

FindZebra: A search engine for rare diseases

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Abstract

Background: The web has become a primary information resource about illnesses and treatments for both medical and non-medical users. Standard web search is by far the most common interface for such information. It is therefore of interest to find out how well web search engines work for diagnostic queries and what factors contribute to successes and failures. Among diseases, rare (or orphan) diseases represent an especially challenging and thus interesting class to diagnose as each is rare, diverse in symptoms and usually has scattered resources associated with it.

Methods: We use an evaluation approach for web search engines for rare disease diagnosis which includes 56 real life diagnostic cases, state-of-the-art evaluation measures, and curated information resources. In addition, we introduce FindZebra, a specialized (vertical) rare disease search engine. FindZebra is powered by open source search technology and uses curated

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NOTICE: this is the author's version of a work that was accepted for publication in International Journal of Medical Informatics. Changes resulting from the publishing process, such as peer review, editing, corrections, structural formatting, and other quality control mechanisms may not be reflected in this document. Changes may have been made to this work since it was submitted for publication. A definitive version was subsequently published and is available online since 23 February 2013, DOI:10.1016/j.bbr.2011.03.031.

freely available online medical information.

Results: FindZebra outperforms Google Search in both default setup and customised to the resources used by FindZebra. We extend FindZebra with specialized functionalities exploiting medical ontological information and UMLS medical concepts to demonstrate different ways of displaying the retrieved results to medical experts.

Conclusions: Our results indicate that a specialized search engine can improve the diagnostic quality without compromising the ease of use of the currently widely popular web search engines. The proposed evaluation approach can be valuable for future development and benchmarking. The FindZebra search engine is available at <http://www.findzebra.com/>.

Keywords: Rare diseases, Specialized search engine, Information retrieval, Evaluation of web search engines

1. Introduction

The web has become a primary source of information about illnesses or treatments [1], with an exponential growth in both volume and amount of entries available [2]. Important resources in locating medical information online are information retrieval systems, more commonly known as search engines. A December 2009 poll found that 66% of web users have searched for medical information online [3]. This class of search activities, which goes beyond simple fact retrieval, is referred to as exploratory health search [4, 5]. It can be carried out by both expert and non-expert medical users.

A typical example of an expert medical user is a clinician. Diagnostic health search can also be seen as a coarse form of hypothetico-deductive reasoning [1], where web search engines guide the iterative cycle of hypotheses about a disease being formulated from evidence, followed by the collection of additional discriminating evidence. According to recent studies, an increasing number of clinicians use web search engines to assist them in solving difficult medical cases, for instance when confronted with rare (or orphan) diseases [6]. The exact definition of rare diseases in terms of prevalence threshold and requirement for severity varies across the globe, but a disease is, in general, said to be rare if it affects fewer than approximately one in two thousand individuals. A study² conducted by the European Organisation for

²<http://archive.eurordis.org/article.php3?idarticle=454>.

Rare Diseases (EURORDIS), showed that 40% of rare disease patients were wrongly diagnosed before the correct diagnosis was given, and that 25% of patients had diagnostic delays ranging between 5 and 30 years.

The current popularity of web search engines (primarily Google) and medical databases (primarily PubMed) for aiding in diagnosis may appear a bit surprising, as these tools are not optimised for this task. For example, a diagnostic query may be quite long, whereas web search engines are typically optimised for very short queries (2–3 terms long). Queries consist of lists of patient symptoms, often expressed as multi-word units. However, search engines often make term independence assumptions in order to increase efficiency. For instance, web search engines may not distinguish between “sleep deficiency, increased sexual appetite” and “sexual deficiency, increased sleep”, hence returning non-relevant results. Some symptoms listed in the clinician’s query may not apply to the correct disease, and conversely, some pertinent symptoms for the correct disease may be missing from the query because they are masked under different conditions. However, search engines are designed to maximise the match between all the query terms and the returned documents.

In short, the clinicians’ queries on rare diseases are likely to be more feature-rich but also harder for a search engine than ordinary web search queries, and should ideally be processed as such. Furthermore, the popularity-based metrics derived from hyperlinking (PageRank), user visit rates, or other forms of user recommendation that are commonly used by search engines are not likely to benefit the retrieval of rare diseases. These practices tend to favour webpages with many in-links (backlinks) or results often viewed by users (implicit feedback). Information on rare diseases, on the other hand, is generally likely to be very sparse and less hyperlinked than other medical content. Finally, efficiency concerns may lead to brute-force index pruning for web search, e.g. by removing from the index low frequency terms, or terms that are unusually long, such as “hydrochlorofluorocarbons” ([7], Chapter 5). Such practices may be particularly damaging for rare disease search, as the medical terminology involved may be exceptionally rare or formed by heavy term compounding. It is probably fair to conclude that familiarity, and the ease of use compared to traditional information search and diagnostic support systems (reviewed below) are the main factors contributing to the current popularity of general purpose web search engines in the clinical setting.

Motivated by these observations we asked to what degree can web search

engines actually be used for rare disease diagnosis and what are the main contributing factors that determine success and failure. To try to answer these questions it is necessary to go through a number of steps. First of all an evaluation approach has to be set up. It should consist of cases of varying degrees of difficulty and retrieval performance measures to allow for quantitative comparisons between methods. Furthermore, the web search engine algorithms are not public so one can only to a limited degree change settings and thus interpret why a query returns a given set of results. Google offers a search engine customisation product called Google Custom Search Engine³ which has a few options for customisation that can be used to emphasise particular resources and thus determine how the choice of the information source (the index) influences the performance. If emphasising resources known to be authoritative in the rare disease domain improves the performance then one can conclude the huge index used by Google Web Search introduces noise. However, this will not give information along the “algorithm dimension”. We therefore made FindZebra, a search engine specifically designed to retrieve rare disease information for clinicians. It uses a specially curated dataset of rare disease information, which is crawled from freely available online authoritative resources. This means that FindZebra searches for rare disease information from a repository of “clean”, specialized resources, unlike web search engines that search the whole web and are hence likely to return spurious, commercial and less relevant results. The same index will be used for the customised versions of Google thus allowing us to gain an insight on the adequacy of the Google Search algorithm in rare disease diagnosis.

The rest of this article is organised as follows: Section 2 discusses background work on collecting and retrieving medical information automatically with a focus on rare disease data. Section 3 presents the evaluation approach. Section 4 presents our search engine, FindZebra and the information resources used for its index. Section 5 describes the evaluation, benchmarking FindZebra, different versions of Google Search, and PubMed against each other. Section 6 discusses the results and finally Section 7 summarises the findings of the paper.

³<http://www.google.com/cse/>.

2. Background

Historically, the task of retrieving medical information has relied on authoritative resources, such as the 1879 Index Medicus (which ceased publication in 2004) [2]. Since that time, the amount, availability and authority of medical resources have changed radically. More medical information is becoming freely available on the web; however, the authority of this information is not always easy to trace. A study by Eysenbach and Kohler [8] found that many users searching for medical information online largely ignored the credibility of web sites (in terms of source, design, scientific or official appearance, phraseology, and ease of use). Several researchers have also noted a need for improving the medical information on the web. Lewis' [9] qualitative study into young peoples' use of the web for medical information showed that users are often sceptical about the information they encounter. Nevertheless, there is evidence that young clinicians in particular are increasingly using the web to help them take medical decisions [10]. Such findings demonstrate some of the conflicting opinions around the level and credibility of medical information on the web. In response to these issues, some organisations have initiated efforts to improve the general quality of medical information on the web, such as the Health on the Net Foundation,⁴ or ways of augmenting web pages or search results with tools to support credibility assessment [11].

Scepticism about the level and credibility of medical information on the web has motivated research in the direction of specialized medical web portals, repositories, database and search systems. The inadequacy of standard search technology for the task of medical retrieval has long been known. For instance, an earlier study [12] on how physicians use search systems to support clinical question answering and decision making revealed that search technology was inadequate for this purpose and generally retrieved less than half of the relevant articles on a given topic (a finding also supported by more recent studies, e.g. [5]).

Furthermore, studies of expert users while they performed search tasks inside and outside their domains of expertise [13] or using general purpose versus specialized medical search engines [4], identified domain-specific search strategies in each domain, and that such search knowledge is not automatically acquired from general-purpose search engines. Overall, the consensus seems to be that standard web search engines are not optimal for finding

⁴<http://www.hon.ch>

medical information online.

The retrieval of rare disease information is an even bigger problem, and efforts to address it date back to the 1990s. DXplain [14], an early diagnostic support system that went online in 1996, was one of the first systems to display rare diseases separately from the rest. DXplain contained probabilities for over 4900 clinical manifestations associated with over 2200 unique diseases, yielding a total of over 230,000 unique disease interconnections. Another early effort was the London Dysmorphology Database, which contained information on rare dysmorphic syndromes and went online in 1999. This system provided the clinician with a manageable list of possible genetic syndromes (many of which are rare) for a particular case, with references, photographic information, and the possibility to register undiagnosed or unreported cases [15]. Further resources on rare diseases include the Online Mendelian Inheritance in Man (OMIM) database,⁵ which specialises in human genes and genetic phenotypes and contains information for all Mendelian disorders and over 12,000 genes. Another major resource for rare diseases is the Orphanet database,⁶ which contains information on more than 5900 rare diseases, and provides a service for retrieving data for rare diseases based on clinical signs or genes. Other databases on topics associated with rare diseases include POSSUMweb,⁷ which is a dysmorphology database that contains textual and photographic information on more than 3000 malformations, metabolic, teratogenic, chromosomal and skeletal syndromes. Phenomizer,⁸ a tool that uses the Human Phenotype Ontology (HPO), correlates phenotypic abnormalities with genetic disorders (OMIM entries) and contains around 9900 features and 5020 diseases. Furthermore, there are clinical decision support systems that aid in the diagnosis of one, or a few difficult to diagnose diseases [16], but their use is limited to verifying a diagnostic hypothesis, and the lack of standardisation hampers the integration of multiple such systems [17].

