DEVELOPING A GUIDELINE-BASED DECISION SUPPORT SYSTEM TO DIAGNOSIS OF PRIMARY IMMUNODEFICIENCY DISEASES

Fateme Sepehri^{1,2} , Mostafa Langarizadeh³ , Laleh Sharifi⁴ , Gholamreza Azizi⁵ , Reza Safdari^{*2} , Asghar Aghamohammadi^{*6}

¹ Department of Health Information Technology, Mousavi Hospital, Zanjan University of Medical Sciences, Zanjan, Iran.

² Department of Health Information Management, School of Allied Medical Sciences, Tehran University of Medical Sciences, Tehran, Iran.

³ Department of Health Information Management, School of Health Management and Information Science, Iran University of Medical Sciences, Tehran, Iran.

⁴ Uro-Oncology Research Center, Tehran University of Medical Sciences, Tehran, Iran.

⁵ Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran.

⁶ Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran.

Article Info

Article type:
Research

Article History:
Received: 2019-01-15
Revised: 2019-02-25
Accepted: 2019-03-16

* Corresponding author:

Reza Safdari
Department of Health Information
Management, School of Allied Medical
Sciences, Tehran University of Medical
Sciences, Tehran, Iran.
E-mail: rsafdari@tums.ac.ir

Asghar Aghamohammadi
Research Center for Immunodeficiencies,
Pediatrics Center of Excellence, Children's
Medical Center, Tehran University of
Medical Sciences, Tehran, Iran.
E-mail: aghamohammadi@tums.ac.ir

ABSTRACT

Introduction:

Primary immunodeficiency diseases (PID) are generally rare genetic disorders affecting the immune system. Overlapping PIDs symptoms and signs is a challenge to diagnosis and treatment. On the other hand, remembering of all diagnosis criteria is difficult for practitioners. The purpose of this research is developing guideline-based clinical decision support system for diagnosis of primary immune deficiency diseases, to assist practitioner in order to diagnose of disease in early stage and to minimize complications of such diseases.

Material and Methods:

To provide data a checklist was used and most important demographic information, symptoms, family history, physical findings and laboratory findings to diagnose eight common PIDs extracted from guidelines and literature under specialists opinion. The diagnosis inference model design and develop in Protégé (version 3.4.8) frame based ontology modeling using "Noy and McGuinness" method. Then the mobile based inference model in Eclipse (SDK version 3.7.1) software has been developed and clinical decision support system of primary immunodeficiency has been created.

Results:

To design the diagnosis inference model in Protégé software, data were classified in 5 main classes and 24 subclasses as hierarchical. Then, specific properties of each class, and determine the value of each property. Then define Instances of each class and initialized instance properties. Then use this model to develop CDSS based on mobile in Eclipse software. At the end, the inference model and the CDSS test with 110 patient's record data and both of them recognized all 110 patient correctly such as specialist recognition.

Conclusion:

Guideline-based decision support systems help to detect diseases correctly, quickly and early. Guideline-based decision support systems are very reliable to practitioner, because guidelines are accepted to their. These systems reduce the forget probability of diagnosis stages and percentage error of diagnosis by practitioner and increase the accuracy of diagnosis.

Keywords:

Primary Immunodeficiency Diseases (PID), Inference Model, Protégé, Frame-Based Ontology, Guideline-Based Clinical Decision Support System.

How to cite this paper

Sepehri F, Langarizadeh M, Sharifi L, Azizi G, Safdari R, Aghamohammadi A. Developing A Guideline-based Decision Support System to Diagnosis of Primary Immunodeficiency Diseases. Front Health Inform. 2019; 8(1): e11. DOI: [10.30699/fhi.v8i1.184](https://doi.org/10.30699/fhi.v8i1.184)

INTRODUCTION

Primary immunodeficiency diseases (PID) are a genetically heterogeneous group disorders that affect distinct components of both humoral and cellular arms of the immune system [1-5]. Overlapping signs and symptoms of these diseases is a challenge for diagnosis and treatment [6-9]. Awareness of the symptoms and considering the possibility of a PID in differential diagnosis as the diagnosis key in many cases, help to rapid recognition and more appropriate treatment of patients [10, 11]. Timely recognition and treatment reduced mortality and increased lifespan and quality of life of the patients [6, 12-15]. For practitioners to memorize all effective criteria to diagnosis is difficult, so developing computerized program based on diagnosis criteria, improves significantly the quality of care [16-18].

