A Clinical Decision Support System for Personalized Medicine

Johannes Idelhauser, Bernhard Humm, Ulrich Beez
Department of Computer Science
Hochschule Darmstadt – University of Applied Sciences
Haardtring 100, 64295 Darmstadt, Germany
e-mail: johannes.idelhauser@stud.h-da.de, {bernhard.humm / ulrich.beez}@h-da.de

Paul Walsh
NSilico Lifescience Ltd.
Bishopstown, Co. Cork, Ireland
e-mail: paul.walsh@nsilico.com

Keywords: Clinical Decision Support System, Electronic Health Record, Information Retrieval

Abstract: Given the rapidly growing number of medical publications and resources, consultants face challenges in keeping up-to-date with current research and patient care best practices. This paper presents the concept and prototypical implementation of a Clinical Decision Support System (CDSS) for personalized medicine. It satisfies information needs of consultants at the point of care by integrating secondary medical resources based on a concrete patient's Electronic Health Record (EHR). Particular focus has been on the usability of the CDSS allowing consultants to quickly and intuitively gather relevant information with minimal system interaction. An initial assessment of the CDSS by medical professionals indicate its benefit.

1 Introduction

Given the rapidly growing number of medical publications and resources, consultants face challenges in keeping up-to-date with current research and patient care best practices. Ongoing research and new treatment options require practitioners to keep up-to-date to ensure good treatment outcomes and prevent malpractice lawsuits (Marchant and Lindor, 2013). Physicians' information needs at the point of care range from refreshing and confirming knowledge over logistical questions like drug dosage to teaching and personal learning (Maggio et al., 2014).

Personalized medicine aims at tailoring medical decisions, practices, interventions or products to the individual patient based on their predicted response or risk of disease (Academy of Medical Sciences, 2015). While tailoring the treatment to individual patients is common practise in medicine, the term has been recently used for informatics approaches in medicine that use large amounts of patient data, particularly genomics data, for selecting appropriate therapies.

This paper presents the concept and prototypical implementation of a Clinical Decision Support System (CDSS) (Kawamoto et al., 2005) for personalized medicine. It satisfies information needs of consultants at the point of care by aggregating and integrating primary and secondary medical resources based on a concrete patient's Electronic Health Record (EHR), thus paving the way for personalized medicine. The CDSS is intended to be integrated into an EHR application to be used at the point of care.

The remainder of this paper is structured as follows. Section 2 specifies the problem statement in terms of requirements. Section 3 is the core of the paper describing the concept and prototypical implementation of the CDSS. Section 4 evaluates our approach. Section 5 compares our approach with related work. Section 6 concludes the paper and indicates future work.

2 Problem Statement

Having consulted extensively with clinicians involved in the treatment of melanoma, we have identified the following requirements:

1. Functional Requirements
    1. Relevant: The CDSS shall satisfy the consultants' information demand with relevant, helpful and latest medical information.
    2. Personalized: The information provided shall be tailored to the medical condition of a particular patient.
    3. Pro-active: The CDSS shall offer information pro-actively without additional data entry by the user.
    4. Easily comprehensible: shall provide a quick overview of all information available as well as the possibility to easily acquire more detailed information where needed.
    5. Workflow: The CDSS shall not interfere with the consultant's EHR workflow.
2. Non-Functional Requirements
    1. Usable: The CDSS shall be intuitive to use and self-explanatory.
    2. Low response time: The response time for all interactions with the CDSS shall be less than 1s.
    3. Extensible: The ongoing extension of the CDSS with new information sources shall be facilitated with moderate implementation effort.

3 A Clinical Decision Support System for Personalized Medicine

3.1 User Interaction Model

Physicians' information needs at the point of care include refreshing and confirming knowledge and logistical questions, e.g., medication dosage, idea generation and personal learning (Maggio et al., 2014). To satisfy these needs, physicians tend to access primary literature in the form of abstracts and full-text as well as secondary literature in the form of summaries and reviews (Maggio et al., 2013). In order to provide an intuitive way for physicians and other health professionals to access this information, the proposed CDSS leverages several information services that each try to satisfy different information needs. Those information services are organized in web page panels that the users can customize and fit to their needs by deciding which service panels should be displayed and which should be hidden. Additionally the order and size of the panels can be adapted to the user's individual needs while the resulting layout is persisted over different sessions for the individual user.

3.1.1 Literature Service

One of the main services in the CDSS is the literature service to find and display relevant primary medical literature that is related to the patient at hand (Figure 1).