The above are either diagnostic support or database systems, not search engines. The major difference between them is that database systems tend to process relational databases (well-structured data) whereas search engines tend to process unstructured data such as raw text or PDF files. The main

⁵<http://www.ncbi.nlm.nih.gov/omim>

⁶<http://www.orpha.net>

⁷<http://www.possum.net.au>

⁸<http://compbio.charite.de/phenomizer>

data structure used in database systems is the relational table with well-defined values for each row and column. The main data structure used in search engines is the inverted index (index of terms, document-IDs entries) with a corresponding postings list (list of documents that contain a term) for each term. In most modern databases one can enable full-text search for text columns by building a type of inverted index and enabling Boolean or vector space search, effectively combining core database with search engine technology. See Chapter 10 in [7] for more information on the fundamental differences between database systems and search engines in terms of retrieval model, data structures and query language.

The use of database systems for clinical diagnosis is not without problems. For instance, the search by clinical signs service provided by both Orphanet and Phenomizer is done using a controlled vocabulary (thesaurus). To search for a diagnosis in Orphanet, the user has to go through multiple steps. Going through a thesaurus and finding the right match can be a complex process that lengthens the diagnostic time, negatively impacts usability, and limits integration in the clinical environment. Similarly, in Phenomizer, the patient symptoms and signs must be selected from a predefined list compiled from the HPO ontology. Similarly, PubMed⁹ is not a fully fledged IR system, but a medical database that comprises more than 21 million entries of biomedical literature from MEDLINE, life science journals, and online books. PubMed's results are not ranked based on query relevance, but only on publication date, author name or other article meta-information that is not necessarily relevant in the search for a diagnosis. Moreover, when submitting a query without additional Boolean operators, only articles containing all query terms are retrieved, dramatically reducing the number of retrieved documents. A study of how medical experts use MEDLINE to gather evidence for clinical question-answering showed that users were only moderately successful [18].

Search engines with the exclusive purpose of retrieving information from specialized websites on rare diseases have been previously developed. For instance, the Rare Disease engine¹⁰ uses Google Custom Search Engine restricted to retrieve rare disease information. Another example is the Rare Disease Communities engine,¹¹ which aggregates search results from the eu-

⁹<http://www.ncbi.nlm.nih.gov/pubmed>

¹⁰<http://www.raredisease.org>

¹¹<http://www.rareconnect.org/en/search>

rordis.org, orpha.net, rarediseases.org and rarediseases.info.nih.gov websites. The attraction of medical search engines is that they are easy to use, fast, accessible, and their indices are continuously updated. While most of the medical database systems take as input complex structured queries requiring expert training, web search engines simply accept free-text queries. Moreover, medical database systems often return only results that exactly match the user query, whereas search engines may also use approximate matching algorithms. This is especially important for difficult cases where symptoms can be missing or misleading. Despite the existence of specialized systems such as Orphanet, OMIM, Phenomizer or POSSUMweb, the general purpose Google Search is repeatedly mentioned in literature as a valuable tool for diagnosing difficult and rare disease cases [6, 19–21]. Among the advantages of using Google in this setting are its comprehensive index, its ease of use, and the medical personnel’s familiarity with it. Its main disadvantage in the scope of clinical diagnosis is that the results contain noise, with many being non-relevant (e.g. pages from non-authoritative sources such as forums and personal blogs, information on alternative medicine or sponsored content [22]).

The problem with general search engine algorithms in the context of clinical diagnosis is, as discussed above, that they are designed and optimised for web search. So even if popular, searching for diagnoses in Google or PubMed is still time-consuming; a specialized search engine could decrease search time and improve performance.

3. Evaluation approach

The evaluation follows the standard paradigm of measuring functions of precision and recall at certain cut-off levels on a set of user queries [23]. In the evaluation we want to address two properties of the different systems simultaneously, namely the quality of the dataset (the index) and quality of information retrieval algorithms for our particular task. We can to a large degree separate the two by using the Google Custom Search functionality. In this Section we describe the diagnostic queries, the curated rare disease index, the public web search engines (variants of Google Search) and database used (PubMed) together with the assessment and evaluation metrics. The description of our own search engine FindZebra is given in Section 4.

3.1. *Diagnostic queries*

In total, 56 queries were used, which were created from difficult clinical cases, where the query text was extracted directly from the patient symptoms listed in the clinical cases. The composition of the 56 queries is as follows: 5 queries were created by a clinician (HLJ) on the basis of his expert knowledge; 25 queries were created from articles in the Orphanet Journal of Rare Diseases (OJRD) by RD and PP and curated by HLJ and 26 queries were taken from the British Medical Journal (BMJ) article of Tang and Ng [20]. All diagnoses except 4 from Tang and Ng are classified as rare. The full text and source of each query is included as an additional file to this article. The queries created from the Orphanet Journal of Rare Diseases are already indexed by Google so using this set poses a methodological problem as the source paper is likely to be highly ranked by Google Search. However, it turned out to be difficult to obtain “de novo” cases with a definite diagnosis so we opted for this approach to get a sufficiently large validation set and report “leave-source-out” result in these cases. The 26 queries of Tang and Ng are noticeably shorter, more vague and less realistic for medical professionals than the rest of our queries – however we include them in this experiment to facilitate comparison with the work of Tang and Ng.

3.2. *The curated rare disease index*

In order to create a high quality dataset of rare disease information, a number of authoritative, carefully curated medical resources were selected. Specifically, 33,144 documents were crawled from the resources shown in Table 1. We estimate that this dataset covers well over 90% of Orphanet’s list of rare diseases and more than 50% when restricting to exact name matches. Resources maintained or curated by non-medical experts, such as blogs or support groups, were not included in the dataset. However, medically curated patient organisation resources, such as Madisons,¹² were included. We chose not to include PubMed because it risked introducing too much irrelevant material, as we found no scalable and accurate way of selecting only those PubMed articles covering rare disease topics.

3.3. *Web search engines and database*

The publicly available search engines and database we tested our queries on are:

¹²<http://www.madisonsfoundation.org>

Resource	Entries
Online Mendelian Inheritance in Man (OMIM) http://www.ncbi.nlm.nih.gov/omim	20,369
Genetic and Rare Diseases Information Center (GARD) http://rarediseases.info.nih.gov/GARD	4578
Orphanet http://www.orpha.net	2967
Wikipedia http://www.wikipedia.org/	2239
National Organization for Rare Disorders (NORD) http://rarediseases.org	1230
Genetics Home Reference http://ghr.nlm.nih.gov	626
Madisons Foundation Rare Paediatric Disease Database http://www.madisonsfoundation.org	522
About.com Rare Disease Database http://rarediseases.about.com	316
Health on the Net Foundation Rare Disease Database http://www.hon.ch	183
Swedish National Board of Health and Welfare www.socialstyrelsen.se/rarediseases	114

Table 1: This table displays the resources used to compile the dataset of rare disease information used in this work.

1. Google Search¹³, which retrieves information from the web as indexed by Google.
2. Google Custom Search set up to retrieve information from the web but emphasizes the sources of the curated rare disease index. We call this Google Custom in the following.
3. Google Custom Search set up to retrieve information only from the sources of the curated rare disease index. We call this Google Restricted in the following.
4. PubMed.

The two Google Search Custom Search variants use the freely available Google Custom Search functionality. Note that Google imposes a limit on query length: any query longer than 32 terms is automatically truncated to the first 32 terms. Only one query in our collection is longer than 32 terms.

3.4. Assessment and evaluation metrics

The top 20 retrieved documents for each query were assessed by the authors as either relevant or non-relevant as follows:

- relevant documents should address predominantly the correct disease in the title or within the first 400 words, and name it using any of its synonyms listed in Orphanet;
- in cases of inherited diseases, e.g. autosomal neonatal form of Adrenoleukodystrophy, documents treating the main disease, e.g. X-linked Adrenoleukodystrophy, are relevant;
- documents treating different types of the correct disease, e.g. Loeys–Dietz syndrome type 1A instead of Loeys–Dietz syndrome type II, are relevant;
- documents treating predominantly other diseases and mentioning the correct disease as an alternative diagnostic or pointing to it are not relevant;

¹³<http://www.google.com>. The details of its ranking algorithm are not publicly known, however PageRank plays an important role, see Udi Manber, "Introduction to Google Search Quality"

- documents listing many diseases are not relevant if the correct disease is listed after the first 10.

Based on the above assessments, we computed the following evaluation metrics, all of which are standard in search engine evaluation: the average retrieval precision at rank k ($P@k$) and the mean reciprocal rank (MRR). $P@k$ is the percentage of retrieved documents that are relevant after k documents (whether relevant or non-relevant) have been retrieved, averaged over all queries:

$$P@k = \frac{1}{N} \sum_{i=1}^N \frac{|\{Rel\} \cap \{k\}|}{|\{k\}|} \quad (1)$$

where N is the number of queries and Rel the relevant documents for query i . This measure closely correlates with user satisfaction. However, it has been criticised because the constant cut-off of k represents very different recall levels for different queries [24]. For this reason, we also use MRR [25], which corresponds to the multiplicative inverse of the rank of the first relevant document retrieved. Specifically, the reciprocal rank for a given query is the reciprocal of the rank position of the highest ranking relevant document for the query. MRR is the average of the reciprocal rank over queries:

$$MRR = \frac{1}{N} \sum_{i=1}^N \frac{1}{r_i} \quad (2)$$

where N is the number of queries and r_i is the highest position of a relevant document for query i . This measure focuses on the retrieval quality of the very top of the ranked list. In addition to the above measures, we also report the number of queries for which at least one relevant document is retrieved for ranks 1–10 and 1–20.