Ontology is a tool for representation and share the knowledge of a field through modeling and create a framework of concepts and relations among them. Ontology used in many medical fields and clinical decision support systems, medical expert systems and biomedical literature data bases [19].

In this study ontology was used to develop the inference model in order to diagnosis of PIDs. Then the inference model was developed using Eclipse (SDK version 3.7.1) software and clinical decision support system of primary immunodeficiency based on mobile has been created.

MATERIAL AND METHODS

The study focused on eight common disease of primary immunodeficiency include Common Variable Immune Deficiency (CVID), X-Linked Agammaglobulinemia (Bruton's) (XLA), Selective IgA Deficiency (SIgA), CD40L deficiency, UNG deficiency, Isolated immunoglobulin (Ig) G Subclass deficiency, Specific antibody deficiency (SAD) with normal Ig concentrations and normal numbers of B cells and Transient hypogammaglobulinemia (THI) of infancy with normal numbers of B cells. Based on clinical guidelines and medical literatures in PID [20-22], we designed a checklist to extract and classified most important signs and symptoms, family history, and laboratory data for eight main type of primary antibody deficiencies (PADs) (Table 1). To evaluate the quality of checklist, data for 10 cases in different type of PIDs were tested.

Table 1: most important signs and symptoms, family history, and laboratory data for eight selected of PIDs

Disease	Symptoms	Family history	Signs	Lab Data
1. CVID	1. Recurrent infections 2. Pneumonia 3. Acute Otitis media 4. Auto immunity 5. Diarrhea 6. Osteomyelitis 7. Sinusitis 8. meningitis 9. Onset Age>4 10. Malignancies 11. Granulomatosis 12. Vitiligo	1. Parents relative 2. male or female	1. lymph nodes: Lymphadenopathy or Normal 2. tonsil: Normal 3. Spleen: Large or Normal 4. Liver: Large or Normal 5. Clubbing: has or not 6. Auscultation of Lungs: has or not	1. IgG: low 2. Isohemagglutinin: low 3. B lymphocyte: normal 4. T lymphocyte: normal 5. Specific AB: normal or low
2. XLA	1. Recurrent infections 2. Pneumonia 3. Acute Otitis media 4. Auto immunity 5. Diarrhea 6. Osteomyelitis 7. Sinusitis 8. Dermatomiositis 9. Encephalitis 10. Enteroviral	1. Parents relative or not 2. male 3. Mother grandfather or uncle have XLA	1. lymph nodes: Hasn't 2. tonsil: Atrophy 3. Spleen: small	1. IgG: low 2. IgM: low 3. IgA: low 4. Isohemagglutinin: low 5. B lymphocyte: low 6. T lymphocyte: normal or high 7. Btk Mutation 8. Specific AB: low
3. IGA	1. Recurrent infections 2. Pneumonia 3. Acute Otitis media 4. Auto immunity 5. Diarrhea 6. Osteomyelitis 7. Sinusitis 8. Onset Age>4 9. Allergies 10. Anaphylaxis	1. Parents relative 2. male or female	1. lymph nodes: Normal 2. tonsil: Normal 3. Spleen: Normal or Large 4. Liver: Normal or Large	1. IgG: normal 2. IgM: normal 3. IgA: low 4. B lymphocyte: normal 5. T lymphocyte: normal 6. Specific AB: normal
4. HIGM CD40lig	1. Recurrent infections 2. Pneumonia	1. Parents not relative	1. lymph nodes: Hasn't 2. tonsil: Atrophy	1. IgG: low 2. IgM: normal or high