Figure 1. Interaction concept to display related medical publications (literature service)

The literature service displays automatically generated filters to quickly navigate the literature search results. The filters are displayed on the left whereas the medical literature is shown on the right. For each medical publication its title, journal and publication date is displayed. In the context of evidence-based medicine (EBM), publications with a high degree of evidence are to be prefered in patient care (Hung et al., 2015). As such, publications that are reviews or clinical trials are shown with a marker indicating their publication type. This also aligns with a study from 2013 that logged and analysed data queries in a hospital and found that "[a]lmost a third of the articles [...] accessed were reviews." (Maggio et al., 2013). For quick orientation and relevance assessment, terms that appear in the patient's EHR are highlighted in the literature service. To help the literature relevance assessment process, a teaser text is displayed when hovering the mouse pointer over the eye icon after each publication title. In order to give the users a way to give feedback on the relevance of a publication and improve the literature search, icons with a thumbs-up and a thumbs-down are provided.

3.1.2 Evidence-Based Medical Recommendations

Evidence-based medicine describes the assessment and use of the best available research for decision making in patient treatment and diagnosis. This is done by focusing on well-designed, conducted research with a strong level of evidence like systematic reviews or randomized controlled trials (Hung et al., 2015). Existing web-based clinical decision support systems specialize on providing evidence-based treatment guidelines and summaries written by medical experts that reflect the current state of research. Obst et al. (2013) assessed the use of such a service named UpToDate.com and suggested that physicians often have little time and that navigating the service could at times be time consuming. They also noted that the summaries were sometimes written confusingly and that it took too long to quickly grasp the desired information.

The EBM recommendation service (Figure 2) therefore queries different secondary information sources for patient-related evidence-based summaries and reviews and extracts the most important sections that describe the patient's issue. If the users wish to see the extracted sections in context, they can follow the links and visit the original text.

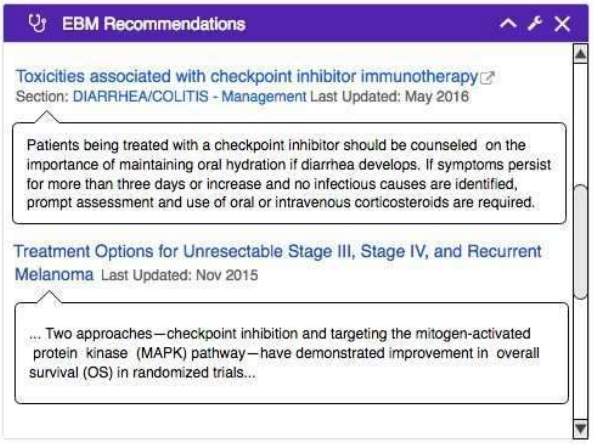

Figure 2. EBM recommendations service

3.1.3 Drug Information Service

Other important information in patient care is material on drugs and their interactions "at the point of drug prescribing" (Rahmner et al., 2012). Therefore, the drug information service provides information normally available in medication package leaflet inserts and secondary decision support services in a more accessible and structured way (Figure 3, left). The provided information includes dosage data for different age groups and pre-filled calculators to compute the correct dosage based on the age and weight of the patient. Other information consists of warnings, adverse effects, pregnancy, pharmacology, administration guidelines, material for patient education and pill images and prices. Selecting a drug for displaying can be done in an autosuggest-supported field that ranks already prescribed medication higher, but allows also searching for medication not yet prescribed.

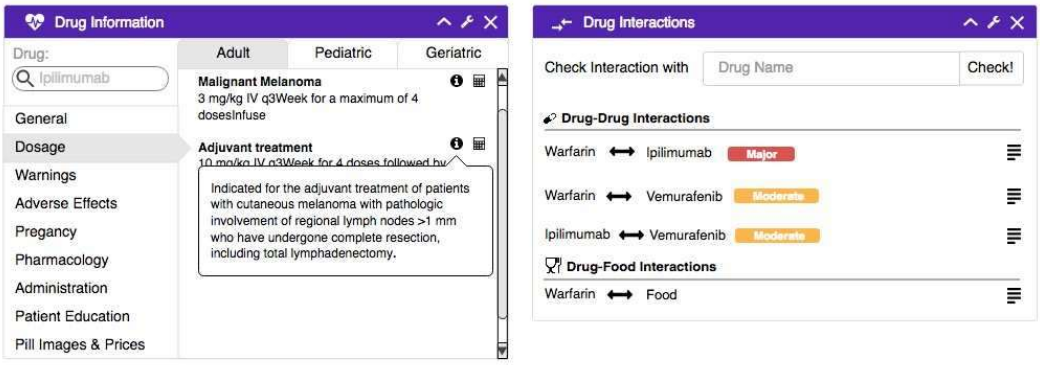

Figure 3. Drug information service

As physicians indicated they wanted to see automatically generated alerts for severe drug interactions and adverse effects (Rahmner et al., 2012), an alert is displayed prominently (Figure 3, top) . For more information on how to manage the interaction or alternative drugs, an appropriate link is provided. Non-severe drug interactions as well as drug-food interactions are displayed in an own panel where the users have the possibility to check interaction with other, not yet prescribed drugs (Figure 3, right).

