageSideEffect (?p,Gliclazide_very-rare_ADR)
10	Patient(?p) ^ isPrescribed(?p, Glimepiride) -> hasEducationMessageSideEffect (?p,Glimepiride_very_common_side_effect) ^ hasEducationMessageSideEffect (?p,Glimepiride_uncommon_ADR) ^ hasEducationMessageSideEffect (?p,Glimepiride_very-rare_ADR)
11	Patient(?p) ^ isPrescribed(?p, Glyburide) -> hasEducationMessageSideEffect (?p,Glyburide_common_side_effect) ^ hasEducationMessageSideEffect (?p,Glyburide_uncommon_ADR) ^ hasEducationMessageSideEffect (?p,Glyburide_rare_ADR) ^ hasEducationMessageSideEffect (?p,Glyburide_very_rare_ADR)
	Drug-Drug Interactions Rules
12	Patient(?p) ^ swrlb:equal(?Total_med, 1) ^isPrescribed(?p,Metformin) ^hasTotalMedication(?p, ?Total_med) -

	>hasDrugDrugInteraction(?p,Msg_no_interaction)
13	Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p,Trandolapril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) ->hasDrugDrugInteraction(?p,Metformin_ACE_inhibitors)
14	Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p,Ramipril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) ->hasDrugDrugInteraction(?p,Metformin_ACE_inhibitors)
15	Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p,Quinapril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) ->hasDrugDrugInteraction(?p,Metformin_ACE_inhibitors)
16	Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p,Perindopril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) ->hasDrugDrugInteraction(?p,Metformin_ACE_inhibitors)
17	Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p,Lisinopril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) ->hasDrugDrugInteraction(?p,Metformin_ACE_inhibitors)
18	Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p,Fosinopril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) ->hasDrugDrugInteraction(?p,Metformin_ACE_inhibitors)
19	Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p,Enalapril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) ->hasDrugDrugInteraction(?p,Metformin_ACE_inhibitors)
20	Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p,Cilazapril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) ->hasDrugDrugInteraction(?p,Metformin_ACE_inhibitors)
21	Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p,Captopril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) ->hasDrugDrugInteraction(?p,Metformin_ACE_inhibitors)
22	Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p,Benazepril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) ->hasDrugDrugInteraction(?p,Metformin_ACE_inhibitors)
23	Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p,Bumetanide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Metformin_diuretics)
24	Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p,Furosemide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Metformin_diuretics)
25	Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p,Hydrochlorothiazide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Metformin_diuretics)
26	Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p,Indapamide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Metformin_diuretics)
27	Patient(?p) ^ isPrescribed(?p, Metformin) ^ isPrescribed(?p,Metolazone) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Metformin_diuretics)
28	Patient(?p) ^ swrlb:equal(?Total_med, 1) ^isPrescribed(?p,Alogliptin) ^hasTotalMedication(?p, ?Total_med) ->hasDrugDrugInteraction(?p,Msg_no_interaction)
29	Patient(?p) ^ swrlb:equal(?Total_med, 1) ^isPrescribed(?p,Canagliflozin) ^hasTotalMedication(?p, ?Total_med) ->hasDrugDrugInteraction(?p,Msg_no_interaction
30	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^

	isPrescribed(?p,Bumetanide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Canagliflozin_loop_diuretics)
31	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^ isPrescribed(?p,Furosemide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Canagliflozin_loop_diuretics)
32	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^ isPrescribed(?p,Furosemide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Canagliflozin_loop_diuretics)
33	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^ isPrescribed(?p,Trandolapril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Canagliflozin_ACE_inhibitors)
34	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^ isPrescribed(?p,Ramipril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Canagliflozin_ACE_inhibitors)
35	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^ isPrescribed(?p,Quinapril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Canagliflozin_ACE_inhibitors)
36	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^ isPrescribed(?p,Lisinopril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Canagliflozin_ACE_inhibitors)
37	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^ isPrescribed(?p,Fosinopril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Canagliflozin_ACE_inhibitors)
38	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^ isPrescribed(?p,Enalapril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Canagliflozin_ACE_inhibitors)
39	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^ isPrescribed(?p,Cilazapril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Canagliflozin_ACE_inhibitors)
40	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^ isPrescribed(?p,Captopril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Canagliflozin_ACE_inhibitors)
41	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^ isPrescribed(?p,Benazepril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Canagliflozin_ACE_inhibitors)
42	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^ isPrescribed(?p,Candesartan) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Canagliflozin_ARBs)
43	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^ isPrescribed(?p,Eprosartan) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Canagliflozin_ARBs)

44	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^ isPrescribed(?p,Irbesartan) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Canagliflozin_ARBs)
45	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^ isPrescribed(?p,Losartan) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Canagliflozin_ARBs)
46	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^ isPrescribed(?p,Valsartan) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Canagliflozin_ARBs)
47	Patient(?p) ^ swrlb:equal(?Total_med, 1) ^ isPrescribed(?p,Dapagliflozin) ^hasTotalMedication(?p, ?Total_med) ->hasDrugDrugInteraction(?p,Msg_no_interaction)
48	Patient(?p) ^ isPrescribed(?p, Dapagliflozin) ^ isPrescribed(?p,Gliclazide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p, Dapagliflozin_sulfonylureas)
49	Patient(?p) ^ isPrescribed(?p, Dapagliflozin) ^ isPrescribed(?p,Glimepiride) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p, Dapagliflozin_sulfonylureas)