Disease and	Symptoms	Family history	Signs	Lab Data
	3. Acute Otitis media 4. Auto immunity 5. Diarrhea 6. Osteomyelitis 7. Sinusitis 8. Pneumocystis Serovici Pneumonia	2. male 3. Mother grandfather or uncle have HIGM CD 40ligand	3. Spleen: small	3. IgA: low 4. Isohemagglutinin: low 5. Specific AB: low
5. HIGM UNG, AID	1. Recurrent infections 2. Pneumonia 3. Acute Otitis media 4. Auto immunity 5. Diarrhea 6. Osteomyelitis 7. Sinusitis	1. Parents relative 2. male or female	1. lymph nodes: Hypertrophy 2. tonsil: Hypertrophy 3. Spleen: Large 4. Liver: Large	1. IgG: low 2. IgM: normal or high 3. IgA: low 4. Isohemagglutinin: low 5. Specific AB: low
6. IGsub class	1. Recurrent infections 2. Pneumonia 3. Acute Otitis media 4. Auto immunity 5. Diarrhea 6. Osteomyelitis 7. Sinusitis	1. Parents relative 2. male or female	1. lymph nodes: Normal 2. tonsil: Normal 3. Spleen: Normal 4. Liver: Normal	1. IgG: normal 2. IgM: normal 3. IgA: normal 4. IgG1: low 5. IgG2: low 6. IgG3: low 7. IgG4: normal 8. B lymphocyte: normal 9. T lymphocyte: normal 10. Isohemagglutinin: normal 11. Specific AB: normal or low
7. SAD	1. Recurrent infections 2. Pneumonia 3. Acute Otitis media 4. Auto immunity 5. Diarrhea 6. Osteomyelitis 7. Sinusitis	1. Parents relative 2. male or female	1. lymph nodes: Normal 2. tonsil: Normal 3. Spleen: Normal 4. Liver: Normal	1. IgG: normal 2. IgM: normal 3. IgA: normal 4. Isohemagglutinin: low 5. B lymphocyte: normal 6. T lymphocyte: normal 7. Antipneumococys AB: low
8. THI	1. Recurrent infections 2. Pneumonia 3. Acute Otitis media 4. Auto immunity 5. Diarrhea 6. Osteomyelitis 7. Sinusitis 8. Onset Age < 5	1. Parents relative or not 2. male or female	1. lymph nodes: Normal 2. tonsil: Normal 3. Spleen: Normal 4. Liver: Normal	1. IgG: low 2. IgM: normal 3. IgA: normal 4. B lymphocyte: normal 5. T lymphocyte: normal 6. Isohemagglutinin: normal 7. Specific AB: normal 8. IgG1, IgG2, IgG3: normal

Frame based ontology modeling (to create the inference model) and "Noy and McGuinness" method was used to develop the inference model. Noy and McGuinness method includes seven stages as followings:

1. Determine the domain and scope of the ontology
2. Consider reusing existing ontologies
3. Enumerate important terms in the ontology
4. Define the classes and the class hierarchy
5. Define the properties of classes-slots
6. Define the facets of the slots
7. Create instances [23].

Determine the domain and scope of the ontology

The aim of this study is developing inference model that could help physicians in diagnose of eight selected disease according to the signs and symptoms of patients. The study area is eight primary immunodeficiency diseases of and its signs and symptoms.

Consider reusing existing ontologies

Today, rarely an ontology is developed from scratch [24]. In this study, expert's knowledge is used to develop the ontology.

Enumerate important terms in the ontology

Make a list of related terms that are expected to be in ontology is the first step of ontology definition [24]. In this study, a list of related terms including eight primary immunodeficiency diseases and their symptoms, signs and lab data to diagnosis were

extracted from clinical guidelines and medical literature under the immunodeficiency specialist supervision.

Define the classes and the class hierarchy

After identifying related terms, such terms should be

classified as a hierarchy [24]. Classes define a set of instances that have common features [25]. In this study, based on this definition, classes were determined and entered in the classes tab of protégé software (Fig 1). In Fig 1 ANTIBODY_PRODUCTION_DEFECTS class is the main class that contains eight PID diseases as instances.