To "make drug information more searchable" (Rahmner et al., 2012) and for example allow checking if a patient's symptom could be drug related, an adverse effects panel is introduced

(Figure 4). It automatically identifies drug-related comorbidities that are registred in the EHR but also allows searching for symptoms not yet recorded. An option to read more provides information on how to manage this effect, when it will occur or how long it will last.

Figure 4. Searchable Adverse Effects

3.1.4 Clinical Trials Service and News Service

Especially in cancer care the participation in clinical trials is an option for patients of all clinical stages as new findings lead to the development of many new drugs (National Cancer Institute, 2016). A clinical trials service is therefore introduced that searches for nearby clinical trials fitting the patient (Fiure. 5, left).

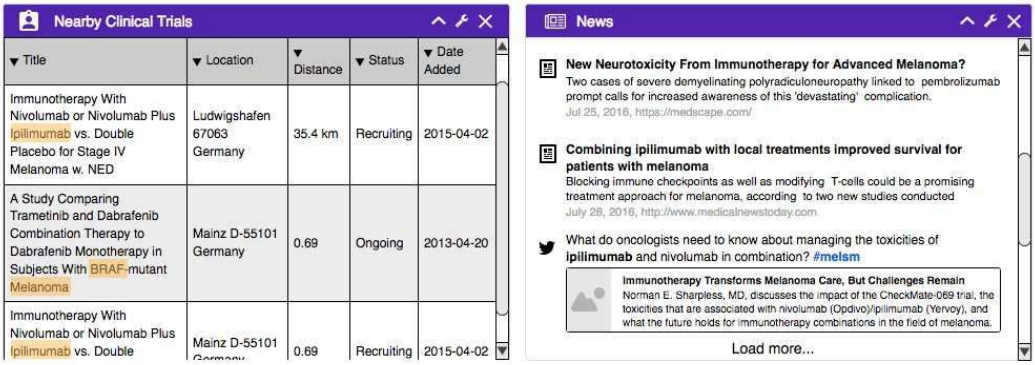

Figure 5. Clinical trials locator service and news service

Finally, a news service provides recent news on treatments, drugs, legislative information or other scientific breakthroughs that can be related to the current EHR (Figure 5, right).

3.2 Information Sources

In order to provide the CDSS services, several potential information sources were identified. The selection of information sources is a critical part in any CDSS application as they are the basis for the trust given them by physicians. As a patient's health might also depend on this information, the quality and correctness of the information is obligatory. This section introduces a summary of identified potentially relevant sources for CDSS.

3.2.1 Literature Service

There are an abundant amount of databases and search services for the health domain. Table 1 lists only a few of them that would be an option to use for the literature service.

Name	Description	API	Access	Size
Google Scholar	Search engine for scientific publications of all fields. Automatically crawls many journals.	no	commercial	estimated at 160 million articles
Ovid	Science search platform that includes many databases, including MEDLINE.	?	subscription	?
PubMed	Search engine mainly accessing MEDLINE database and focused on health topics. Query expansion by use of MeSH ontology.	yes	public & free	> 24.6 million records, about 500,000 new records each year
ScienceDirect	Website with access to large database of scientific publications from many fields.	yes	free (abstracts), subscription (full-text)	12 million records from 3,500 journals and 34,000 eBooks
Scopus	Database with abstracts and citations from many academic journals and many scientific fields, not focused on health topics.	yes	paid subscription	~55 million records
Springer API	Access to all Springer published journals, also includes BioMedCentral open-access publications.	yes	partly free, partly subscription	~2,000 journals and >6,500 books per year, access to >10 million online documents

Table 1. Literature data sources

3.2.2 Evidence-based Medical Recommendations

As evidence-based reviews or summaries should be written by medical experts to ensure quality and reliability, most services require a commercial licence or paid subscription to access them. Only a few public and free sources could be found in the scope of this thesis (Table 2).