50	Patient(?p) ^ isPrescribed(?p, Dapagliflozin) ^ isPrescribed(?p,Glyburide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p, Dapagliflozin_sulfonylureas)
51	Patient(?p) ^ swrlb:equal(?Total_med, 1) ^ isPrescribed(?p,Empagliflozin) ^hasTotalMedication(?p, ?Total_med) ->hasDrugDrugInteraction(?p,Msg_no_interaction)
52	Patient(?p) ^ isPrescribed(?p, Empagliflozin) ^ isPrescribed(?p,Gliclazide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p, Empagliflozin_sulfonylureas)
53	Patient(?p) ^ isPrescribed(?p, Empagliflozin) ^ isPrescribed(?p,Glimepiride) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p, Empagliflozin_sulfonylureas)
54	Patient(?p) ^ isPrescribed(?p, Empagliflozin) ^ isPrescribed(?p,Glyburide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p, Empagliflozin_sulfonylureas)
55	Patient(?p) ^ swrlb:equal(?Total_med, 1) ^ isPrescribed(?p,Linagliptin) ^hasTotalMedication(?p, ?Total_med) ->hasDrugDrugInteraction(?p,Msg_no_interaction)
56	Patient(?p) ^ isPrescribed(?p, Linagliptin) ^ isPrescribed(?p,Gliclazide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p, Linagliptin_sulfonylureas)
57	Patient(?p) ^ isPrescribed(?p, Linagliptin) ^ isPrescribed(?p,Glimepiride) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p, Linagliptin_sulfonylureas)
58	Patient(?p) ^ isPrescribed(?p, Linagliptin) ^ isPrescribed(?p,Glyburide) ^ hasTotalMedication(?p, ?Total_med) ^

	swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p, Linagliptin_sulfonylureas)
59	Patient(?p) ^ swrlb:equal(?Total_med, 1) ^ isPrescribed(?p,Saxagliptin) ^hasTotalMedication(?p, ?Total_med) ->hasDrugDrugInteraction(?p,Msg_no_interaction)
60	Patient(?p) ^ swrlb:equal(?Total_med, 1) ^ isPrescribed(?p,Sitagliptin) ^hasTotalMedication(?p, ?Total_med) ->hasDrugDrugInteraction(?p,Msg_no_interaction)
61	Patient(?p) ^ isPrescribed(?p, Sitagliptin) ^ isPrescribed(?p,Gliclazide) ^ isPrescribed(?p,Metformin)^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p, Sitagliptin_metformin_sulfonylureas)
62	Patient(?p) ^ isPrescribed(?p, Sitagliptin) ^ isPrescribed(?p,Glimepiride) ^ isPrescribed(?p,Metformin)^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p, Sitagliptin_metformin_sulfonylureas)
63	Patient(?p) ^ isPrescribed(?p, Sitagliptin) ^ isPrescribed(?p,Glyburide) ^ isPrescribed(?p,Metformin)^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p, Sitagliptin_metformin_sulfonylureas)
64	Patient(?p) ^ swrlb:equal(?Total_med, 1) ^ isPrescribed(?p,Gliclazide) ^hasTotalMedication(?p, ?Total_med) ->hasDrugDrugInteraction(?p,Msg_no_interaction)
65	Patient(?p) ^ isPrescribed(?p, Gliclazide) ^ isPrescribed(?p,Bumetanide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Gliclazide_diuretics)
66	Patient(?p) ^ isPrescribed(?p, Gliclazide) ^ isPrescribed(?p,Furosemide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Gliclazide_diuretics)
67	Patient(?p) ^ isPrescribed(?p, Gliclazide) ^ isPrescribed(?p,Hydrochlorothiazide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Gliclazide_diuretics)
68	Patient(?p) ^ isPrescribed(?p, Gliclazide) ^ isPrescribed(?p,Indapamide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Gliclazide_diuretics)
69	Patient(?p) ^ isPrescribed(?p, Gliclazide) ^ isPrescribed(?p,Metolazone) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Gliclazide_diuretics)
70	Patient(?p) ^ swrlb:equal(?Total_med, 1) ^ isPrescribed(?p,Glimepiride) ^hasTotalMedication(?p, ?Total_med) ->hasDrugDrugInteraction(?p,Msg_no_interaction)
71	Patient(?p) ^ swrlb:equal(?Total_med, 1) ^ isPrescribed(?p,Glyburide) ^hasTotalMedication(?p, ?Total_med) ->hasDrugDrugInteraction(?p,Msg_no_interaction)
72	Patient(?p) ^ isPrescribed(?p, Glyburide) ^ isPrescribed(?p,Bumetanide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Glyburide_diuretics)
73	Patient(?p) ^ isPrescribed(?p, Glyburide) ^ isPrescribed(?p,Furosemide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Glyburide_diuretics)

74	Patient(?p) ^ isPrescribed(?p, Glyburide) ^ isPrescribed(?p,Hydrochlorothiazide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Glyburide_diuretics)
75	Patient(?p) ^ isPrescribed(?p, Glyburide) ^ isPrescribed(?p,Indapamide) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Glyburide_diuretics)
76	Patient(?p) ^ isPrescribed(?p, Glyburide) ^ isPrescribed(?p,Metolazone) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Glyburide_diuretics)
77	Patient(?p) ^ isPrescribed(?p, Glyburide) ^ isPrescribed(?p,Trandolapril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Glyburide_ACE_inhibitors)
78	Patient(?p) ^ isPrescribed(?p, Glyburide) ^ isPrescribed(?p,Ramipril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Glyburide_ACE_inhibitors)
79	Patient(?p) ^ isPrescribed(?p, Glyburide) ^ isPrescribed(?p,Quinapril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Glyburide_ACE_inhibitors)
80	Patient(?p) ^ isPrescribed(?p, Glyburide) ^ isPrescribed(?p,Perindopril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Glyburide_ACE_inhibitors)
81	Patient(?p) ^ isPrescribed(?p, Glyburide) ^ isPrescribed(?p,Lisinopril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Glyburide_ACE_inhibitors)
82	Patient(?p) ^ isPrescribed(?p, Glyburide) ^ isPrescribed(?p,Fosinopril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Glyburide_ACE_inhibitors)
83	Patient(?p) ^ isPrescribed(?p, Glyburide) ^ isPrescribed(?p,Enalapril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Glyburide_ACE_inhibitors)
84	Patient(?p) ^ isPrescribed(?p, Glyburide) ^ isPrescribed(?p,Cilazapril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Glyburide_ACE_inhibitors)
85	Patient(?p) ^ isPrescribed(?p, Glyburide) ^ isPrescribed(?p,Captopril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Glyburide_ACE_inhibitors)
86	Patient(?p) ^ isPrescribed(?p, Glyburide) ^ isPrescribed(?p,Benazepril) ^ hasTotalMedication(?p, ?Total_med) ^ swrlb:notEqual(?Total_med, 1) -> hasDrugDrugInteraction(?p,Glyburide_ACE_inhibitors)
Special Consideration Rules	
87	Patient(?p) ^ isPrescribed(?p,Metformin) ^hasRiskFactor(?p,Elderly) ->hasSpecialConsideration(?p,Consideration_metformin_elderly)
88	Patient(?p) ^ isPrescribed(?p,Metformin) ^hasRiskFactor(?p,Binge_drinking) ->hasSpecialConsideration(?p,Consideration_metformin_alcohol)
89	Patient(?p) ^hasDrugDrugInteraction(?p,Metformin_diuretics) ->hasSpecialConsideration(?p,Consideration_metformin_diuretics)
90	Patient(?p) ^hasDrugDrugInteraction(?p,Metformin_ACE_inhibitors) ->hasSpecialConsideration(?p,Consideration_metformin_ACE_inhibitors)
91	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^hasRiskFactor(?p,Elderly) ->hasSpecialConsideration(?p,Consideration_canagliflozin_elderly)
92	Patient(?p) ^ isPrescribed(?p,Canagliflozin)

	^hasRiskFactor(?p,Binge_drinking) - >hasSpecialConsideration(?p,Consideration_canagliflozin_alcohol)