Fig 1: Classes and the class hierarchy of inference model

Define the properties of classes-slots

Properties are links and relationships between classes [19, 24]. Object type Property is used for the relationship between instances (individuals) of two class. Data type Property defines data type values for instances (individuals) of a class [25]. Properties (slots) of ANTIBODY_PRODUCTION_DEFECTS class are shown in Fig 1. For example, LabDats_Info slot is an Object type Property that made instances of LabDats class usable in instances of ANTIBODY_PRODUCTION_DEFECTS class. OnsetAge slot is a Data type Property with value type of integer.

Define the facets of the slots

For properties (slots) can define facets. Slots can have different facets describing the value type, allowed values, the number of the values (cardinality), and other features of the values the slot can take [23]. For example, the OnsetAge slot can have multiple values

because some of the primary immunodeficiency diseases occur in particular time range. The slot Symptoms_Info can have multiple values and the values are instances of the class Symptoms.

Create instances

Instances are considered as members of a class [25-28]. An ontology with individual instances of classes constitute a knowledge base [23]. Actually ontology is used to organize the instances [24]. Defining an individual instance of a class requires 1) choosing a class, 2) creating an individual instance of that class, and 3) filling in the slot values [19, 23]. For example, the eight selected primary immunodeficiency diseases are instances of ANTIBODY_PRODUCTION_DEFECTS class with them slots such as symptoms, family history, signs and laboratory finding.

Whereas the model is not useable for all, After developing of diagnosis inference model in Protégé

(version 3.4.8) frame based ontology modeling using "Noy and McGuinness" method, develop the inference model in Eclipse (SDK version 3.7.1) software and development mobile application of Clinical decision support system of primary immunodeficiency (Android 2.1) that physicians can use this application.

RESULTS

The diagnosis inference model developed in 5 main class and 24 subclass as hierarchical. Eight primary immunodeficiency diseases as instances of ANTIBODY_PRODUCTION_DEFECTS class, with their properties that is their symptoms, signs, family

history and laboratory data, consist the knowledge base, so question and answer done on ANTIBODY_PRODUCTION_DEFECTS class. To execute the inference model use the query tab of protégé software. The symptoms and signs and laboratory data is entered as input and the diseases that have related symptoms is returned as output by model. Whereas this model is developed with deterministic data and information and based on knowledge, the model responds correctly to the question that related knowledge exist in the knowledge base and did not return any answer where the related knowledge not exist in knowledge base. In Fig 2 a query of the inference model is shown.

Fig 2: Execute the inference model in query tab by entering symptoms, signs and laboratory data

At the end, evaluate functionality of the inference model and application to investigate that could them correctly analyzed and recognized eight PID diseases correctly or not (Fig 3 and 4). So over than 100 cases in different type of PIDs that were used to evaluate

the quality of checklist, both of inference model and mobile application were tested with 10 patient's record data, that both of them diagnosed 110 patients correctly such as specialist. Results of 10 samples are shown in Table 2.

Fig 3: Execute the mobile application of CDSS by entering symptoms, signs and laboratory data

Fig 4: Result of executemobile application of CDSS

Table 2: Inference Model and Software Test Results with Ten Patients Case

Patient ID	1	2	3	4	5
Patient Symptoms	1. age: 2 2. Acute Otitis media 3. IgG : Low 4. SpecificAB : Normal	1. age: 3 2. male 3. Recurrent infections 4. tonsil : small 5. IgG : Low 6. BCell : Low	1. age:6 2. Pneumonia 3. IgG : Normal 4. IgM : Normal 5. IgA : Low	1. age: 7 2. Pneumonia 3. Diarrhea 4. IgG : Low 5. BCell : Normal	1. age: 5 2. male 3. Recurrent infections 4. tonsil : small 5. IgG : Low 6. IgA : Low 7. IgM : Normal
Diagnosis by model and System	THI	XLA	IgA	CVID	CD40Ligand
Diagnosis by specialist	Correct	Correct	Correct	Correct	Correct