Name	Description	API	Access	Volume
BMJ Best Practice	Evidence-based information to offer step-by-step guidance on diagnosis, prognosis, treatment and prevention.	yes	subscription	?
DynaMedPlus	Evidence-based clinical overviews and recommendations. Content updated daily. Also offers calculators, decision trees and unit and dose converters.	yes	subscription	> 3,200 topics and > 500 journals
EBMeDS	Platform-Independent web service CDSS with EBM module	yes	commercial	
Medscape / eMedicine	Largest clinical knowledge base available freely. Articles updated yearly. Also available as mobile application.	no	free, registration required	~6,800 articles
Physician Data Query	Cancer database from the U.S. *National Cancer Institute*. Contains peer-reviewed information on cancer treatment in the form of summaries for patients and professionals.	no	public	Only cancer domain
UpToDate	Popular evidence-based POC tool for a wide range of disciplines but targeted on internal medicine. Extensive peer-review process to ensure accurate and precise recommendations.	yes	subscription, some articles free	~8,500 topics

Table 2. EBM resources

3.2.3 Drug Information

There are few public resources for drug information that are also accessible via an API. Table 3 shows services that could be used in the context of the CDSS proposed in this work. Other not listed services include DrugBank (accessible over RxNav), ResearchAE.com, SIDER, NDF-RT, Epocrates or the OpenFDA API.

As Peters et al. (2015) stated, the data quality of some public resources might be a problem in clinical settings. They compared the two public drug interaction services DrugBank and NDF-RT and found a limited overlap between their drug interaction information. The commercial service used to compare against provided better coverage of the test data then both of the free services

combined. Assuming the commercial drug information services provide a better data quality, one would have to select one of those as data source. Additionally, as of September 2016, the public data source NDF-RT removed the drug interaction information from their service.

Name	Description	API	Access	Drug Information	Drug Interactions	Adverse Events	Drug Announcements/Recalls
DailyMed	Website by U.S. National Library of Medicine (NLM), provides high quality and up-to-date drug labels. Updated daily by FDA. Documents use structured XML format.	yes	public & free	✓	✓	✓	
MedlinePlus Connect	Service by NLM, provides unstructured natural language drug information/labelling and health topic overviews	yes**	public & free	✓*		✓*	
Medscape	Many clinical information resources available over website or mobile app. Articles updated yearly.	no	free, registration required	✓	✓	✓	
RxNav	Provides access to different drug resources like *RxNorm*, *NDF-RT* and *DrugBank*. Drug normalisation over different codes and systems by using *RxNorm*, drug interactions from *DrugBank*.	yes	public & free		✓		
Wolters Kluwer Clinical Drug Information	Commercial drug information APIs including interaction, adverse effects, indications and mapping to RxNorm.	yes	commercial	✓	✓	✓	

Table 3. Drug information sources

3.2.4 Clinical Trials

Several information sources for clinical trials were identified (Table 3).

Name	Description	API	Access	Type	Country
ClinicalTrials.gov	Trial registry from US National Institute of Health. 39% are U.S. only trials.	no*	Public & free	Register	Worldwide with a focus on U.S. (39%)
EU Clinical Trials Register	Clinical Trials Register for trials in the EU	no*	Public & free	Register	European Union
German Clinical Trials Register	German clinical trial register. Also imports trials from clincaltrials.gov that are located in Germany	no*	Public & free	Register	Germany
WHO International Clinical Trials Registry Platform	Search portal to central database with links to original records. Regular fetch of trials from currently 16 data providers, including sources mentioned earlier	no*	Public & free	Search Service	Worldwide

Table 4. Potential clinical trials sources

As the clinical trials' location plays a vital role in assessing their relevance, a service is needed that is not solely focused on one or a few countries. As the WHO registry platform seems to aggregate data from many national registers and other services, the choice would most likely fall on the WHO service.

3.2.5 News

Many online services offer medical news, e.g. MedScape, ScienceDaily or Medical News Today. Usually their content is not accessible over an API and there can also be legal issues prohibiting any “unauthorized copy, reproduction, distribution, publication, display, modification, or transmission of any part of this Service" (ScienceDaily, 2016).

An alternative to this might be the online social networking service Twitter which is used by many medical news sites and professionals.

3.3 Software Architecture

The CDSS is intended to be integrated into an EHR application. The application is organized in a three layer architecture where each layer consists of components that encapsulate logically separable units (Figure 5).