4. FindZebra: a search engine for rare diseases

Our search engine is called FindZebra, as zebra is a name often given to rare diseases by medical professionals [26]. The interface of the search engine located at `findzebra.com` is very similar to that of standard web search engines so it should be straightforward to use by anyone familiar with web search. FindZebra is based on Indri [27], a state-of-the-art open source experimental information retrieval system. Specifically, we use Indri’s indexing and retrieval functions, on top of which we build an interface and several

functionalities specifically tailored to rare disease diagnosis by clinicians. As corpus we use the curated rare disease resources described in Section 3.2. The retrieval time of our system was less than 0.5s per query on a virtual machine allocated with 1 GB RAM, on an Intel Xeon E5530 clocked at 2.40 GHz. Since the available information will change continuously, the index of the search engine will be updated every 3 months. The technical details of FindZebra’s standard search functionality are described in Section 4.1 and the added functionality based upon UMLS medical concepts is described in Section 4.2.

4.1. Standard search

The system ranks documents decreasingly by their estimated relevance to the user query using the state-of-the-art query likelihood ranking model of the Language Model framework [28] with Jelinek-Mercer and Dirichlet smoothing [29]. The respective equations for Jelinek-Mercer and Dirichlet smoothing are:

$$p(q_i|D) = \prod_{i=1}^N (1 - \lambda) \frac{f_{q_i, D}}{|D|} + \lambda \frac{cq_i}{|C|} \quad (3)$$

$$p(q_i|D) = \prod_{i=1}^N \frac{f_{q_i, D} + \mu \frac{cq_i}{|C|}}{|D| + \mu} \quad (4)$$

where $p(q_i|D)$ is the probability of query term q_i given document D , $f_{q_i, D}$ is the frequency of q_i in D , cq_i is the frequency of q_i in the collection of all documents, $|D|$ is the number of terms in document D , $|C|$ is the number of documents in the collection of all documents, λ is the Jelinek-Mercer smoothing parameter ($0 \leq \lambda \leq 1$), and μ is the Dirichlet smoothing parameter. Parameters were set to default settings ($\lambda = 0.01$, $\mu = 2500$, $\mu = 0.9$, as described in [29]). These settings could be tuned in order to optimise the system’s performance, for instance by ranging the parameter values across their respective ranges. We did not tune these parameters at this stage in order to avoid over-fitting our system’s performance to our data.

This retrieval model performs basic text search without addressing term dependence and we chose it because it is the best-performing model in this category according to recent Text Retrieval Evaluation Conference (TREC) findings [30]. Documents are retrieved from the curated rare disease dataset described in Section 3.2 and displayed to the user in a simple interface. It is also possible to specify whether the documents should be retrieved from the

whole rare and genetic disease dataset or only the rare disease resources of the dataset.

4.2. Using the UMLS medical concepts in search

Motivated by the goal of facilitating medical diagnostic search, FindZebra also offers the options of (a) clustering the retrieved documents by UMLS medical concepts (diseases) derived from the document title, and (b) ranking UMLS concepts as opposed to documents. Both options aim to facilitate cases where the search engine retrieves several documents covering the same disease. The aim is to select and group these documents in flexible ways that, on the one hand, can facilitate a user’s navigation through the retrieved results, and on the other hand, allow the display of a potentially more diverse set of results (which considers the top j retrieved documents) than standard search (which is limited to the top n retrieved results). We used $j = 50$ and $n = 20$ in FindZebra.

The mapping of documents to UMLS medical concepts was performed with MetaMap,¹⁴ a standard tool of the US National Library of Medicine, which uses freely accessible medical ontologies and classifications recognised by the US National Institute of Health. We only select the maximum scoring mappings for each document. In order to achieve a near complete mapping of the articles we used the following three-step procedure. Allowing overmatches and truncate to mappings with matching scores above a certain threshold (600), 90% of titles were matched to concepts. For the remaining unmapped titles we reduced the length of the OMIM titles to the first disease name variant and ran MetaMap with the same parameters. In the final step for the remaining unmapped articles, we ran MetaMap using a larger subset of the Metathesaurus, the datasets in Category 0. In the end 99.75% of the titles were mapped to medical concepts.

FindZebra accepts UMLS concept identifiers as queries. In that case, documents are retrieved by matching the UMLS concept identifiers in the query to the UMLS concept identifiers that correspond to the document titles. This correspondence is already indexed in the system, and hence there is no extra delay at retrieval time.

¹⁴<http://metamap.nlm.nih.gov>. Subset of UMLS Metathesaurus 2011AA including 6 disease-related sources: ICD10CM, OMIM, Disease Database, DXP, QMR and RAM. The subset was extracted using MetamorphoSys, the UMLS customisation tool and uses UMLS Metathesaurus

Method	MRR	P@10	P@20	Unanswered queries	
				in top 10	in top 20
FindZebra	0.385	0.125	0.089	35 (62.5%)	38 (67.9%)
Google Search	0.206	0.07	0.056	16 (28.6%)	18 (32.1%)
Google Custom	0.206	0.088	0.071	17 (30.4%)	21 (37.5%)
Google Restricted	0.098	0.013	0.006	6 (10.7%)	6 (10.7%)
PubMed	0.128	0.021	0.016	7 (12.5%)	9 (16.07%)

Table 2: This table shows the performance of our system against three different versions of the Google Search engine in terms of retrieval precision at rank k ($P@k$), the mean reciprocal rank (MRR) and the fraction of queries with the correct result in top k .

FindZebra can also cluster the top $j = 50$ retrieved documents according to their UMLS concepts. Clustering is performed by simply grouping together the retrieved documents associated with the same medical concept (i.e. disease) and using the highest ranking document to represent the cluster. If clicked, each cluster expands to reveal information on the documents it contains sorted by rank, thus allowing to zoom in on documents of interest. This option offers a quick summary of the main retrieved medical conditions.

The system can furthermore rank UMLS medical concepts directly. In that case, the search results consist of a list of UMLS medical concepts which, when clicked, point to their corresponding documents. We calculate the ranking score for UMLS concept i , C_i , by the following formula:

$$Score(C_i) = |C_i| + \sum_{d \in C_i} \frac{1}{R_d} \quad (5)$$

where $|C_i|$ is the number of documents containing concept C_i , the sum goes over all documents containing the concept, and R_d is the rank of the document according to the query. This alternative display is another succinct way of visualising the main medical concepts related to the user query. An example of the use of UMLS concepts in FindZebra is given in Section 5.1.

5. Evaluation

We evaluate and compare FindZebra and the four other systems presented in Section 3.3 from two perspectives. On the one hand following the standard paradigm of computing statistical measures of precision and recall,

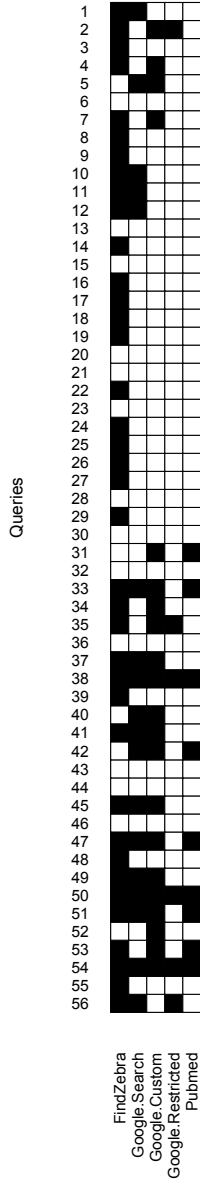


Figure 1: An overview of the queries for each of the five systems, represented as a binary matrix.

a commonly used approach in evaluating information retrieval systems. Table 2 shows the retrieval precision at rank k ($P@k$) and the mean reciprocal rank (MRR) of our experiments averaged for all 56 queries. The result for each query is given in Supplementary Table 2 [31–50]. Secondly, we analyse the results returned for the queries by each of the systems in order to get a deeper understanding of the strength and weaknesses of each approach. This should also have particular value to clinicians.

As can be seen in Figure 1, there is a clear distinction on how the systems perform overall, depending on the origin of the queries. Supplementary Table 3 summarizes the performance of all approaches in terms of queries for which the correct result appears in the top 20 ranks. The results show that all other systems except FindZebra have difficulty in addressing queries from OJRD. For these queries, FindZebra returns correct results for 17 of the 25 queries (68%), whereas Google Search and Google Custom return correct results for 3 (12%) and one (4%), respectively. For the OJRD queries, neither Google Restricted, nor PubMed manage to return correct results for any of the queries. For the HLJ queries, FindZebra still has a lead, managing to return correct results for 4 of the 5 queries (80%), with Google Search returning correct results for 2 (40%), Google Custom returning correct results for 3 (60%), Google Restricted returning correct results for one (20%) and PubMed for none. For the BMJ queries, which were specifically devised for Google Search, the differences between systems are less pronounced. FindZebra and Google Custom are leading, both returning correct results for 17 of the 26 BMJ queries (65%), with Google Search returning correct results for 13 (50%), Google Restricted 5 (19%) and PubMed 9 (35%).

In 13 of the 56 queries, none of the systems was

able to return the correct result. Of these, 8 were from OJRD and the remaining 5 were from BMJ. It is interesting to note that for both OJRD and BMJ queries, there have been comments from clinicians that some queries are particularly difficult to address. Specifically, HLJ identified 3 queries from OJRD (13, 20, and 21) where the symptoms are probably not specific enough to identify the correct cause. Additionally, Tang and Ng commented on the difficulty of 3 other queries (36, 39, and 43), noting that the first two are less likely to be successful because they cover a complex disease with non-specific symptoms, while the last one is less likely to be correctly addressed, because it covers a rare presentation of a common disease. Of these 6 queries labelled as particularly difficult, only FindZebra is able to find the correct result to one (query 39) at rank 8.