Patient ID	6	7	8	9	10
Patient Symptoms	1. age: 6 2. Pneumonia 3. IgG : Normal 4. IgA : Normal 5. IgM : Normal 6. BCell : Normal	1. age: 8 2. Pneumonia 3. IgG : Normal 4. IgA : Normal 5. IgM : Normal 6. IgG2: low 7. BCell: Normal	1. age: 4 2. female 3. Pneumonia 3. IgG : Low 4. IgA : Normal 5. IgM : Normal 6. BCell : Normal 7. sub class IgG : Normal 8. SpecificAB: Normal	1. age: 7 2. Pneumonia 3. IgG: Low 4. IgA: Low 5. IgM: high 6. Specific AB: Low 7. Diarrhea	1. age: 4 2. male 3. Pneumonia 4. IgG : Normal 5. IgA : Normal 6. IgM : Normal 7. BCell : Normal 8. IgG3: low
Diagnosis by model and System	SAD, IgSubClass	IgSubClass	THI	UNG-AID, CD40Ligand	IgSubClass
Diagnosis by specialist	Correct	Correct	Correct	Correct	Correct

DISCUSSION

in this study data is limit and follow the Closed World

Assumption (in the closed world assumption is true if its negation is not provable [24] and terms should be considered unique, so the best method is frame-based modeling that used in artificial intelligence,

expert systems and knowledge bases [29].

Eslami and et al. developed a computerized program designed to diagnose primary headache based on international classification of headache disorders, 2nd edition (ICHD-II) criteria for use by physicians. Of 80 patients, the software was able to come up with correct results in 78 cases. In other words, this software permitted the diagnosis of more than 97% of the patients similar to the physician's [16].

Yin and et al. proposed a computerized headache guideline method using SAGE module and developed a decision support system for headache diagnosis. 282 previously diagnosed cases from EMR were used to evaluate the diagnostic accuracy of the system, the result is: migraine 94.1%, tension-type headache 89%, cluster headache 90.9% and chronic daily headache 93.0% [17].

Dong and et al. developed a headache CDSS based on ICHD-3 beta and validated it in a prospective study that included 543 headache patients. The CDSS correctly recognized 99.4% of migraine without aura, 100% of migraine with aura, 95.2% of chronic migraine, and 62.7% of probable migraine. This system also correctly identified 87.2% of patients with tension-type headache (TTH), which infrequent episodic TTH was diagnosed in 92.3%, frequent episodic TTH was diagnosed in 98.0%, chronic TTH in 90.0%, and probable TTH in 60.9%. The correct diagnostic rates of cluster headache and new daily persistent headache (NDPH) were 90.0% and 100%, respectively. In addition, the system recognized 100% of patients with medication overuse headache [30].

CONCLUSION

In this study and previous studies, software's are developing with deterministic data, they recognized correctly with high accuracy. Also integrating clinical guidelines and diagnostic criteria with information systems and electronic medical records, increase following clinical guideline, improve the quality of patient care, ensure patient safety and reduce costs.

AUTHOR'S CONTRIBUTION

All the authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this study.