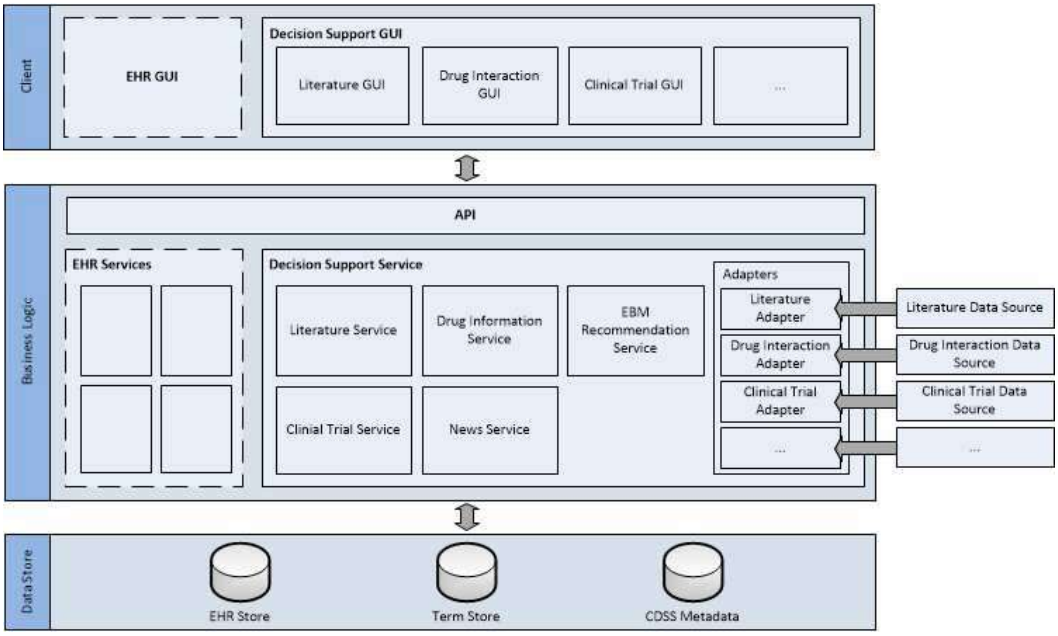

Figure 5. System architecture

On the client side, the Decision Support GUI is implemented alongside the EHR GUI. The different CDSS service are subcomponents of a single decision support module.

The business logic of the Decision Support System consists of the different service components as well as different adapters to connect to the information sources. The services store and use data from the EHR and the Term Store and persist data in the CDSS Metadata store.

3.4 Prototype Implementation

The literature service and drug information service have been implemented prototypically as part of an EHR application for melanoma treatment (Humm and Walsh, 2015) (Beez et al., 2015). The application is implemented in C# using .NET and MS SQL Server on the server side, and in HTML5 / CSS / JavaScript on the client side, using Bootstrap and AngularJS. As data source for the literature service PubMed was selected. Drug interaction data is acquired by querying DrugBank

over the RxNav drug interaction API. In the following sections, we describe the implementation of the literature service in more detail. See Figure 6 for the detailed architecture.

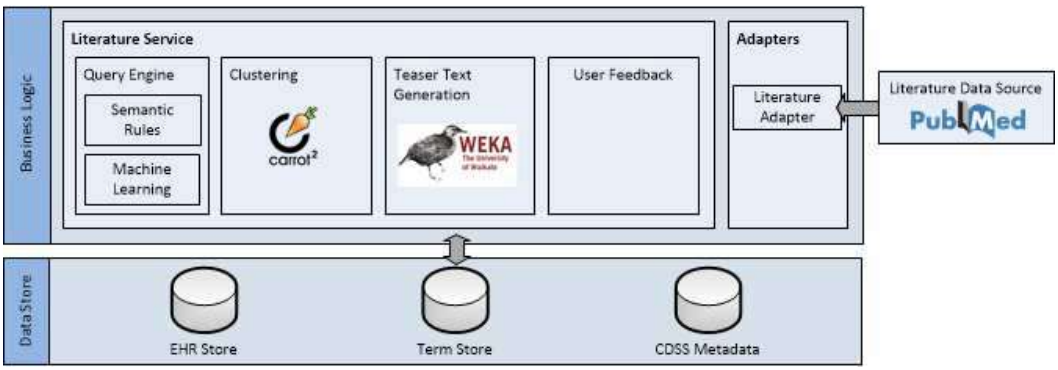

Figure 6. Literature service architecture

3.4.1 Query Engine

As PubMed is selected as the source for the literature service, we need a query in the literature source's query language to find and display publications. To generate the query from the EHR, two strategies are employed: use of semantic rules for creating queries from EHR attributes and machine learning.