In 17 of the 56 queries, FindZebra is the only system with a correct result, with 13 of these queries from OJRD. Google Custom is the only system to return correct results for query 52. None of the other systems manages to be alone in returning correct results for any of the queries. There are 5 queries that are not addressed correctly by FindZebra, but for which one or more of the other systems return correct results. In fact, Google Custom returns correct results for all the 5 queries, with Google Search returning correct results for 3, and PubMed managing to return correct results for 2 of them.

5.1. Use of UMLS medical concepts example

The option of clustering documents by UMLS concepts is better suited for medical professionals who wish to quickly read about the correct diagnosis; instead of having to browse all the retrieved documents, they can focus on the cluster of documents that contains the correct diagnosis. Consider, for example, query 25 (see Supplementary Table 1), for which none of the Google Search options return a relevant result, and for which FindZebra standard search returns two relevant documents with the correct diagnosis at ranks 4 and 10. By selecting the option of clustering documents by UMLS medical concepts for this query, the correct diagnosis shows up as the main title of the third cluster. This cluster contains three documents on that disease that were originally at ranks 4, 10 and 27. Hence, whereas standard search retrieves two relevant documents at rank 4 at best, this clustering option retrieves three relevant documents at rank 3.

The option of ranking UMLS concepts as opposed to documents is better suited for medical professionals who wish to quickly browse diagnoses and their corresponding UMLS concepts, without spending time reading their

descriptions. For query 25 seen above, this option identifies the correct UMLS concept *C0268579 Ketotic Hyperglycinemia, Propionic Acidemia, propionyl-CoA carboxylase deficiency, PCC Deficiency* and ranks it as the second most relevant concept to this query (as opposed to rank 4 with standard search). Similarly, for query 18, this option identifies the correct UMLS concept and displays it at rank 5 (as opposed to rank 10 with standard search).

6. Discussion

One of Google’s advantages in web search is its specialized ranking algorithm optimised to work with a large sized index. Our finding, that FindZebra outperforms Google overall for this task and especially when restricted to the sites of our collection (Google Restricted), suggests that Google ranking algorithm is suboptimal for the task at hand. The poor Google Restricted results highlight this because in this case FindZebra and Google are using the same limited, focused data. When broadening the data collection indexed by Google using again a Google Custom Search, but which searches the entire web, only emphasising the documents in the limited collection (Google Custom), the performance of Google is improved but still inferior to the evaluation results obtained for FindZebra. PubMed also has a large index, containing a comprehensive resource of medical articles, however the search approach is different, as results cannot be ranked by relevance but exact match is expected. While this can be overcome by boolean queries, the query complexity becomes quite high and the amount spent on constructing such queries would be more than what is thought of reasonable in medical literature.

It is probably the case that neither PubMed nor Google handle long queries very well, as is the case with long lists of symptoms and observations. This might explain why FindZebra is able to achieve better results for HLJ and OJRD queries, which have an average query length of 28 and 21 words, respectively. For BMJ queries, which have a much lower average query length of 5 words, being devised specifically for Google Search, FindZebra is on equal footing with Google Custom, with Google Search, Google Restricted and PubMed performing considerably better than on the OJRD queries.

In addition to retrieving relevant documents at higher ranks than Google, our system also returns correct results for more queries in the top 20 retrieved documents (67.9%) than any of the Google variants we tested (37.5% at best). For the specific task described in this work, we can argue that the

most important success consideration is for the correct diagnosis to appear at the top of the diagnostic hypotheses returned by the system. In our case, we not only get in 67.9% of the cases the correct result in top 20, but it is important to also note that the returned results are actually disease hypotheses, streamlining the clinician’s diagnostic process.

The MRR scores show that on average the correct diagnosis appears above rank 3 with our system (0.385), at around rank 5 with Google Search (0.206) and lower for Google Restricted, Google Custom and PubMed. Standard Google Search can thus, to some degree, compensate for the optimal design (in this context) by its larger index. What the MRR actually means for a clinician is that, with FindZebra, when selecting the diagnostic hypotheses, it would be enough to include on average only the first three disease hypotheses retrieved using the system. Moreover, as the results correspond to diseases, transforming a search result into a diagnostic hypothesis should be straightforward. Each result is associated with a description of the disease from a reputable source. Compare this to Google, where results can be retrieved from various types of sources and reading through search results snippets might not be as straightforward.

The evaluation has revealed 5 queries (5, 31, 40, 42, and 52) for which Google Custom returns the correct result and FindZebra not. This result shows that FindZebra, despite being the overall better, still has limitations. The FindZebra index did not include documents for diseases for query 40 and 42, but we have multiple documents for the others. It is notable that 4 of the 5 queries are BMJ queries, which are considerably shorter than both HLJ and OJRD queries. One work-around for short queries would be to enrich the query with synonyms and conceptually similar medical terms. This technique, known as query expansion, is commonly employed in information retrieval systems and also by Google¹⁵ The articles retrieved by Google Custom pointing to the correct diagnosis were in all 5 cases not indexed by FindZebra. This suggests that adding more sources, such as UpToDate and Medline Plus, could improve the system. However, we have yet to assess how the performance is affected by the number of sources used and how each source contributes to the overall quality of the system.

Finally, it is worthwhile discussing how well our evaluation approach can

¹⁵<http://googleblog.blogspot.com/2010/01/helping-computers-understand-language.html>.

mimic a real diagnostic situation. The main limitation is that it is hard to achieve a query completely blind to the diagnosis because it is known at the time of the construction of the query. The queries are based upon descriptions of the symptoms from case stories. Knowing the diagnosis will probably to some degree bias the description of symptoms. To illustrate how such a bias may occur, the authors of the BMJ queries state that "...although we were blinded to the correct diagnosis, one author was a respiratory and sleep trainee and the other a rheumatologist; sometimes the diagnoses were evident to us, and this could have affected our choice of search terms" [20].

Another aspect is to what degree expert knowledge goes into construction of the queries. From an efficiency point of view we would like the work going into this to be as little as possible. However, the key to successful retrieval is the clinician's ability to represent observations on symptoms in terms that resonate with the general usage as well as with the ranking algorithm used. It is not clear that a typical description of a case appearing in a journal fits web search well. The authors of the BMJ queries are quite clear that medical judgement went into creating their queries: "We chose between three to five search terms for each case, depending on symptoms and signs that we felt would not return a non-specific result. We selected "statistically improbable phrases" whenever possible" [20]. When comparing to the original cases taken from the New England Journal of Medicine referenced in [20], it is apparent that the authors did more than just select symptoms from the original reports. They often changed the words, used synonyms, and employed high-level knowledge to arrive at the BMJ queries. For the OJRD queries we used the original descriptions from the article. It could therefore be of interest to follow the same procedure for the BMJ queries and compare performance before and after the adaptation to web search. We suspect that the original longer descriptions of the cases would probably be beneficial for FindZebra but not for Google Search.

7. Summary and conclusion

Effective text processing tools are very important to aid biomedical researchers. There has been a remarkable surge of new advances in biomedical language processing, and web search engines in particular are becoming increasingly popular for the task of diagnosing difficult cases. In this article we have asked ourselves how effective is web search actually for diagnosis? We therefore designed an evaluation approach and focussed on the most popular

resources used namely Google Search and PubMed. In order to address what determine successes and failures of these resources we developed FindZebra, a specialized search engine for rare diseases, customised for rare disease diagnosis by clinicians in terms of the selection of curated data resources, system interface, indexing (e.g. associating UMLS medical concept identifiers to indexed documents) and retrieval functionalities. The evaluation convincingly showed that FindZebra outperformed Google on standardised performance metrics, specifically precision at rank k (with $k = 10, 20$), mean reciprocal rank and the percentage of queries for which the correct result was returned.

A lesson of this study and similar work in this field is that the ranking algorithm used by large-scale web search engines like Google are not optimized for particular unusual domains, making it feasible to build improved specialized search engines. Hence, one of the contributions of this work is to demonstrate how one can ‘do more with less’: we simply used an open source information retrieval system with standard settings and freely available on-line medical information. The perspective of combining the ease-of-use of web search with specialized domain knowledge should be attractive to specialists in many areas as it has the potential to greatly improve the quality of search as our work of diagnosis of rare diseases has demonstrated.

There are several ways to move this work forward. On one side we may go further along the path set out in this work by using more advanced information retrieval models and collect data from additional authoritative sources. A perhaps even better strategy would be to work on the data acquisition side and directly and correctly collect symptom-diagnosis association data. In setting up our evaluation approach we found it surprisingly difficult to collect queries with an associated diagnosis. Initiatives in the medical community to systematically collect this kind of data in an unbiased way would be a valuable source for better information retrieval system performance and precision assessment.

Authors contribution

R.D., P.P., C.L. and O.W. overall contributed equally to the project. R.D. and P.P. collected the data, set up the search engine, performed the evaluation under the guidance of C.L. and O.W. C.L. and O.W. wrote the paper assisted by R.D. and P.P. The remainder of the authors commented on the paper. O.W. conceived the project and the other authors primarily R.D., P.P. and C.L. contributed to further development of the project.

Conflicts of interest

None declared

Acknowledgements

The authors wish to thank MD Lennart Friis-Hansen for the initial inspiration for the project.

Appendix: Supplementary material

Supplementary Table 1 - Queries

This table displays the real-life medical cases of rare diseases used for the experimental evaluation of this work. The sources are HLJ (MD Henrik L. Jørgensen), References [31] to [50] are from the Orphanet Journal of Rare Diseases (OJRD) and BMJ is referring to the British Medical Journal (BMJ) article of Tang and Ng [20].

