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Doknosis: A differential diagnosis tool for physicians

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Independent Study Project

Despite modernization in many areas of medicine, creating a differential diagnosis remains subjective and qualitative. Our goal is to create a differential diagnostic tool for clinicians that is both accurate and accessible. For this project, my main contribution was to enter relevant findings for about 700 medical conditions into the database, coded by the frequency with which each finding is observed. This database was uploaded to the Doknosis tool at Doknosis.org, to be used by the diagnosis-ranking algorithm. We have subsequently continued to refine the database, algorithm and web interface. To evaluate the current utility of the project, I have chosen representative cases, entered the relevant symptoms into the site, and determined the approximate accuracy of the program.

Purpose and Methods

Our site allows the user to input features of a patient's presentation and receive a list of possible diagnoses. These features include signs, symptoms, demographics, risk factors, lab findings, travel history and past medical history. The potential diagnostic conditions include both infectious and sporadic diseases as well as drug side effects. Features in the database are weighted based on the rate they occur in patients with that diagnosis. This information was taken from trusted medical sources such as UpToDate and Medscape's Drugs and Diseases database. A section of one database entry is shown below.

Syringomyelia or syringobulbia

- trauma:0.2
- malignancy:0.4
- cranial nerve palsy:0.5
- CSF obstruction:0.5
- Arnold-Chiari malformation:0.4
- male:0.6
- female:0.4
- child:0.01
- insidious onset:0.8
- acute onset:0.2
- dissociated sensory loss:0.9
- decreased pain sensation :0.9
- decreased temperature sensation:0.9
- preserved light touch sensation:0.9
- preserved vibratory sensation:0.7
- intact proprioception:0.7
- shawl-like distribution:0.7
- upper extremity atrophy:0.7
- upper extremity weakness:0.7
- dysphagia:0.4
- nystagmus:0.4
- painless ulcers of hands:0.7
- hyporeflexia of arms:0.6

If the prevalence of a finding was not stated quantitatively in the literature, we assigned an estimate using a standardized system to translate qualitative statements into relative numbers:

1 Always	0.75 Common	0.5 Probable	0.25 Infrequent	0.1 Rare	0 Never
Gender specific (e.g. OB/GYN)	"Classic" "Usually" "Mainly"	"Can"	"May cause" "May reveal" "May be" "Less common"	"Has occurred" "Occasionally"	Gender specific

Translation of qualitative statements to quantitative frequency

Armed with this database, the program uses multiple algorithmic approaches to identify possible diagnoses, depending on the available data. The results are not intended to replace the judgment of the clinician when diagnosing the patient, but rather to aid in creating a broad differential so that rare but serious conditions are not forgotten. The tool should enable clinicians to integrate statistics from a number of reliable sources through a simple, open-source tool, empowering informed differentials and improving both patient care and physician efficiency.

Evaluation

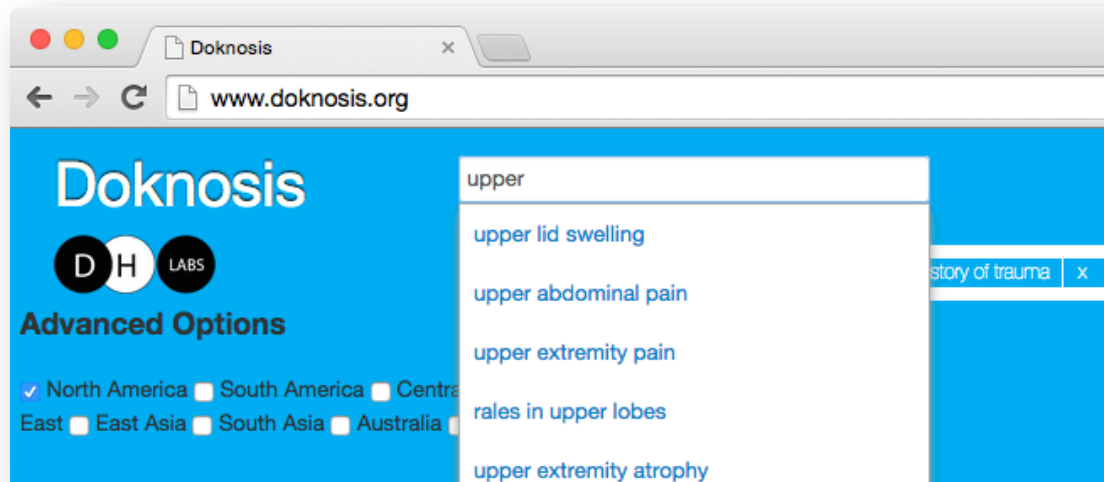
I wanted to evaluate diagnostic performance for common presentations of important diseases. Most published cases studies seemed unique or esoteric, so I opted to use cases from the USMLE Step 2 CK question bank. These practice questions prepare medical students for part of their medical boards examinations, taken after their first year of clinical rotations. They consist of case summaries with multiple-choice answers. These questions are copyrighted and require a subscription for access, so I cannot reproduce them here, but I will include the question IDs in Appendix A for reference.