Semantic rules

From the ca. 100 attributes that are currently used in the EHR application, not all are helpful for getting personalized literature suggestions for a concrete patient (Figure 7).

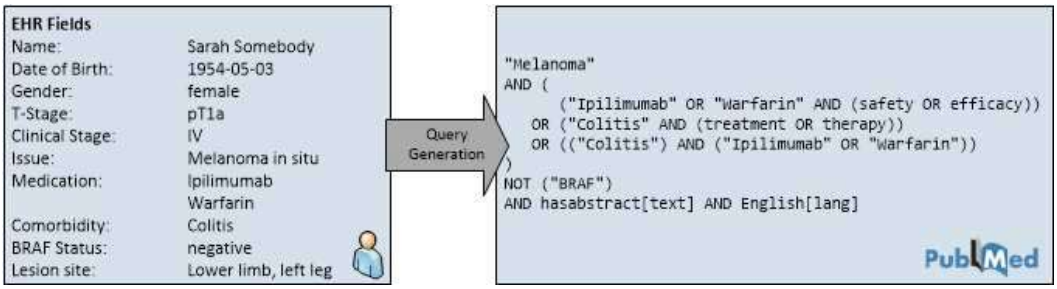

Figure 7. Sample query generation from an EHR

Fields with no relevance like the patient's name are omitted in query generation whereas relevant fields like the issue, medications or comorbidities are included using rules. One rule to search for publications that address the safety or efficacy aspects of one of the medications prescribed, combines all medication with an "OR" and adds "(safety OR efficacy)" to the medication subquery. Another rule combines the comorbidities field with the medication to search for drug-related adverse effects and their treatment. To ensure data quality and only search for recent literature, restrictions are added to the query like the "hasabstract[text]" to only show publications that contain an abstract.

Machine Learning Approach

The presented rule-based approach returns good results in various cases as fields like comorbidity, medication and issue are always relevant. However, in using a rules approach only a predefined field of possible questions can be answered and other fields like age, gender or the clinical stage could also in certain contexts return relevant literature. Additionally, the above mentioned terms "safety" and "efficacy" are only one example of additional query terms. Other terms that are not captured in the semantic rules could also become relevant. We therefore apply a query expansion method by automatically refining queries based on user feedback. This is done using a machine learning approach. Examples for additional query terms from the current prototype implementation include "adverse effects" and "drug therapy". Also, other attributes may become relevant in the future, e.g., the publication type "Review".

To facilitate machine learning, Accord.NET's [1] one-against-all multi label Support Vector Machine (SVM) is used to predict suitable search terms. Training data consists of user feedback data on the relevance of a literature given a specific EHR. As input vector, a bag-of-words (BoW) is built from all EHR terms. The output labels are extracted from the literature using the EHR's medical ontology.

Both strategies are used in parallel and their results are combined using an heuristic approach. The final query is passed to the literature adapter that retrieves the publications from PubMed and parses the retrieved XML document to an internal object representation. Publications are then ranked utilizing their PubMed rank in combination with explicit and implicit user feedback.

3.4.2 Clustering

Different users are interested in different topics and want to have different questions answered. A one-fit-for-all ranking is, therefore, not sufficient. To accommodate this, the result set is clustered to allow filtering the publications according to different semantic criteria. Example filter labels include "Ipilimumab-induced Colitis", "Adverse Effects" and "Overall Survival" (Figure 8).

Figure 8. Partial screenshot of automatically generated filter labels

For clustering the publications, the open source search engine clustering server "Carrot2" is used. It utilizes the specialized "Lingo" algorithm that automatically creates meaningful cluster labels from the publications' titles and abstracts (Osiński et al., 2004). The generated cluster labels are then filtered using the EHR application's medical ontology as well as a custom whitelist.

[1] http://accord-framework.net

3.4.3 Teaser Text Generation

If a publication title catches a consultant's attention, he may choose to read a teaser text in order to easily assess its relevance. This teaser text should be about three sentences long and contain the conclusion of the publication. Usually, abstracts consist of at least 500 or more words and not all of them have their conclusion displayed in a structured form. Therefore, for publications for which the conclusion is not explicitly marked, a machine learning algorithm is employed to predict the concluding sentences. The implementation uses the libSVM algorithm and the open source machine learning software Weka.

3.4.4 User Feedback

There are two kinds of user feedback gathered in this application, active and passive. Active feedback is generated by the users clicking on thumbs-up or thumbs-down icons in the client. Passive feedback is gathered by logging and interpreting all clicks on a publication. All feedback is stored in the CDSS Metadata store and is used for the ranking of publications and clusters as well as for creating training data for machine learning.