No	Query	Diagnosis	Source
1	Boy, normal birth, deformity of both big toes (missing joint), quick development of bone tumor near spine and osteogenesis at biopsy	Fibrodysplasia ossificans progressiva	HLJ
2	Normally developed boy age 5, progressive development of talking difficulties, seizures, ataxia, adrenal insufficiency and degeneration of visual and auditory functions	Adrenoleukodystrophy autosomal neonatal form	HLJ
3	Boy age 14, yellow, keratotic plaques on the skin of palms and soles going up onto the dorsal side. Both hands and feet are affected	Papillon Lefevre syndrome	HLJ
4	Jewish boy age 16, monthly seizures, sleep deficiency, aggressive and irritable when woken, highly increased sexual appetite and hunger	Kleine Levin Syndrome	HLJ
5	Male child, malformations at birth, midfacial retraction with a deep groove under the eyes, and hypertelorism, short nose with a low nasal bridge and large lowset ears, wide mouth and retrognathia, Hypertrichosis with bright reddish hair and a median frontal cutaneous angioma, short neck with redundant skin, Bilateral inguinal hernias, hypospadias with a megameatus, and cryptorchidism	Schinz-Giedion Syndrome	HLJ
6	6 year old, girl, weight length head circumference below the third percentile, atrophic and hyperpigmented skin lesions, pointed nose, aberrant thumbs with diminished flexion, bilateral glue ears, purulent rhinitis	Rothmund-Thomson syndrome	[31]
7	13 year old, teenage girl, skeletal muscle defects (muscle weakness), mild mental retardation, ophthalmoparesis	Autosomal recessive centronuclear myopathy (ARCNM)	[32]
8	14 year old, teenage boy, mild mental retardation, proximal muscle weakness, unable to walk (wheelchair-bound), premature ventricular complexes, ophthalmoparesis	Autosomal recessive centronuclear myopathy (ARCNM)	[32]
9	35 year old, female, progressive disturbance of gait (difficulties in walking), recurrent diarrhea, bronchitis, growth retardation, mild retardation of psychomotor development in infancy, bilateral juvenile cataracts, swelling of the Achilles tendons, high arched feet, exaggerated tendon reflexes	Cerebrotendinous xanthomatosis (CTX)	[33]
10	25 year old, woman, conjunctival hyperaemia, interstitial keratitis, moderate bilateral sensorineural hearing loss, tinnitus, dizziness, nausea and vertigo	Cogan's syndrome	[34]
11	11 year old, boy, severe psychomotor retardation, seizures, strabismus, inverted nipples, dilated cardiomyopathy, hypotonia, wheelchair-bound	CDG (Congenital Disorders of Glycosylation) syndrome type Ic. (<i>Synonyms: Carbohydrate deficient glycoprotein syndrome type Ic, Congenital disorder of glycosylation type Ic (or Ic)</i>)	[35]
12	17 year old, woman, congenital right pulmonary hypoplasia, right hip dysplasia, absence of uterus, rudimentary uterine horn	Mayer-Rokitansky-Küster-Hauser syndrome	[36]
13	10 year old, girl, thrombocytopenia, splenomegaly, headache, itching rubeoliform rash	Congenital hepatic fibrosis (CHF)	[37]
14	11 year old, girl, intermittent abdominal pain, mild dorsal scoliosis, low serum phosphate/hypophosphatemia, hypercalcuria, elevated serum 1,25 dihydroxyvitamin D	Hypophosphatemic rickets with hypercalciuria	[38]
15	4 month old, boy, epistaxis, haematemesis, haematochezia, subconjunctival bleeding, petechiae, haematomas, haemangioma, slightly enlarged liver, elevated serum transaminases	Type I tyrosinemia. (<i>Synonyms: Fumarylacetoacetase deficiency, Hepatorenal tyrosinosis/tyrosinemia</i>)	[39]
16	7 year old, boy, dysmorphic signs, blue sclerae, high-arched palate, bifid uvula, joint hypermobility, muscular hypotrophy, translucent skin, aortic root dilatation, camptodactyly and ulnar deviation	Loeys-Dietz syndrome (LDS) type I	[40]
17	48 year old, woman, aortic aneurysm, haematoma, translucent skin, bilateral venous varicosities, recurrent wrist dislocations	Loeys-Dietz syndrome (LDS) type II	[40]
18	8 months old, male, progressive signs of respiratory distress, tachypnea, pulmonary hypertension, tortuosity of aortic arch, facial dysmorphisms	Arterial tortuosity syndrome (ATS)	[41]
19	5 year old, male, dyspnoea, asthenia, pulmonary hypertension, severe stenoses elongation and tortuosity of pulmonary arteries branches aortic arch sovraortic trunks and iliac arteries, dysmorphic features, joints hypermobility	Arterial tortuosity syndrome (ATS)	[41]
20	64 year old, male, inflammatory back pain, flares of arthritis, multisegmental spondylitis	Whipple's disease. (<i>Synonyms: Intestinal lipodystrophy, Intestinal lipophagie granulomatosis, Secondary non-tropical sprue</i>)	[42]
21	70 year old, male, massive hemoptysis, respiratory distress, anemia, hemodynamic instability, renal failure, intense headache, arthralgia, myalgias, ecchymoses over	Pulmonary hemorrhage syndrome associated with dengue fever/dengue	[43]

	arms and abdomen, acidosis, pleural effusions, blood tinged secretion from lungs	hemorrhagic fever	
22	46 year old, female, ptosis, acanthocytosis, history of diarrhea, ataxia, paresthesia	Abetalipoproteinemia (ABL). (<i>Synonyms: Bassen-Kornzweig disease, Homozygous familial hypobetalipoproteinemia (HoFHBL)</i>)	[44]
23	16 year old, girl, persistent diarrhea, acanthocytosis, mild dysarthria, reduced muscle bulk, bilateral proximal muscle weakness, absent deep-tendon reflexes, upgoing plantar reflexes, reduced sensitivity to light, dysdiadochokinesia	Abetalipoproteinemia (ABL). (<i>Synonyms: Bassen-Kornzweig disease, Homozygous familial hypobetalipoproteinemia (HoFHBL)</i>)	[44]
24	teenager, girl, hypotonia, dehydration, acidosis, massive ketonuria, hyperammonemia	Methylmalonic acidemia (MMA). (<i>Synonyms: Methylmalonic aciduria</i>)	[45]
25	girl, hypotonia, seizures, dehydration, polypnea, acidosis, massive ketonuria, hyperammonemia	Propionic acidemia (PA). (<i>Synonyms: Propionic aciduria, Ketotic glycinemia, Propionyl-CoA carboxylase deficiency</i>)	[45]
26	27 year old, woman, blindness, obesity, type 2 diabetes, renal dysfunction, chronic pyelonephritis, hypertension, hirsutism, retinitis pigmentosa, cataract	Alstrom syndrome (Alström syndrome)	[46]
27	17 year old, boy, lysinuric protein intolerance, mild restrictive functional impairment, digital clubbing, atypical abdominal and thoracic pain, ground glass attenuation, interlobular septa thickening, moderate restrictive ventilatory defect, mild anemia, thrombocytopenia, increase in lactate dehydrogenase	Pulmonary alveolar proteinosis (PAP)	[47]
28	girl, pronounced microcephaly, short stature, psychomotoric delay, distinctive facial appearance, thrombocytopenia, anemia, leukocytopenia, pancytopenia, growth retardation, telecanthus, epicanthal folds, ptosis, infections of the inner ear and respiratory tract, hypoplastic marrow with cellular dysplasia	Ligase IV deficiency syndrome (LIG4 syndrome) (<i>Synonyms: Ligase 4 syndrome</i>)	[48]
29	5 year old, boy, congenital malformations, malformations of the hands and feet, bilateral strabismus, small tongue, impaired coordination, expressionless face, prominent forehead, depressed nasal bridge, hypoplastic thumbs, bilateral adactyly of the feet, short stature, severe myopia	Oromandibular-limb hypogenesis-Möbius syndrome	[49]
30	21 year old, female, irregular menses, menorrhagia, hand and foot malformation, ovarian cyst, basic cognitive function	Terminal deletion of chromosome 4q	[50]
31	Acute Aortic regurgitation, depression, abscess	Infective endocarditis	BMJ
32	oesophageal cancer, refractory hic cups, nausea, vomiting	Linitis plastica with bowel obstruction	BMJ
33	hypertension, adrenal mass	Cushings secondary to adrenal adenoma	BMJ
34	hip lesion, older child	Osteoid osteoma	BMJ
35	HRCT centrilobular nodules, acute respiratory failure	Hot tub lung secondary to M avium	BMJ
36	fever, bilateral thigh pain, weakness	Ehrlichiosis	BMJ
37	fever, anterior mediastinal mass and central necrosis	Lymphoma	BMJ
38	multiple spinal tumours, skin tumours	Neurofibromatosis type 1	BMJ
39	ulcerative colitis, blurred vision, fever	Vasculitis	BMJ
40	nephrotic syndrome, Bence Jones, ventricular failure	Amyloid light chain	BMJ
41	hypertension, papilledema, headache, renal mass, cafe au lait	Pheochromocytoma	BMJ
42	sickle cell, pulmonary infiltrates, back pain	Acute chest syndrome	BMJ
43	fibroma, astrocytoma, tumor, leiomyoma, scoliosis	Endometriosis	BMJ
44	pulmonary infiltrates, cns lesion	Aspiration pneumonia and brain abscess (polymicrobial)	BMJ
45	CLL, encephalitis	West Nile fever	BMJ
46	portal vein thrombosis, cancer	Pylephlebitis	BMJ
47	cardiac arrest, exercise, young	Hypertrophic Obstructive Cardiomyopathy (HOCM)	BMJ
48	ataxia, confusion, insomnia, death	Creutzfeldt-Jakob disease (CJD)	BMJ
49	wheeze wt loss, ANCA, haemoptysis, haematuria	Churg Strauss	BMJ
50	myopathy, neoplasia, dysphagia, rash, periorbital swelling	Dermatomyositis secondary to NHL	BMJ
51	renal transplant, fever, cat, lymphadenopathy	Cat scratch disease	BMJ
52	buttock rash, renal failure, edema	Cryoglobulinaemia	BMJ
53	polyps, telangiectasia, epistaxis, anemia	MADH4 mutation (HTT + juvenile polyposis)	BMJ
54	bullous skin conditions, respiratory failure, carbamazepine	Toxic Epidermal Necrolysis Syndrome	BMJ

		(TENS)	
55	seizure, confusion, dysphasia, T2 lesions	MELAS	BMJ
56	cardiac arrest sleep	Brugada	BMJ

Supplementary Table 2 - Evaluation Results (Detailed)

This table breaks down the results of Table 2 for each query. Rank 1st relevant is the rank of the first relevant document (the lower the rank number, the better the performance). Relevant @10/20 is the number of relevant documents in the top 10/20 ranks (the higher the number, the better the performance).