93	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^ hasRiskFactor(?p,Heart_failure) - >hasSpecialConsideration(?p,Consideration_canagliflozin_heart_failure)
94	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^ hasRiskFactor(?p,Cardiovascular_disease) - >hasSpecialConsideration(?p,Consideration_canagliflozin_cardiovascular_disease)
95	Patient(?p) ^ isPrescribed(?p, Canagliflozin) ^ hasRiskFactor(?p,Diabetes_kidney_disease) - >hasSpecialConsideration(?p,Consideration_canagliflozin_diabetic_kidney_disease)
96	Patient(?p) ^hasDrugDrugInteraction(?p,Canagliflozin_ACE_inhibitors) - >hasSpecialConsideration(?p,Consideration_canagliflozin_ACE_inhibitors)
97	Patient(?p) ^hasDrugDrugInteraction(?p,Canagliflozin_ARBs) - >hasSpecialConsideration(?p,Consideration_canagliflozin_ARBs)
98	Patient(?p) ^hasDrugDrugInteraction(?p,Canagliflozin_loop_diuretics) - >hasSpecialConsideration(?p,Consideration_canagliflozin_loop_diuretics)
99	Patient(?p) ^hasDrugDrugInteraction(?p,Dapagliflozin_sulfonylureas) - >hasSpecialConsideration(?p,Consideration_dapagliflozin_sulfonylureas)
100	Patient(?p) ^ isPrescribed(?p,Empagliflozin) ^hasRiskFactor(?p,Binge_drinking) - >hasSpecialConsideration(?p,Consideration_empagliflozin_alcohol)
101	Patient(?p) ^hasDrugDrugInteraction(?p,Empagliflozin_sulfonylureas) - >hasSpecialConsideration(?p,Consideration_empagliflozin_sulfonylureas)
102	Patient(?p) ^hasDrugDrugInteraction(?p,Linagliptin_sulfonylureas) - >hasSpecialConsideration(?p,Consideration_linagliptin_sulfonylureas)
103	Patient(?p) ^ isPrescribed(?p, Saxagliptin) ^ hasRiskFactor(?p,Chronic_kidney_disease) - >hasSpecialConsideration(?p,Consideration_saxagliptin_chronic_kidney_disease)
104	Patient(?p) ^hasDrugDrugInteraction(?p,Sitagliptin_metformin_sulfonylureas) - >hasSpecialConsideration(?p,Consideration_sitagliptin_metformin_sulfonylureas)
105	Patient(?p) ^ isPrescribed(?p, Gliclazide) ^hasRiskFactor(?p,Elderly) - >hasSpecialConsideration(?p,Consideration_gliclazide_elderly)
106	Patient(?p) ^ isPrescribed(?p,Gliclazide) ^hasRiskFactor(?p,Binge_drinking) - >hasSpecialConsideration(?p,Consideration_gliclazide_alcohol)
107	Patient(?p) ^hasDrugDrugInteraction(?p,Gliclazide_diuretics) - >hasSpecialConsideration(?p,Consideration_gliclazide_diuretics)
108	Patient(?p) ^ isPrescribed(?p, Gliclazide) ^ hasRiskFactor(?p,Impaired_renal_function) - >hasSpecialConsideration(?p,Consideration_gliclazide_impaired_renal_function)
109	Patient(?p) ^ isPrescribed(?p, Glimepiride) ^hasRiskFactor(?p,Elderly) - >hasSpecialConsideration(?p,Consideration_glimepiride_elderly)
110	Patient(?p) ^ isPrescribed(?p,Glimepiride) ^hasRiskFactor(?p,Binge_drinking) - >hasSpecialConsideration(?p,Consideration_glimepiride_alcohol)
111	Patient(?p) ^hasDrugDrugInteraction(?p,Glyburide_diuretics) - >hasSpecialConsideration(?p,Consideration_glyburide_diuretics)
112	Patient(?p) ^hasDrugDrugInteraction(?p,Glyburide_ACE_inhibitors) -

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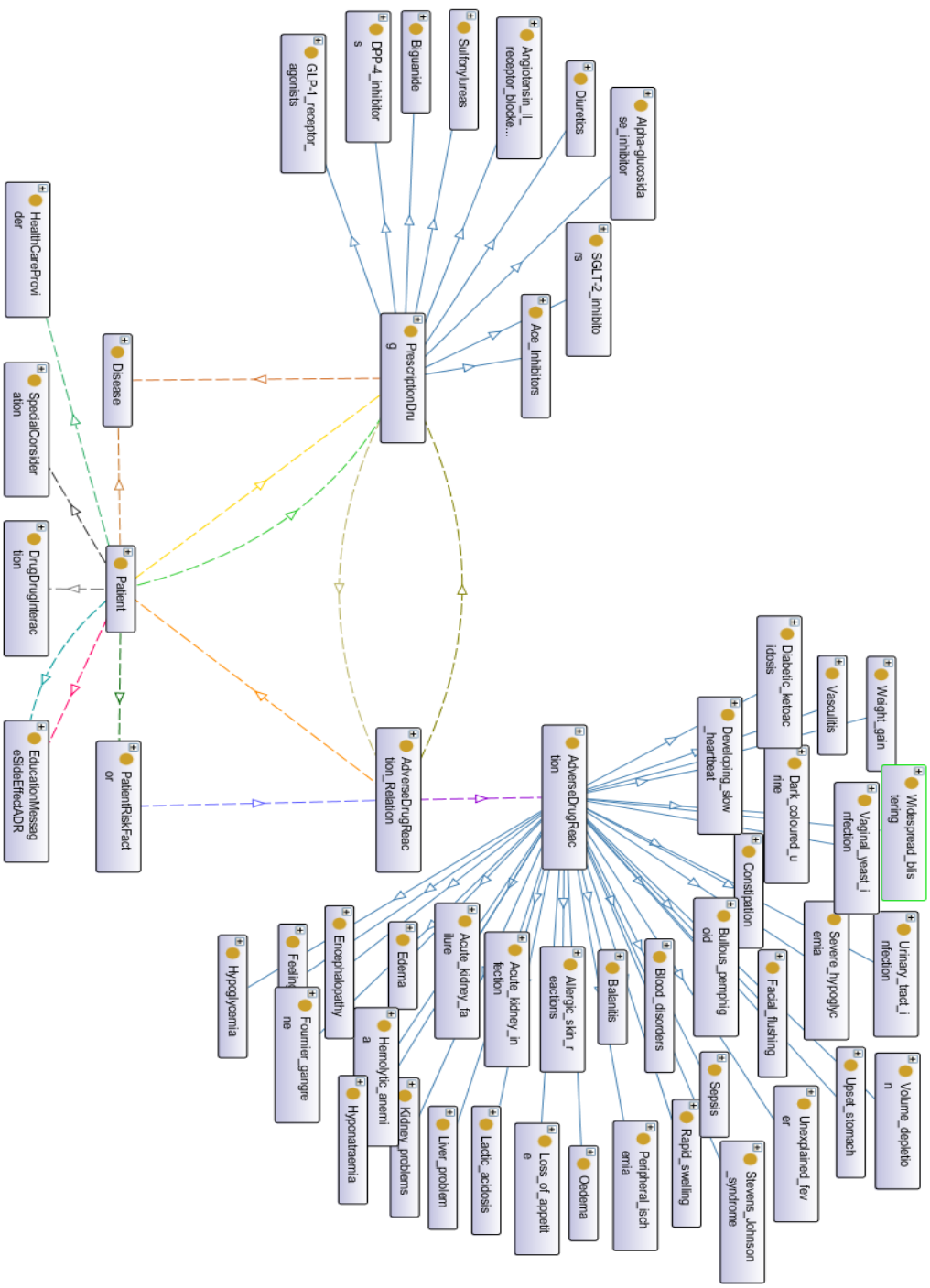
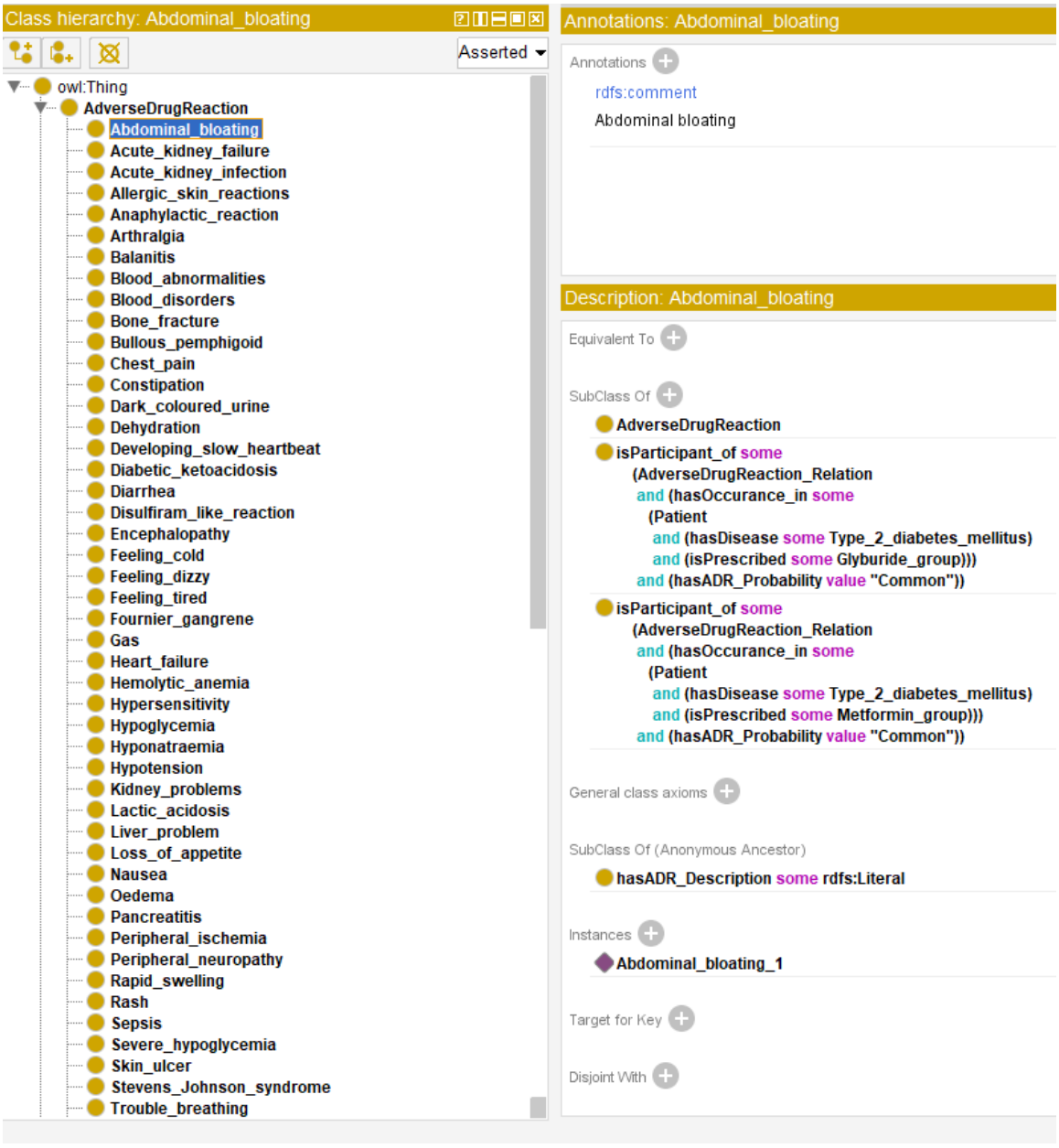
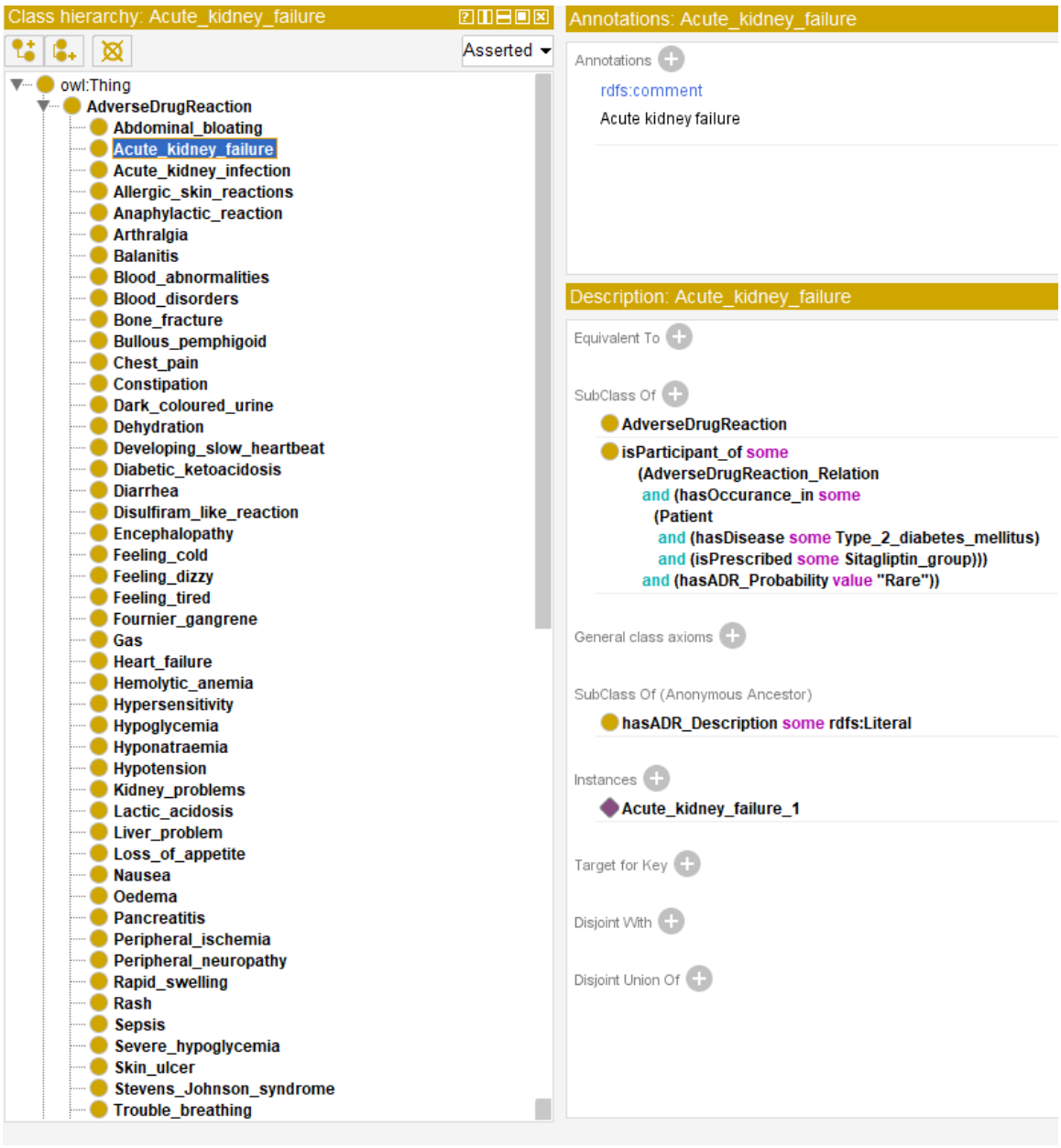
>hasSpecialConsideration(?p,Consideration_glyburide_ACE_inhibitors)
```

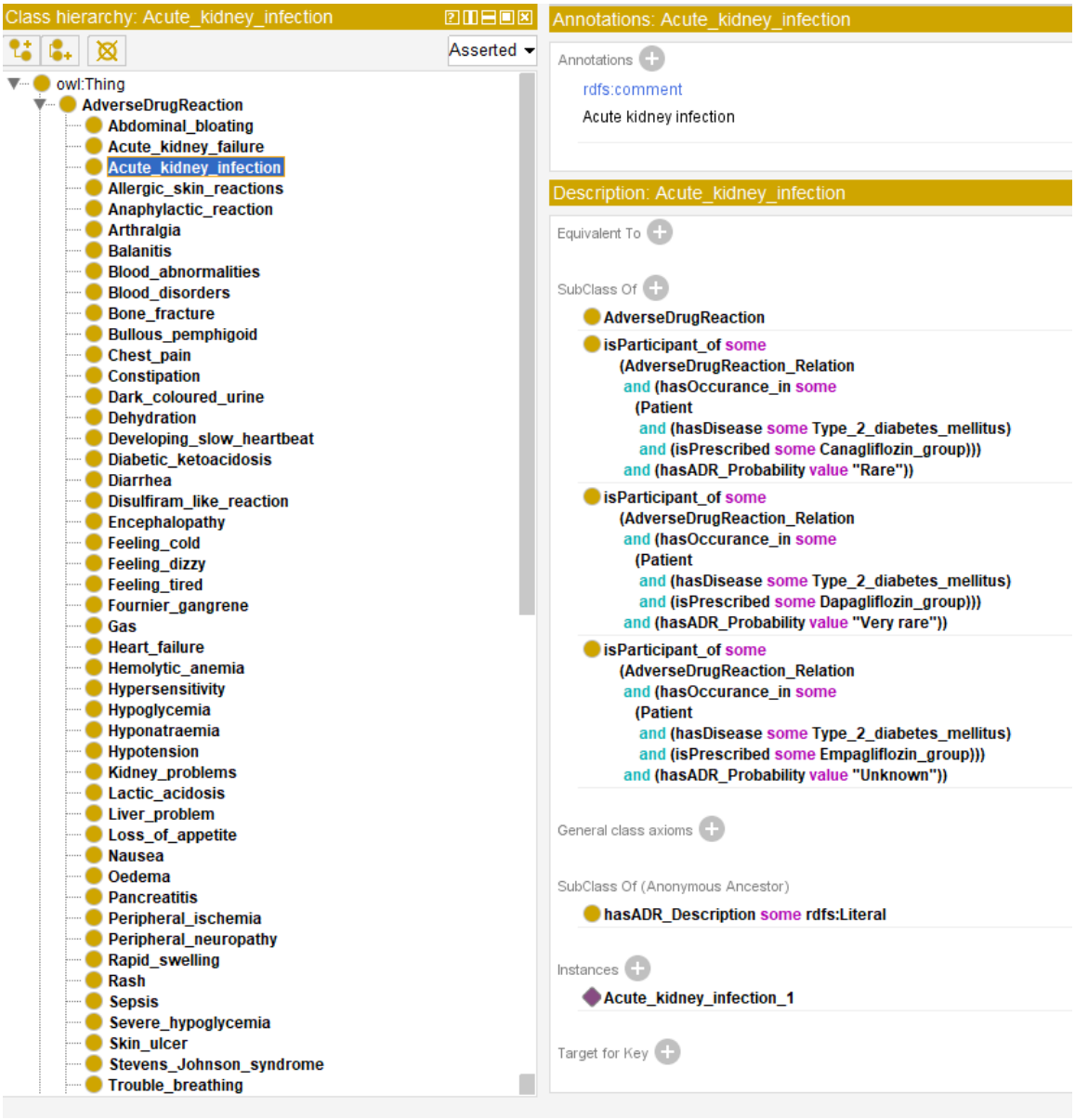
APPENDIX C: ONTOGRAF VIEW OF THE ADM ONTOLOGY

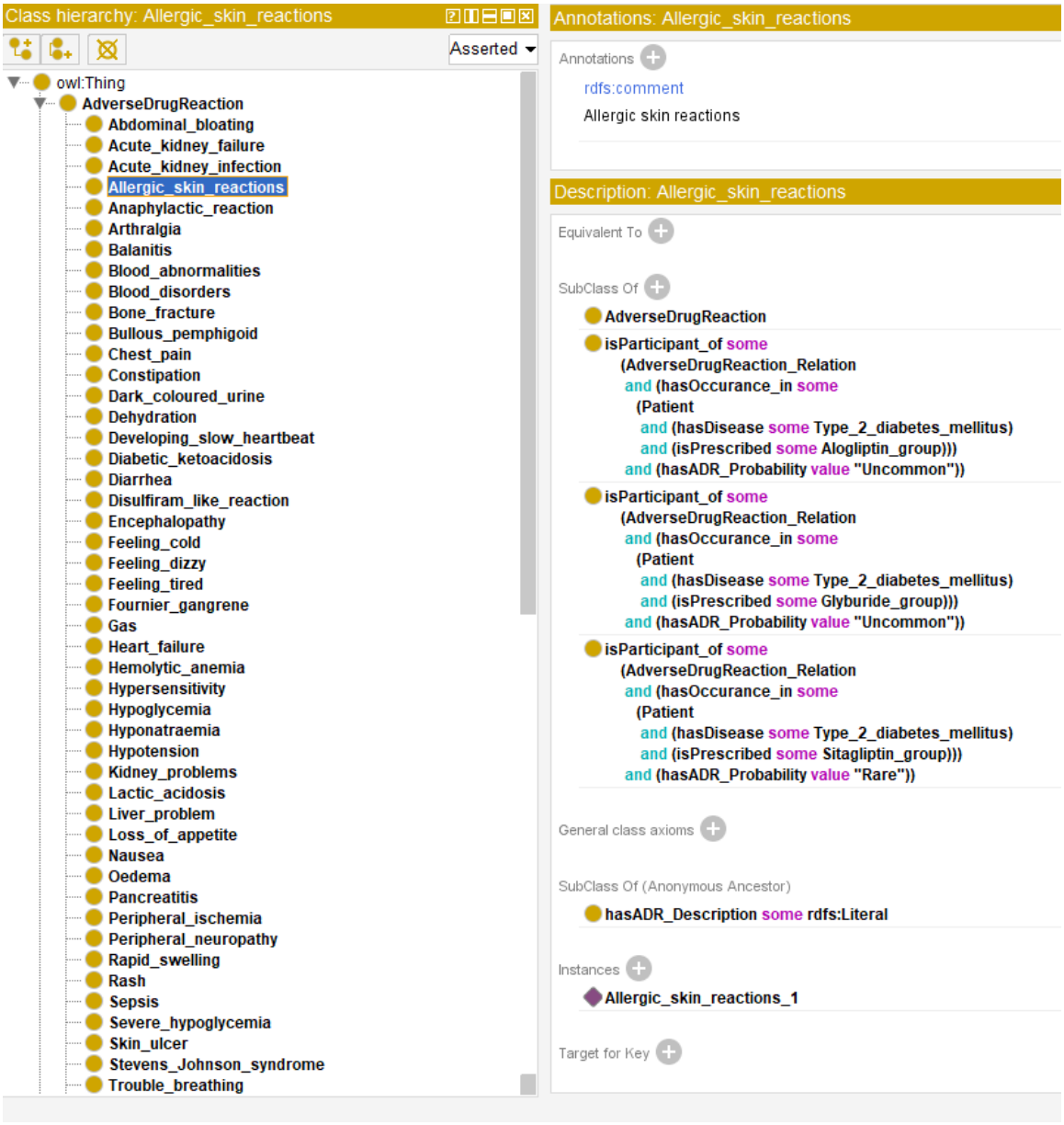


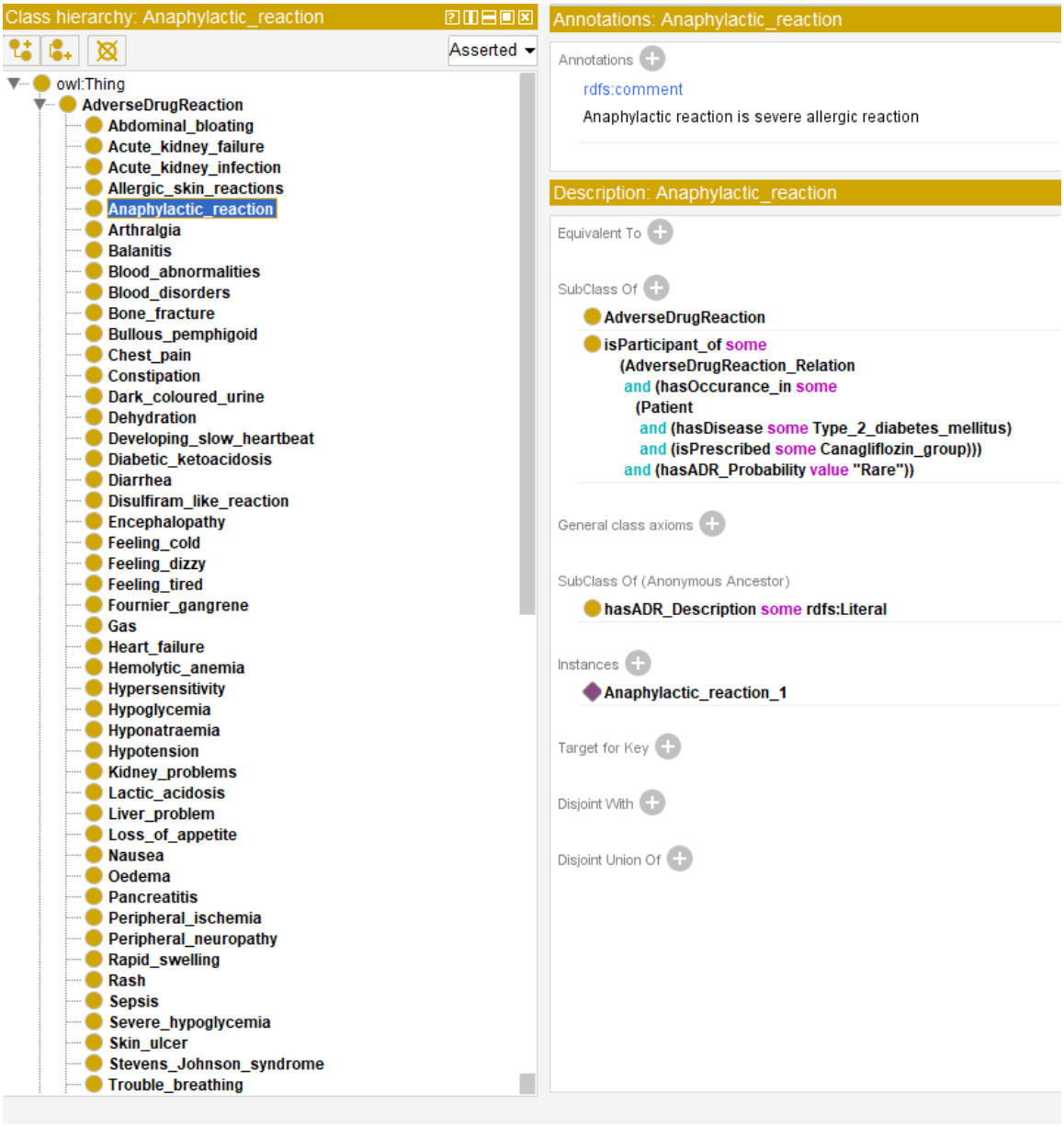
APPENDIX D: PROPERTIES OF ADVERSEDRUGREACTION SUBCLASSES

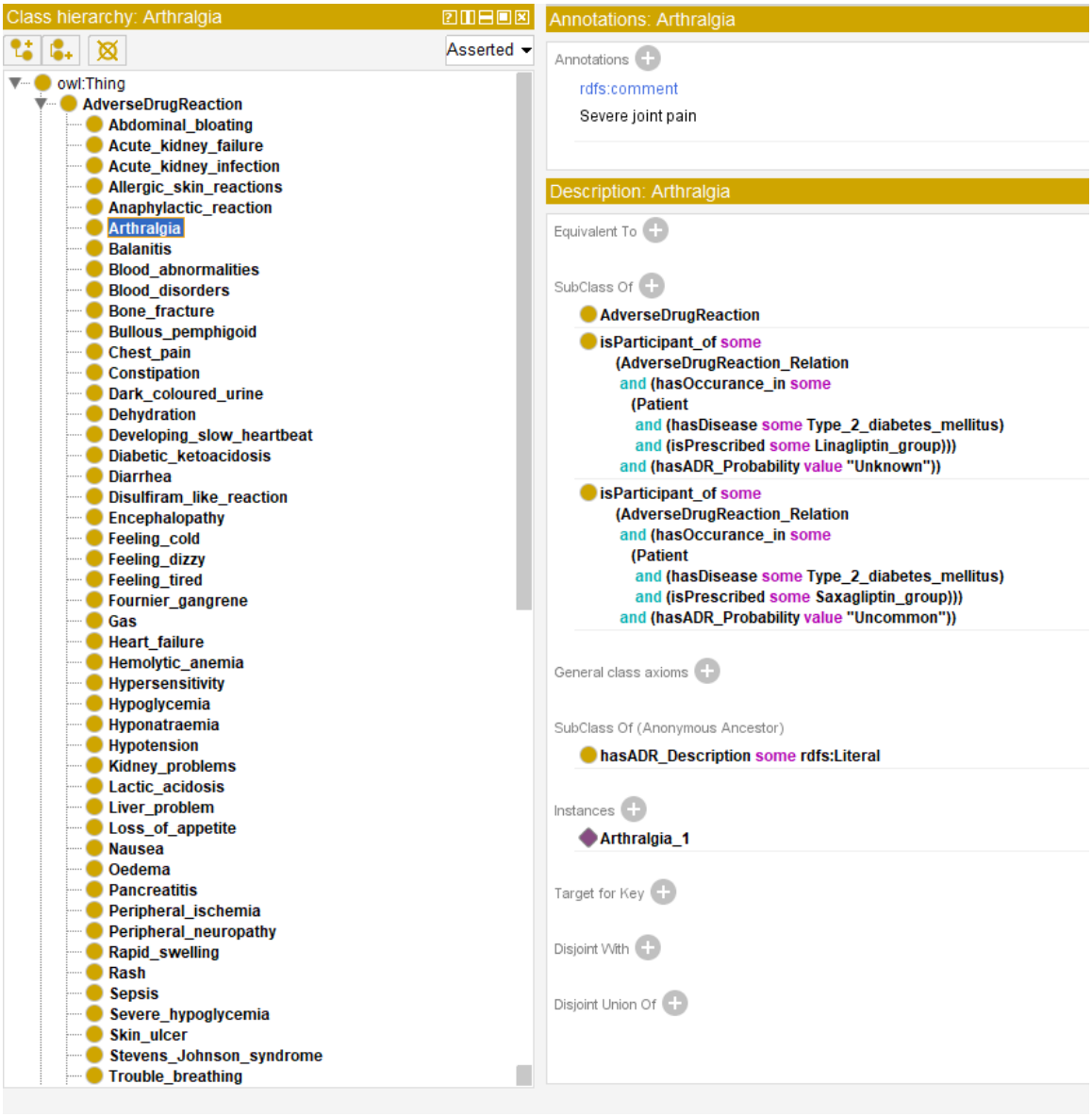


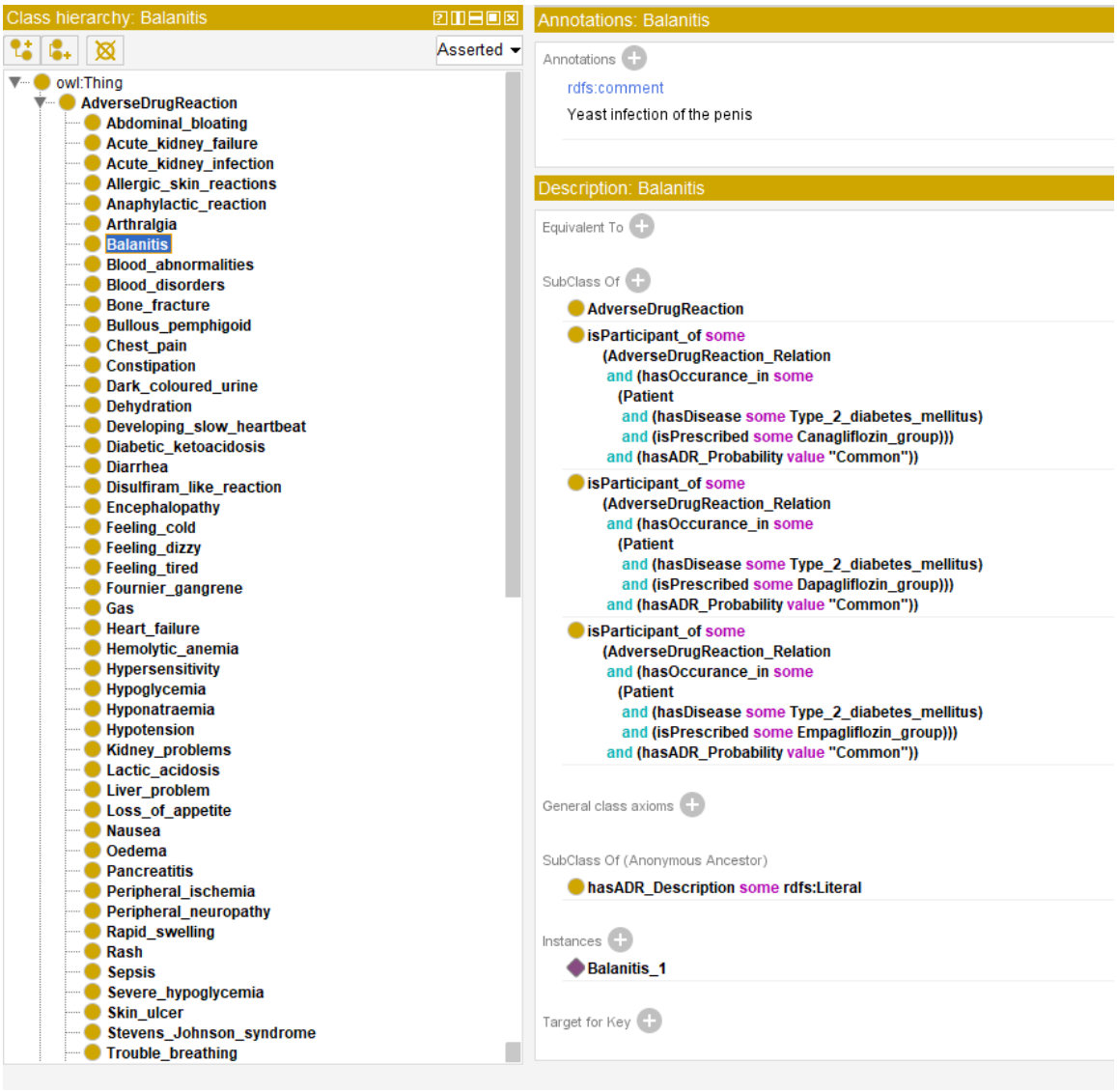

Class hierarchy: Acute_kidney_failure
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Acute_kidney_failure
Annotations
rdfs:comment
Acute kidney failure
Description: Acute_kidney_failure
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Sitagliptin_group)))
and (hasADR_Probability value "Rare"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Acute_kidney_failure_1
Target for Key
Disjoint With
Disjoint Union Of

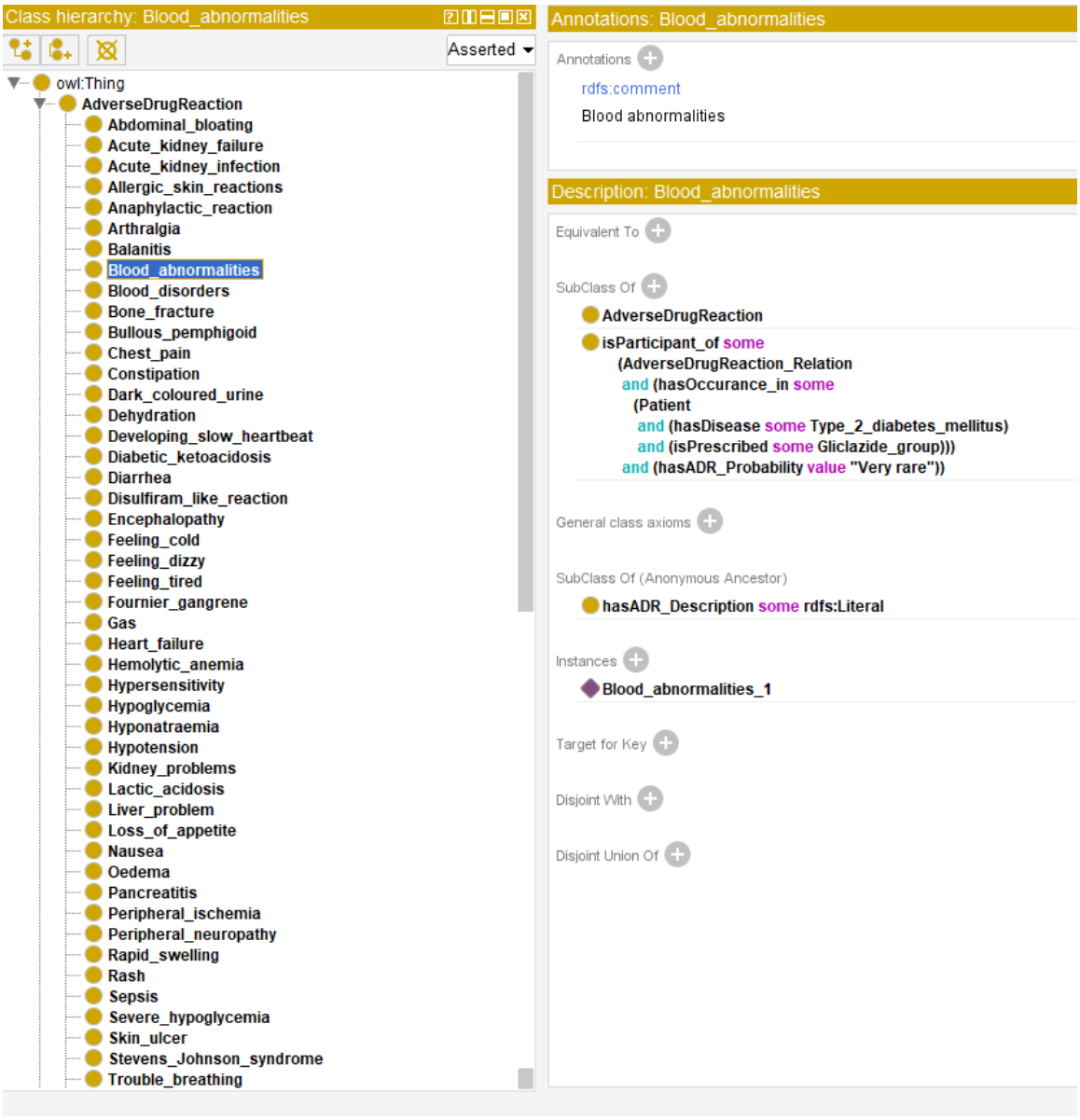

Class hierarchy: Acute_kidney_infection
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Acute_kidney_infection
Annotations
rdfs:comment
Acute kidney infection
Description: Acute_kidney_infection
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some (AdverseDrugReaction_Relation and (hasOccurance_in some (Patient and (hasDisease some Type_2_diabetes_mellitus) and (isPrescribed some Canagliflozin_group))) and (hasADR_Probability value "Rare"))
isParticipant_of some (AdverseDrugReaction_Relation and (hasOccurance_in some (Patient and (hasDisease some Type_2_diabetes_mellitus) and (isPrescribed some Dapagliflozin_group))) and (hasADR_Probability value "Very rare"))
isParticipant_of some (AdverseDrugReaction_Relation and (hasOccurance_in some (Patient and (hasDisease some Type_2_diabetes_mellitus) and (isPrescribed some Empagliflozin_group))) and (hasADR_Probability value "Unknown"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Acute_kidney_infection_1
Target for Key

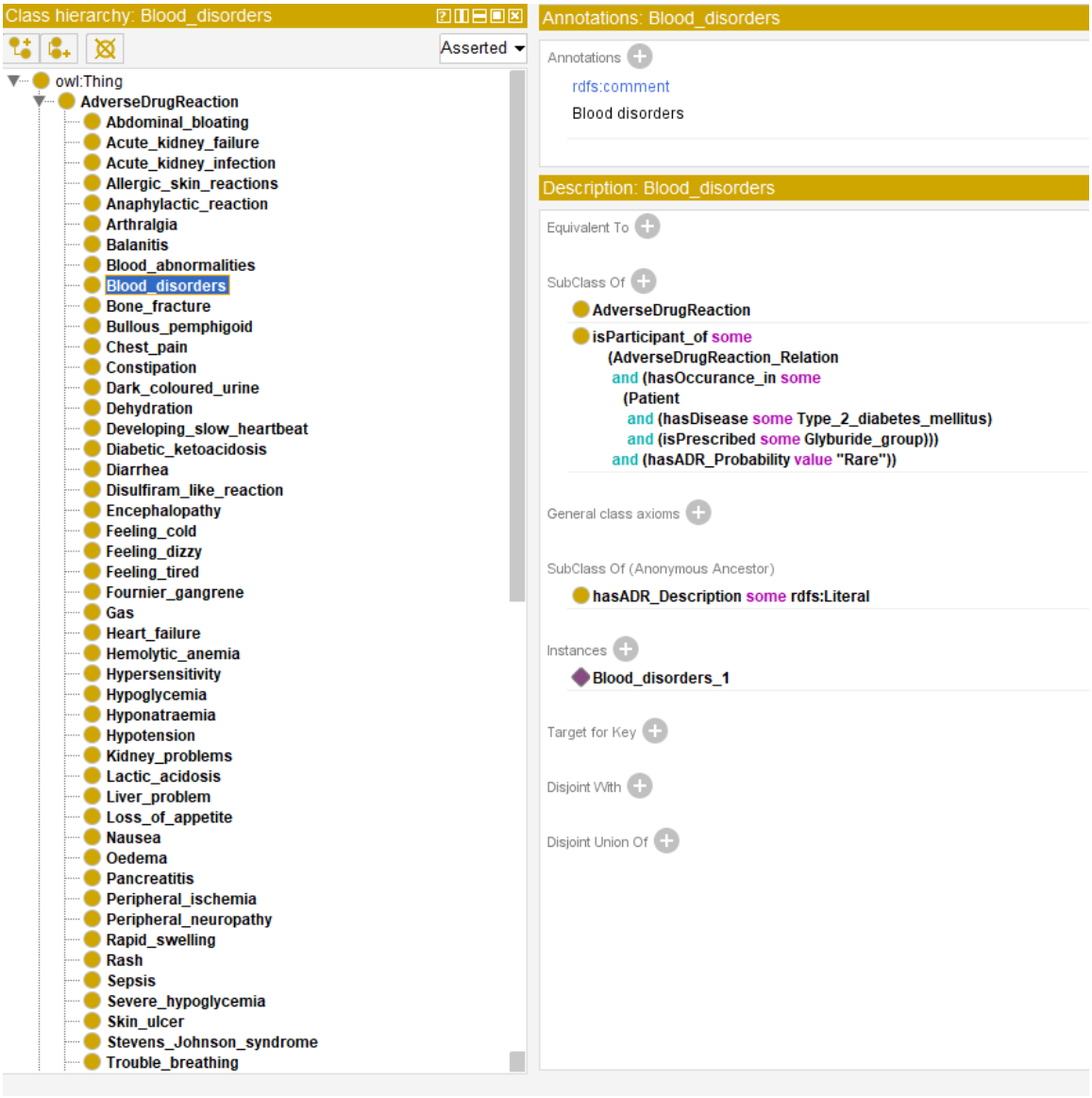

Class hierarchy: Allergic_skin_reactions
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Allergic_skin_reactions
Annotations
rdfs:comment
Allergic skin reactions
Description: Allergic_skin_reactions
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Alogliptin_group)))
and (hasADR_Probability value "Uncommon"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Glyburide_group)))
and (hasADR_Probability value "Uncommon"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Sitagliptin_group)))
and (hasADR_Probability value "Rare"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Allergic_skin_reactions_1
Target for Key

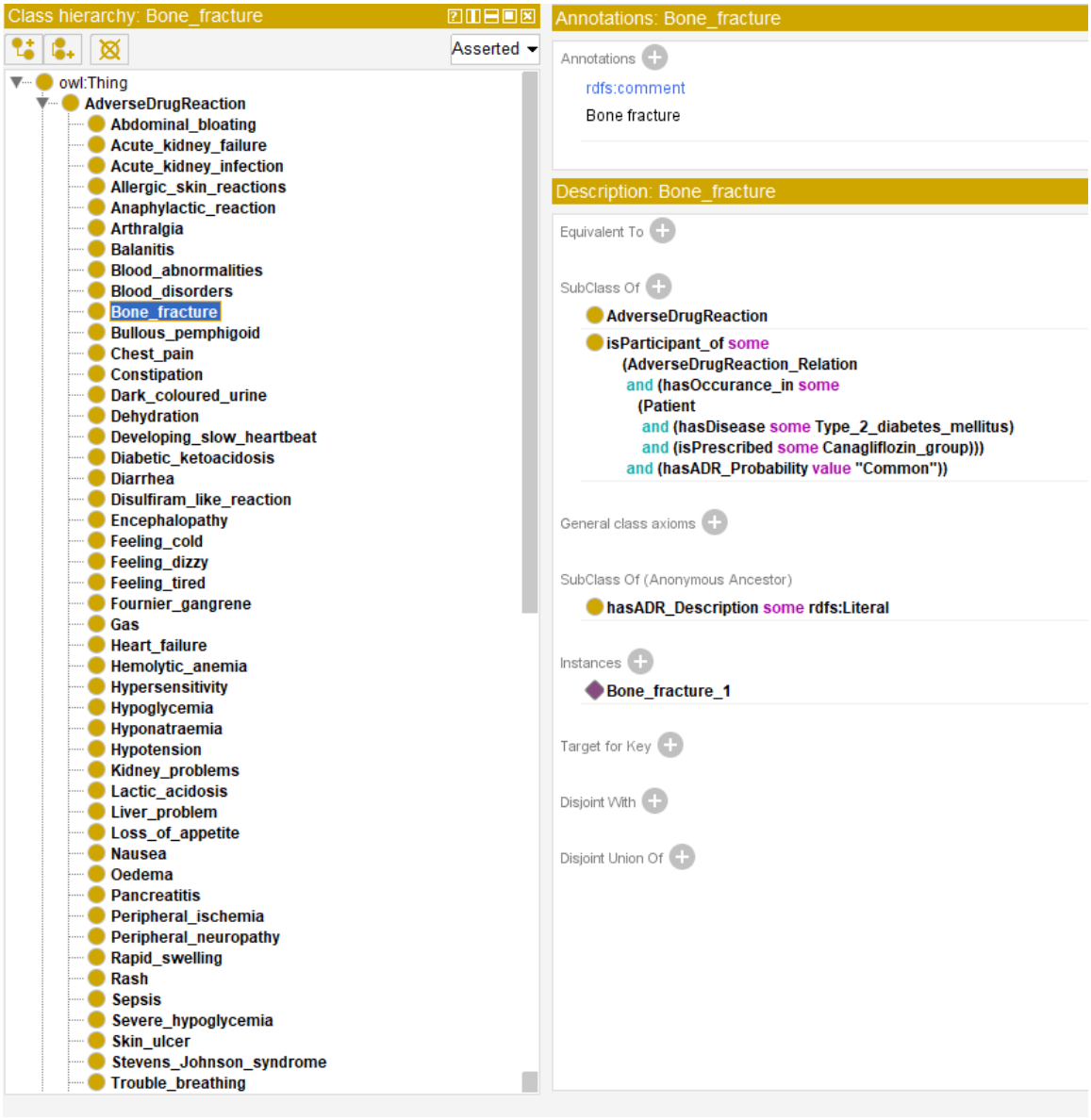

Class hierarchy: Anaphylactic_reaction
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Anaphylactic_reaction
Annotations
rdfs:comment
Anaphylactic reaction is severe allergic reaction
Description: Anaphylactic_reaction
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Canagliflozin_group)))
and (hasADR_Probability value "Rare"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Anaphylactic_reaction_1
Target for Key
Disjoint With
Disjoint Union Of

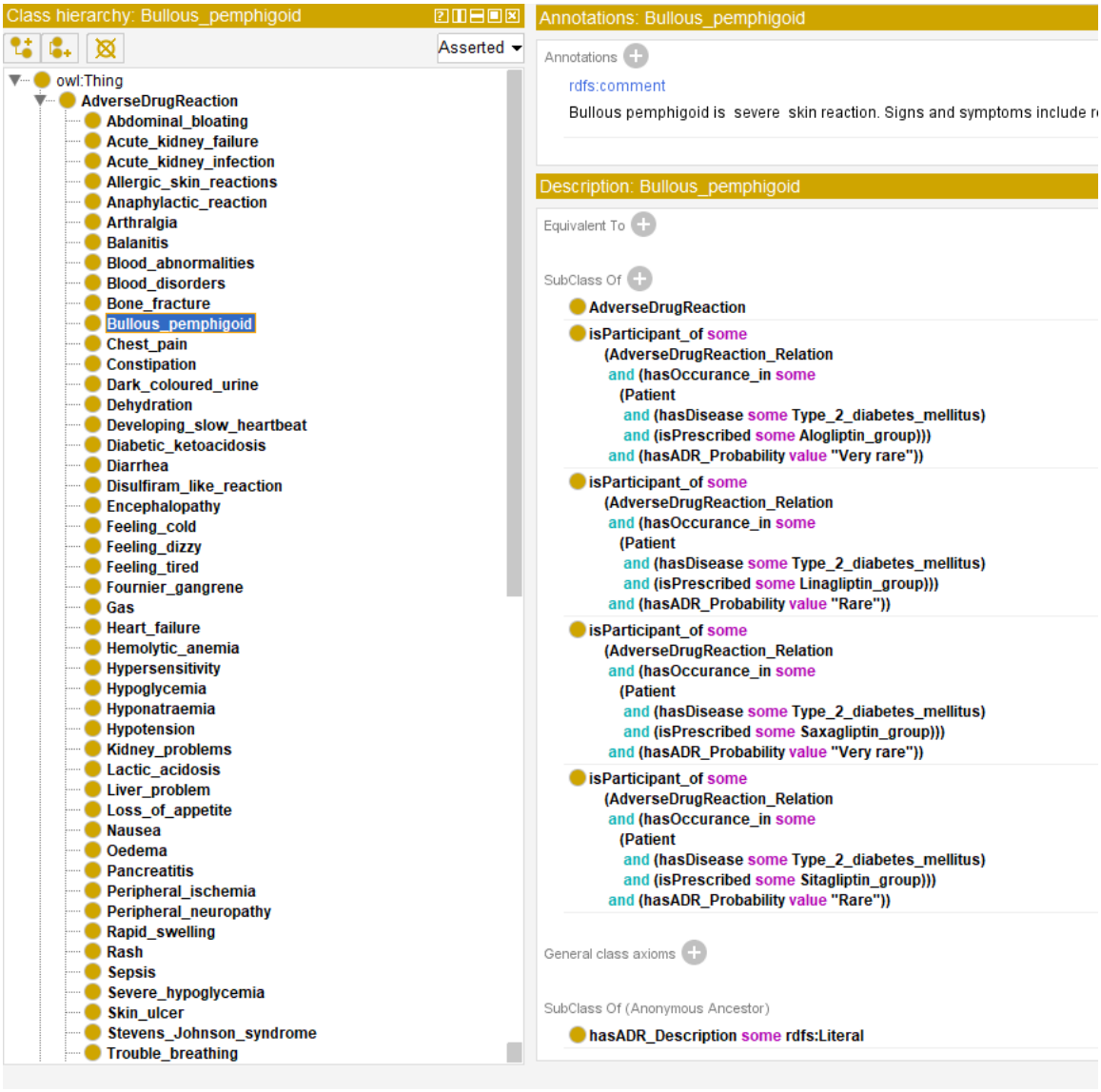

Class hierarchy: Arthralgia
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Arthralgia
Annotations
rdfs:comment
Severe joint pain
Description: Arthralgia
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Linagliptin_group)))
and (hasADR_Probability value "Unknown"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Saxagliptin_group)))
and (hasADR_Probability value "Uncommon"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Arthralgia_1
Target for Key
Disjoint With
Disjoint Union Of

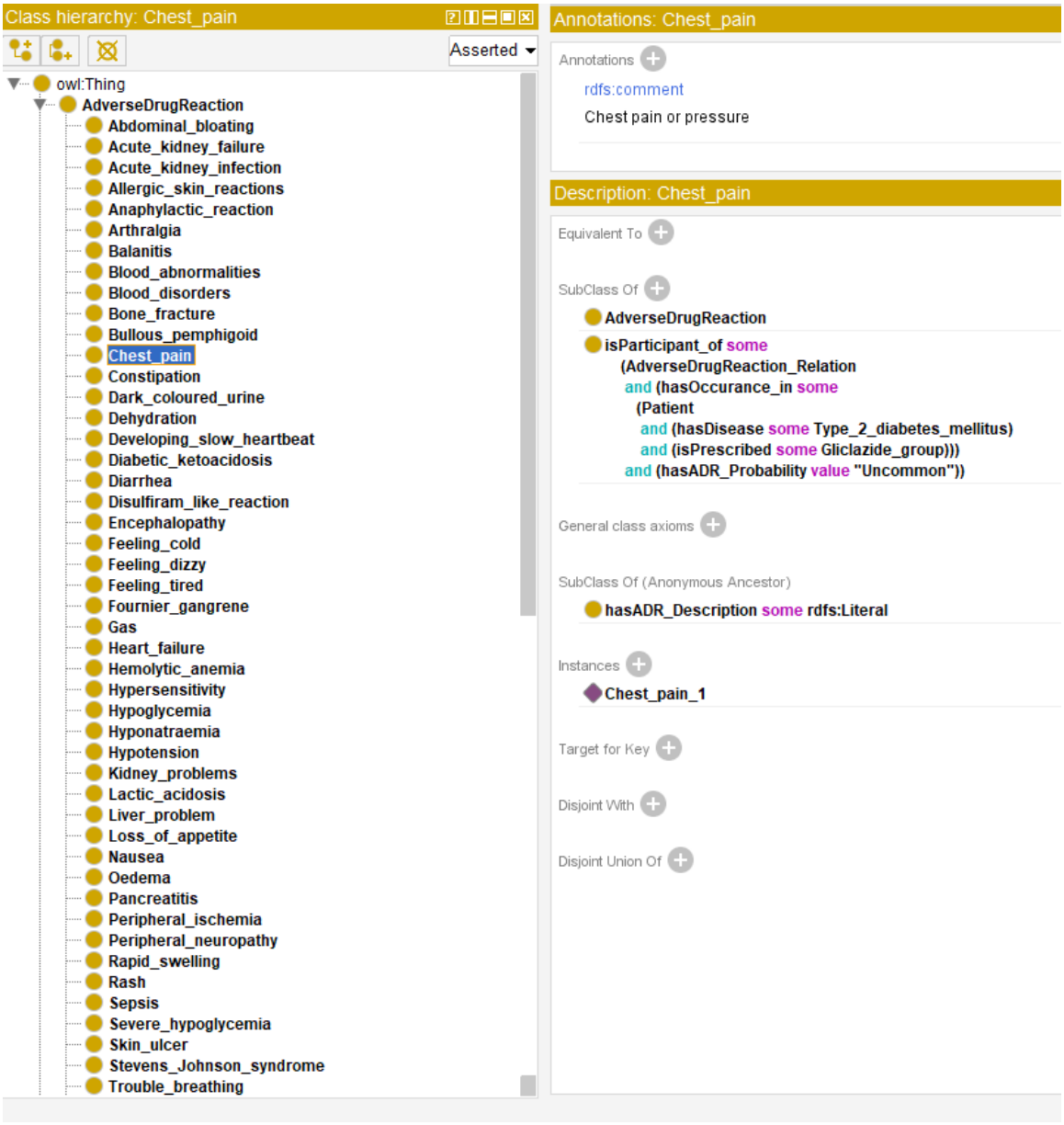

Class hierarchy: Balanitis
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Balanitis
Annotations
rdfs:comment
Yeast infection of the penis
Description: Balanitis
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Canagliflozin_group)))