I went through 176 questions randomly selected from the entire bank (4 sets of 44 questions) and found 47 that asked for a diagnosis. I attempted to input the symptoms and other associated features from the question stem into Doknosis as best as possible, often including redundant findings to be as specific as possible. For example, I included both "low fever" and "low-grade fever" where appropriate, as these are likely to be consolidated in the future. After I was satisfied with the input, I went down the list of likely diagnoses until I found one that matched an answer choice from the question. If this answer was incorrect, I looked for the correct answer in the top 20 results on Doknosis. If the correct answer was not present in these results, I searched the Doknosis database for any entries related to that disease or condition. I recorded the correct answer, matching database entry (if present), rank of correct answer (if present in top 20), the answer chosen by the algorithm, student accuracy (reported by USMLE World), entered findings, and number of multiple-choice options [Appendix A]. I used the opportunity to make improvements to the database, but did not modify the version of the database used for subsequent queries for this experiment.

Example Case

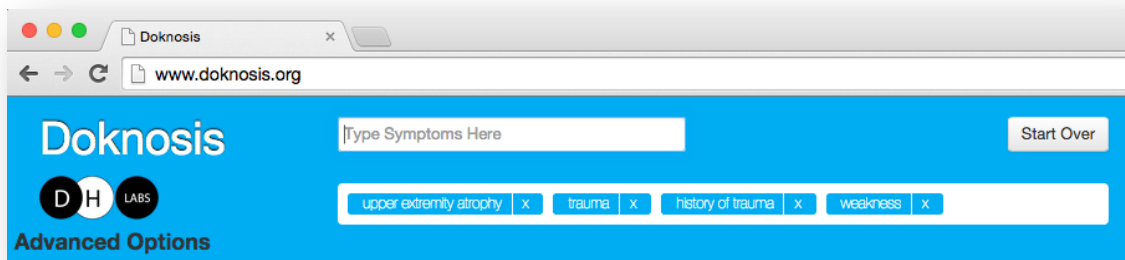
Unfortunately I am unable to reproduce any questions from the bank, so I will demonstrate entry and feedback from the Doknosis site.

Entering a finding:



Findings are typed into the entry box and selected from a list of all matching findings in the database. Suggestions appear while typing and contain the exact text at any point (not just the beginning).

Entered Findings:



Each finding is added here and can be removed individually. Order does not influence results.

Results List:

Most Likely: Syringomyelia and syringobulbia	
Name	Score
Syringomyelia and syringobulbia	2.7
Fat embolism (traumatic)	2.5
Air embolism (traumatic)	2
Crushed chest	2
Chronic post-traumatic headache	2
Dissociative motor disorders	1.99
Dislocation of ankle joint	1.9
Dislocation of acromioclavicular joint	1.9
Dislocation of finger	1.9
Fracture of lower end of both ulna and radius	1.9

Conditions are ranked by probability. The user can select to include diseases, drug toxicities, or both. Currently, up to 20 conditions can be displayed.