Query	FindZebra			Google Search			Google Custom			Google Restricted			PubMed		
	Rank 1st rel.	Relevant		Rank 1st rel.	Relevant		Rank 1st rel.	Relevant		Rank 1st rel.	Relevant		Rank 1st rel.	Relevant	
		@10	@20		@10	@20		@10	@20		@10	@20		@10	@20
1	1	2	2	10	1	1	-	0	0	-	0	0	-	0	0
2	2	2	4	-	0	0	1	1	2	1	1	1	-	0	0
3	9	1	1	-	0	0	-	0	0	-	0	0	-	0	0
4	1	3	4	-	0	0	1	1	1	-	0	0	-	0	0
5	-	0	0	1	2	2	1	1	1	-	0	0	-	0	0
6	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
7	1	2	2	-	0	0	17	0	1	-	0	0	-	0	0
8	2	2	2	-	0	0	-	0	0	-	0	0	-	0	0
9	6	1	1	-	0	0	-	0	0	-	0	0	-	0	0
10	7	1	1	7	1	2	-	0	0	-	0	0	-	0	0
11	1	2	3	3	2	2	-	0	0	-	0	0	-	0	0
12	5	2	2	10	1	1	-	0	0	-	0	0	-	0	0
13	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
14	1	4	6	-	0	0	-	0	0	-	0	0	-	0	0
15	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
16	1	4	5	-	0	0	-	0	0	-	0	0	-	0	0
17	5	2	4	-	0	0	-	0	0	-	0	0	-	0	0
18	10	1	1	-	0	0	-	0	0	-	0	0	-	0	0
19	1	2	3	-	0	0	-	0	0	-	0	0	-	0	0
20	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
21	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
22	1	5	6	-	0	0	-	0	0	-	0	0	-	0	0
23	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
24	1	4	5	-	0	0	-	0	0	-	0	0	-	0	0
25	4	2	2	-	0	0	-	0	0	-	0	0	-	0	0
26	2	2	2	-	0	0	-	0	0	-	0	0	-	0	0
27	1	2	3	-	0	0	-	0	0	-	0	0	-	0	0
28	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
29	1	1	1	-	0	0	-	0	0	-	0	0	-	0	0
30	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
31	-	0	0	-	0	0	4	4	6	-	0	0	1	1	1
32	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
33	10	1	2	1	1	1	7	1	2	-	0	0	1	3	3
34	19	0	1	-	0	0	9	1	1	-	0	0	-	0	0
35	7	1	1	-	0	0	3	2	2	1	1	1	-	0	0
36	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
37	7	1	1	1	2	2	4	1	4	-	0	0	-	0	0
38	1	1	3	4	2	4	1	3	3	1	2	2	11	0	3
39	8	1	1	-	0	0	-	0	0	-	0	0	-	0	0
40	-	0	0	1	5	10	1	5	10	-	0	0	-	0	0
41	13	0	1	13	0	1	5	2	2	-	0	0	-	0	0
42	-	0	0	2	5	8	4	2	5	-	0	0	1	1	1
43	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
44	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
45	17	0	2	18	0	1	15	0	1	-	0	0	-	0	0
46	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
47	5	2	3	1	1	1	12	0	1	-	0	0	12	0	3
48	1	2	4	-	0	0	-	0	0	-	0	0	-	0	0
49	3	1	1	1	2	2	16	0	1	-	0	0	-	0	0
50	1	2	3	1	6	12	1	8	11	1	1	1	1	1	1
51	1	2	4	1	5	7	1	8	12	-	0	0	1	3	3
52	-	0	0	-	0	0	1	2	2	-	0	0	-	0	0
53	1	3	5	-	0	0	2	3	4	-	0	0	1	2	2

54	1	3	4	1	2	5	1	3	4	1	1	1	1	1	1
55	3	1	1	-	0	0	-	0	0	-	0	0	-	0	0
56	3	2	3	1	1	1	-	0	0	2	1	1	-	0	0

Supplementary Table 3 - queries for which correct/relevant results were returned (detailed)

This table breaks down the results for the queries by system. The following is a list of comments about specific difficult queries. HLJ on query 13: These symptoms could be caused by many different diseases including some fairly common ones. It might not be the best case story for your purposes. On the other hand, I think that it will be interesting to see what the system will come up with here. HLJ on query 20: This case is interesting but I doubt the system will work here. In a patient of 64 years, these symptoms could be caused by a multitude of diseases, most of them much more common than the rare infectious disease. HLJ on query 21: This one is also interesting, although not that uncommon. Several other similar infections could produce a picture like this, so I am looking forward to the proposals of the system. BMJ authors on query 36: less likely to be successful because of complex disease with non-specific symptoms. BMJ authors on query 43: less likely to be successful because of common disease with rare presentation.

Query Source	Query No	Search Terms	Final diagnosis	Systems with relevant results	FindZebra	Google Search	Google Custom	Google Restricted	Pubmed
HLJ	1	Boy, normal birth, deformity of both big toes (missing joint), quick development of bone tumor near spine and osteogenesis at biopsy	Fibrodysplasia ossificans progressiva	2	1	1	0	0	0
HLJ	2	Normally developed boy age 5, progressive development of talking difficulties, seizures, ataxia, adrenal insufficiency and degeneration of visual and auditory functions	Adrenoleukodystrophy autosomal neonatal form	3	1	0	1	1	0
HLJ	3	Boy age 14, yellow, keratotic plaques on the skin of palms and soles going up onto the dorsal side. Both hands and feet are affected	Papillon Lefevre syndrome	1	1	0	0	0	0
HLJ	4	Jewish boy age 16, monthly seizures, sleep deficiency, aggressive and irritable when woken, highly increased sexual appetite and hunger	Kleine Levin Syndrome	2	1	0	1	0	0
HLJ	5	Male child, malformations at birth, midfacial retraction with a deep groove under the eyes, and hypertelorism, short nose with a low nasal bridge and large lowset ears, wide mouth and retrognathia. Hypertrichosis with bright reddish hair and a median frontal cutaneous angioma, short neck with redundant skin, Bilateral inguinal hernias, hypospadias with a megameatus, and cryptorchidism	Schinz-Giedion Syndrome	2	0	1	1	0	0
OJRD	6	6 year old, girl, weight length head circumference below the third percentile, atrophic and hyperpigmented skin lesions, pointed nose, aberrant thumbs with diminished flexion, bilateral glue ears, purulent rhinitis	Rothmund-Thomson syndrome	0	0	0	0	0	0
OJRD	7	13 year old, teenage girl, skeletal muscle defects (muscle weakness), mild mental retardation, ophthalmoparesis	Autosomal recessive centronuclear myopathy (ARCNM)	2	1	0	1	0	0
OJRD	8	14 year old, teenage boy, mild mental retardation, proximal muscle weakness, unable to walk (wheelchair-bound), premature ventricular complexes, ophthalmoparesis	Autosomal recessive centronuclear myopathy (ARCNM)	1	1	0	0	0	0
OJRD	9	35 year old, female, progressive disturbance of gait (difficulties in walking), recurrent diarrhea, bronchitis, growth retardation, mild retardation of psychomotor development in infancy, bilateral juvenile cataracts, swelling of the Achilles tendons, high arched feet, exaggerated tendon reflexes	Cerebrotendinous xanthomatosis (CTX) Synonym: Sterol 27-hydroxylase deficiency	1	1	0	0	0	0
OJRD	10	25 year old, woman, conjunctival hyperaemia, interstitial keratitis, moderate bilateral sensorineural hearing loss, tinnitus, dizziness, nausea and vertigo	Cogan's syndrome	2	1	1	0	0	0