and (hasADR_Probability value "Common"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Dapagliflozin_group)))
and (hasADR_Probability value "Common"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Empagliflozin_group)))
and (hasADR_Probability value "Common"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Balanitis_1
Target for Key

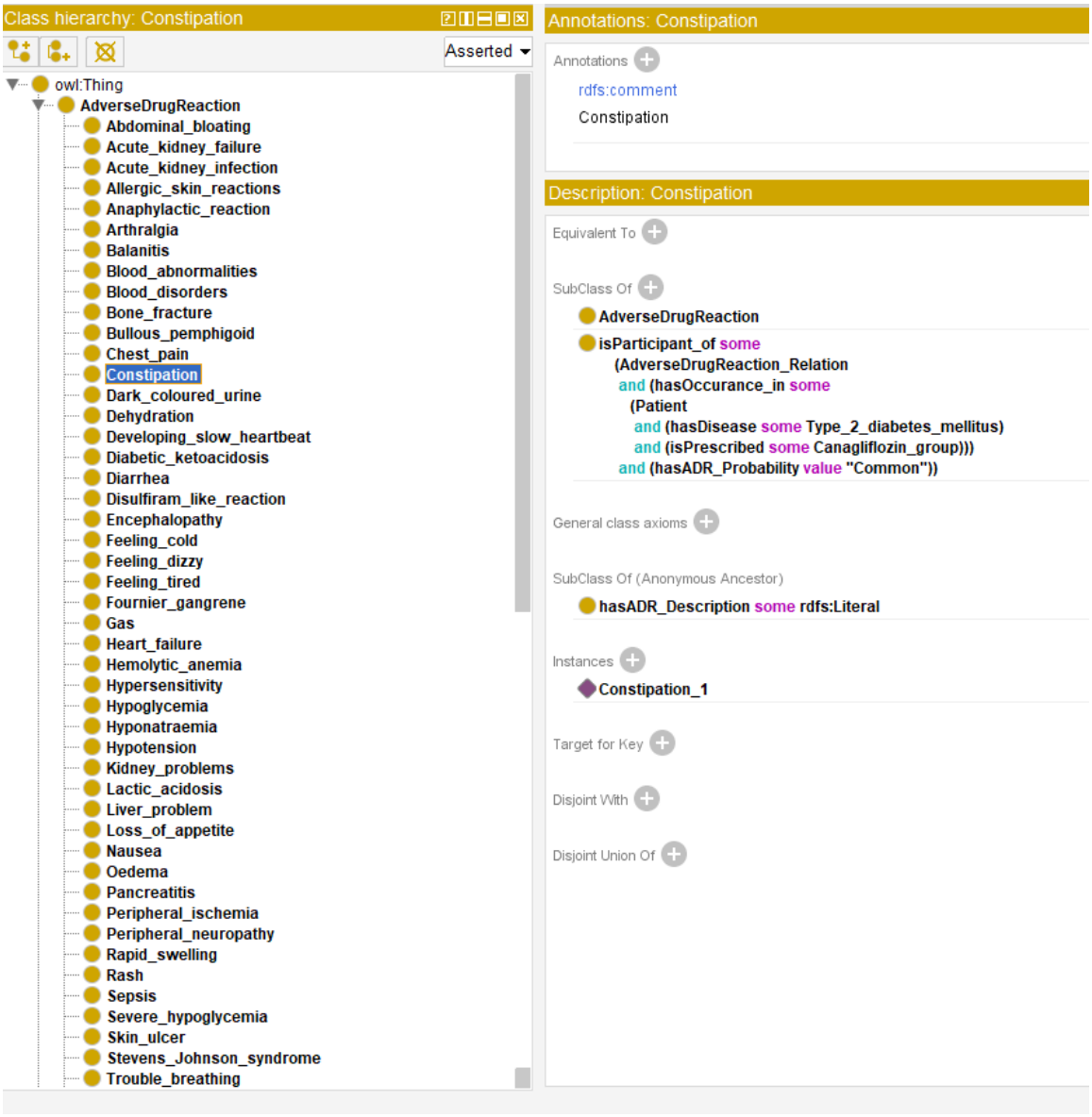

Class hierarchy: Blood_abnormalities
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Blood_abnormalities
Annotations
rdfs:comment
Blood abnormalities
Description: Blood_abnormalities
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Gliclazide_group)))
and (hasADR_Probability value "Very rare"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Blood_abnormalities_1
Target for Key
Disjoint With
Disjoint Union Of

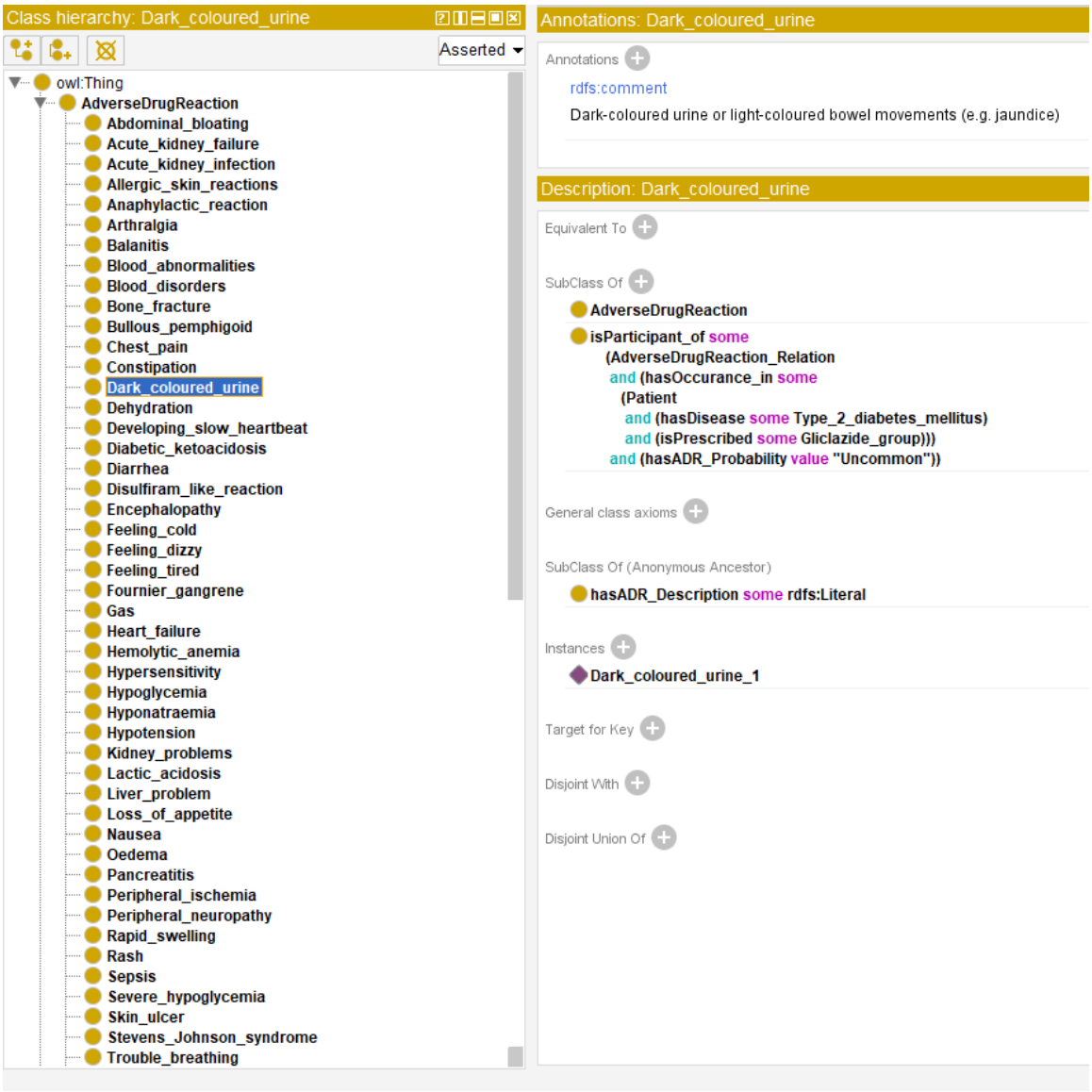

Class hierarchy: Blood_disorders
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Blood_disorders
Annotations
rdfs:comment
Blood disorders
Description: Blood_disorders
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Glyburide_group)))
and (hasADR_Probability value "Rare"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Blood_disorders_1
Target for Key
Disjoint With
Disjoint Union Of

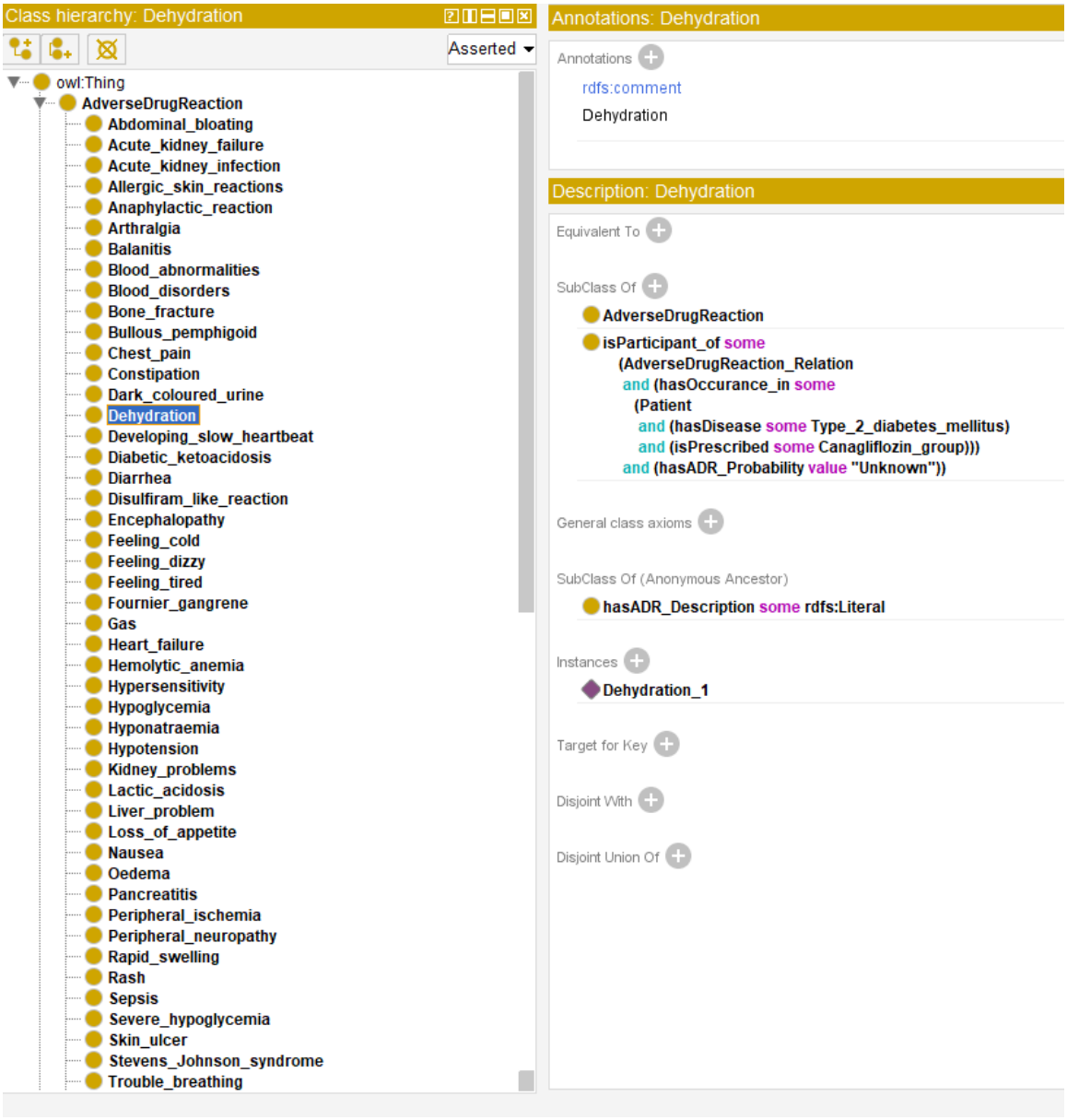

Class hierarchy: Bone_fracture
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Bone_fracture
Annotations
rdfs:comment
Bone fracture
Description: Bone_fracture
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Canagliflozin_group)))
and (hasADR_Probability value "Common"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Bone_fracture_1
Target for Key
Disjoint With
Disjoint Union Of

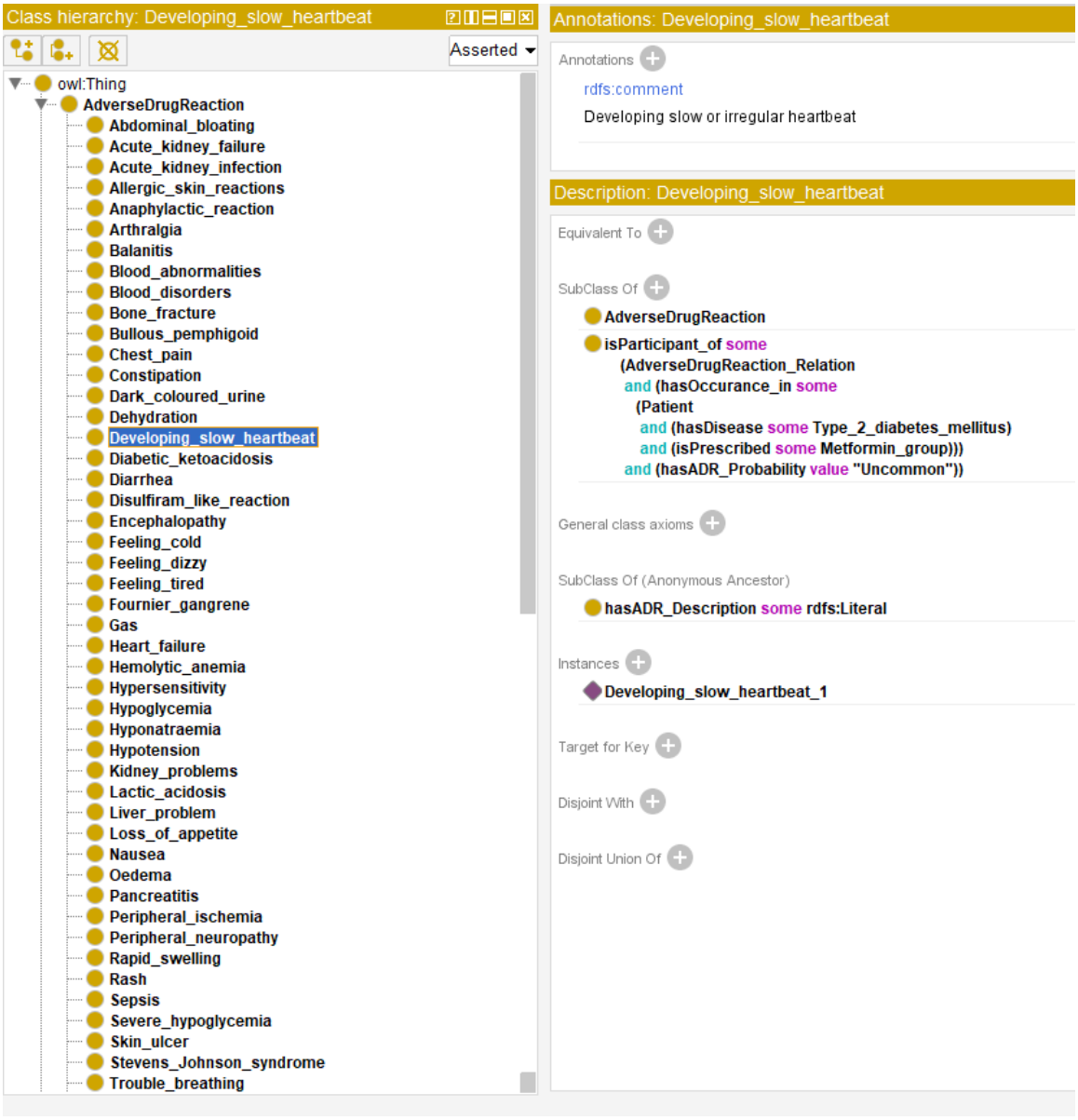

Class hierarchy: Bullous_pemphigoid
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Bullous_pemphigoid
Annotations
rdfs:comment
Bullous pemphigoid is severe skin reaction. Signs and symptoms include r
Description: Bullous_pemphigoid
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Alogliptin_group)))
and (hasADR_Probability value "Very rare"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Linagliptin_group)))
and (hasADR_Probability value "Rare"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Saxagliptin_group)))
and (hasADR_Probability value "Very rare"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Sitagliptin_group)))
and (hasADR_Probability value "Rare"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal

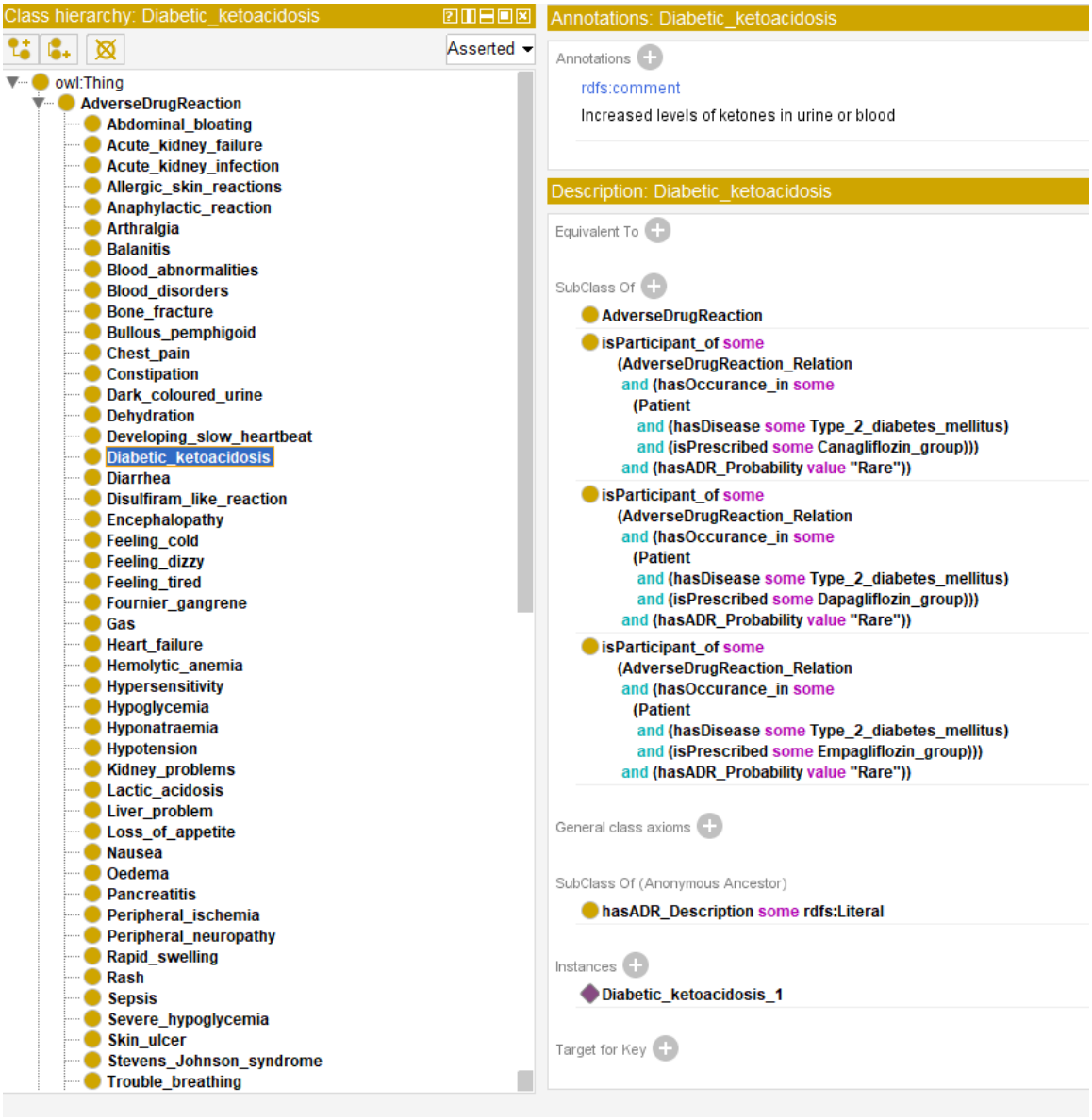

Class hierarchy: Chest_pain
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Chest_pain
Annotations
rdfs:comment
Chest pain or pressure
Description: Chest_pain
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Gliclazide_group)))
and (hasADR_Probability value "Uncommon"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Chest_pain_1
Target for Key
Disjoint With
Disjoint Union Of

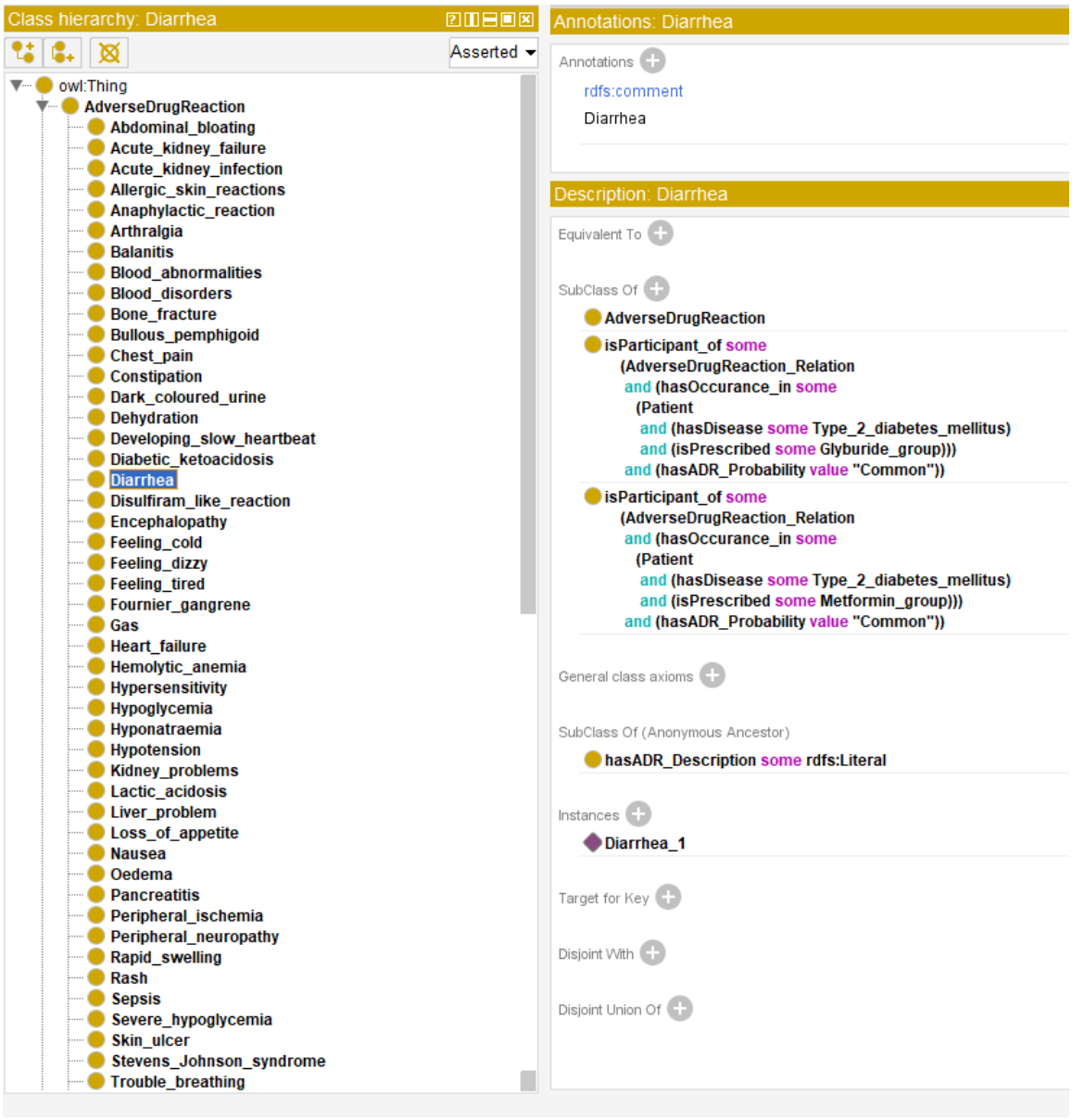

Class hierarchy: Constipation
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Constipation
Annotations
rdfs:comment
Constipation
Description: Constipation
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Canagliflozin_group)))
and (hasADR_Probability value "Common"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Constipation_1
Target for Key
Disjoint With
Disjoint Union Of

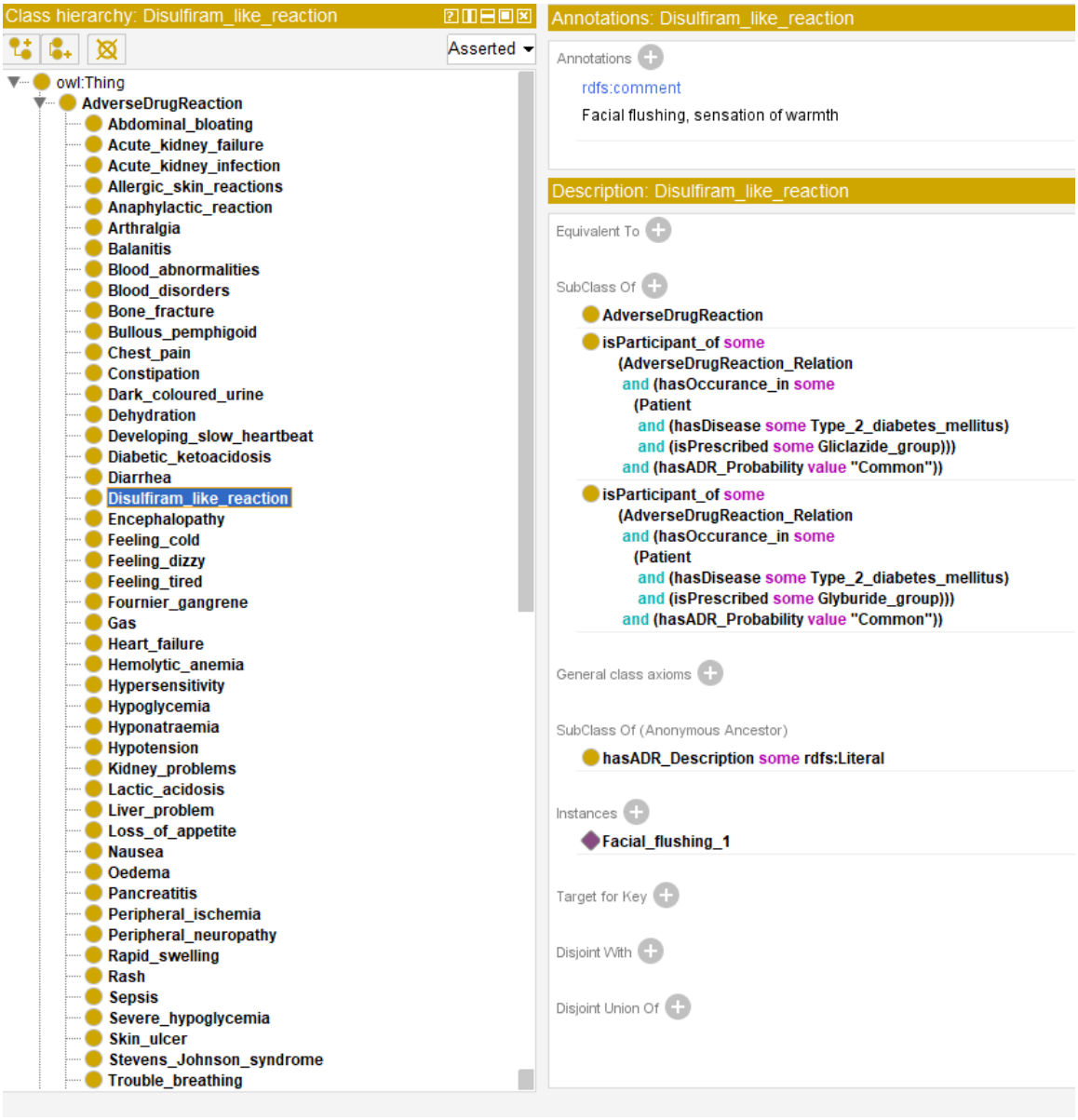

Class hierarchy: Dark_coloured_urine
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Dark_coloured_urine
Annotations
rdfs:comment
Dark-coloured urine or light-coloured bowel movements (e.g. jaundice)
Description: Dark_coloured_urine
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Gliclazide_group)))
and (hasADR_Probability value "Uncommon"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Dark_coloured_urine_1
Target for Key
Disjoint With
Disjoint Union Of

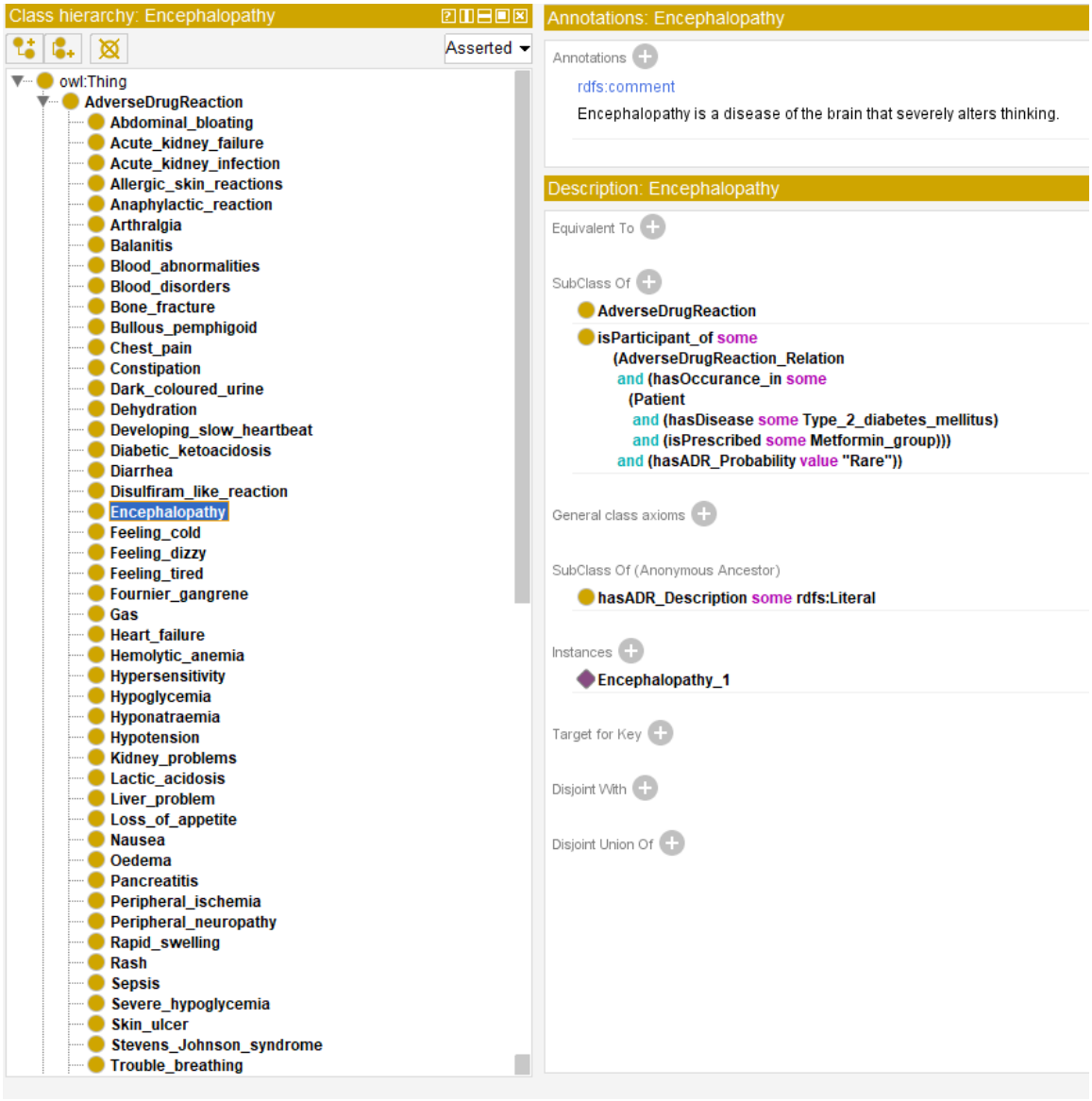

Class hierarchy: Dehydration
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Dehydration
Annotations
rdfs:comment
Dehydration
Description: Dehydration
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Canagliflozin_group)))
and (hasADR_Probability value "Unknown"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Dehydration_1
Target for Key
Disjoint With
Disjoint Union Of

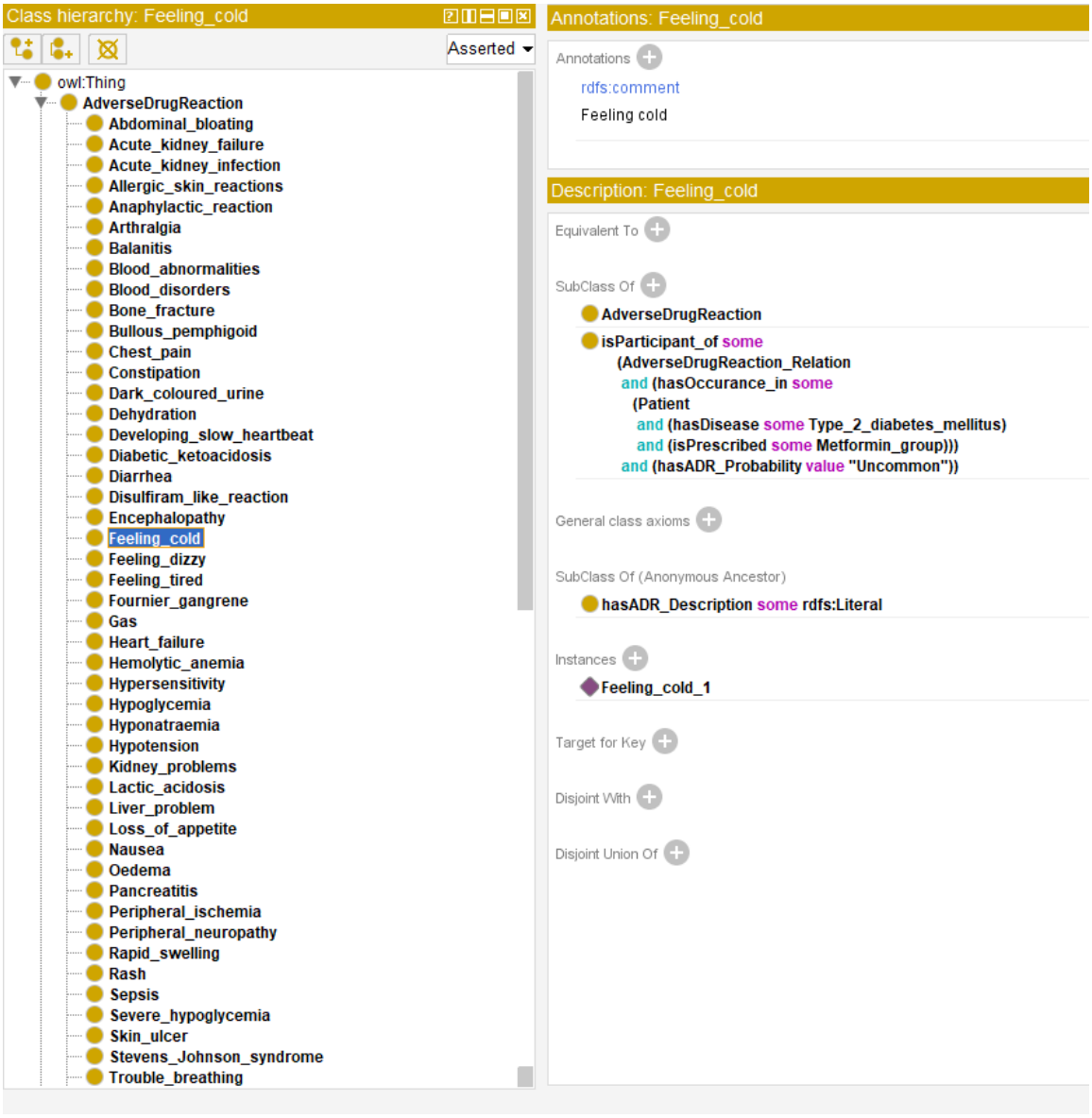

Class hierarchy: Developing_slow_heartbeat
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Developing_slow_heartbeat
Annotations
rdfs:comment
Developing slow or irregular heartbeat
Description: Developing_slow_heartbeat
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Metformin_group)))
and (hasADR_Probability value "Uncommon"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Developing_slow_heartbeat_1
Target for Key
Disjoint With
Disjoint Union Of

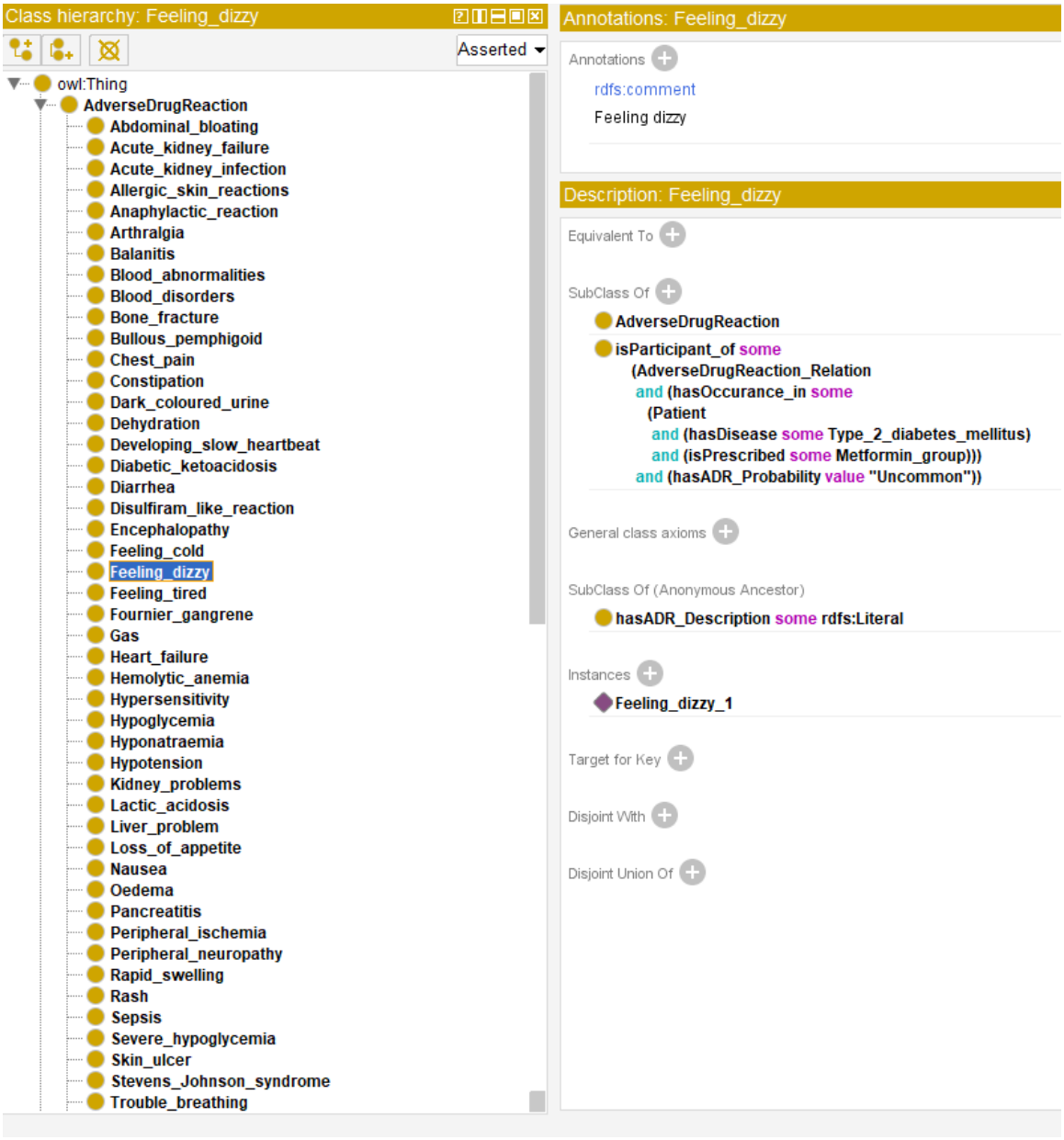

Class hierarchy: Diabetic_ketoacidosis
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Diabetic_ketoacidosis
Annotations
rdfs:comment
Increased levels of ketones in urine or blood
Description: Diabetic_ketoacidosis
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Canagliflozin_group)))
and (hasADR_Probability value "Rare"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Dapagliflozin_group)))
and (hasADR_Probability value "Rare"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Empagliflozin_group)))
and (hasADR_Probability value "Rare"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Diabetic_ketoacidosis_1
Target for Key

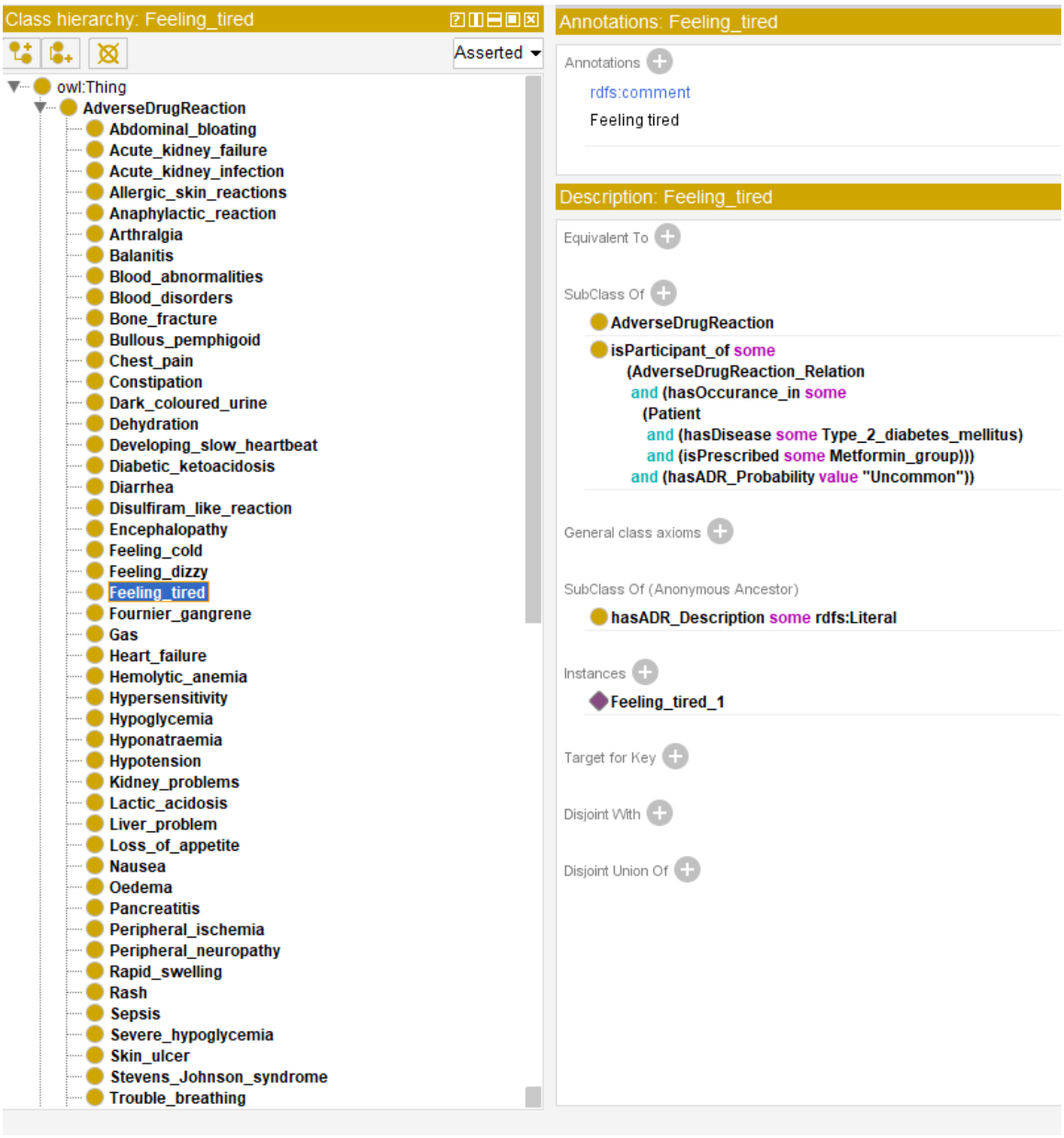

Class hierarchy: Diarrhea
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Diarrhea
Annotations
rdfs:comment
Diarrhea
Description: Diarrhea
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Glyburide_group)))
and (hasADR_Probability value "Common"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Metformin_group)))
and (hasADR_Probability value "Common"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Diarrhea_1
Target for Key
Disjoint With
Disjoint Union Of

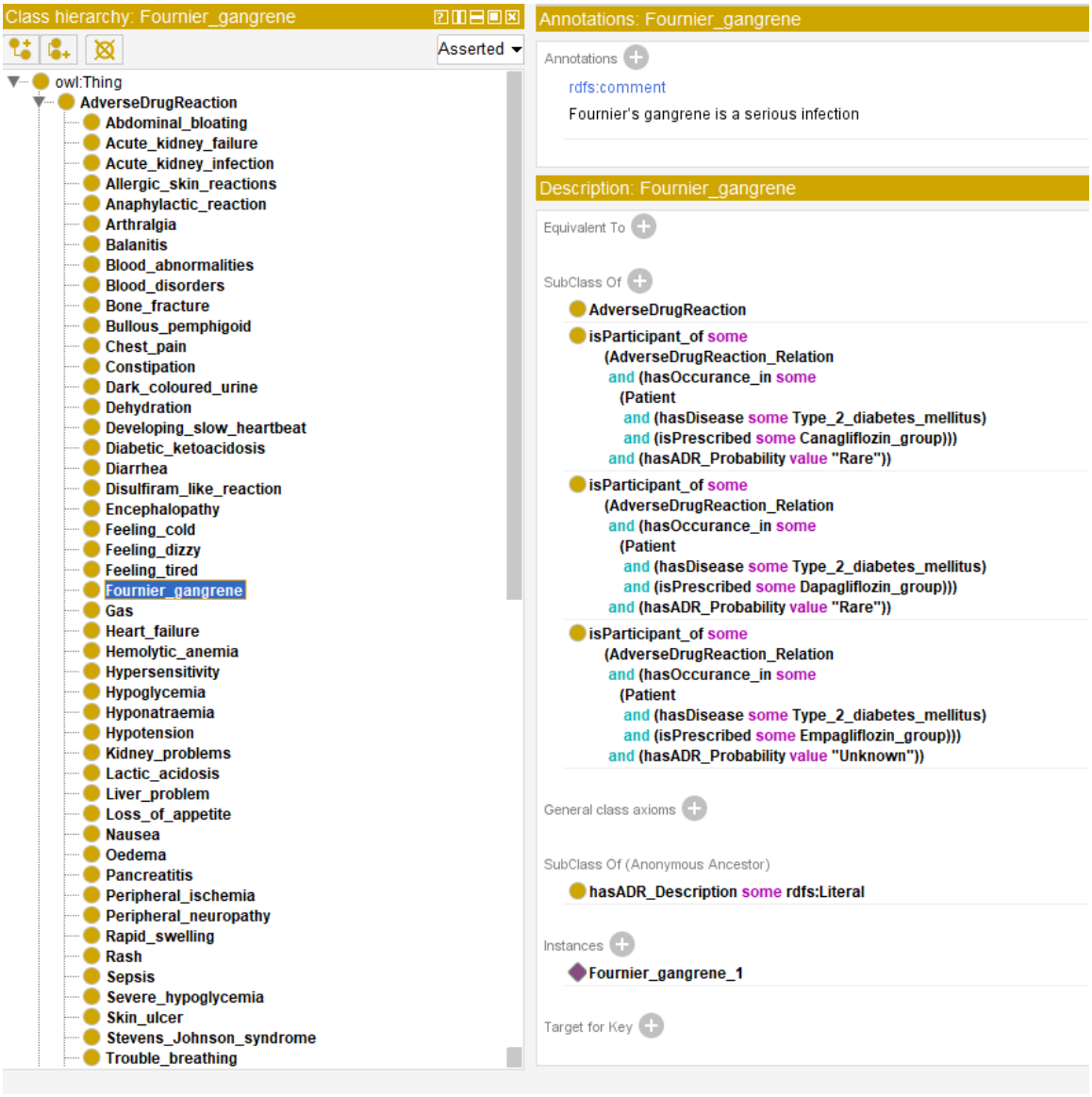

Class hierarchy: Disulfiram_like_reaction
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Disulfiram_like_reaction
Annotations
rdfs:comment
Facial flushing, sensation of warmth
Description: Disulfiram_like_reaction
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Gliclazide_group)))
and (hasADR_Probability value "Common"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Glyburide_group)))
and (hasADR_Probability value "Common"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Facial_flushing_1
Target for Key
Disjoint With
Disjoint Union Of

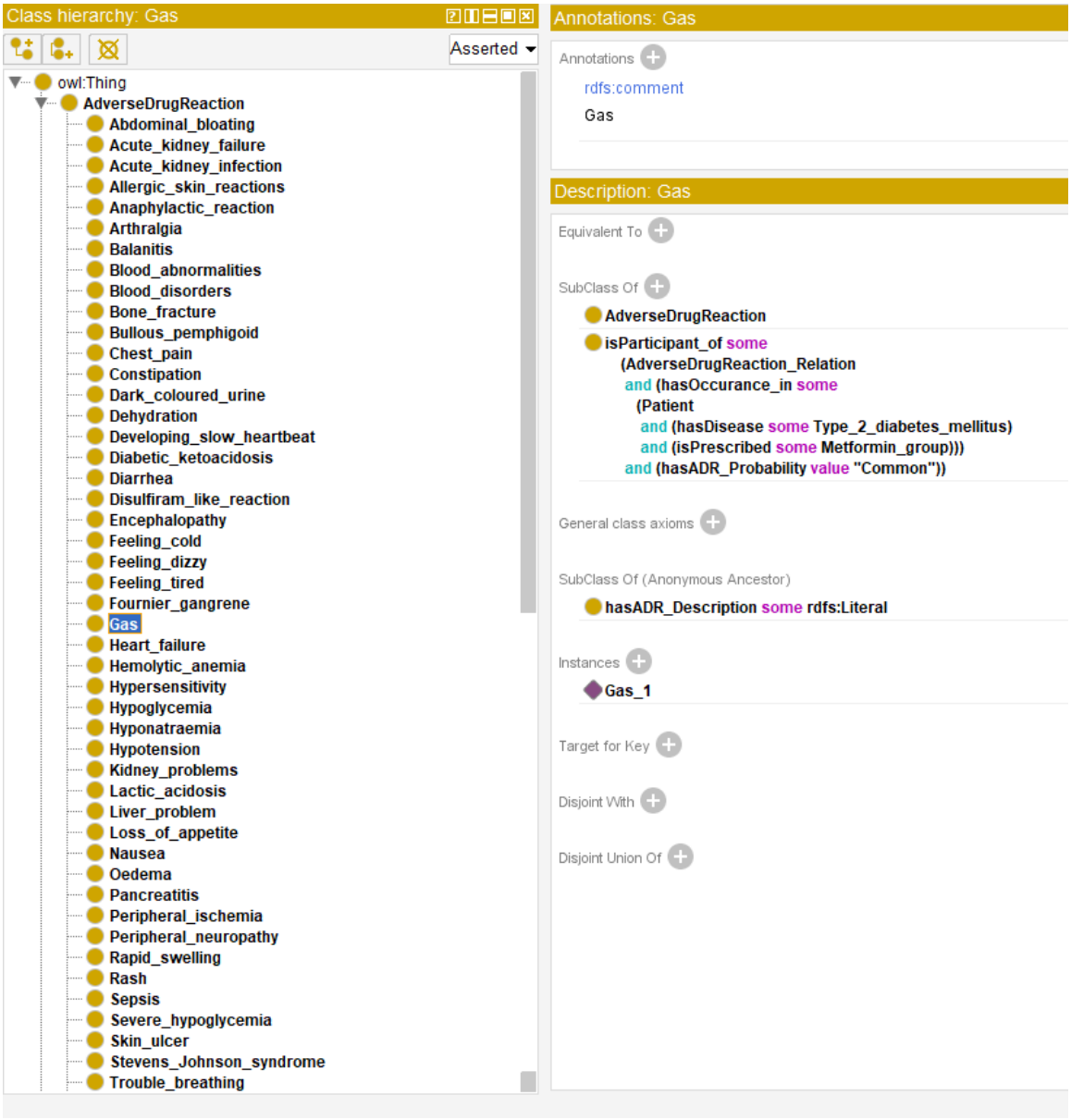

Class hierarchy: Encephalopathy
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Encephalopathy
Annotations
rdfs:comment
Encephalopathy is a disease of the brain that severely alters thinking.