4 Evaluation

We compare concept and the prototypical implementation with the requirements stated in Section 2. Requirement 1.2 (personalized) and 1.3 (pro-active) are obviously met since the CDSS information is displayed automatically based on the EHR currently being handled. Also, requirement 1.5 is met, since the CDSS panels can be separated from the EHR dialogs. Assessing the Requirement 1.1 (relevant), 1.4 (easily comprehensible) and 2.1 (usable) is less obvious and needs feedback from users. Therefore, we have conducted an initial survey with 4 medical students and 1 resident physicians.

Users were given the task to prepare for a multidisciplinary team (MDT) meeting using the different CDSS modules. Subsequently, they were to fill out a questionnaire to assess the usability aspects and relevance of the CDSS services implemented in the prototype as well as in the interaction concept.

Initial usability observations indicate positive feedback. Positively feedback mentioned was the display of the teaser text for assessing literature relevance, the drug interaction information, searchable adverse effects as well as the automatically generated filters. The usability test also revealed some weak points that were, subsequently, improved. For example, the teaser text's icon position was initially not prominent enough and was easily overlooked. Therefore, its position was moved after the literature's title and a legend was added (Figure 1). However, the survey was only an initial one and relevance assessment by medical students might be skewed due to their lack of clinical experience. In the future, a comprehensive survey with physicians working in the melanoma domain is planned.

When opening EHR for the first time initial loading of literature data may take up to 15 seconds. However, as this happens asynchronously while the consultant is working with EHR this will not interfere with the EHR workflow. As soon as all data is loaded and the physician enters the CDSS, each interaction is less than 500 ms which meets Requirement 2.2 (low response time) clearly. With caching strategies this initial loading time may also be reduced.

Concerning Requirement 2.3 (extensible), the component-based system architecture and the use of adapters to access information sources enables the extension of the CDSS and implement other decision support modules with moderate implementation effort. For a new data source one would have to implement an additional adapter which results in about 100 lines of code (LOC). For a new decision support module the service on the server and the client GUI would have to be implemented. For the client this would require about 300 LOC. The server implementation depends on the module's complexity, e.g. the literature service is ~2,500 LOC whereas the interaction service is ~200 LOC.

5 Related Work

The idea of CDSS is not new and there exist many services accessible over the browser and/or smartphone applications. Their scope ranges from drug information, drug interaction and diseases to guidelines, pill identification and alternative medications. Example services include UpToDate, Epocrates, MedScape and First Databank. Often, the integration of theses services into an EHR system consists of providing a standard search field that enables the users to search and visit the CDSS service's main webpage. Some EHR systems like Athenahealth's EHR include context-sensitive drug monographs that provide information like dosing, adverse effects and other key safety data directly in the EHR [2]. However, there are systems that include include the patient's context in the CDSS search. The integration of UpToDate into various EHR systems provides such a future by displaying an info button in various EHR locations and providing an automatic search [3]. However, this function delivers standard UpToDate results pages and problems mentioned earlier in this work like confusingly written texts and difficulties navigating the long summaries remain (Obst et al., 2013).

Finland's Evidence based Medicine electronic Decision Support (Nyberg, 2012) is a platform-independent online service that accepts structured EHR data as input and returns clinical decision support data like links to guidelines, therapeutic suggestions, clinical reminders and alerts. These rules can be created by experts in a web-based editor and scoped per organization or globally. It can also populate forms and calculators with patient specific data. They do not include a literature search service but provide other services like the drug alerts that are similar to services presented in this work. Additional services like the knowledge assistant would be relevant in the context of this work and could later be integrated into our proposed CDSS.

Alternative approaches for the task of finding literature fitting to a patient's case has been described in different publications. Perez-Rey et al. (2012) propose a visual browser extension that allows the user to select a subset of extracted search terms from a natural language medical record. These selected terms will then be used to search PubMed. However, the selection of search terms is not automatic or pro-active as the user has to interact with the application to build the search.

[2] http://www.athenahealth.com/enterprise/epocrates/clinical-decision-support

[3] http://www.uptodate.com/home/hl7

Soldaini et al. (2015) propose a CDSS that tries to find fitting medical literature for medical case reports instead of EHRs. They consider the natural language case report as the query and apply query reformulation techniques like query reduction by identifying medical terms and expansion by using pseudo relevance feedback to build the search. They try to best answer the case report (~60 words) by providing relevant literature. In contrast to this work they do not use PubMed as search engine but use a local search server.