OJRD	11	11 year old, boy, severe psychomotor retardation, seizures, strabismus, inverted nipples, dilated cardiomyopathy, hypotonia, wheelchair-bound	CDG (Congenital Disorders of Glycosylation) syndrome type 1c Synonyms: Carbohydrate deficient glycoprotein syndrome type 1c, Congenital disorder of glycosylation type 1c (or 1c)	2	1	1	0	0	0
OJRD	12	17 year old, woman, congenital right pulmonary hypoplasia, right hip dysplasia, absence of uterus, rudimentary uterine horn	Mayer-Rokitansky-Küster-Hauser syndrome	2	1	1	0	0	0
OJRD	13	10 year old, girl, thrombocytopenia, splenomegaly, headache, itching rubeoliform rash	Congenital hepatic fibrosis (CHF)	0	0	0	0	0	0
OJRD	14	11 year old, girl, intermittent abdominal pain, mild dorsal scoliosis, low serum phosphate / hypophosphatemia, hypercalcuria, elevated serum 1.25 dihydroxyvitamin D	Hypophosphatemic rickets with hypercalciuria	1	1	0	0	0	0
OJRD	15	4 month old, boy, epistaxis, haematemesis, haematochezia, subconjunctival bleeding, petechiae, haematomas, haemangioma, slightly enlarged liver, elevated serum transaminases	Type I tyrosinemia Synonyms: Fumarylacetoacetase deficiency, Hepatorenal tryosinosis / tyrosinemia	0	0	0	0	0	0
OJRD	16	7 year old, boy, dysmorphic signs, blue sclerae, high-arched palate, bifid uvula, joint hypermobility, muscular hypotrophy, translucent skin, aortic root dilatation, campodactyly and ulnar deviation	Loeys-Dietz syndrome (LDS) type I	1	1	0	0	0	0
OJRD	17	48 year old, woman, aortic aneurysm, haematoma, translucent skin, bilateral venous varicosities, recurrent wrist dislocations	Loeys-Dietz syndrome (LDS) type II	1	1	0	0	0	0
OJRD	18	8 months old, male, progressive signs of respiratory distress, tachypnea, pulmonary hypertension, tortuosity of aortic arch, facial dysmorphisms	Arterial tortuosity syndrome (ATS)	1	1	0	0	0	0
OJRD	19	5 year old, male, dyspnoea, asthenia, pulmonary hypertension, severe stenoses elongation and tortuosity of pulmonary arteries branches aortic arch sovraortic trunks and iliac arteries, dysmorphic features, joints hypermobility	Arterial tortuosity syndrome (ATS)	1	1	0	0	0	0
OJRD	20	64 year old, male, inflammatory back pain, flares of arthritis, multisegmental spondylitis	Whipple's disease Synonyms: Intestinal lipodystrophy, Intestinal lipophagic granulomatosis, Secondary non-tropical sprue	0	0	0	0	0	0
OJRD	21	70 year old, male, massive hemoptysis, respiratory distress, anemia, hemodynamic instability, renal failure, intense headache, arthralgia, myalgias, ecchymoses over arms and abdomen, acidosis, pleural effusions, blood tinged secretion from lungs	Pulmonary hemorrhage syndrome associated with dengue fever /dengue hemorrhagic fever	0	0	0	0	0	0
OJRD	22	46 year old, female, ptosis, acanthocytosis, history of diarrhea, ataxia, paresthesia	Abetalipoproteinemia (ABL) Synonyms: Bassen-Kornzweig disease, Homozygous familial hypobetalipoproteinemia (HoFHBL)	1	1	0	0	0	0
OJRD	23	16 year old, girl, persistent diarrhea, acanthocytosis, mild dysarthria, reduced muscle bulk, bilateral proximal muscle weakness, absent deep-tendon reflexes, upgoing plantar reflexes, reduced sensitivity to light, dysidiadochokinesia	Abetalipoproteinemia (ABL) Synonyms: Bassen-Kornzweig disease, Homozygous familial hypobetalipoproteinemia (HoFHBL)	0	0	0	0	0	0
OJRD	24	teenager, girl, hypotonia, dehydration,	Methylmalonic acidemia	1	1	0	0	0	0

		acidosis, massive ketonuria, hyperammonemia	(MMA) Synonyms: Methylmalonic aciduria						
OJRD	25	girl, hypotonia, seizures, dehydration, polypnea, acidosis, massive ketonuria, hyperammonemia	Propionic acidemia (PA) Synonyms: Propionic aciduria, Ketotic glycinemia, Propionyl-CoA carboxylase deficiency	1	1	0	0	0	0
OJRD	26	27 year old, woman, blindness, obesity, type 2 diabetes, renal dysfunction, chronic pyelonephritis, hypertension, hirsutism, retinitis pigmentosa, cataract	Alstrom syndrome (Alström syndrome)	1	1	0	0	0	0
OJRD	27	17 year old, boy, lysinuric protein intolerance, mild restrictive functional impairment, digital clubbing, atypical abdominal and thoracic pain, ground glass attenuation, interlobular septa thickening, moderate restrictive ventilatory defect, mild anemia, thrombocytopenia, increase in lactate dehydrogenase	Pulmonary alveolar proteinosis (PAP)	1	1	0	0	0	0
OJRD	28	girl, pronounced microcephaly, short stature, psychomotoric delay, distinctive facial appearance, thrombocytopenia, anemia, leukocytopenia, pancytopenia, growth retardation, telecanthus, epicanthal folds, ptosis, infections of the inner ear and respiratory tract, hypoplastic marrow with cellular dysplasia	Ligase IV deficiency syndrome (LIG4 syndrome) Synonyms: Ligase 4 syndrome	0	0	0	0	0	0
OJRD	29	5 year old, boy, congenital malformations, malformations of the hands and feet, bilateral strabismus, small tongue, impaired coordination, expressionless face, prominent forehead, depressed nasal bridge, hypoplastic thumbs, bilateral adactyly of the feet, short stature, severe myopia	Oromandibular-limb hypogenesis-Möbius syndrome	1	1	0	0	0	0
OJRD	30	21 year old, female, irregular menses, menorrhagia, hand and foot malformation, ovarian cyst, basic cognitive function	Terminal deletion of chromosome 4q	0	0	0	0	0	0
BMJ	31	Acute Aortic regurgitation, depression, abscess	Infective endocarditis	2	0	0	1	0	1
BMJ	32	oesophageal cancer, refractory hic cups, nausea, vomiting	Linitis plastica with bowel obstruction	0	0	0	0	0	0
BMJ	33	hypertension, adrenal mass	Cushings secondary to adrenal adenoma	4	1	1	1	0	1
BMJ	34	hip lesion, older child	Osteoid osteoma	2	1	0	1	0	0
BMJ	35	HRCT centrilobular nodules, acute respiratory failure	Hot tub lung secondary to M avium	3	1	0	1	1	0
BMJ	36	fever, bilateral thigh pain, weakness	Ehrlichiosis	0	0	0	0	0	0
BMJ	37	fever, anterior mediastinal mass and central necrosis	Lymphoma	3	1	1	1	0	0
BMJ	38	multiple spinal tumours, skin tumours	Neurofibromatosis type 1	5	1	1	1	1	1
BMJ	39	ulcerative colitis, blurred vision, fever	Vasculitis	1	1	0	0	0	0
BMJ	40	nephrotic syndrome, Bence Jones, ventricular failure	Amyloid light chain	2	0	1	1	0	0
BMJ	41	hypertension, papilledema, headache, renal mass, café au lait	Pheochromocytoma	3	1	1	1	0	0
BMJ	42	sickle cell, pulmonary infiltrates, back pain	Acute chest syndrome	3	0	1	1	0	1
BMJ	43	fibroma, astrocytoma, tumor, leiomyoma, scoliosis	Endometriosis	0	0	0	0	0	0
BMJ	44	pulmonary infiltrates, cns lesion	Aspiration pneumonia and brain abscess (polymicrobial)	0	0	0	0	0	0
BMJ	45	CLL, encephalitis	West Nile fever	3	1	1	1	0	0
BMJ	46	portal vein thrombosis, cancer	Pylephlebitis	0	0	0	0	0	0
BMJ	47	cardiac arrest, exercise, young	Hypertrophic Obstructive Cardiomyopathy (HOCM)	4	1	1	1	0	1
BMJ	48	ataxia, confusion, insomnia, death	Creutzfeldt-Jakob disease (CJD)	1	1	0	0	0	0
BMJ	49	wheeze wt loss, ANCA, haemoptysis, haematuria	Churg Strauss	3	1	1	1	0	0
BMJ	50	myopathy, neoplasia, dysphagia, rash,	Dermatomyositis	5	1	1	1	1	1

		periorbital swelling	secondary to NHL						
BMJ	51	renal transplant, fever, cat, lymphadenopathy	Cat scratch disease	4	1	1	1	0	1
BMJ	52	buttock rash, renal failure, edema	Cryoglobulinaemia	1	0	0	1	0	0
BMJ	53	polyps, telangiectasia, epistaxis, anemia	MADH4 mutation (HTT + juvenile polyposis)	3	1	0	1	0	1
BMJ	54	bullous skin conditions, respiratory failure, carbamazepine	Toxic Epidermal Necrolysis Syndrome (TENS)	5	1	1	1	1	1
BMJ	55	seizure, confusion, dysphasia, T2 lesions	MELAS	1	1	0	0	0	0
BMJ	56	cardiac arrest sleep	Brugada	3	1	1	0	1	0

References

- [1] Cartright M, White RW, Horvitz E. Intentions and attention in exploratory health search. In: Proc ACM SIGIR. 2011, p. 65–74.
- [2] Hunter L, Cohen KB. Biomedical language processing: What’s beyond pubmed? *Molecular cell* 2006;21(5):589–94.
- [3] Purcell K, Rainie L, Mitchell A, Rosenstiel T, Olmstead K. Understanding the participatory news consumer. Pew Internet and American Life Project 2010;1.
- [4] Spink A, Yang Y, Jansen J, Nykanen P, Lorence DP, Ozmutlu S, et al. A study of medical and health queries to web search engines. *Health Information & Libraries Journal* 2004;21(1):44–51.
- [5] White RW, Horvitz E. Cyberchondria: studies of the escalation of medical concerns in web search. *ACM Transactions on Information Systems (TOIS)* 2009;27(4):23.
- [6] Bouwman MG, Teunissen QG, Wijburg FA, Linthorst GE. ‘doctor google’ending the diagnostic odyssey in lysosomal storage disorders: parents using internet search engines as an efficient diagnostic strategy in rare diseases. *Archives of disease in childhood* 2010;95(8):642–4.
- [7] Manning CD, Raghavan P, Schütze H. Introduction to information retrieval; vol. 1. Cambridge University Press Cambridge; 2008.
- [8] Eysenbach G, Köhler C. How do consumers search for and appraise health information on the world wide web? qualitative study using focus groups, usability tests, and in-depth interviews. *Bmj* 2002;324(7337):573–7.
- [9] Lewis T. Seeking health information on the internet: lifestyle choice or bad attack of cyberchondria? *Media, Culture & Society* 2006;28(4):521–39.
- [10] Hughes B, Joshi I, Lemonde H, Wareham J. Junior physician’s use of web 2.0 for information seeking and medical education: a qualitative study. *International journal of medical informatics* 2009;78(10):645–55.