Description: Encephalopathy
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Metformin_group)))
and (hasADR_Probability value "Rare"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Encephalopathy_1
Target for Key
Disjoint With
Disjoint Union Of

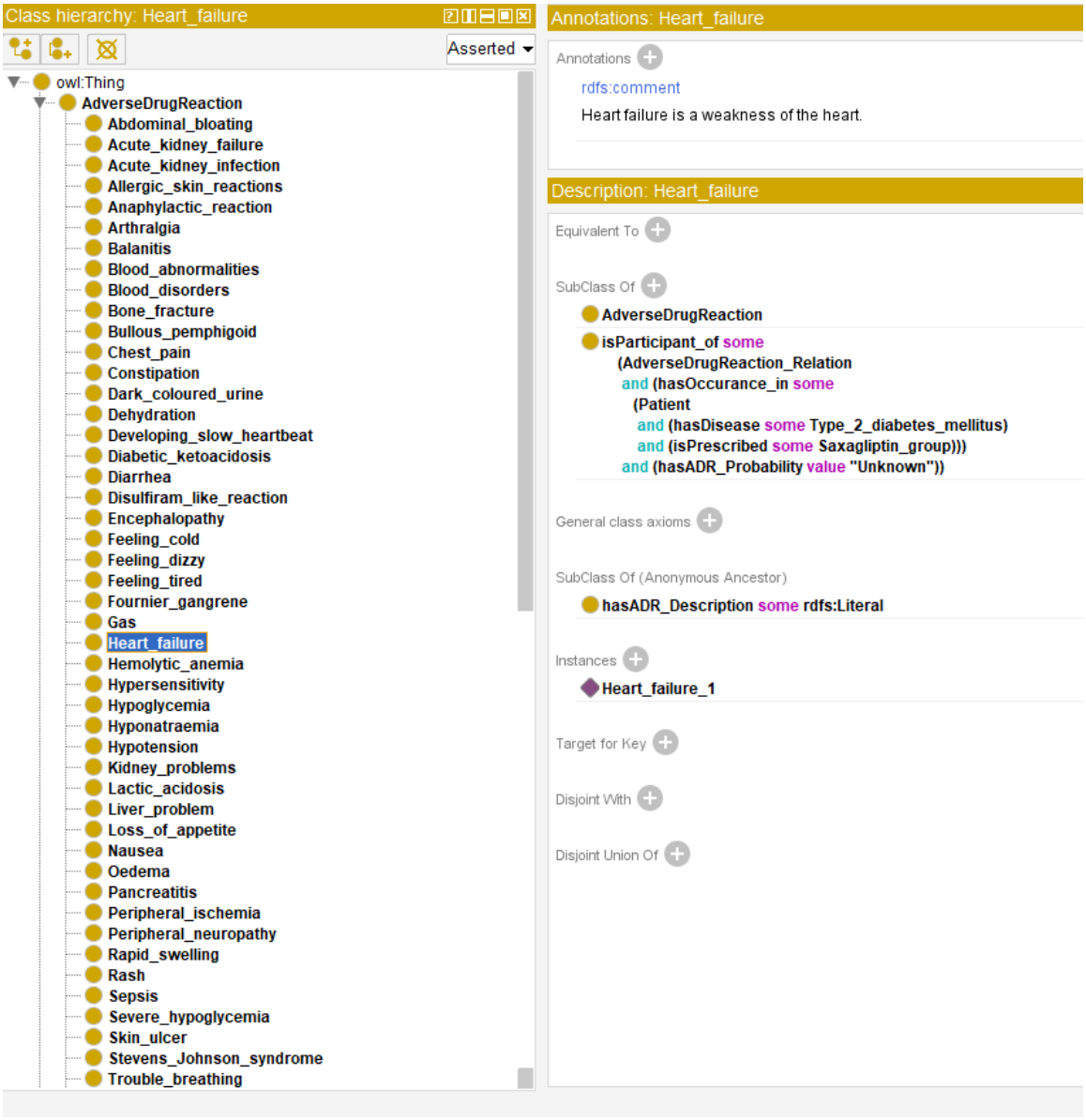

Class hierarchy: Feeling_cold
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Feeling_cold
Annotations
rdfs:comment
Feeling cold
Description: Feeling_cold
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Metformin_group)))
and (hasADR_Probability value "Uncommon"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Feeling_cold_1
Target for Key
Disjoint With
Disjoint Union Of

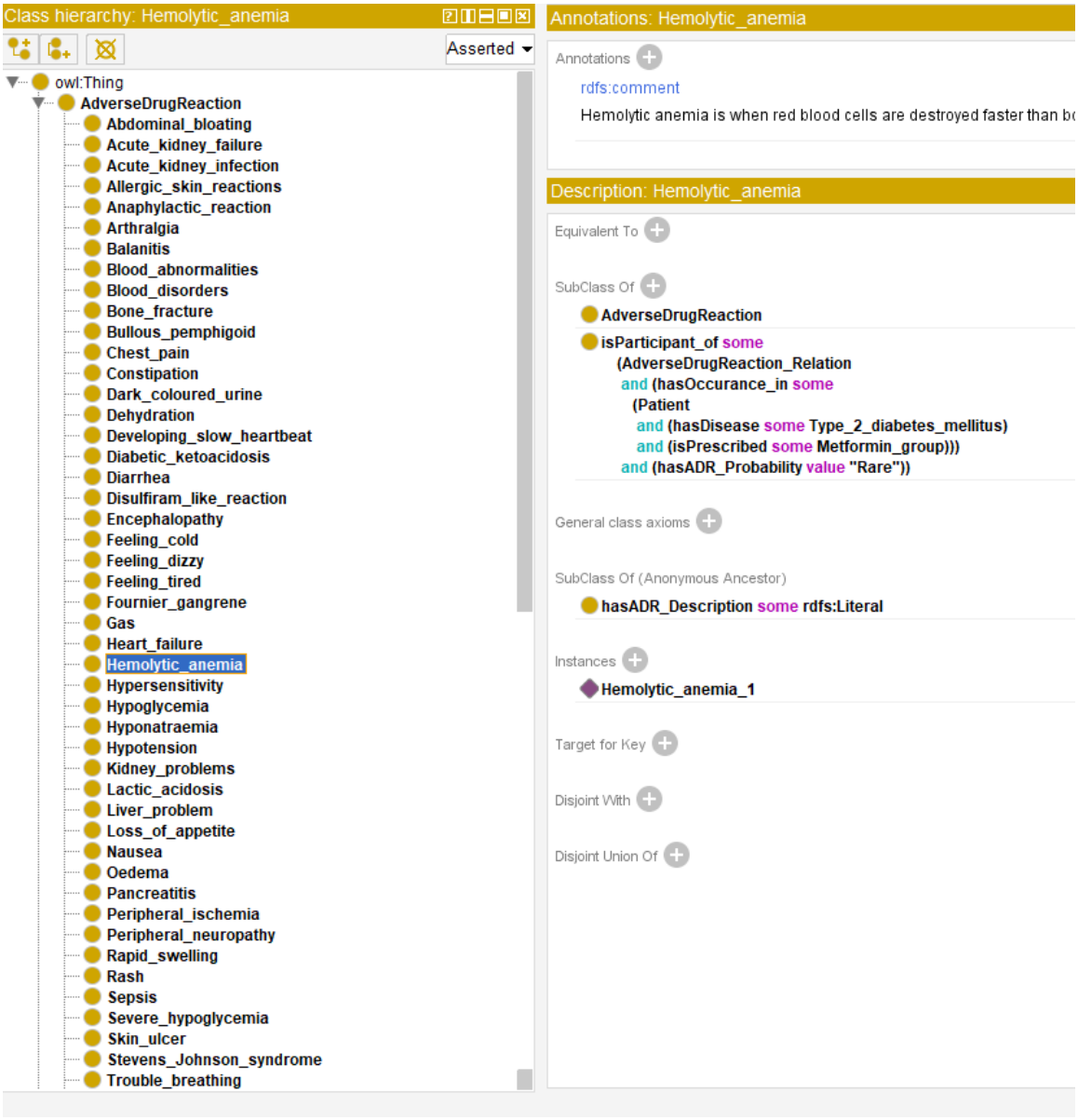

Class hierarchy: Feeling_dizzy
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Feeling_dizzy
Annotations
rdfs:comment
Feeling dizzy
Description: Feeling_dizzy
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Metformin_group)))
and (hasADR_Probability value "Uncommon"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Feeling_dizzy_1
Target for Key
Disjoint With
Disjoint Union Of

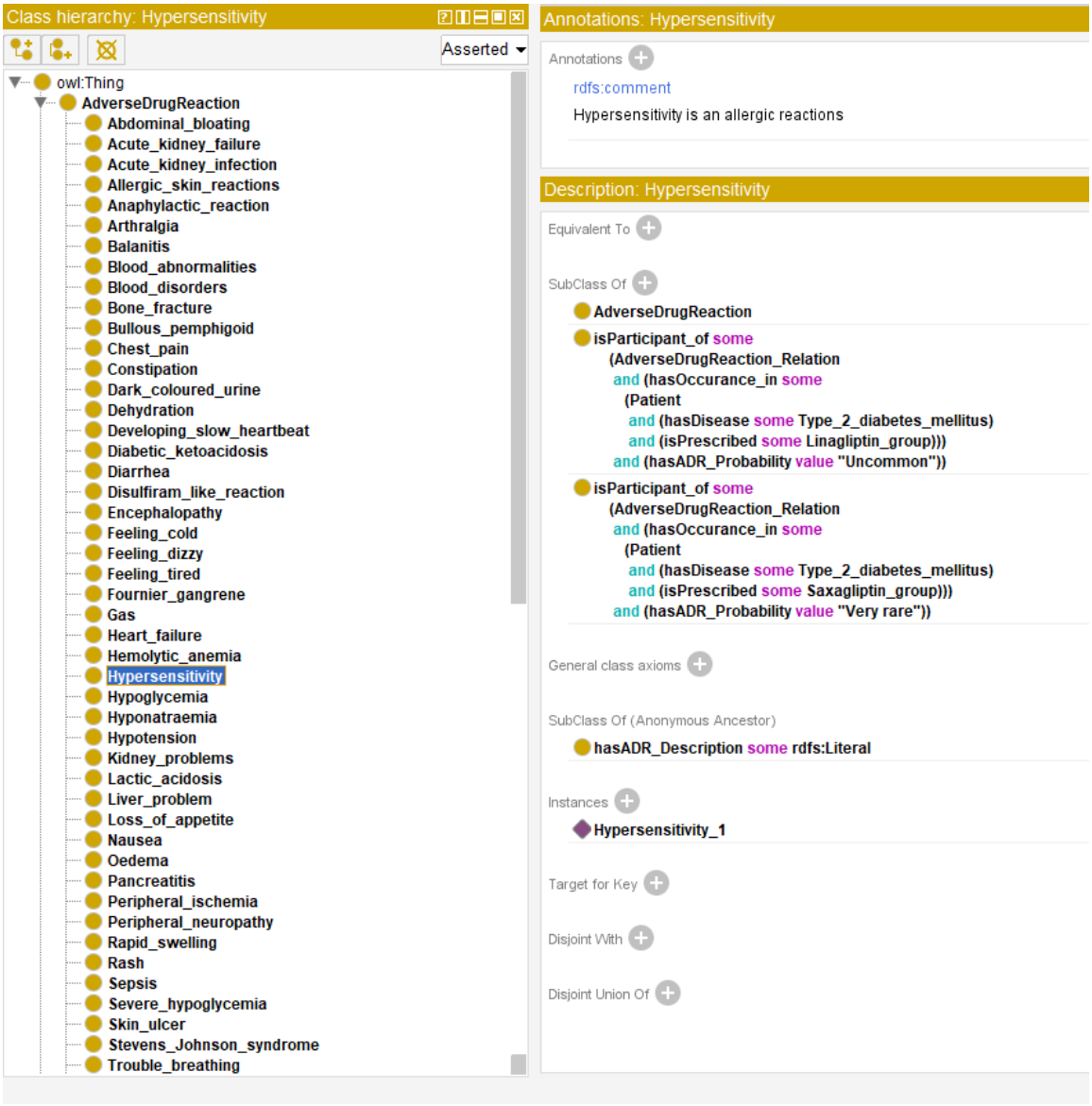

Class hierarchy: Feeling_tired
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Feeling_tired
Annotations
rdfs:comment
Feeling tired
Description: Feeling_tired
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Metformin_group)))
and (hasADR_Probability value "Uncommon"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Feeling_tired_1
Target for Key
Disjoint With
Disjoint Union Of

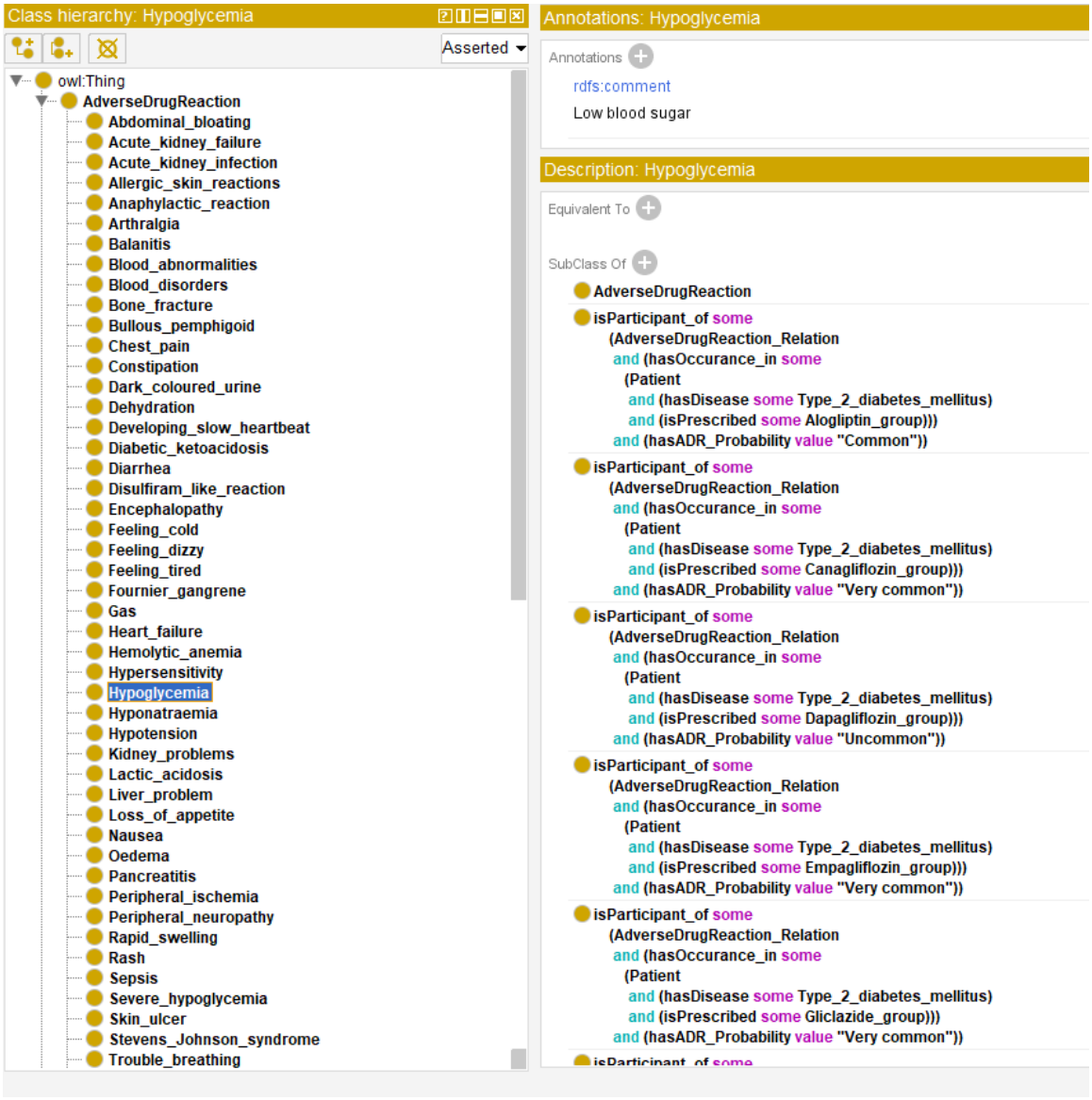

Class hierarchy: Fournier_gangrene
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Fournier_gangrene
Annotations
rdfs:comment
Fournier's gangrene is a serious infection
Description: Fournier_gangrene
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Canagliflozin_group)))
and (hasADR_Probability value "Rare"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Dapagliflozin_group)))
and (hasADR_Probability value "Rare"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Empagliflozin_group)))
and (hasADR_Probability value "Unknown"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Fournier_gangrene_1
Target for Key

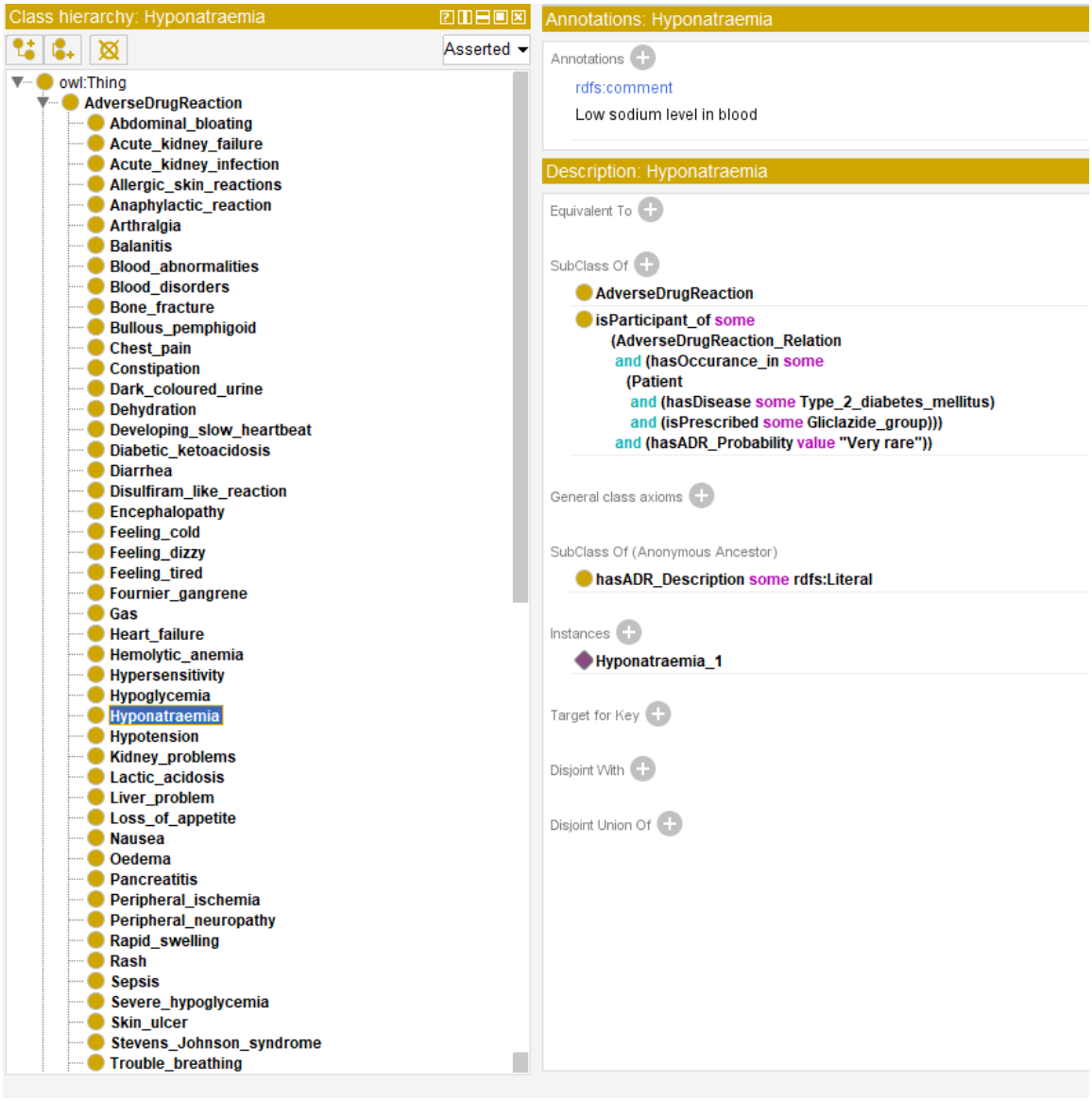

Class hierarchy: Gas
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Gas
Annotations
rdfs:comment
Gas
Description: Gas
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Metformin_group)))
and (hasADR_Probability value "Common"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Gas_1
Target for Key
Disjoint With
Disjoint Union Of

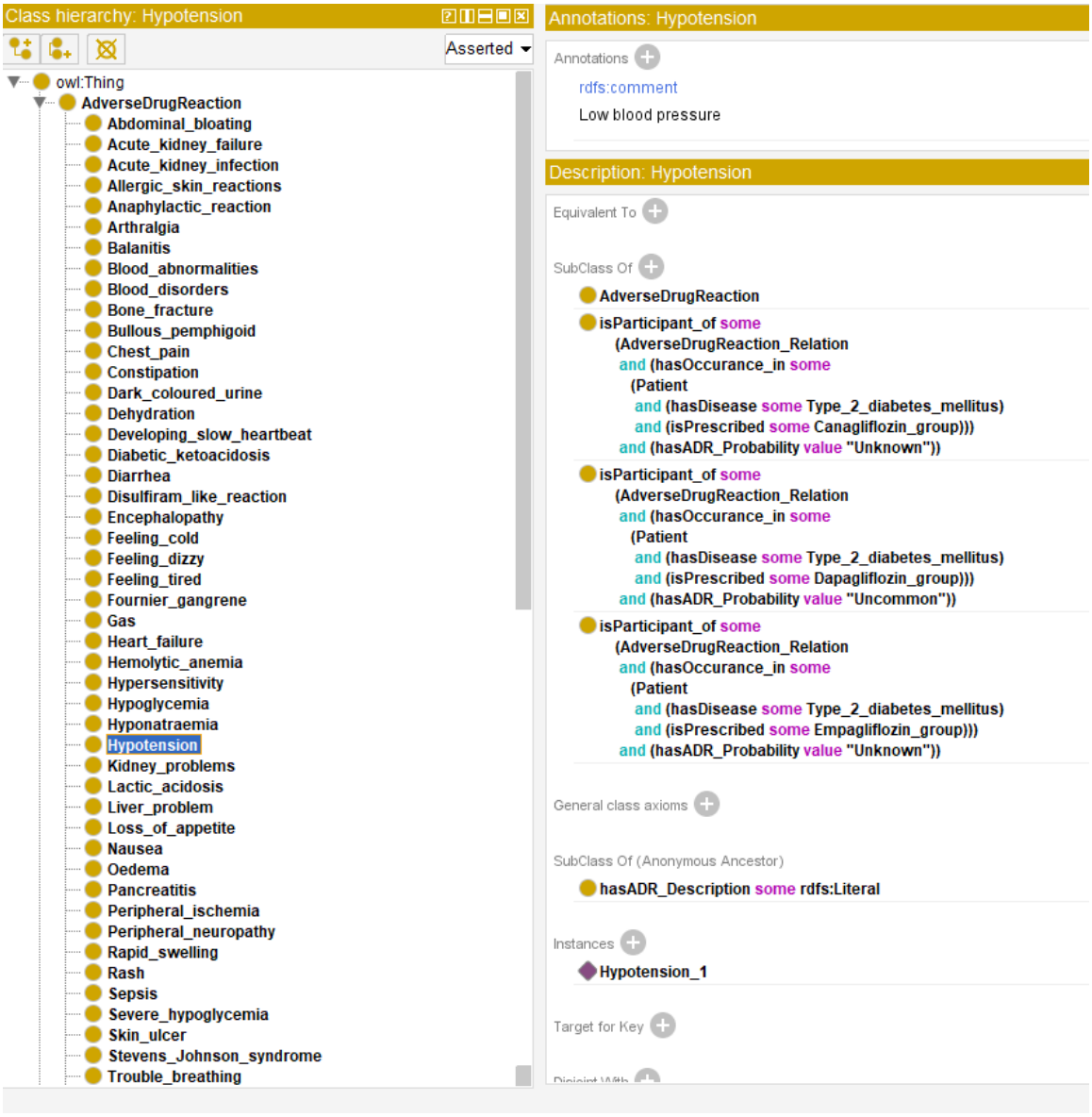

Class hierarchy: Heart_failure
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Heart_failure
Annotations
rdfs:comment
Heart failure is a weakness of the heart.
Description: Heart_failure
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Saxagliptin_group)))
and (hasADR_Probability value "Unknown"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Heart_failure_1
Target for Key
Disjoint With
Disjoint Union Of

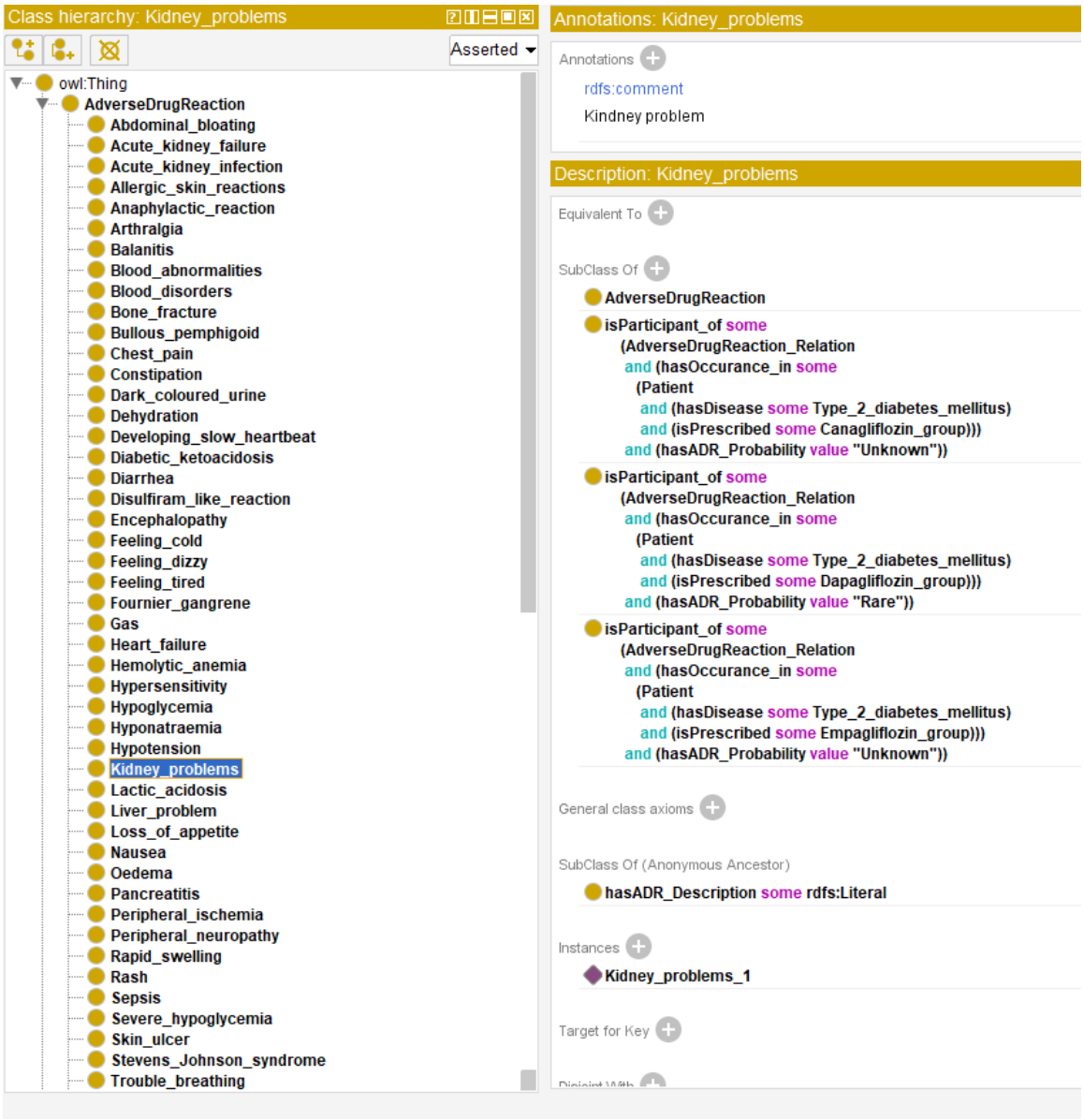

Class hierarchy: Hemolytic_anemia
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Hemolytic_anemia
Annotations
rdfs:comment
Hemolytic anemia is when red blood cells are destroyed faster than b
Description: Hemolytic_anemia
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Metformin_group)))
and (hasADR_Probability value "Rare"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Hemolytic_anemia_1
Target for Key
Disjoint With
Disjoint Union Of

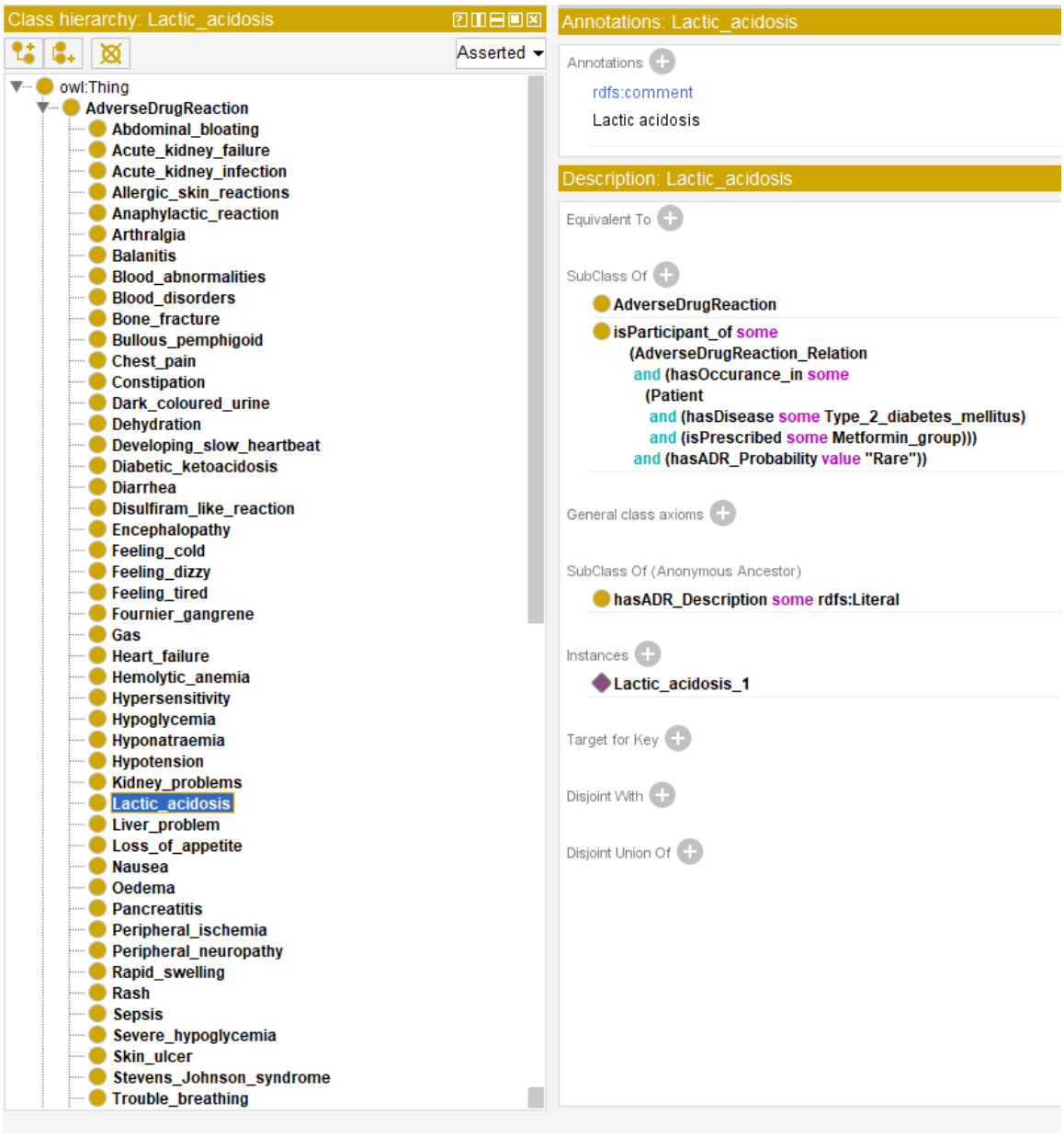

Class hierarchy: Hypersensitivity
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Hypersensitivity
Annotations
rdfs:comment
Hypersensitivity is an allergic reactions
Description: Hypersensitivity
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Linagliptin_group)))
and (hasADR_Probability value "Uncommon"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Saxagliptin_group)))
and (hasADR_Probability value "Very rare"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Hypersensitivity_1
Target for Key
Disjoint With
Disjoint Union Of

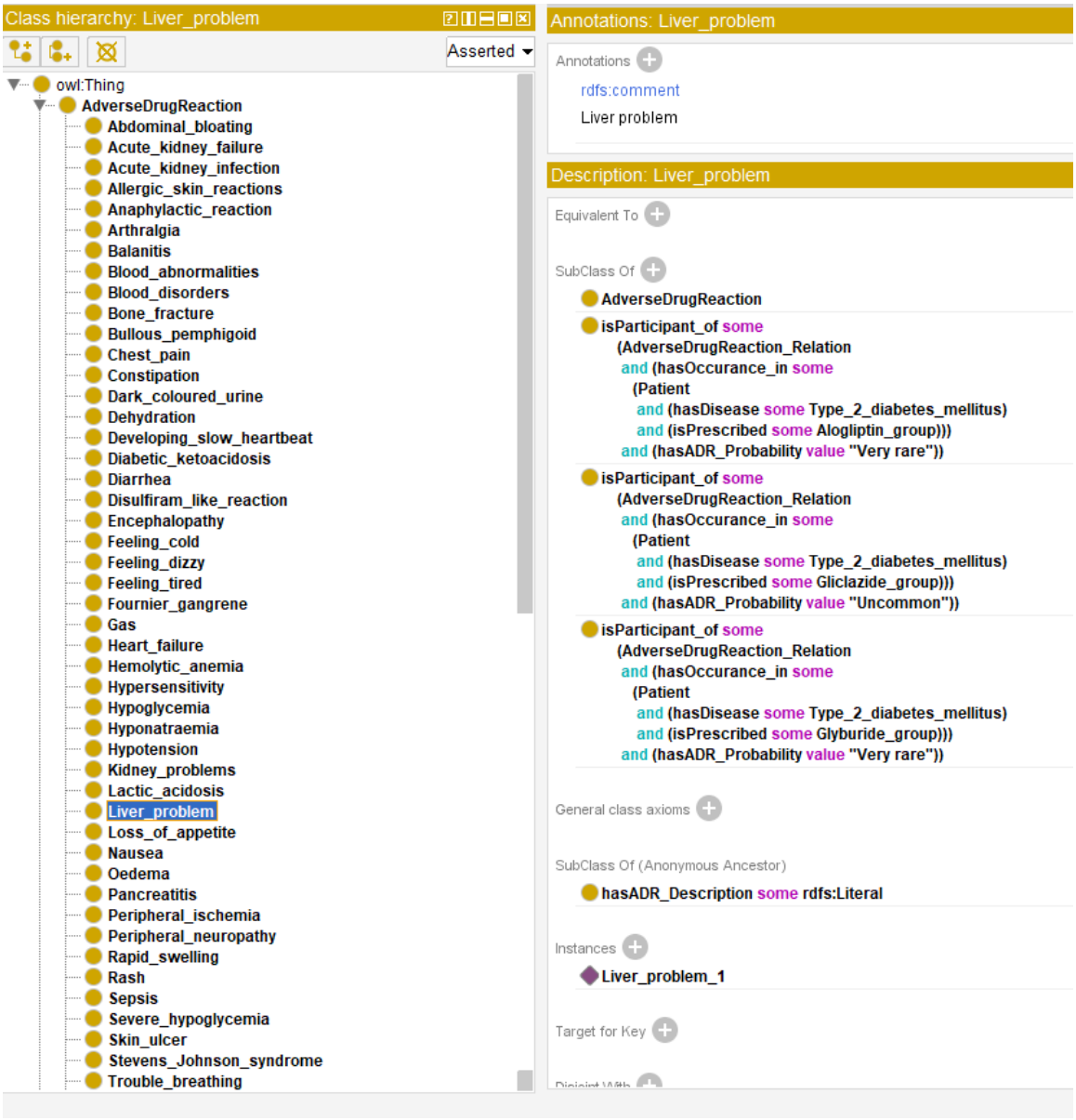

Class hierarchy: Hypoglycemia
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Hypoglycemia
Annotations
rdfs:comment
Low blood sugar
Description: Hypoglycemia
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some (AdverseDrugReaction_Relation and (hasOccurance_in some (Patient and (hasDisease some Type_2_diabetes_mellitus) and (isPrescribed some Alogliptin_group))) and (hasADR_Probability value "Common"))
isParticipant_of some (AdverseDrugReaction_Relation and (hasOccurance_in some (Patient and (hasDisease some Type_2_diabetes_mellitus) and (isPrescribed some Canagliflozin_group))) and (hasADR_Probability value "Very common"))
isParticipant_of some (AdverseDrugReaction_Relation and (hasOccurance_in some (Patient and (hasDisease some Type_2_diabetes_mellitus) and (isPrescribed some Dapagliflozin_group))) and (hasADR_Probability value "Uncommon"))
isParticipant_of some (AdverseDrugReaction_Relation and (hasOccurance_in some (Patient and (hasDisease some Type_2_diabetes_mellitus) and (isPrescribed some Empagliflozin_group))) and (hasADR_Probability value "Very common"))
isParticipant_of some (AdverseDrugReaction_Relation and (hasOccurance_in some (Patient and (hasDisease some Type_2_diabetes_mellitus) and (isPrescribed some Gliclazide_group))) and (hasADR_Probability value "Very common"))

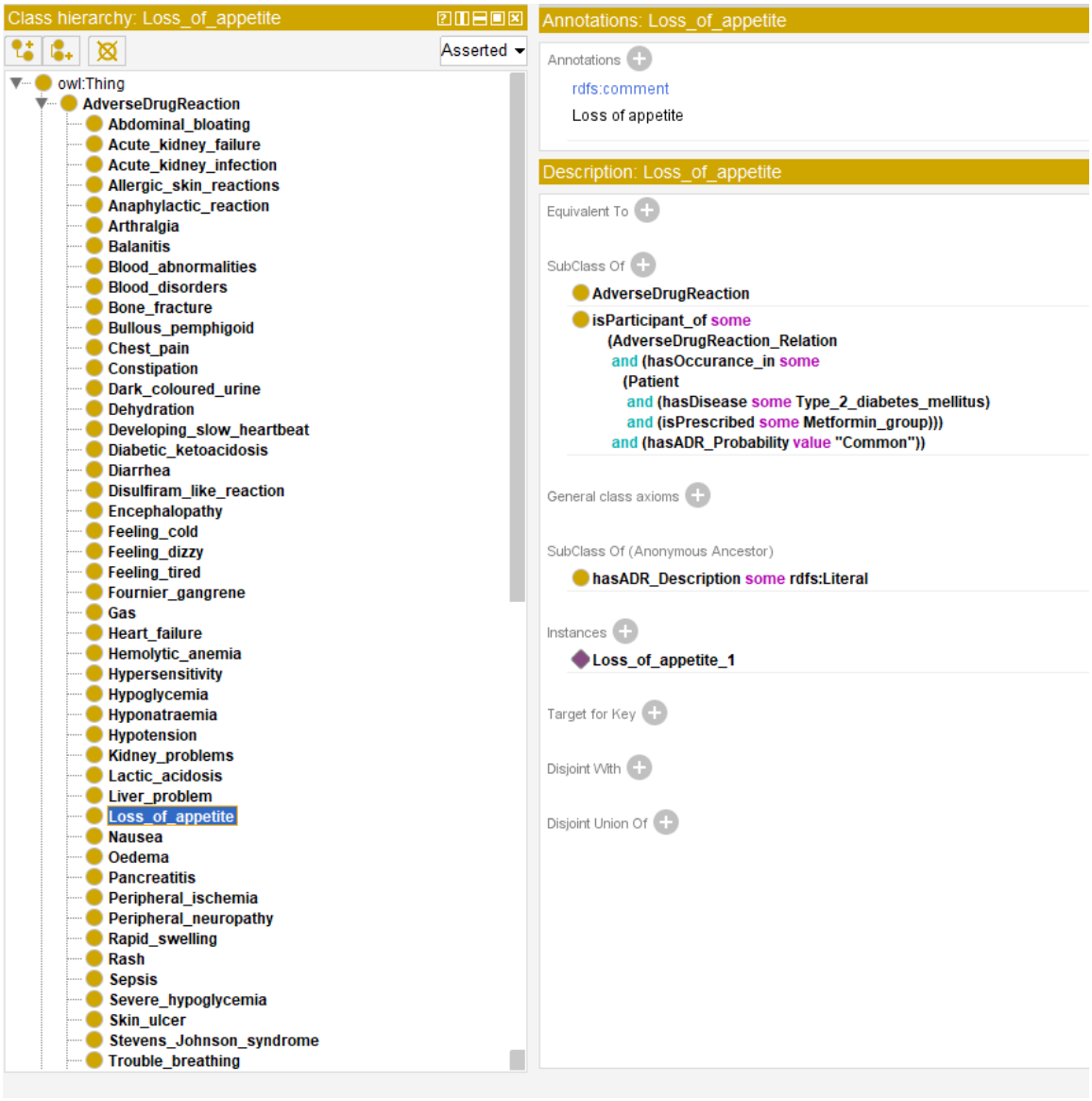

Class hierarchy: Hyponatraemia
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Hyponatraemia
Annotations
rdfs:comment
Low sodium level in blood
Description: Hyponatraemia
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Gliclazide_group)))
and (hasADR_Probability value "Very rare"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Hyponatraemia_1
Target for Key
Disjoint With
Disjoint Union Of

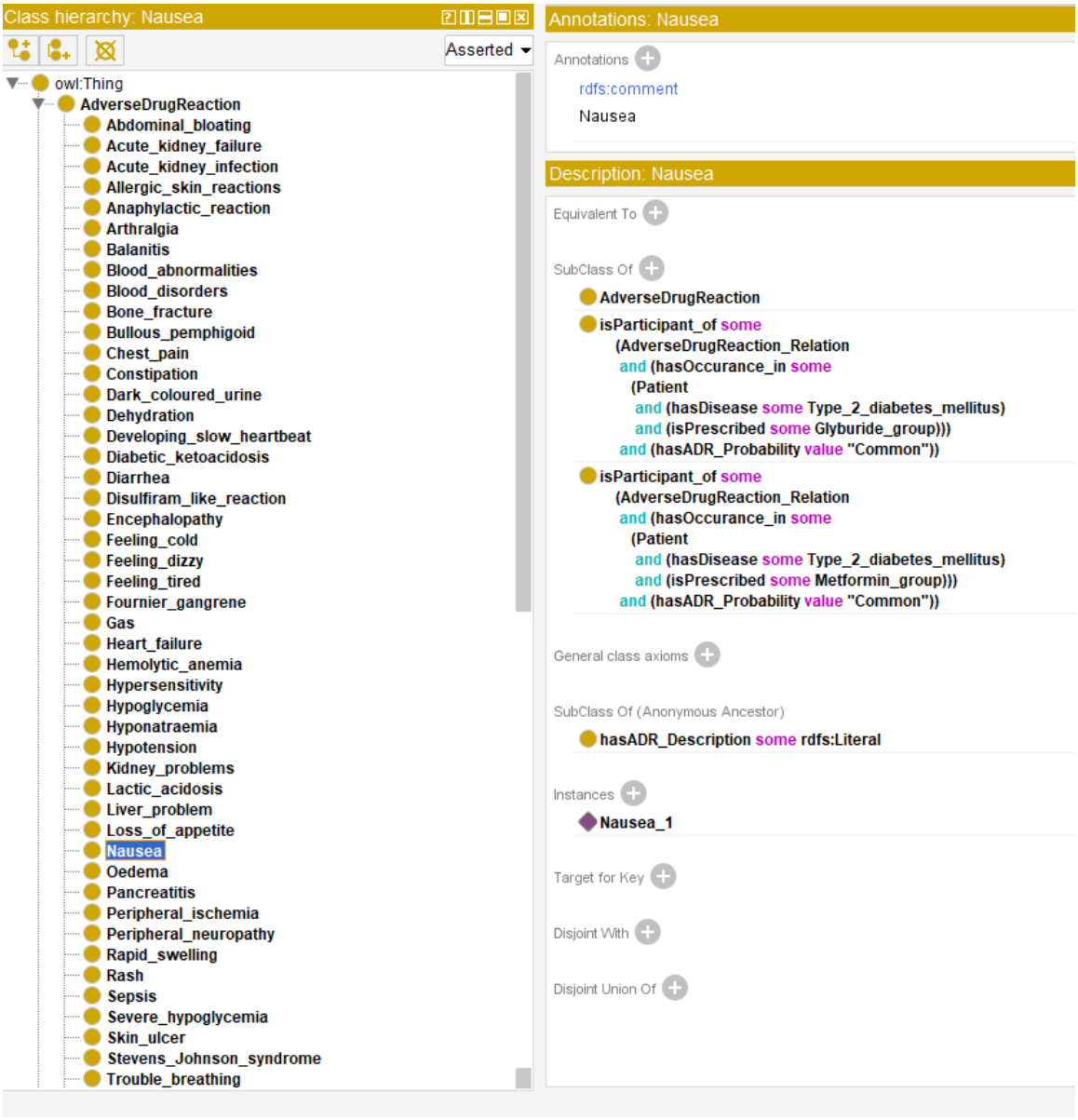

Class hierarchy: Hypotension