Results

47 diagnosis-based questions were used. These questions had between 4-15 multiple-choice options. Of the 47 diagnosis-based questions, 19 were related to a diagnosis that was not yet present in our database. Of the remaining 28, Doknosis had the answer in its top 20 results 57% of the time, and answered correctly 50% of the time. For the same 28 questions, students were correct 69% of the time.

Characterization of questions

	# (%)	Student Accuracy ¹	Average # of choices	Average rank of correct answer
In database	28 (60%) ²	69%	6.2	-
Answer in top 20	16 (57%) ³	73%	5.7	2.7
Answered correctly	14 (50%) ³	75%	5.8	1.7
Not in top 20	12 (43%) ³	64%	7.0	-
Not in database	19 (40%) ²	59%	6.1	-
Total	47	65%	6.2	-

¹Percent of students that answered correctly, as reported by USMLE World

²Percent of all questions (47 questions)

³Percent of questions represented in the database (28 questions)

R-Squared Values	All	In DB
Student vs. algo	0.122	0.128
Difficulty vs. DB inclusion	0.100	-
# of choices vs. difficulty	0.011	0.000
# of choices vs. algo	0.021	0.062
# of choices vs. DB inclusion	0.001	-

R squared correlation analysis. Algo = Doknosis algorithm performance, DB = database

Discussion

I used R-squared (R^2 , or coefficient of determination) analysis to evaluate correlation between various properties of each question, such as difficulty and number of answer choices.

Question Difficulty

I used student accuracy as an indirect measure of question difficulty. Algorithm accuracy appeared to correlate with question difficulty, as average student score was lower on questions that the algorithm failed to recognize. By R^2 analysis, student accuracy was 12.8% predictive of algorithm performance. Questions that were absent from our database were also more difficult on average than those that were, with a correlation of 10%. This indicates that inclusion in our database may have some relation to difficulty; so perhaps difficult questions represented more obscure topics that were less likely to be included.

Number of Choices

Because not all questions had the same number of choices, I wanted to ensure that this was not a confounding factor. Although it is commonly stated that more answer choices makes a question more difficult for students, there was only a 1.1% correlation. As I was evaluating the algorithm just based on its ability to include the correct answer in its results, one would not expect it to be affected by the number of wrong choices. Although the average was higher, the R^2 correlation was only 6.2%. Questions with relevant entries in the database had roughly the same amount of answer choices as those that did not, and number of choices was only 0.1% predictive of inclusion. This indicates that number of choices was likely not a confounding factor in this evaluation.

Conclusion

These results show the potential of this early version of the database. Future areas for improvement should focus on adding more conditions, improving finding recognition, and ease of use.

Accurate identification depends on the presence of the condition in the database. We started with what we thought was a comprehensive list, but the results show that there are many conditions that still need to be added. Some conditions were too general, such as “nephrotic syndrome,” and will need to be subdivided. Working with the UWorld question bank could continue to provide an effective resource.

Once a condition is in the database, the algorithm has to be able to match its symptoms to the entered findings, which can be improved by adding connections between symptoms and revising previous entries. Currently, the algorithm can’t recognize relations between findings. For example, it doesn’t know that “arm weakness” should also count as “weakness.” Future versions will have an “ontological dictionary” to map relationships between related terms, automatically including them in the search. We also need to allow users to distinguish symptoms from history, such as “hypertension” vs. “history of hypertension,” or “myocardial infarction” vs. “history of myocardial infarction.” For medication toxicities, this evaluation was limited to only 5 questions, but I did notice that it is often difficult to indicate that the patient is taking a specific medication.

Even if the database is comprehensive, it must be simple and accessible in order to be useful. Other improvements could include suggesting related findings, allowing the indication of absent findings, and automatically importing findings from an Electronic Medical Record (EMR).

The program is already quite effective, and with improvement in these directions, the accuracy and usability of the program will make it a helpful tool for doctors and students.

References

Test cases taken from [USMLEWorld Step 2CK QBank](#) without reproduction in accordance with “Terms of Use” at http://www.uworld.com/terms_conditions.aspx, accessed May 2-3, 2015 using “USMLEWorld Qbank” software version 4.0 for Mac

Appendix A – Detailed Results

Entered findings are listed below each row, with parentheses indicating useful findings that could not be entered into Doknosis.