REFERENCES

1. Mohammadinejad P, Pourhamdi S, Abolhassani H, Mirminachi B, Havaei A, Masoom SN, et al. Primary antibody deficiency in a tertiary referral hospital: A 30-year experiment. *J Investig Allergol Clin Immunol.* 2015; 25(6): 416-25. PMID: 26817138. [PubMed]
2. Mohammadinejad P, Mirminachi B, Sadeghi B, Movahedi M, Gharagozlou M, Mohammadi J, et al. Distribution of primary immunodeficiency disorders diagnosed in a tertiary referral center, Tehran, Iran (2006-2013). *Iran J Immunol.* 2014; 11(4): 282-91. PMID: 25549596 DOI: 10.1111/ijaai.3136 [PubMed]
3. Aghamohammadi A, Mohammadinejad P, Abolhassani H, Mirminachi B, Movahedi M, Gharagozlou M, et al. Primary immunodeficiency disorders in Iran: update and new insights from the third report of the national registry. *J clin immuno.* 2014; 34(4): 478-90. PMID: 24659230 DOI: 10.1007/s10875-014-0001-z [PubMed]
4. Abolhassani H, Aghamohammadi A, Pourjabbar S, Salehi Sadaghiani M, Nikayin S, Rabiee A, et al. Psychiatric aspects of primary immunodeficiency diseases: The parental study. *Iran J Allergy Asthma Immunol.* 2013; 12(2): 176-81. PMID: 23754357 [PubMed]
5. Mir Saeid Ghazi B, Aghamohammadi A, Kouhi A, Farhoudi A, Moin M, Rezaei N, et al. Mortality in primary immunodeficient patients, registered in Iranian primary immunodeficiency registry. *Iran J Allergy Asthma Immunol.* 2004; 3(1): 31-6. PMID: 17301389 DOI: 03.01/ijaai.3136 [PubMed]
6. Nabavi M, Arshi S, Bermanian MH, Aghamohammadi A, Mansouri D, Hedayat M, et al. Long-term follow-up of ninety eight Iranian patients with primary immune deficiency in a single tertiary centre. *Allergol Immunopathol (Madr).* 2016; 44(4): 322-30. PMID: 26803694 DOI: 10.1016/j.aller.2015.09.006 [PubMed]
7. Mohammadinejad P, Ataeinia B, Kaynejad K, Zeinoddini A, Sadeghi B, Hosseini M, et al. Antibiotic resistance in patients with primary immunodeficiency disorders versus immunocompetent patients. *Expert Rev Clin Immunol.* 2015; 11(10): 1163-72. PMID: 26289374 DOI: 10.1586/1744666X.2015.1075396 [PubMed]
8. Aghamohammadi A, Moghaddam ZG, Abolhassani H, Hallaji Z, Mortazavi H, Pourhamdi S, et al. Investigation of underlying primary immunodeficiencies in patients with severe atopic dermatitis. *Allergol Immunopathol (Madr).* 2014; 42(4): 336-41. PMID: 23735167 DOI: 10.1016/j.aller.2013.02.004 [PubMed]
9. Rezaei N, Mohammadinejad P, Aghamohammadi A. The demographics of primary immunodeficiency diseases across the unique ethnic groups in Iran, and approaches to diagnosis and treatment. *Ann N Y Acad Sci.* 2011; 1238: 24-32. PMID: 22129050 DOI: 10.1111/j.1749-6632.2011.06239.x [PubMed]
10. Abolhassani H, Mirminachi B, Daryabeigi M, Agharahimi Z, Aghamohammadi A, Rabbani A, et al. Evaluation of physicians' awareness of pediatric diseases in Iran. *Iran J Pediatr.* 2014; 24(1): 87-92. PMID: 25793051 [PubMed]
11. Azizi G, Abolhassani H, Asgardoon MH, Shaghaghi S, Negahdari B, Mohammadi J, et al. Managing patients