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Hypotension
Annotations
rdfs:comment
Low blood pressure
Description: Hypotension
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Canagliflozin_group)))
and (hasADR_Probability value "Unknown"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Dapagliflozin_group)))
and (hasADR_Probability value "Uncommon"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Empagliflozin_group)))
and (hasADR_Probability value "Unknown"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Hypotension_1
Target for Key

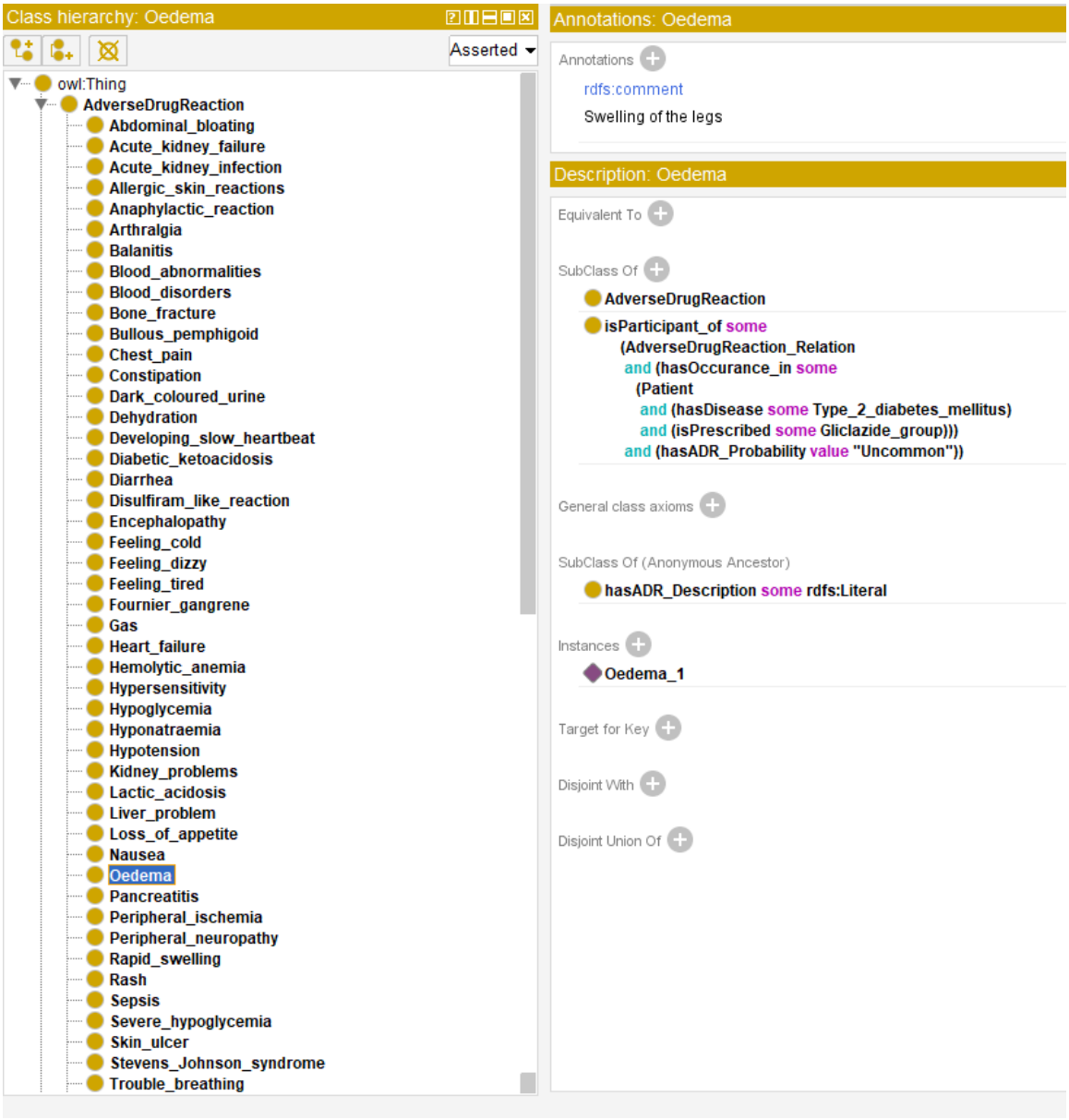

Class hierarchy: Kidney_problems
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Kidney_problems
Annotations
rdfs:comment
Kindney problem
Description: Kidney_problems
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Canagliflozin_group)))
and (hasADR_Probability value "Unknown"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Dapagliflozin_group)))
and (hasADR_Probability value "Rare"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Empagliflozin_group)))
and (hasADR_Probability value "Unknown"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Kidney_problems_1
Target for Key

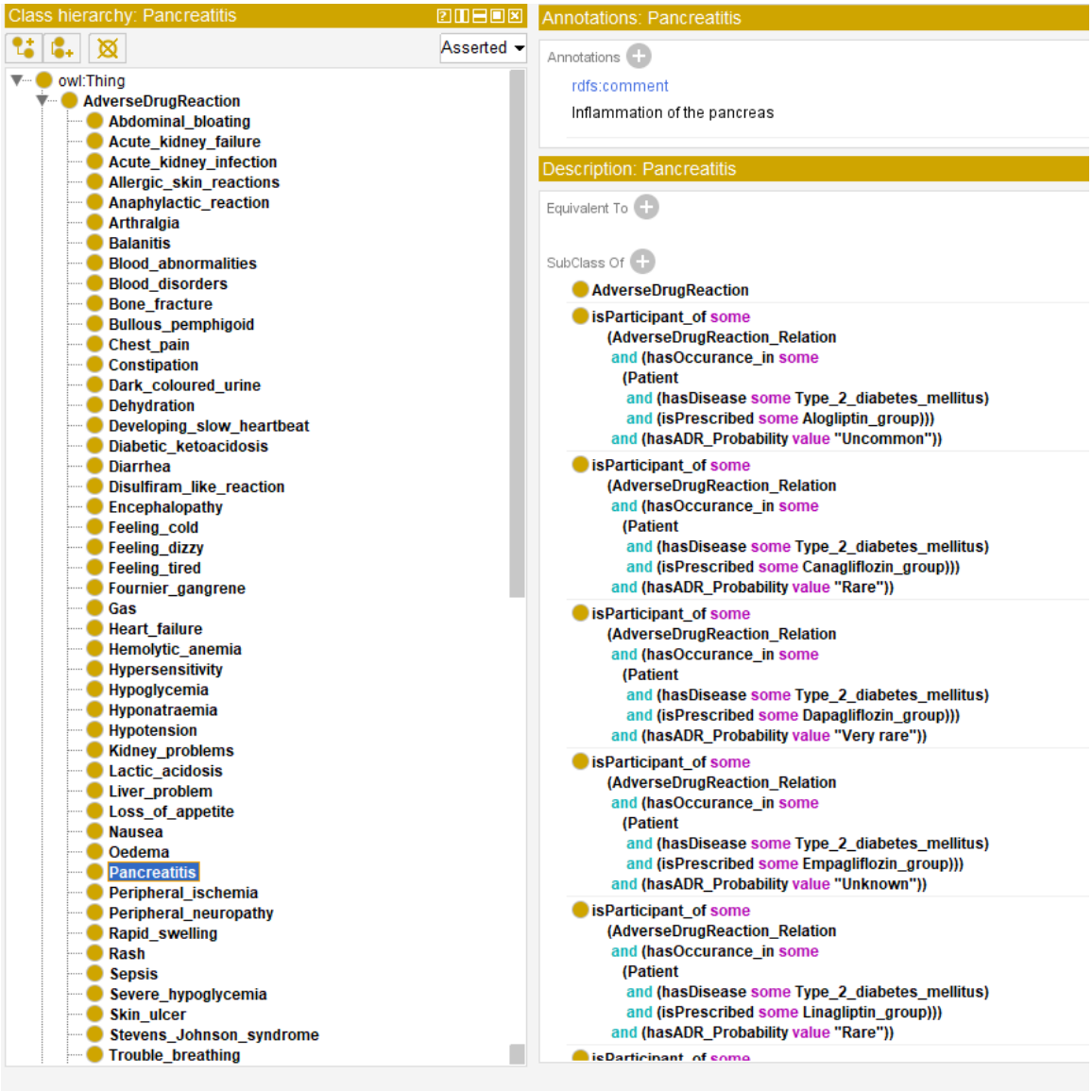

Class hierarchy: Lactic_acidosis
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Lactic_acidosis
Annotations
rdfs:comment
Lactic acidosis
Description: Lactic_acidosis
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Metformin_group)))
and (hasADR_Probability value "Rare"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Lactic_acidosis_1
Target for Key
Disjoint With
Disjoint Union Of

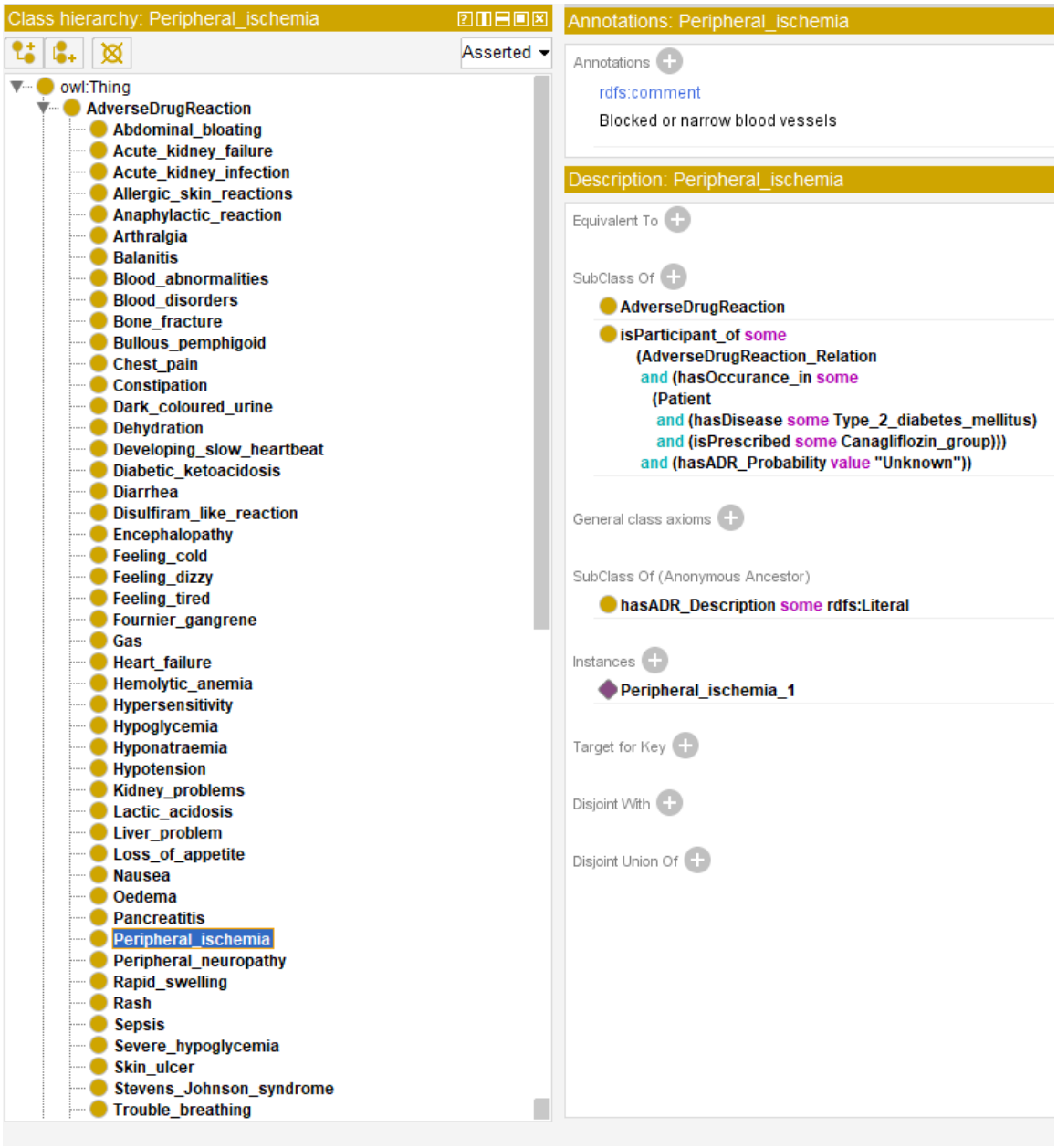

Class hierarchy: Liver_problem
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Liver_problem
Annotations
rdfs:comment
Liver problem
Description: Liver_problem
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Alogliptin_group)))
and (hasADR_Probability value "Very rare"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Gliclazide_group)))
and (hasADR_Probability value "Uncommon"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Glyburide_group)))
and (hasADR_Probability value "Very rare"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Liver_problem_1
Target for Key

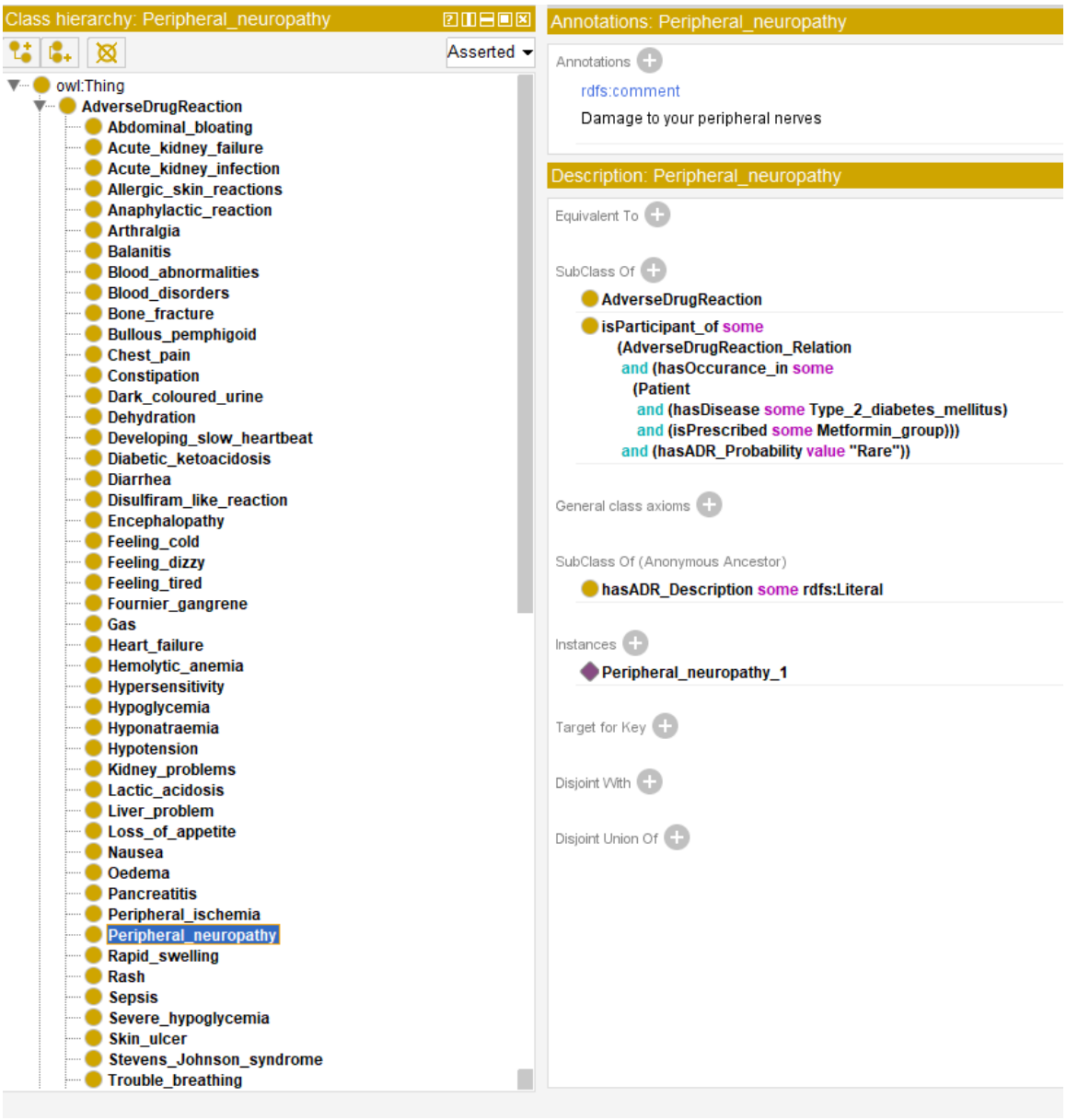

Class hierarchy: Loss_of_appetite
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Loss_of_appetite
Annotations
rdfs:comment
Loss of appetite
Description: Loss_of_appetite
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Metformin_group)))
and (hasADR_Probability value "Common"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Loss_of_appetite_1
Target for Key
Disjoint With
Disjoint Union Of

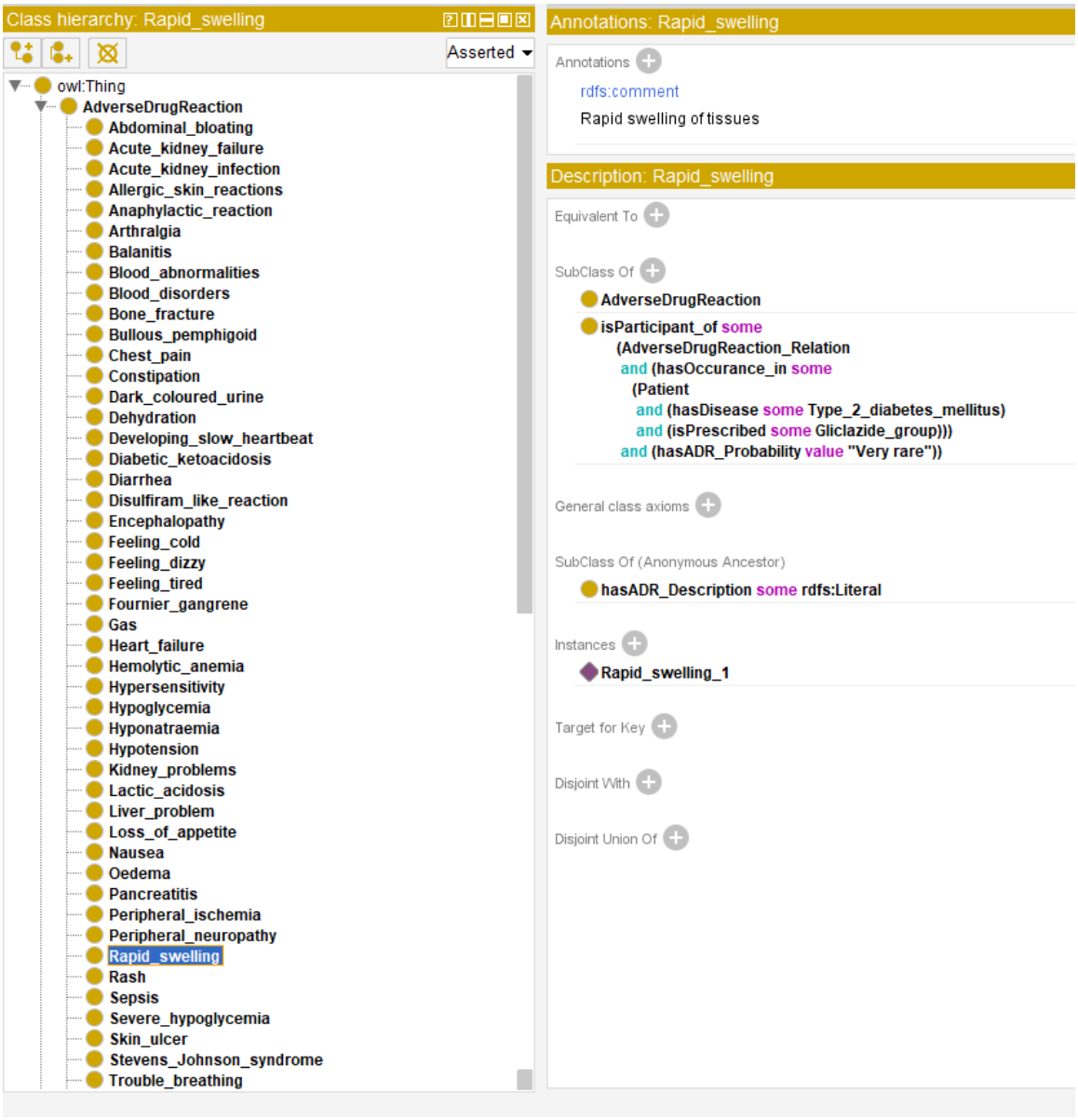

Class hierarchy: Nausea
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Nausea
Annotations
rdfs:comment
Nausea
Description: Nausea
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Glyburide_group)))
and (hasADR_Probability value "Common"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Metformin_group)))
and (hasADR_Probability value "Common"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Nausea_1
Target for Key
Disjoint With
Disjoint Union Of

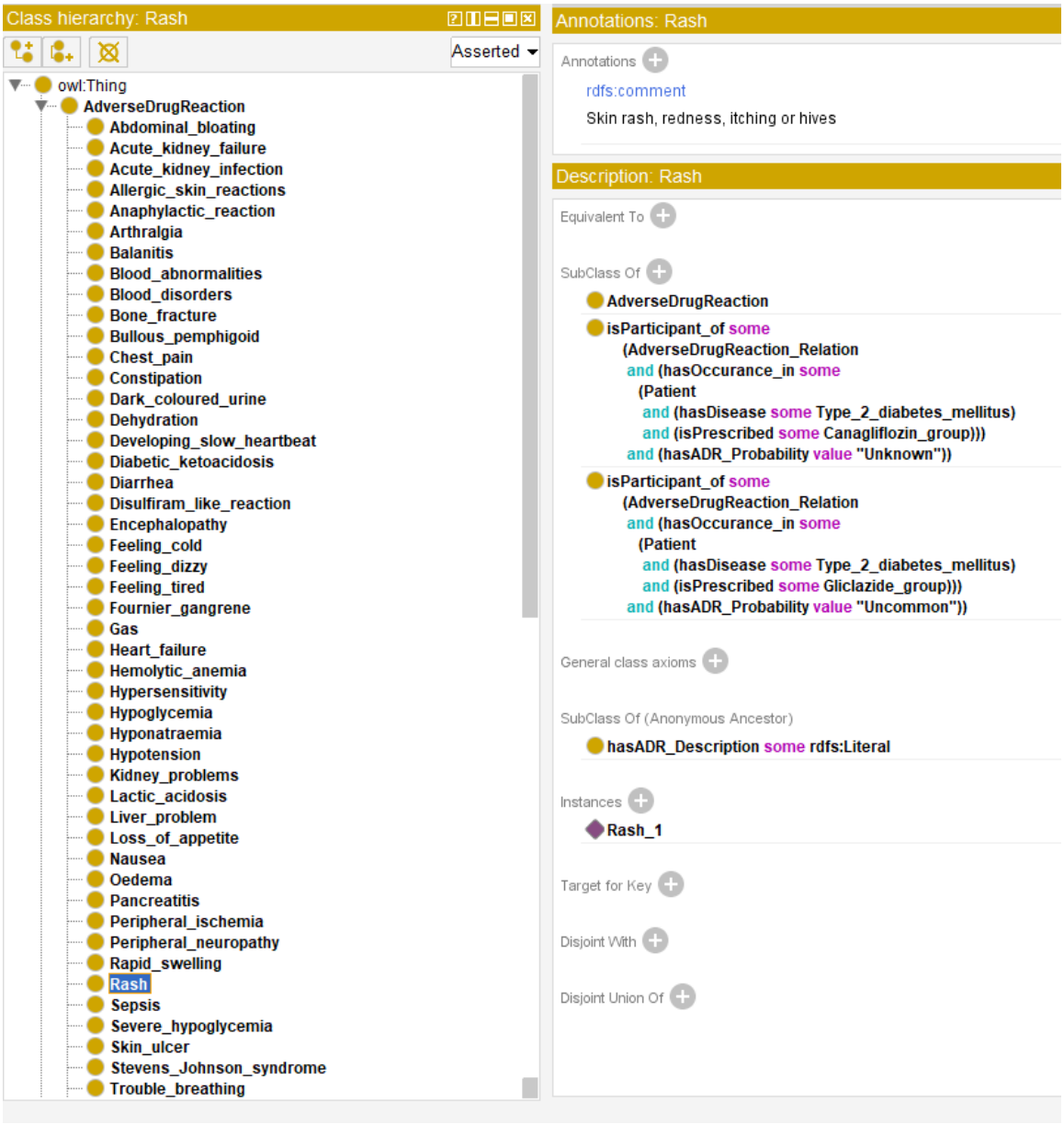

Class hierarchy: Oedema
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Oedema
Annotations
rdfs:comment
Swelling of the legs
Description: Oedema
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Gliclazide_group)))
and (hasADR_Probability value "Uncommon"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Oedema_1
Target for Key
Disjoint With
Disjoint Union Of

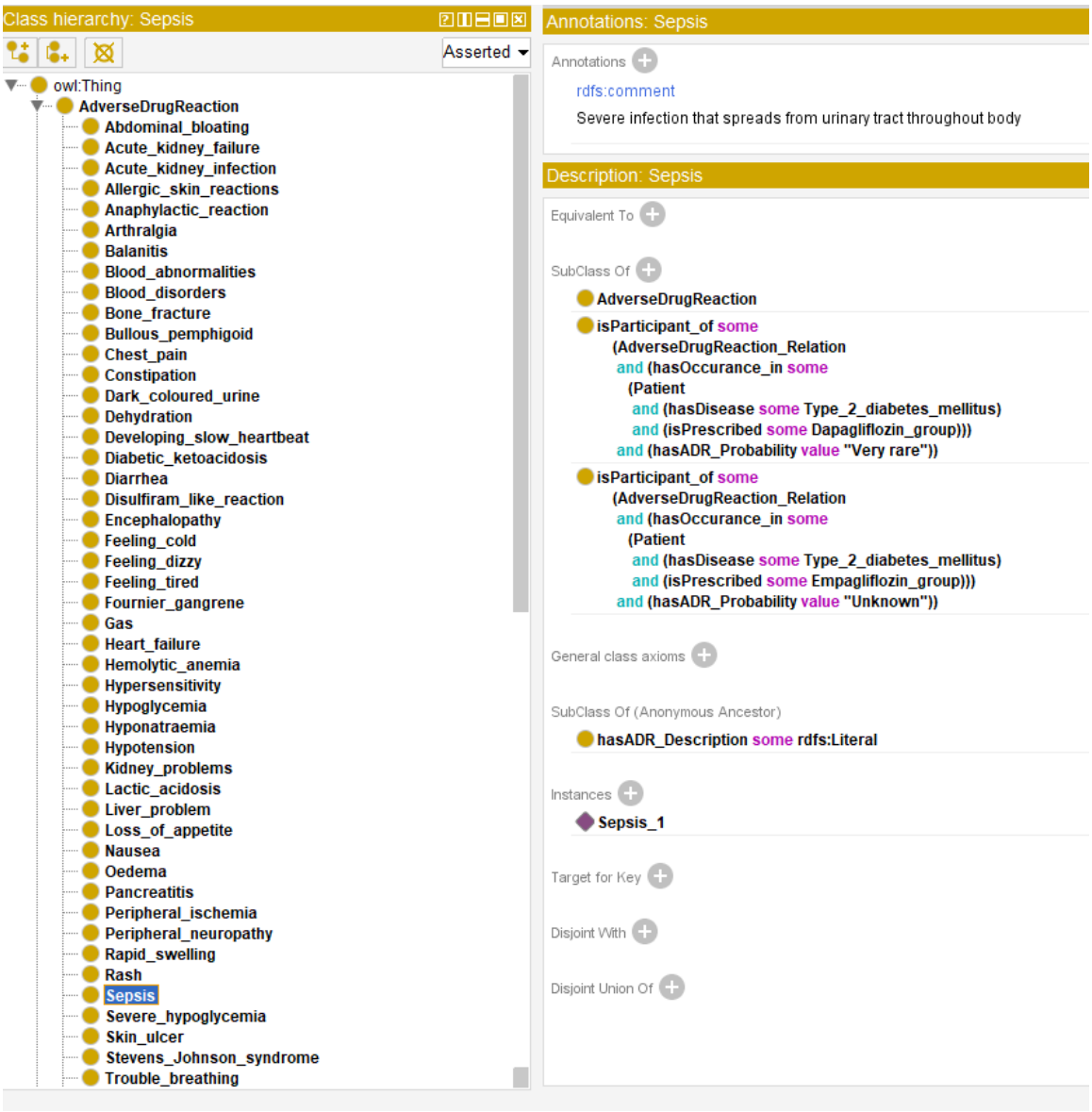

Class hierarchy: Pancreatitis
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Pancreatitis
Annotations
rdfs:comment
Inflammation of the pancreas
Description: Pancreatitis
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Alogliptin_group)))
and (hasADR_Probability value "Uncommon"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Canagliflozin_group)))
and (hasADR_Probability value "Rare"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Dapagliflozin_group)))
and (hasADR_Probability value "Very rare"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Empagliflozin_group)))
and (hasADR_Probability value "Unknown"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Linagliptin_group)))
and (hasADR_Probability value "Rare"))

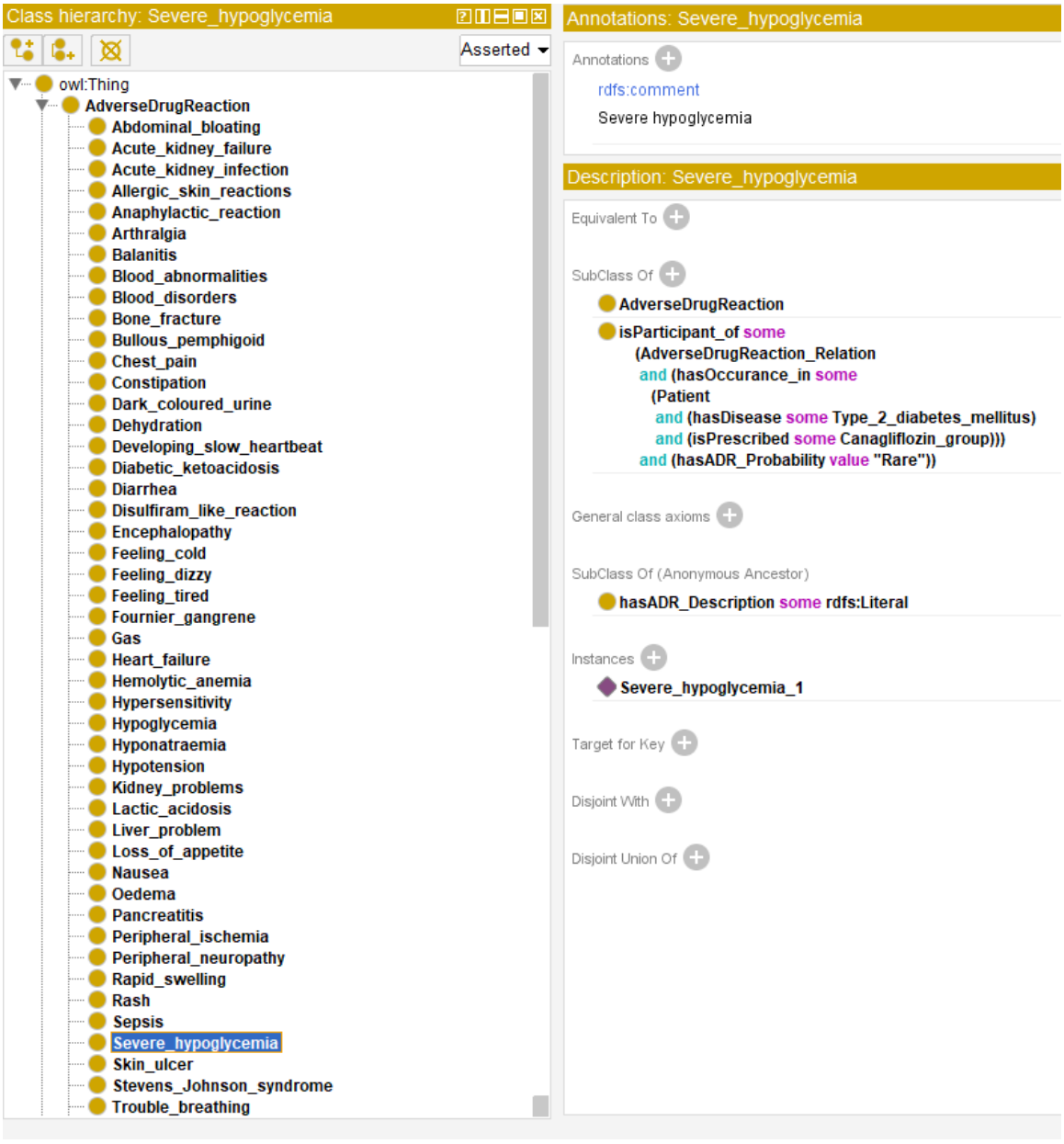

Class hierarchy: Peripheral_ischemia
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Peripheral_ischemia
Annotations
rdfs:comment
Blocked or narrow blood vessels
Description: Peripheral_ischemia
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Canagliflozin_group)))
and (hasADR_Probability value "Unknown"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Peripheral_ischemia_1
Target for Key
Disjoint With
Disjoint Union Of

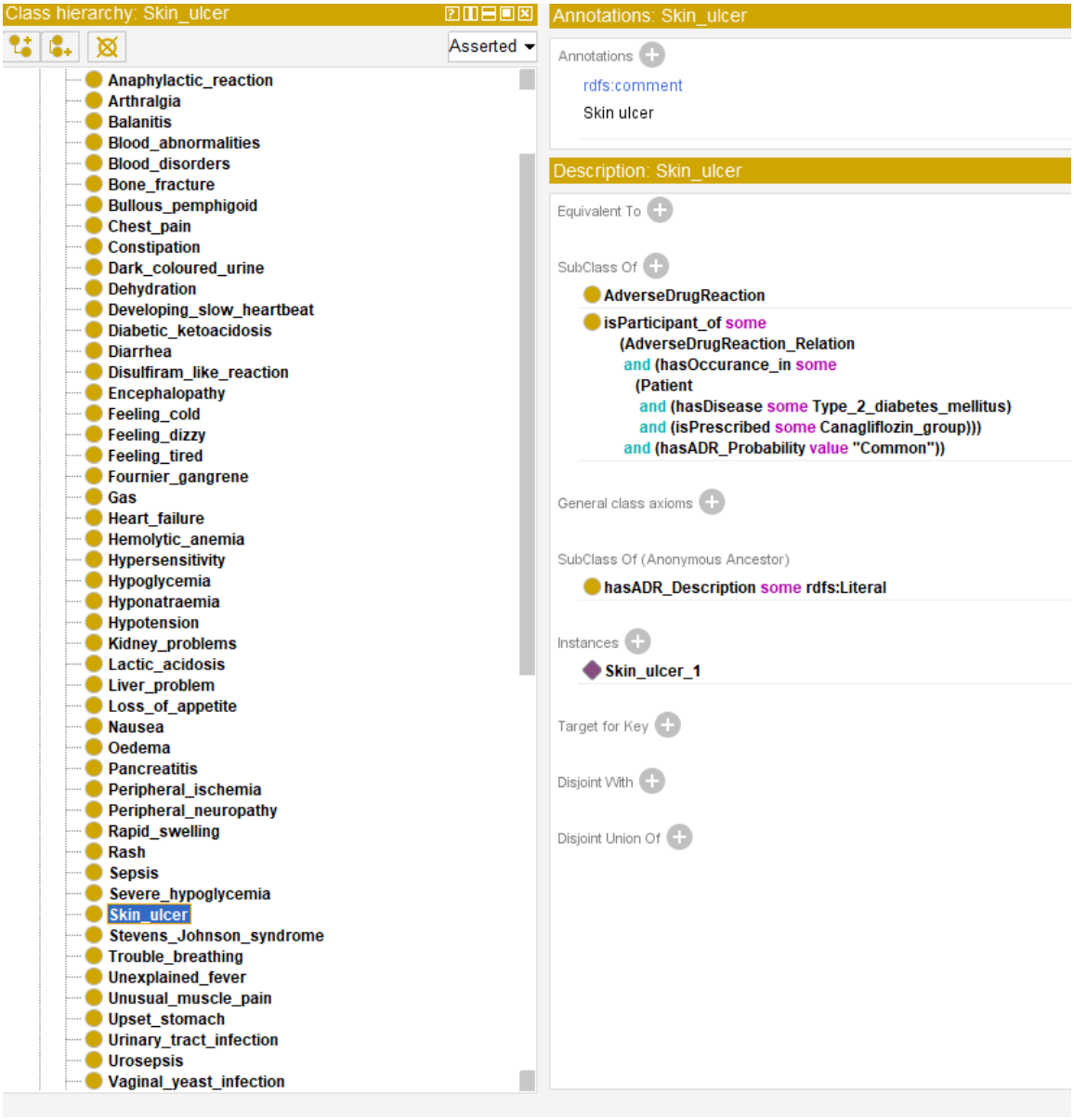

Class hierarchy: Peripheral_neuropathy
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Peripheral_neuropathy
Annotations
rdfs:comment
Damage to your peripheral nerves
Description: Peripheral_neuropathy
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Metformin_group)))
and (hasADR_Probability value "Rare"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Peripheral_neuropathy_1
Target for Key
Disjoint With
Disjoint Union Of

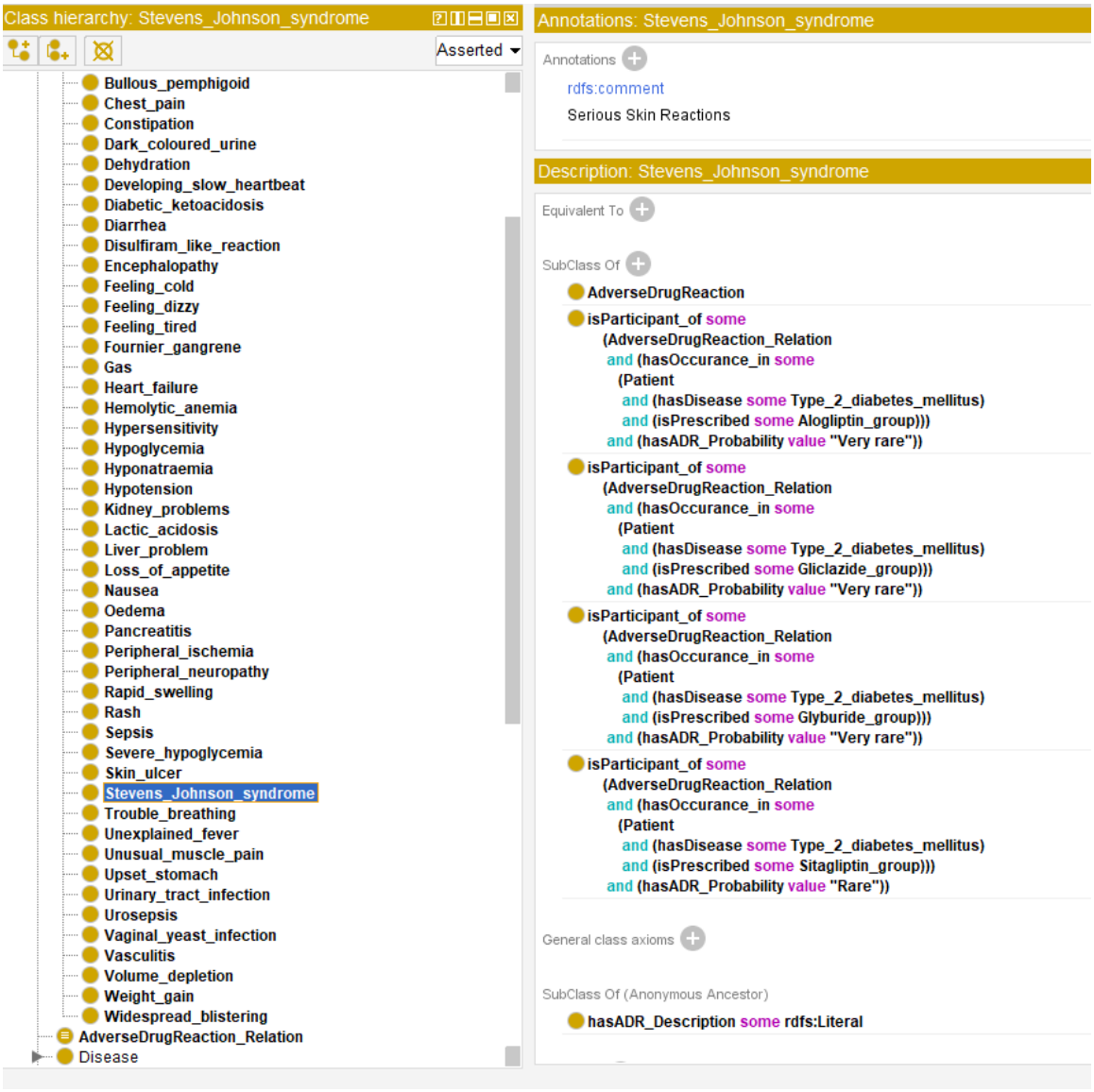

Class hierarchy: Rapid_swelling
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Rapid_swelling
Annotations
rdfs:comment
Rapid swelling of tissues
Description: Rapid_swelling
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Gliclazide_group)))
and (hasADR_Probability value "Very rare"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Rapid_swelling_1
Target for Key
Disjoint With
Disjoint Union Of

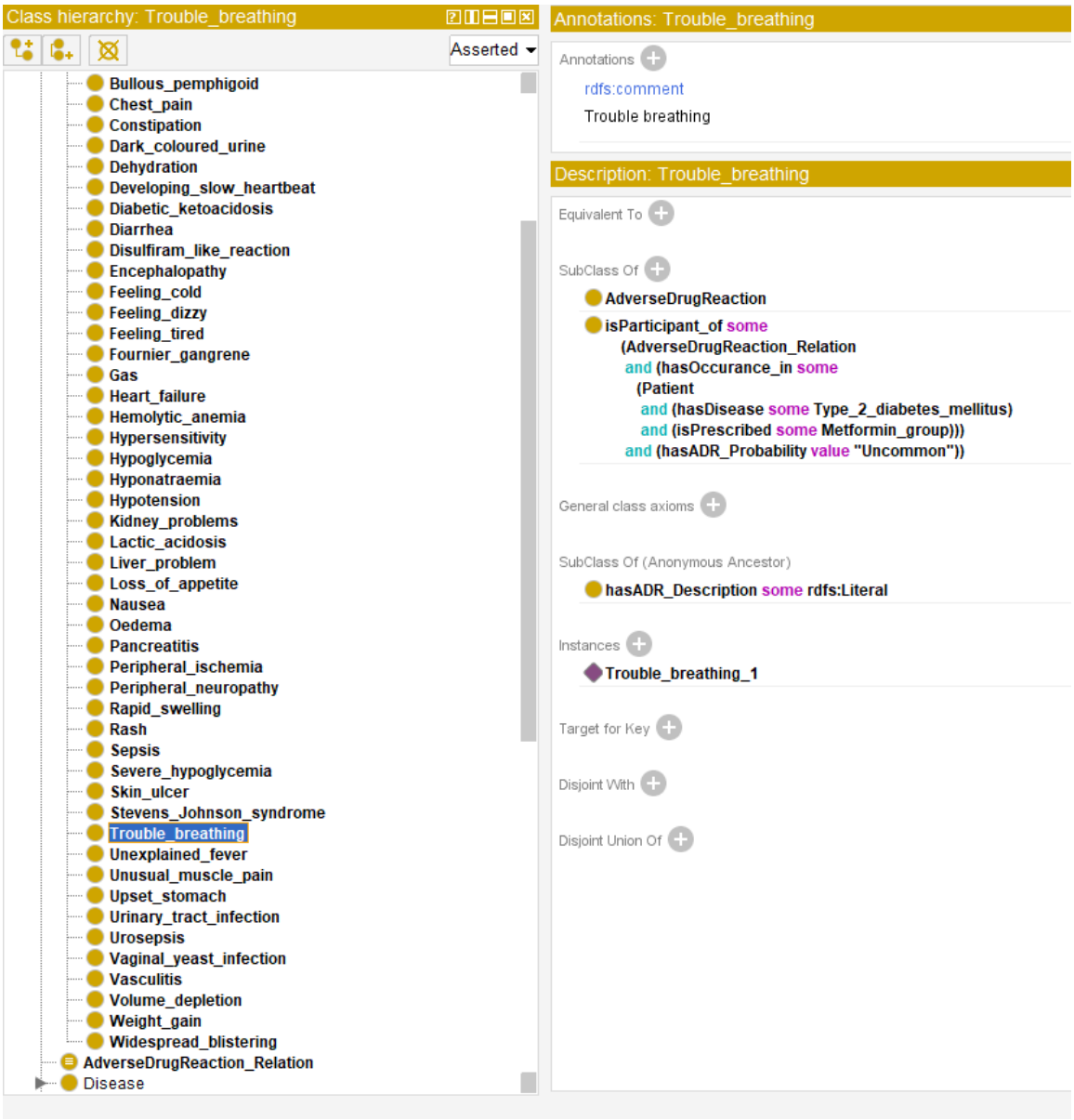

Class hierarchy: Rash
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Rash
Annotations
rdfs:comment