UWorld case ID	Correct answer	Corresponding database entry	Rank of correct entry	Best choice based on results
	Findings			Difficulty
4698	Syringomyelia	syringomyelia or syringobulbia	1	Correct
	upper extremity atrophy, trauma, history of trauma, weakness			69%
3061	Drug-induced interstitial nephritis	Tubulointerstitial nephritis	1	Correct
	white cell casts in urine, arthralgia, rash, recent antibiotic use, fever, sexually active, dysuria, polyuria, urinary frequency, increased urinary frequency, acute renal failure, proteinuria, mild proteinuria, maculopular rash			80%
4463	drug interaction (digoxin)	Digoxin	>20	erosive gastritis
	anorexia, nausea, weakness, amiodarone, atrial fibrillation, history of atrial fibrillation, furosemide, (digoxin)			56%
2746	tinea corporis	tinea corporis	>20	secondary syphilis
	rash, rash on trunk, itching, itchiness, itchy rash, sexually active			68%
4897	delusional disorder	delusional disorder	1	Correct
	paranoia, delusion, nonbizarre delusions			73%
4912 (Audio)	patent ductus arteriosus	None		mitral valve prolapse
	infant, murmur, (washing machine murmur, to and fro murmur)			
3037	blastomycosis	chronic pulmonary blastomycosis (rank 2), blastomycosis (3)	3	disseminated coccidiomycosis (1)
	midwestern united states, fever, night sweats, cough, productive cough, weight loss, subacute, subacute onset, rash, skin lesion, skin lesions, verrucous skin lesions, lytic lesions on bone films, osteolytic lesions, consolidation on cxr			59%
4635	chronic liver disease (alcoholic cirrhosis)	alcoholic cirrhosis	>20	adrenal insufficiency
	sexual dysfunction, male, impotence, weight loss, gynecomastia, low t3, low t4, chronic, hypogonadism, testicular atrophy			66%
4434	acute pancreatitis	alcohol-induced acute pancreatitis (Rank 4)	1	“drug-induced acute pancreatitis”
	abdominal pain, epigastric pain, acute onset of epigastric pain, vomiting, improved by sitting up and leaning forward, hyperlipidemia, smoking history, alcohol use, alcohol, alcoholism, left sided pleural effusion			81%
4640	pilonidal disease	None		None
	pain, swelling, male			65%

3815	behcet's disease	behcet's disease	2	reactive arthropathies (reiter's syndrome) TIED WITH behcet's disease
	oral ulcers, blurry vision, vision changes, anterior uveitis, uveitis, genital ulcers, multiple painful genital ulcers, nodular lesions, hypopigmented lesions			60%
10763	nitroprusside (cyanide) toxicity	None		None
	dyspnea, cough, dry cough, smoking history, alcohol, alcoholism, alcohol use, history of alcohol abuse, history of heavy alcohol use, history of chronic alcohol consumption, elevated creatinine, serum creatinine raised, seizure, hypertension, hypertensive crisis, severe hypertension, confusion, agitation, altered mental status			20%
2233	alport syndrome	None		None
	adolescent, hematuria, lower abdominal pain, pelvic or lower abdominal pain, abdominal pain, deafness in child, deafness, proteinuria, protein in ua, renal failure, child			86%
4388	s aureus endocarditis	None		None
	fever, chills, pleuritic chest pain, dyspnea, positive hiv pcr, positive hiv elisa, positive hiv western blot, tachycardia, crackles on lung exam, crackles in adult, diffuse crackles, crackles, leukocytosis, lung cavitations			39%
2868	hairy cell leukemia	hairy cell leukemia	3	Correct
	lethargy, easy fatigability, pallor, splenomegaly, palpable spleen, palpable splenomegaly, atypical lymphocytes, leukocytosis			87%
3951	aortic regurgitation	aortic (valve) insufficiency	17	aortic stenosis
	dyspnea on exertion, palpitations, widened pulse pressure			65%
3724	fluid-filled cavity in the central spinal cord	syringomyelia or syringobulbia	2	Correct
	arm weakness, weakness, anesthesia, areflexia, preserved vibratory sensation, preserved proprioception			81%
3769	amiodarone (toxicity)	amiodarone	1	Correct
	pulmonary fibrosis, pneumonitis			85%
3574	subacromial bursitis	bursitis of shoulder	>20	bicipital tendinitis
	shoulder pain, history of anterior shoulder pain exacerbated by lifting or elevated pushing or pulling of objects			74%
2713	intracardiac tumor (cardiac myxoma)	None		infective endocarditis
	weakness, hemiparesis, fatigue, fever, low-grade fever, low fever, low grade fever, palpitations, weight loss, murmur, diastolic murmur, (left atrial mass)			61%
3679	flagellated motile organisms	trichomoniasis	2	Correct
	vulvar burning, vulvar pruritis, vaginal discharge, green vaginal discharge, frothy vaginal discharge, thin vaginal discharge, (ph 5.5)			79%