- with side effects and adverse events to immunoglobulin therapy. *Expert Rev Clin Pharmacol*. 2016; 9(1): 91-102. PMID: 26496172 DOI: 10.1586/17512433.2016.1105131 [PubMed]
12. Abolhassani H, Rezaei N, Mohammadinejad P, Mirminachi B, Hammarstrom L, Aghamohammadi A. Important differences in the diagnostic spectrum of primary immunodeficiency in adults versus children. *Expert Rev Clin Immunol*. 2015; 11(2): 289-302. PMID: 25556968 DOI: 10.1586/1744666X.2015.990440 [PubMed]
 13. Abolhassani H, Akbari F, Mirminachi B, Bazregari S, Hedayat E, Rezaei N, et al. Morbidity and mortality of Iranian patients with hyper IgM syndrome: a clinical analysis. *Iran J Immunol*. 2014; 11(2): 123-33. PMID: 24975969 DOI: 10.1111/ijim.12127 [PubMed]
 14. Abolhassani H, Hirbod-Mobarakeh A, Shahinpour S, Panahi M, Mohammadinejad P, Mirminachi B, et al. Mortality and morbidity in patients with X-linked agammaglobulinemia. *Allergol Immunopathol (Madr)*. 2015; 43(1): 62-6. PMID: 24485939 DOI: 10.1016/j.aller.2013.09.013 [PubMed]
 15. Tavakol M, Mohammadinejad P, Baiardini I, Braidó F, Gharagozlou M, Aghamohammadi A, et al. The Persian version of the chronic urticaria quality of life questionnaire: factor analysis, validation, and initial clinical findings. *Iran J Allergy Asthma Immunol*. 2014; 13(4): 278-85. PMID: 24659164 [PubMed]
 16. Eslami V, Rouhani-Esfahani S, Hafezi-Nejad N, Refaiean F, Abdi S, Togha M. A computerized expert system for diagnosing primary headache based on International Classification of Headache Disorder (ICHD-II). *SpringerPlus*. 2013; 2(1): 199-202. PMID: 23710428 DOI: 10.1186/2193-1801-2-199 [PubMed]
 17. Yin Z, Dong Z, Yu S, Lu X, Feng G, Duan H. A guideline-based decision support system for headache diagnosis. *Stud Health Technol Inform*. 2013; 192: 1022-3. PMID: 23920796 [PubMed]
 18. Maizels M, Wolfe WJ. An expert system for headache diagnosis: The Computerized Headache Assessment tool (CHAT). *Headache*. 2008; 48(1): 72-8. PMID: 17868352 DOI: 10.1111/j.1526-4610.2007.00918.x [PubMed]
 19. Zahedi R, Alibeik M, Amin G, Karimi M. Development of ontology representation of medicinal plants in Iran based on Unified Medical Language System (UMLS). [Thesis] Tehran University of Medical Sciences; 2013.
 20. Bonilla FA, Khan DA, Ballas ZK, Chinen J, Frank MM, Hsu JT, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *J Allergy Clin Immunol*. 2015; 136(5): 1186-205. PMID: 26371839 DOI: 10.1016/j.jaci.2015.04.049 [PubMed]
 21. de Vries E. Patient-centred screening for primary immunodeficiency, a multi-stage diagnostic protocol designed for non-immunologists: 2011 update. *Clin Exp Immunol*. 2012; 167(1): 108-19. PMID: 22132890 DOI: 10.1111/j.1365-2249.2011.04461.x [PubMed]
 22. Bousfiha AA, Jeddane L, Ailal F, Al Herz W, Conley ME, Cunningham-Rundles C, et al. A phenotypic approach for IUIS PID classification and diagnosis: guidelines for clinicians at the bedside. *J Clin Immunol*. 2013; 33(6): 1078-87. PMID: 23657403 DOI: 10.1007/s10875-013-9901-6 [PubMed]
 23. Noy NF, McGuinness DL. Ontology development 101: A guide to creating your first ontology. Stanford knowledge systems laboratory technical report [Report No: KSL-01-05]; 2001.
 24. Shadgar B, Osare A, Haratian Nejadi A. Semantic Web-Concepts and techniques. Tehran: Armaghan; 2014.
 25. Sanat Joo A, Fathian A. The methodology for design, construction and implementation of ontology: Approaches, languages and tools (Case study in the field of library and information science ASFAONT design ontology). *Journal of Librarianship and Information Sciences*. 2012; 15(1): 113-142.
 26. Asooshe A, Mehra Sh, Khatibi T, Khakshour Saadat P. Ontology: Methodology, tools and development languages. Tehran: Tarbiyat Modares University Publication Center; 2011.
 27. Ghaffari J, Karami H, Khanian A, Mohammadzadeh E. Primary immuno-deficiencies (PID). *J Mazandaran Univ Med Sci*. 2009; 19 (70) :76-80.
 28. Chen CC, Chen K, Hsu CY, Li YC. Developing guideline-based decision support systems using protégé and jess. *Comput Methods Programs Biomed*. 2011; 102(3): 288-94. PMID: 20594609 DOI: 10.1016/j.cmpb.2010.05.010 [PubMed]
 29. Behkamal B. Semantic Web Tutorial. Ferdowsi University: Web Technology Lab; 2012.
 30. Dong Z, Yin Z, He M, Chen X, Lv X, Yu S. Validation of a guideline-based decision support system for the diagnosis of primary headache disorders based on ICHD-3 beta. *J Headache Pain*. 2014; 15(1): 40-7. PMID: 24934331 DOI: 10.1186/1129-2377-15-40 [PubMed]