Skin rash, redness, itching or hives
Description: Rash
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Canagliflozin_group)))
and (hasADR_Probability value "Unknown"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Gliclazide_group)))
and (hasADR_Probability value "Uncommon"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Rash_1
Target for Key
Disjoint With
Disjoint Union Of

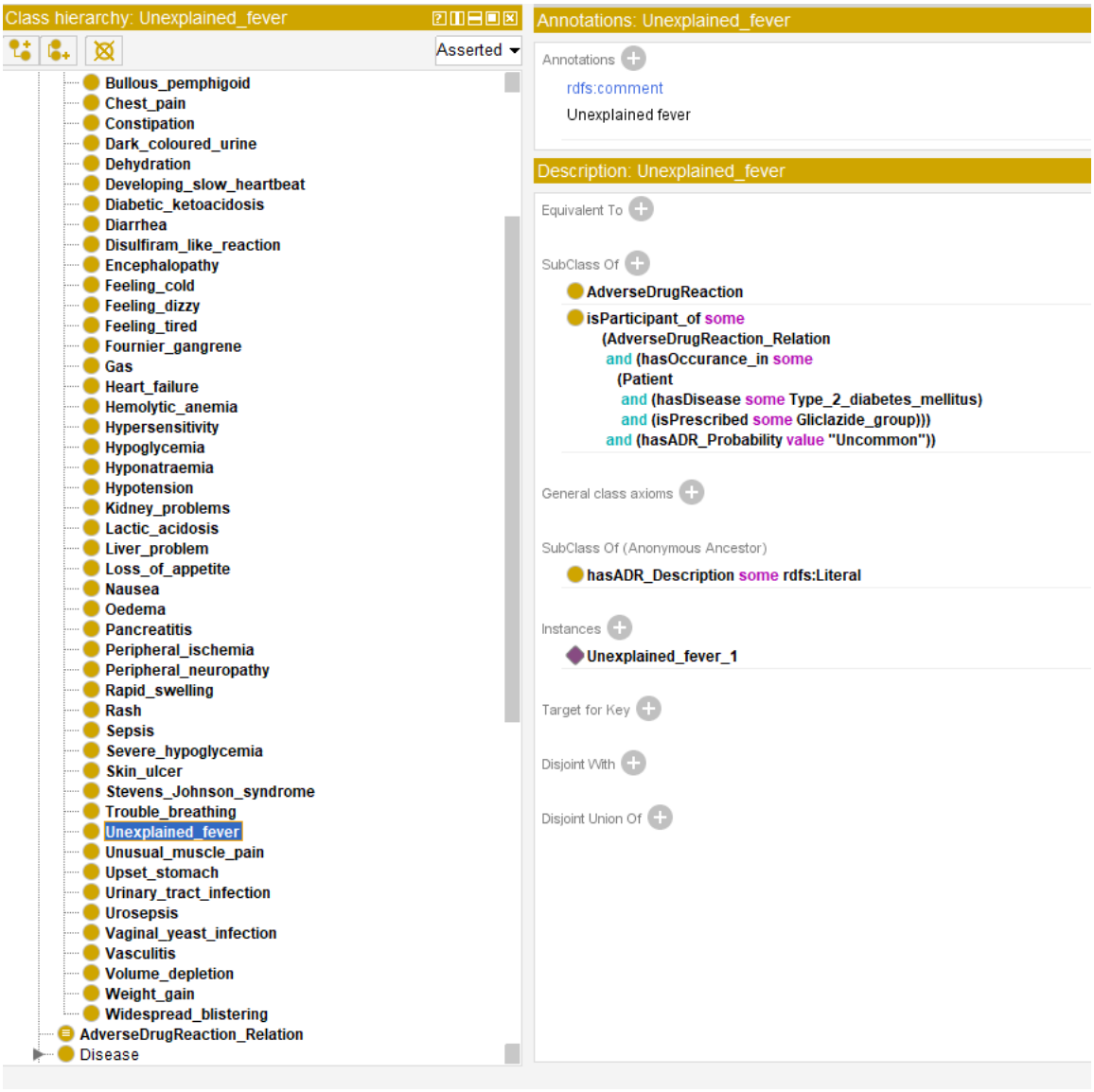

Class hierarchy: Sepsis
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Sepsis
Annotations
rdfs:comment
Severe infection that spreads from urinary tract throughout body
Description: Sepsis
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Dapagliflozin_group)))
and (hasADR_Probability value "Very rare"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Empagliflozin_group)))
and (hasADR_Probability value "Unknown"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Sepsis_1
Target for Key
Disjoint With
Disjoint Union Of

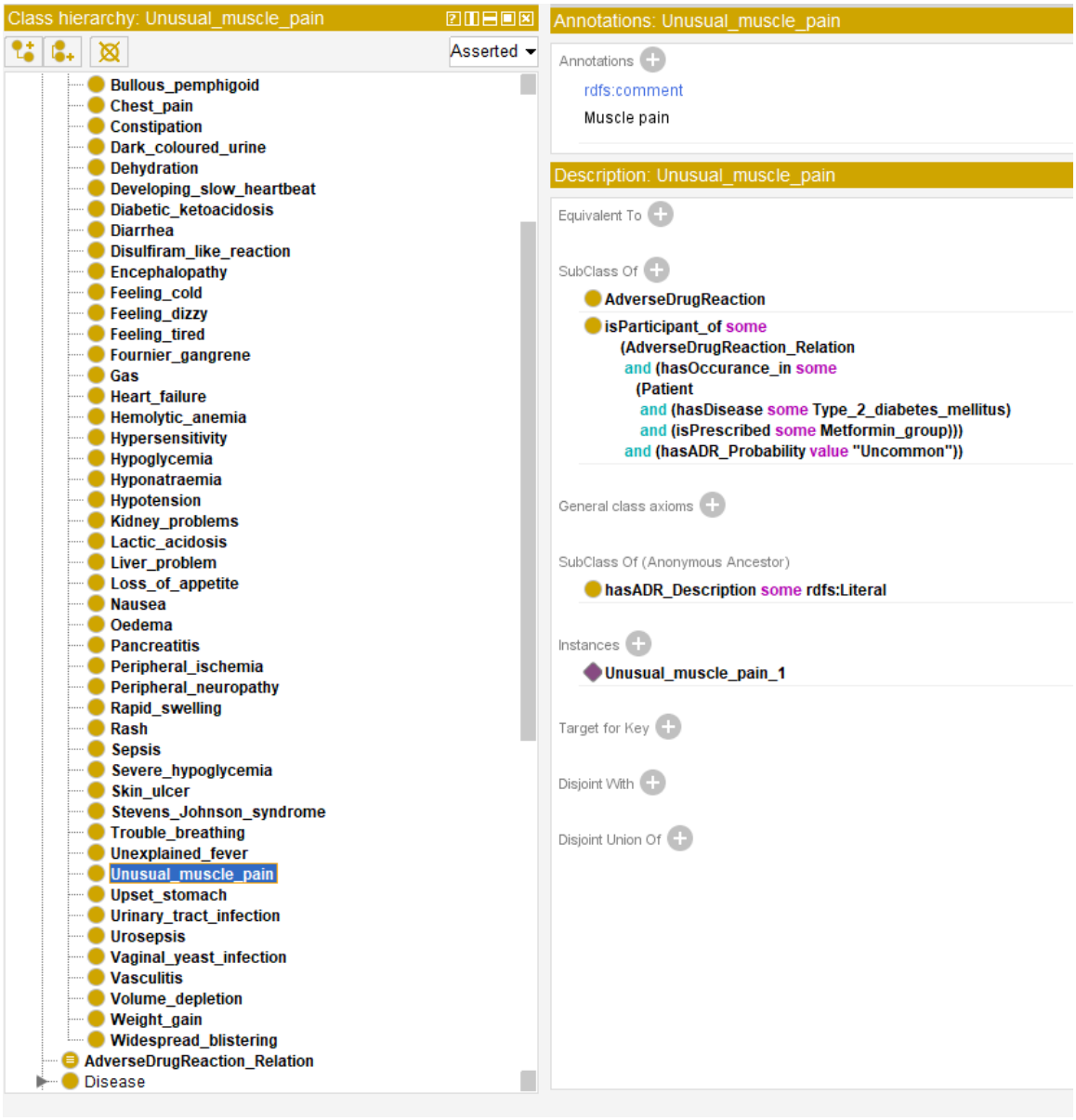

Class hierarchy: Severe_hypoglycemia
Asserted
owl:Thing
AdverseDrugReaction
Abdominal_bloating
Acute_kidney_failure
Acute_kidney_infection
Allergic_skin_reactions
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Annotations: Severe_hypoglycemia
Annotations
rdfs:comment
Severe hypoglycemia
Description: Severe_hypoglycemia
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Canagliflozin_group)))
and (hasADR_Probability value "Rare"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Severe_hypoglycemia_1
Target for Key
Disjoint With
Disjoint Union Of

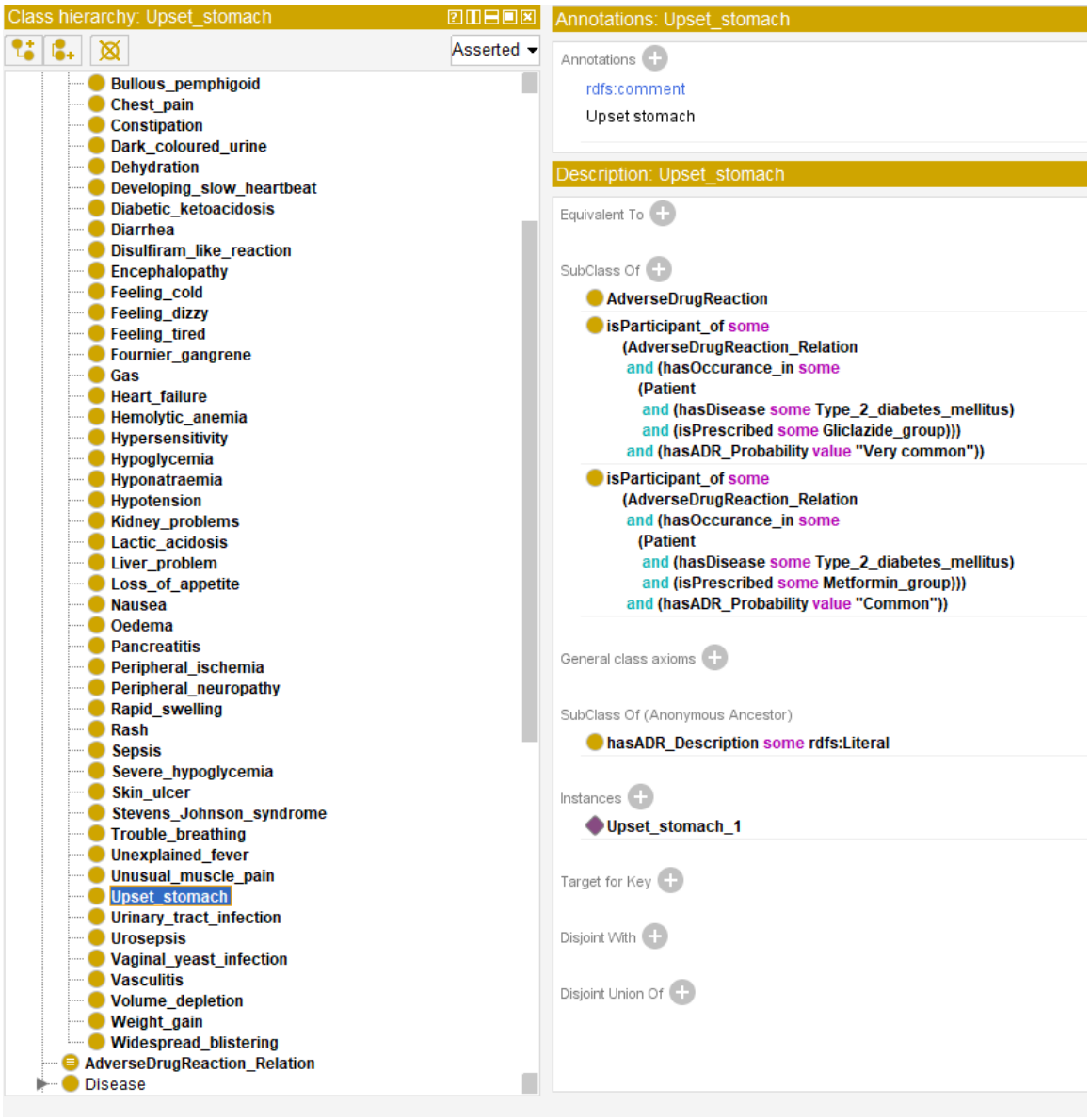

Class hierarchy: Skin_ulcer
Asserted
Anaphylactic_reaction
Arthralgia
Balanitis
Blood_abnormalities
Blood_disorders
Bone_fracture
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Unexplained_fever
Unusual_muscle_pain
Upset_stomach
Urinary_tract_infection
Urosepsis
Vaginal_yeast_infection
Annotations: Skin_ulcer
Annotations
rdfs:comment
Skin ulcer
Description: Skin_ulcer
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Canagliflozin_group)))
and (hasADR_Probability value "Common"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Skin_ulcer_1
Target for Key
Disjoint With
Disjoint Union Of

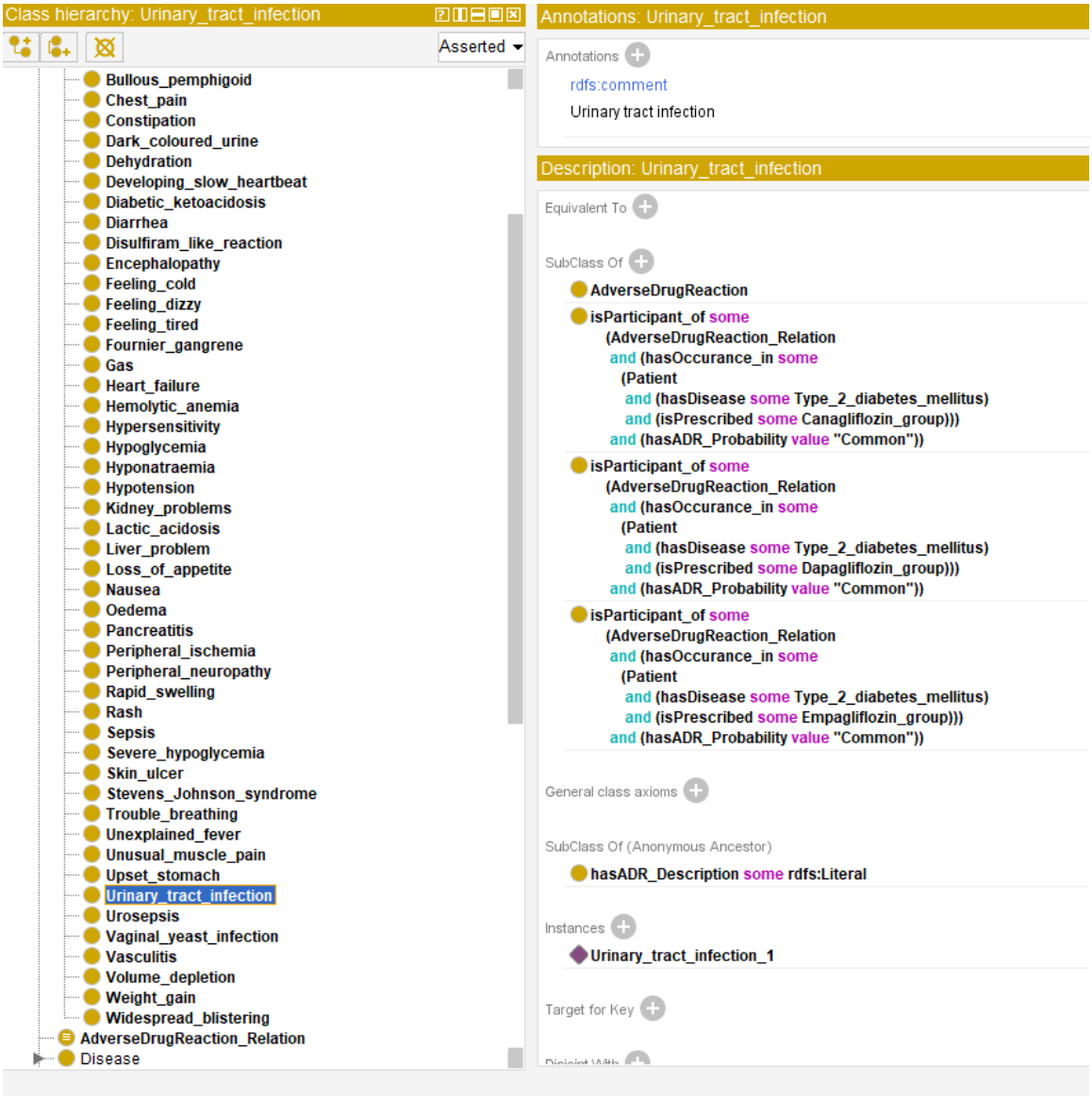

Class hierarchy: Stevens_Johnson_syndrome
Asserted
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Unexplained_fever
Unusual_muscle_pain
Upset_stomach
Urinary_tract_infection
Urosepsis
Vaginal_yeast_infection
Vasculitis
Volume_depletion
Weight_gain
Widespread_blistering
AdverseDrugReaction_Relation
Disease
Annotations: Stevens_Johnson_syndrome
Annotations
rdfs:comment
Serious Skin Reactions
Description: Stevens_Johnson_syndrome
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Alogliptin_group)))
and (hasADR_Probability value "Very rare"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Gliclazide_group)))
and (hasADR_Probability value "Very rare"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Glyburide_group)))
and (hasADR_Probability value "Very rare"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Sitagliptin_group)))
and (hasADR_Probability value "Rare"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal

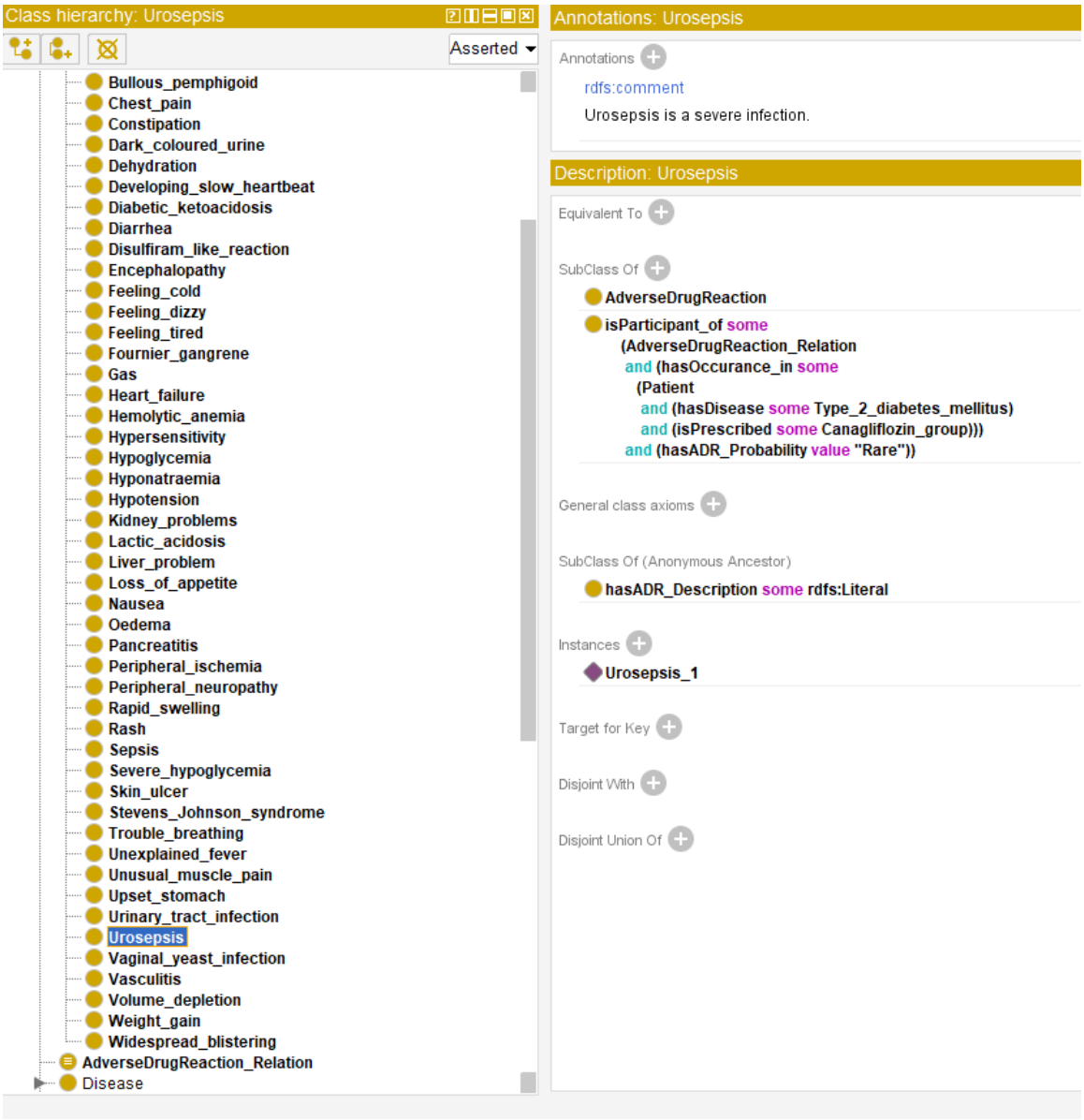

Class hierarchy: Trouble_breathing
Asserted
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Unexplained_fever
Unusual_muscle_pain
Upset_stomach
Urinary_tract_infection
Urosepsis
Vaginal_yeast_infection
Vasculitis
Volume_depletion
Weight_gain
Widespread_blistering
AdverseDrugReaction_Relation
Disease
Annotations: Trouble_breathing
Annotations
rdfs:comment
Trouble breathing
Description: Trouble_breathing
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Metformin_group)))
and (hasADR_Probability value "Uncommon"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Trouble_breathing_1
Target for Key
Disjoint With
Disjoint Union Of

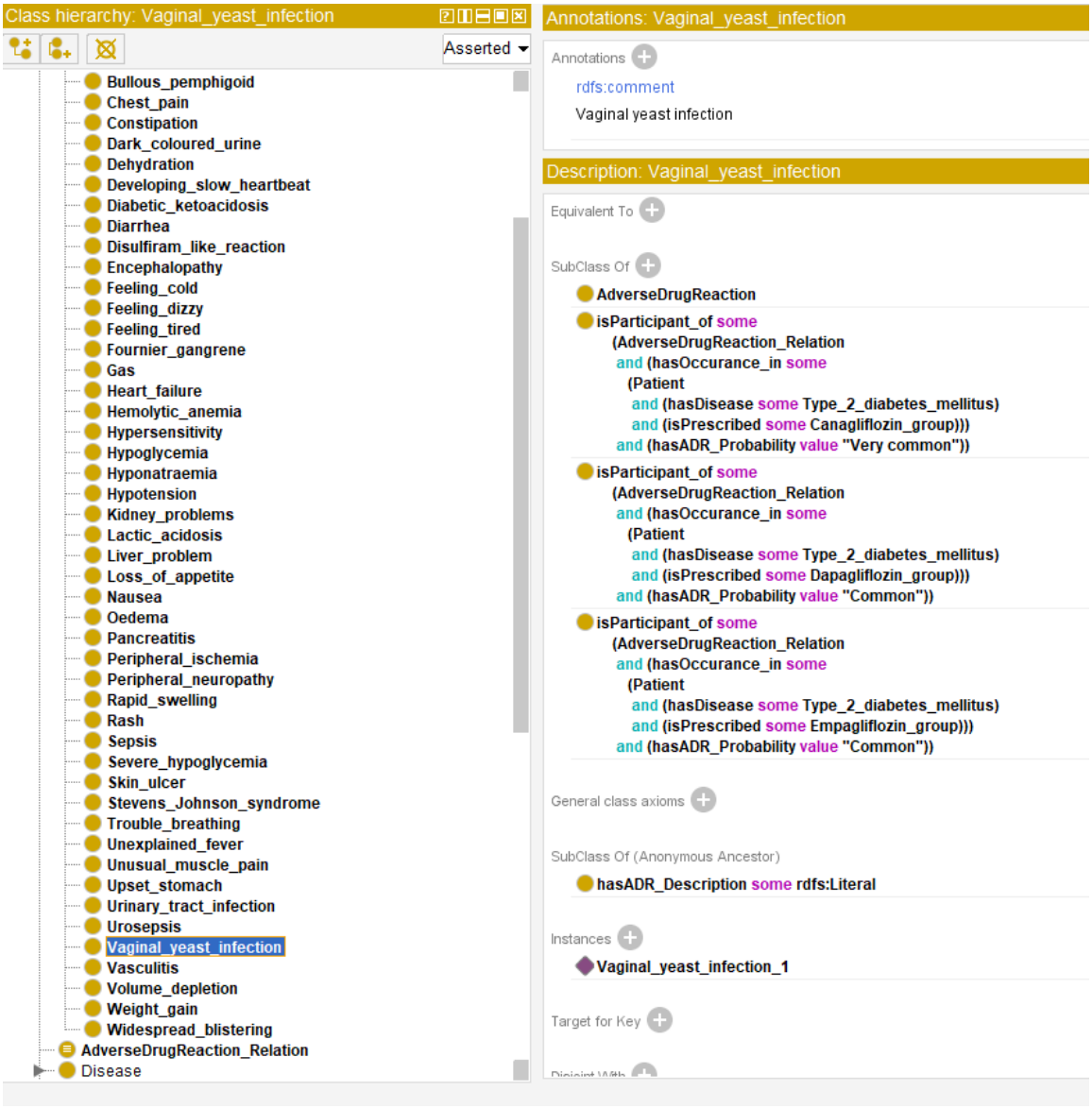

Class hierarchy: Unexplained_fever
Asserted
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Unexplained_fever
Unusual_muscle_pain
Upset_stomach
Urinary_tract_infection
Urosepsis
Vaginal_yeast_infection
Vasculitis
Volume_depletion
Weight_gain
Widespread_blistering
AdverseDrugReaction_Relation
Disease
Annotations: Unexplained_fever
Annotations
rdfs:comment
Unexplained fever
Description: Unexplained_fever
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Gliclazide_group)))
and (hasADR_Probability value "Uncommon"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Unexplained_fever_1
Target for Key
Disjoint With
Disjoint Union Of

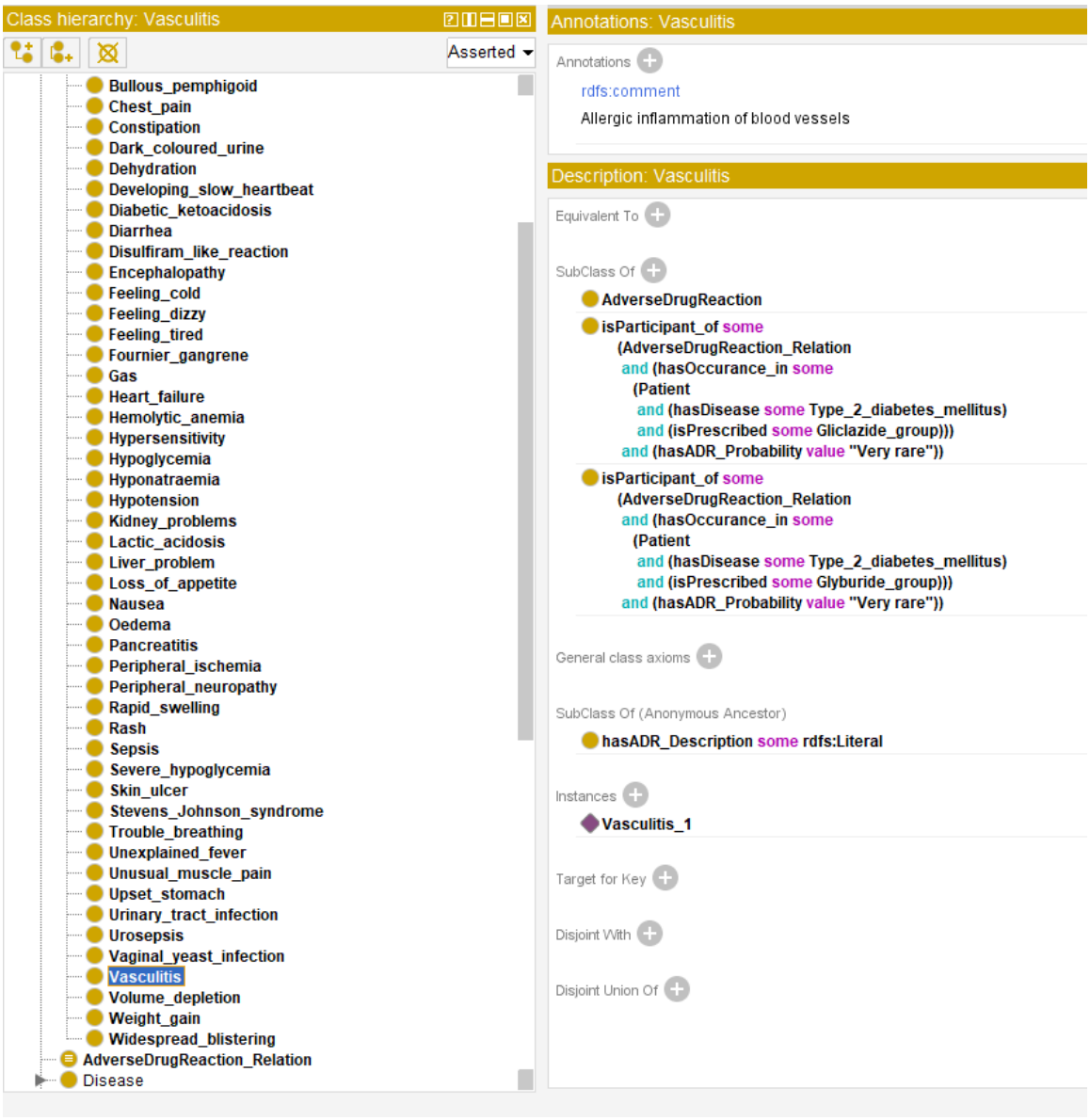

Class hierarchy: Unusual_muscle_pain
Asserted
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Unexplained_fever
Unusual_muscle_pain
Upset_stomach
Urinary_tract_infection
Urosepsis
Vaginal_yeast_infection
Vasculitis
Volume_depletion
Weight_gain
Widespread_blistering
AdverseDrugReaction_Relation
Disease
Annotations: Unusual_muscle_pain
Annotations
rdfs:comment
Muscle pain
Description: Unusual_muscle_pain
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Metformin_group)))
and (hasADR_Probability value "Uncommon"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Unusual_muscle_pain_1
Target for Key
Disjoint With
Disjoint Union Of

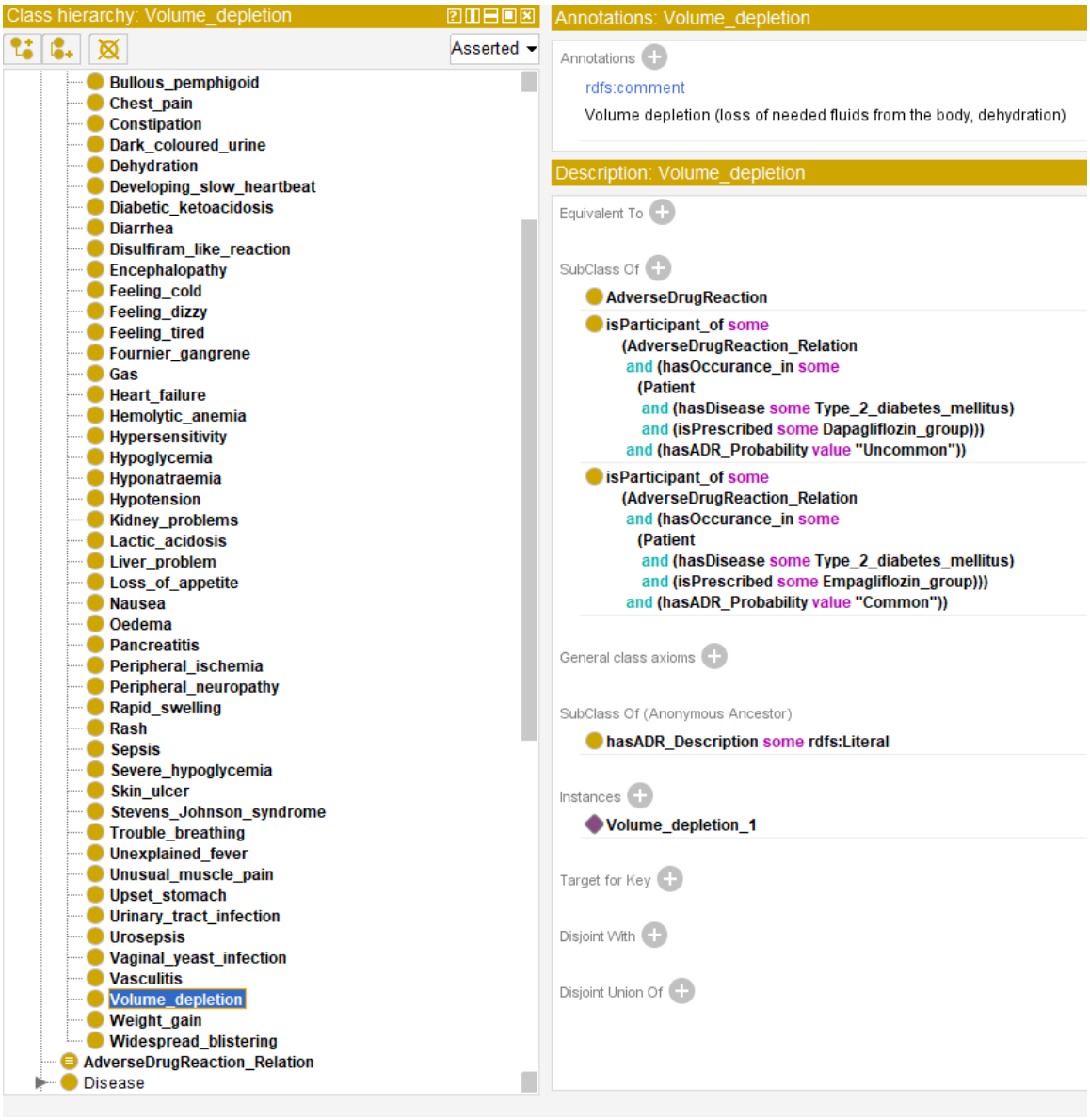

Class hierarchy: Upset_stomach
Asserted
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Unexplained_fever
Unusual_muscle_pain
Upset_stomach
Urinary_tract_infection
Urosepsis
Vaginal_yeast_infection
Vasculitis
Volume_depletion
Weight_gain
Widespread_blistering
AdverseDrugReaction_Relation
Disease
Annotations: Upset_stomach
Annotations
rdfs:comment
Upset stomach
Description: Upset_stomach
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Gliclazide_group)))
and (hasADR_Probability value "Very common"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Metformin_group)))
and (hasADR_Probability value "Common"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Upset_stomach_1
Target for Key
Disjoint With
Disjoint Union Of