- [11] Schwarz J, Morris M. Augmenting web pages and search results to support credibility assessment. In: Proceedings of the 2011 annual conference on Human factors in computing systems. ACM; 2011, p. 1245–54.
- [12] Hersh WR, Hickam DH. How well do physicians use electronic information retrieval systems? JAMA: the journal of the American Medical Association 1998;280(15):1347–52.
- [13] Bhavnani SK. Domain-specific search strategies for the effective retrieval of healthcare and shopping information. In: CHI’02 extended abstracts on Human factors in computing systems. ACM; 2002, p. 610–1.
- [14] Barnett GO, Cimino JJ, Hupp JA, Hoffer EP. An evolving diagnostic decision-support system. Jama 1987;258:67–74.
- [15] Fryer A. London dysmorphology database. Journal of Medical Genetics 1991;28(10):727.
- [16] Tenório JM, Hummel AD, Cohrs FM, Sdepanian VL, Pisa IT, de Fátima Marin H. Artificial intelligence techniques applied to the development of a decision-support system for diagnosing celiac disease. International journal of medical informatics 2011;80(11):793–802.
- [17] Ahmadian L, van Engen-Verheul M, Bakhshi-Raiez F, Peek N, Cornet R, de Keizer NF. The role of standardized data and terminological systems in computerized clinical decision support systems: Literature review and survey. International journal of medical informatics 2011;80(2):81–93.
- [18] Hersh WR, Crabtree MK, Hickam DH, Sacherek L, Friedman CP, Tidmarsh P, et al. Factors associated with success in searching medline and applying evidence to answer clinical questions. Journal of the American Medical Informatics Association 2002;9(3):283–93.
- [19] Lombardi C, Griffiths E, McLeod B, Caviglia A, Penagos M. Search engine as a diagnostic tool in difficult immunological and allergologic cases: is google useful? Internal medicine journal 2009;39(7):459–64.
- [20] Tang H, Ng JHK. Googling for a diagnosis—use of google as a diagnostic aid: internet based study. Bmj 2006;333(7579):1143–5.

- [21] Falagas ME, Ntziora F, Makris GC, Malietzis GA, Rafailidis PI. Do pubmed and google searches help medical students and young doctors reach the correct diagnosis? a pilot study. *European journal of internal medicine* 2009;20(8):788–90.
- [22] Walji M, Sagaram S, Meric-Bernstam F, Johnson CW, Bernstam EV. Searching for cancer-related information online: Unintended retrieval of complementary and alternative medicine information. *International journal of medical informatics* 2005;74(7):685–93.
- [23] Croft WB, Metzler D, Strohman T. *Search engines: Information retrieval in practice*. Addison-Wesley; 2010.
- [24] Buckley C, Voorhees EM. Retrieval evaluation with incomplete information. In: *Proceedings of the 27th annual international ACM SIGIR conference on Research and development in information retrieval*. ACM; 2004, p. 25–32.
- [25] Voorhees E, Tice DM. The trec-8 question answering track evaluation. In: *Proceedings of The Eighth Text REtrieval Conference (TREC-8)*, http://trec.nist.gov/pubs/trec8/t8_proceedings.html. 1999,.
- [26] Haran M, Schattner A. On the clinical encounter with ‘zebras’—the science and art of rare diseases. *European journal of internal medicine* 2011;22(3):235–7.
- [27] Strohman T, Metzler D, Turtle H, Croft WB. Indri: A language model-based search engine for complex queries. In: *Proceedings of the International Conference on Intelligent Analysis*; vol. 2. Citeseer; 2005, p. 2–6.
- [28] Croft WB, Lafferty J. *Language modeling for information retrieval*; vol. 13. Springer; 2003.
- [29] Zhai C, Lafferty J. A study of smoothing methods for language models applied to information retrieval. *ACM Transactions on Information Systems (TOIS)* 2004;22(2):179–214.
- [30] Voorhees EM, Buckland LP, editors. *Proceedings of The Twentieth Text REtrieval Conference, TREC 2011*, Gaithersburg, Maryland, November

15-18, 2011. National Institute of Standards and Technology (NIST); 2011.

- [31] De Somer L, Wouters C, Morren MA, De Vos R, Van Den Oord J, Devriendt K, et al. Granulomatous skin lesions complicating varicella infection in a patient with rothmund-thomson syndrome and immune deficiency: case report. *Orphanet Journal of Rare Diseases* 2010;5(1):37.
- [32] Böhm J, Yiş U, Ortaç R, Çakmakçı H, Kurul SH, Dirik E, et al. Case report of intrafamilial variability in autosomal recessive centronuclear myopathy associated to a novel bin1 stop mutation. *Orphanet J Rare Dis* 2010;5:35.
- [33] Schneider H, Lingesleben A, Vogel HP, Garuti R, Calandra S. A novel mutation in the sterol 27-hydroxylase gene of a woman with autosomal recessive cerebrotendinous xanthomatosis. *Orphanet journal of rare diseases* 2010;5(1):27.
- [34] Orsoni JG, Laganà B, Rubino P, Zavota L, Bacciu S, Mora P. Case report rituximab ameliorated severe hearing loss in cogan's syndrome: a case report. *Orphanet Journal of Rare Diseases* 2010;.
- [35] Al-Owain M, Mohamed S, Kaya N, Zagal A, Matthijs G, Jaeken J. Case report a novel mutation and first report of dilated cardiomyopathy in alg6-cdg (cdg-ic): a case report. *Orphanet Journal of Rare Diseases* 2010;.
- [36] Acién P, Galán F, Manchón I, Ruiz E, Acién M, Alcaraz LA. Hereditary renal adysplasia, pulmonary hypoplasia and mayer-rokitansky-küster-hauser (mrkh) syndrome: a case report. *Orphanet Journal of Rare Diseases* 2010;5:6.
- [37] Poala SB, Bisogno G, Colombatti R. Case report thrombocytopenia and splenomegaly: an unusual presentation of congenital hepatic fibrosis. *Orphanet Journal of Rare Diseases* 2010;.
- [38] Mejia-Gaviria N, Gil-Peña H, Coto E, Pérez-Menéndez TM, Santos F, et al. Genetic and clinical peculiarities in a new family with hereditary hypophosphatemic rickets with hypercalciuria: a case report. *Orphanet J Rare Dis* 2010;5(1):1.

- [39] Cassiman D, Zeevaert R, Holme E, Kvittingen EA, Jaeken J, et al. A novel mutation causing mild, atypical fumarylacetoacetase deficiency (tyrosinemia type i): a case report. *Orphanet journal of rare diseases* 2009;4(1):28.
- [40] Drera B, Ritelli M, Zoppi N, Wischmeijer A, Gnoli M, Fattori R, et al. Loeys-dietz syndrome type i and type ii: clinical findings and novel mutations in two italian patients. *Orphanet J Rare Dis* 2009;4:24.
- [41] Ritelli M, Drera B, Vicchio M, Puppini G, Biban P, Pilati M, et al. Arterial tortuosity syndrome in two italian paediatric patients. *Orphanet J Rare Dis* 2009;4:20.
- [42] Spoerl D, Bär D, Cooper J, Vogt T, Tyndall A, Walker UA. Multisegmental spondylitis due to tropheryma whipplei: Case report. *Orphanet Journal of Rare Diseases* 2009;4(1):13.
- [43] Marchiori E, Ferreira J, Bittencourt CN, de Araújo Neto CA, Zanetti G, Mano CM, et al. Pulmonary hemorrhage syndrome associated with dengue fever, highresolution computed tomography findings: a case report. *Orphanet J Rare Dis* 2009;4(8).
- [44] Zamel R, Khan R, Pollex RL, Hegele RA, et al. Abetalipoproteinemia: two case reports and literature review. *Orphanet J Rare Dis* 2008;3:19.
- [45] Virginie L, Isabelle F, Alain F, Cécile A, Christine VS, Nathalie G. Carglumic acid: an additional therapy in the treatment of organic acidurias with hyperammonemia? *Orphanet Journal of Rare Diseases* ????:3.
- [46] Joy T, Cao H, Black G, Malik R, Charlton-Menys V, Hegele RA, et al. Alstrom syndrome (omim 203800): a case report and literature review. *Orphanet Journal of Rare Diseases* 2007;2(1):49.
- [47] Ceruti M, Rodi G, Stella GM, Adami A, Bolongaro A, Baritussio A, et al. Successful whole lung lavage in pulmonary alveolar proteinosis secondary to lysinuric protein intolerance: a case report. *Orphanet J Rare Dis* 2007;2:14.
- [48] Gruhn B, Seidel J, Zintl F, Varon R, Tönnies H, Neitzel H, et al. Successful bone marrow transplantation in a patient with dna ligase iv deficiency and bone marrow failure. *Orphanet J Rare Dis* 2007;2(5).

- [49] Al Kaissi A, Grill F, Safi H, Ben Ghachem M, Ben Chehida F, Klaushofer K. Craniocervical junction malformation in a child with oromandibular-limb hypogenesis-möbius syndrome. *Orphanet J Rare Dis* 2007;8(2):2.
- [50] Sills ES, Burns M, Parker LD, Carroll LP, Kephart LL, Dyer C, et al. Further phenotypic delineation of subtelomeric (terminal) 4q deletion with emphasis on intracranial and reproductive anatomy. *Orphanet Journal of Rare Diseases* 2007;2(1):9.