4497	vascular ring	None		laryngotracheobronchitis
	infant, ventricular septal defect, stridor, murmur, holosystolic murmur loudest at left sternal border, systolic murmur, pansystolic murmur, (stridor improves with neck extension)			37%
3548	autoimmune destruction of the pancreatic beta cells (DMI)	insulin-dependent diabetes mellitus (Rank 8)	4	"diabetes mellitus"
	child, polydipsia, polyuria, incontinence, urinary incontinence, incontinence of bladder, fatigue, dehydration, (enuresis)			57%
4239	nonclassic CAH (21-hydroxylase deficiency, gonadotropin independent (peripheral))	None		None
	child, acne, (advanced bone age, coarse axillary and pubic hair, severe cystic acne, low LH, negative GNRH stimulation, tall)			24%
4436	family history (sickle cell trait)	sickle-cell trait	>20	"sexual history" (syphilis)
	african american, nocturia, recurrent otitis media, sexually active, (family history)			54%
4306	tuberculosis	tuberculosis	>20	human immunodeficiency virus infection
	weight loss, fever, cough, sputum production, productive cough, nausea, abdominal pain, dizziness, (postural dizziness, subnormal cortisol rise with cosyntropin stimulation test, bilateral adrenal calcification)			75%
2664	benzodiazepine overdose	None		None
	slurred speech, trouble walking, difficulty walking, drowsiness, (history of) insomnia, (history of) migraine, (history of) migraines, history of epilepsy, lethargy, hyporeflexia, (bipolar disorder, history of hypothyroidism, reactive pupils)			53%
3396	shearing of subdural veins (non-accidental trauma)	None		meningeal inflammation
	infant, seizure, grand mal seizure, aka tonic-clonic seizure, seizure in infant, full-term, retinal hemorrhage, (increased head circumference)			67%
2819	self-induced vomiting	bulimia nervosa	3	Correct
	weakness, tingling, tingling sensation, paresthesia, numbness, hypokalemia, hypochloremia, metabolic alkalosis, (alkalosis [unspecified], low urine chloride, low urine sodium)			69%
4241	femoral artery aneurysm	None		"inguinal hernia"
	presentation with isolated knee or thigh pain, pain with walking, pain on walking, history of copd, smoking history, visible bulge in the groin, (pulsatile groin mass, anterior thigh pain)			80%
4114	histoplasmosis	histoplasmosis	>20	pneumocystis pneumonia
	nodules on cxr, nodules on chest x-ray, lung nodules, (mississippi, southern united states, nonsmoker)			73%