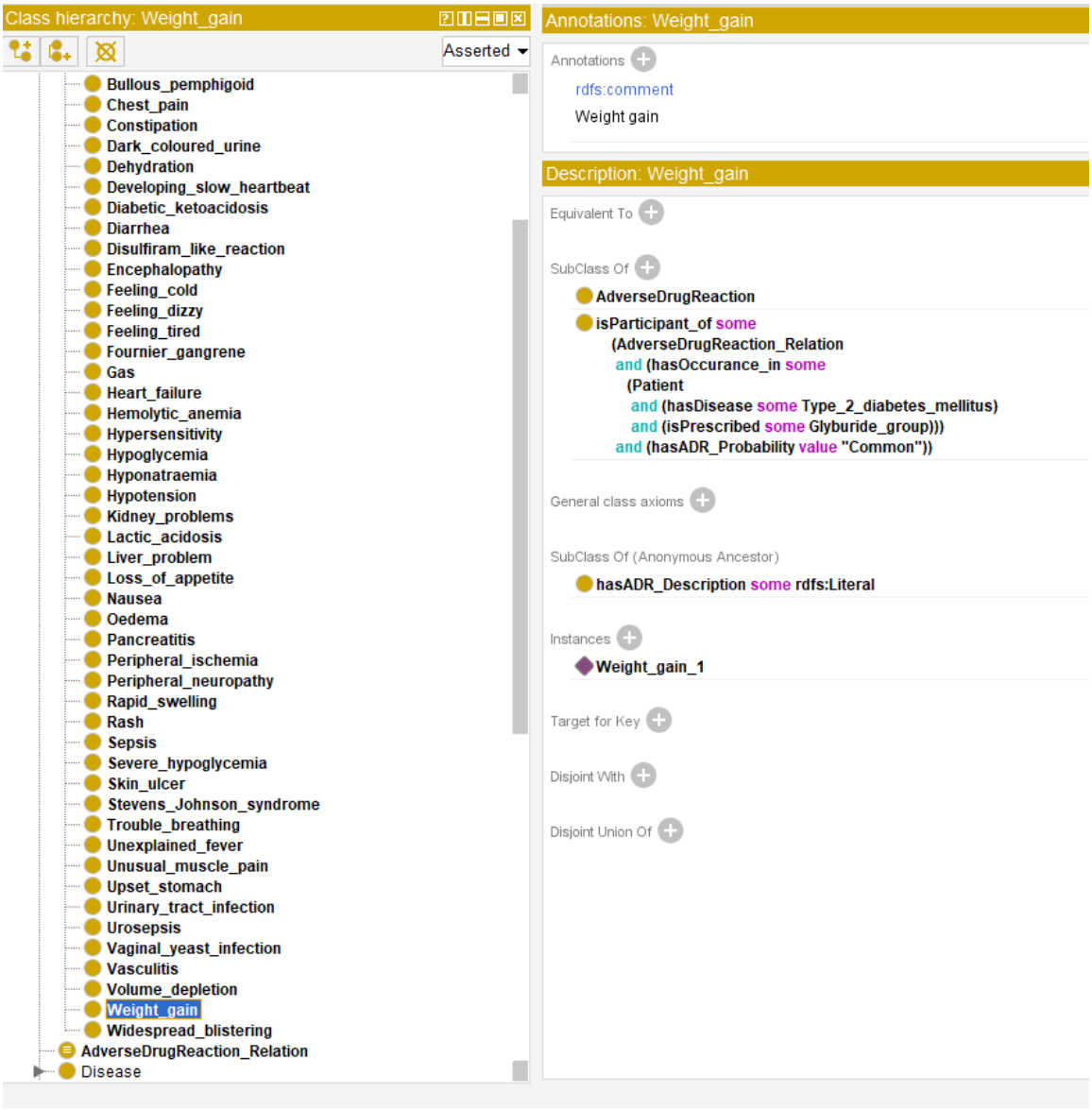

Class hierarchy: Urinary_tract_infection
Asserted
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Unexplained_fever
Unusual_muscle_pain
Upset_stomach
Urinary_tract_infection
Urosepsis
Vaginal_yeast_infection
Vasculitis
Volume_depletion
Weight_gain
Widespread_blistering
AdverseDrugReaction_Relation
Disease
Annotations: Urinary_tract_infection
Annotations
rdfs:comment
Urinary tract infection
Description: Urinary_tract_infection
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Canagliflozin_group)))
and (hasADR_Probability value "Common"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Dapagliflozin_group)))
and (hasADR_Probability value "Common"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Empagliflozin_group)))
and (hasADR_Probability value "Common"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Urinary_tract_infection_1
Target for Key

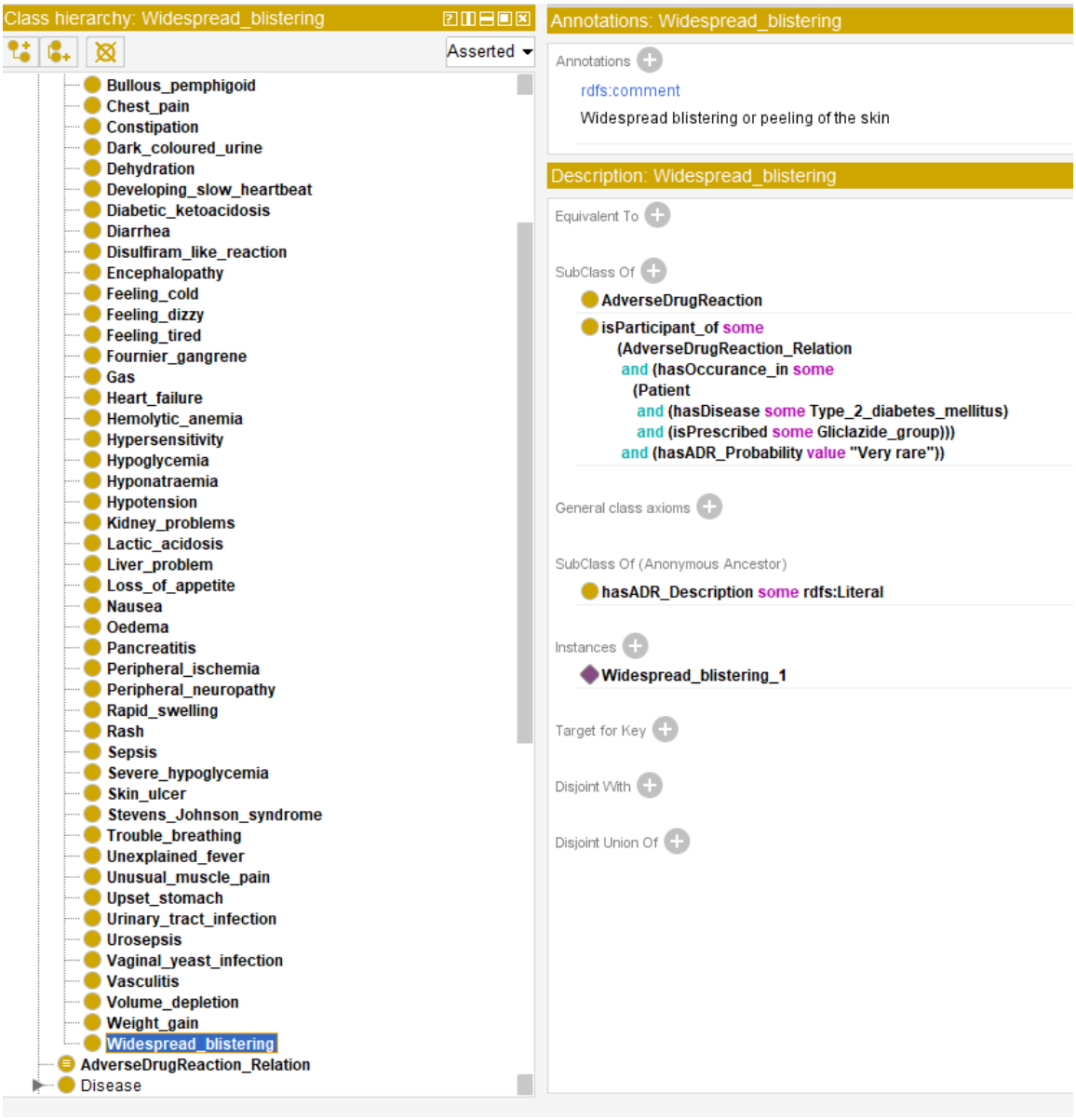

Class hierarchy: Urosepsis
Asserted
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Unexplained_fever
Unusual_muscle_pain
Upset_stomach
Urinary_tract_infection
Urosepsis
Vaginal_yeast_infection
Vasculitis
Volume_depletion
Weight_gain
Widespread_blistering
AdverseDrugReaction_Relation
Disease
Annotations: Urosepsis
Annotations
rdfs:comment
Urosepsis is a severe infection.
Description: Urosepsis
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Canagliflozin_group)))
and (hasADR_Probability value "Rare"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Urosepsis_1
Target for Key
Disjoint With
Disjoint Union Of


Class hierarchy: Vaginal_yeast_infection
Asserted
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Unexplained_fever
Unusual_muscle_pain
Upset_stomach
Urinary_tract_infection
Urosepsis
Vaginal_yeast_infection
Vasculitis
Volume_depletion
Weight_gain
Widespread_blistering
AdverseDrugReaction_Relation
Disease
Annotations: Vaginal_yeast_infection
Annotations
rdfs:comment
Vaginal yeast infection
Description: Vaginal_yeast_infection
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Canagliflozin_group)))
and (hasADR_Probability value "Very common"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Dapagliflozin_group)))
and (hasADR_Probability value "Common"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Empagliflozin_group)))
and (hasADR_Probability value "Common"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Vaginal_yeast_infection_1
Target for Key


Class hierarchy: Vasculitis
Asserted
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Unexplained_fever
Unusual_muscle_pain
Upset_stomach
Urinary_tract_infection
Urosepsis
Vaginal_yeast_infection
Vasculitis
Volume_depletion
Weight_gain
Widespread_blistering
AdverseDrugReaction_Relation
Disease
Annotations: Vasculitis
Annotations
rdfs:comment
Allergic inflammation of blood vessels
Description: Vasculitis
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Gliclazide_group)))
and (hasADR_Probability value "Very rare"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Glyburide_group)))
and (hasADR_Probability value "Very rare"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Vasculitis_1
Target for Key
Disjoint With
Disjoint Union Of


Class hierarchy: Volume_depletion
Asserted
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Unexplained_fever
Unusual_muscle_pain
Upset_stomach
Urinary_tract_infection
Urosepsis
Vaginal_yeast_infection
Vasculitis
Volume_depletion
Weight_gain
Widespread_blistering
AdverseDrugReaction_Relation
Disease
Annotations: Volume_depletion
Annotations
rdfs:comment
Volume depletion (loss of needed fluids from the body, dehydration)
Description: Volume_depletion
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Dapagliflozin_group)))
and (hasADR_Probability value "Uncommon"))
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Empagliflozin_group)))
and (hasADR_Probability value "Common"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Volume_depletion_1
Target for Key
Disjoint With
Disjoint Union Of


Class hierarchy: Weight_gain
Asserted
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Unexplained_fever
Unusual_muscle_pain
Upset_stomach
Urinary_tract_infection
Urosepsis
Vaginal_yeast_infection
Vasculitis
Volume_depletion
Weight_gain
Widespread_blistering
AdverseDrugReaction_Relation
Disease
Annotations: Weight_gain
Annotations
rdfs:comment
Weight gain
Description: Weight_gain
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Glyburide_group)))
and (hasADR_Probability value "Common"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Weight_gain_1
Target for Key
Disjoint With
Disjoint Union Of


Class hierarchy: Widespread_blistering
Asserted
Bullous_pemphigoid
Chest_pain
Constipation
Dark_coloured_urine
Dehydration
Developing_slow_heartbeat
Diabetic_ketoacidosis
Diarrhea
Disulfiram_like_reaction
Encephalopathy
Feeling_cold
Feeling_dizzy
Feeling_tired
Fournier_gangrene
Gas
Heart_failure
Hemolytic_anemia
Hypersensitivity
Hypoglycemia
Hyponatraemia
Hypotension
Kidney_problems
Lactic_acidosis
Liver_problem
Loss_of_appetite
Nausea
Oedema
Pancreatitis
Peripheral_ischemia
Peripheral_neuropathy
Rapid_swelling
Rash
Sepsis
Severe_hypoglycemia
Skin_ulcer
Stevens_Johnson_syndrome
Trouble_breathing
Unexplained_fever
Unusual_muscle_pain
Upset_stomach
Urinary_tract_infection
Urosepsis
Vaginal_yeast_infection
Vasculitis
Volume_depletion
Weight_gain
Widespread_blistering
AdverseDrugReaction_Relation
Disease
Annotations: Widespread_blistering
Annotations
rdfs:comment
Widespread blistering or peeling of the skin
Description: Widespread_blistering
Equivalent To
SubClass Of
AdverseDrugReaction
isParticipant_of some
(AdverseDrugReaction_Relation
and (hasOccurance_in some
(Patient
and (hasDisease some Type_2_diabetes_mellitus)
and (isPrescribed some Gliclazide_group)))
and (hasADR_Probability value "Very rare"))
General class axioms
SubClass Of (Anonymous Ancestor)
hasADR_Description some rdfs:Literal
Instances
Widespread_blistering_1
Target for Key
Disjoint With
Disjoint Union Of