4772	pulmonary embolism	pulmonary embolism	>20	septic shock
	loss of consciousness, trouble walking, difficulty walking, skin infections, diabetic, diabetes mellitus, hypotension, shock, tachycardia, "cold, clammy skin", cool clammy skin, pulmonary hypertension, syncope, (normal pcwp)			66%
3582	whipple's disease	whipple's disease	1	Correct
	diarrhea, abdominal pain, weight loss, bulky diarrhea, foul-smelling diarrhea, abdominal distension, abdominal distention, flatulence, arthralgia, polyarthralgia, chronic cough, cough, lymphadenopathy, generalized lymphadenopathy, hyperpigmentation, hyperpigmentation of skin, diastolic murmur, pas-positive macrophages in intestinal biopsy			76%
3379	Autism spectrum disorder	Childhood Autism	>20	None
	child, male, behavioral changes, poor eye contact, restricted behaviors, solitary			94%
3872	Choanal atresia	None		None
	newborn, difficulty feeding, poor feeding, cyanosis, dyspnea			63%
3940	membranous nephropathy	None		(unable to determine)
	adolcescent, child or adolescent, adolescent or young adult, facial swelling, fatigue, loss of appetite, decreased appetite, decrease in appetite, "history of travel to southeast asia and australia, or middle east, india or china", "history of travel to china, india, malaysia, the philippines, indonesia, or various pacific islands", china, travel to china, periorbital edema, hypoalbuminemia, decreased albumin, decreased serum albumin, hepatitis b infection, proteinuria, nephrotic proteinuria			39%
2452 (xray)	duodenal atresia	None		None
	bilious vomiting, newborn, vomiting, maternal polyhydramnios, delayed passage of meconium, hypotonia, enlarged tongue, protruding tongue, up-slanting palpebral fissure, low-set ears, fifth finger clinodactyly, holosystolic murmur loudest at left sternal border, thrill, precordial thrill, down syndrome, (double bubble)			92%
4331	G6PD Deficiency	None		acute viral hepatitis
	african american, "african american (in us)", fever, jaundice, absominal pain, dark urine, tachycardia, (bite cells on peripheral smear, RBC inclusions on crystal violet stain)			72%
3146	schizoid personality disorder	shizoid personality disorder	1	Correct
	solitary, poor eye contact, (not bothered)			74%
2860	herpes simplex keratitis	herpesviral ocular disease	1	Correct
	eye pain, red eye, eye redness, watery eyes, watering of the eye, vesicles, dendritic ulcer, corneal ulceration			72%

3083	vitamin d overdose	hypervitaminatosis d	>20	adrenal insufficiency
	constipation, abdominal pain, obese, obesity, weight loss, history of atrial fibrillation, dehydration, (warfarin, diltiazem, numerous daily vitamins and minerals)			48%
10670 (Photo)	epidermal inclusion cyst	Epidermal cyst	>20	None
	bump, nonpruritic skin lesions, palpable nodule, subcutaneous nodules, nontender firm subcutaneous nodules			44%
4118	aspiration pneumonia	None		None
	fever, productive cough, putrid sputum, recurrent pneumonia, smoking history, alcoholism, history of alcohol abuse, history of heavy alcohol use, infiltrates on cxr, hypoxemia, consolidation on cxr, crackles, crackles in adult, crackles on lung exam, dyspnea			68%
4486	pyloric stricture	None		None
	central america, travel to central america, nausea, vomiting, suicidality, suicidal behavior, diabetes mellitus - type 2, diabetes mellitus, smoking history, tachycardia, dehydration, presence of a gastric splash, hear four hours or more after the last meal, peptic ulcer disease, (vomiting of partially digested food, history of acid ingestion, early satiety)			55%
4253	cluster headache	cluster headache	>20	migraine
	pain behind the eyes, eye pain, severe eye pain, sharp or stabbing pain, alcoholism, ptosis, ptosis with miosis (partial horner syndrome), miosis, pain awakening patient at night, sudden awakening, intense pain, retroorbital pain			55%
3959	lacunar stroke (hypertension)	None		large artery atherosclerosis
	slurred speech, hand weakness, focal weakness, history of myocardial infarction, aspirin use, other known associations include penicillins, cephalosporins, enalapril, rifampin, nsaid, smoking history, hypertension, dysarthria			54%
2901	spontaneous bacterial peritonitis	None		alcoholic hepatitis
	liver disease, fatigue, ascites, furosemide, (history of) esophageal varices, beta blocker, beta-blocker use, tachycardia, (abdominal discomfort, history of chronic ascites, history of alcoholic liver disease, ascitic fluid with high neutrophils, high serum-ascites albumin gradient (SAAG), no free air on upright cxr)			82%