To the best of our knowledge, no system integrates a literature search system into an EHR to display relevant medical literature. Similarly, we believe there is no implementation of a patient-specific search service for clinical trials.

6 Conclusions and Future Work

Personalised medicine offers great promises for consultants' decision making, potentially resulting in improved patient treatment. Numerous medical information sources are already available which can be utilized, and they are growing rapidly. However, personalized medicine has not yet widely used in day-to-day clinical practise. With the concept and a prototypical implementation of a Clinical Decision Support System (CDSS) for personalized medicine presented in this paper, we intend to make a contribution towards this direction.

Particular focus has been on the usability of the CDSS allowing consultants to quickly and intuitively gather relevant information with minimal system interaction. A number of artificial intelligence (AI) techniques have been used to tailor information to the patient's medical situation and the consultant's information demand.

It is planned to integrate the CDSS presented into a commercial EHR application suite for melanoma treatment. Towards this end, future work is required. Additional information services as presented in the interaction concept need to be implemented. A comprehensive analysis of the CDSS with consultants in the field needs to take place resulting in potential improvements of the concept and the implementation. Then, a trial phase with real patient data is planned to extend the data base for machine learning. We intend to publish insights from these analyses.

May this work eventually help consultants improve patient care.

7 Acknowledgements

This work was funded by the European Commission, Horizon 2020 Marie Skłodowska-Curie Research and Innovation Staff Exchange, under grant no 644186 as part of the project SAGE-CARE (SemAntically integrating Genomics with Electronic health records for Cancer CARE).

References

Academy of Medical Sciences (2015), Stratified, personalised or P4 medicine: a new direction for placing the patient at the centre of healthcare and health education (Technical report). Academy of Medical Sciences. May 2015. Retrieved 24/8/2016.

Beez, U., Humm, B.G. and Walsh, P. (2015), "Semantic AutoSuggest for Electronic Health Records", 2015 International Conference on Computational Science and Computational Intelligence (CSCI), 760-765.

Humm, B.G. and Walsh, P. (2015), “Flexible yet Efficient Management of Electronic Health Records”. 2015 International Conference on Computational Science and Computational Intelligence (CSCI), 771-775.

Hung, B. T., Long, N. P., Hung, L. P., Luan, N. T., Anh, N. H., Nghi, T. D., … Hirayama, K. (2015), “Research Trends in Evidence-Based Medicine: A Joinpoint Regression Analysis of More than 50 Years of Publication Data”, PLoS ONE, 10(4).

Kawamoto, K, Houlihan, C.A., Balas, E.A. and Lobach, D.F. (2005), "Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success", BMJ? British Medical Journal, 330(7494), 765.

Maggio, L. A., Cate, O. T., Moorhead, L. L., Van Stiphout, F., Kramer, B. M., Ter Braak, E., Posley, K., Irby, D. and O'Brien, B. C. (2014), “Characterizing physicians' information needs at the point of care”, Perspectives on Medical Education (Perspect Med Educ), 33(5), 332-42.

Maggio, L. A., Steinberg, R. M., Moorhead, L., O'brien, B. & Willinsky, J. (2013). "Access of primary and secondary literature by health personnel in an academic health center: implications for open access". Journal of the Medical Library Association (J Med Libr Assoc), 101(3), 205-12.

Marchant, G. E. and Lindor, R. A. (2013), “Personalized medicine and genetic malpractice”, Genetics in Medicine (Genet Med), 15(12), 921-2.

National Cancer Institute (2016). Melanoma Treatment. URL: http://www.cancer.gov/types/skin/hp/melanoma-treatment-pdq#section/_885 (visited on 11/09/2016).

Nyberg, P. (2012), “EBMeDS Clinical Decision Support. EBMeDS White Paper”, URL: http://www.ebmeds.org/www/EBMeDS%20White%20Paper.pdf (visited on 12/09/2016).

Obst, O., Hofmann, C., Knüttel, H. and Zöller, P. (2013), “‘Ask a question, get an answer, continue your work!’ – Survey on the use of UpToDate at the universities of Freiburg, Leipzig, Münster and Regensburg”, GMS Medizin—Bibliothek—Information, 13(3), 26.

Osiński, S., Stefanowski, J. and Weiss, D. (2004), “Lingo: Search results clustering algorithm based on singular value decomposition”. In Intelligent information processing and web mining, 359-368, Springer Berlin Heidelberg.

Perez-Rey, D., Jimenez-Castellanos, A., Garcia-Remesal, M., Crespo, J., & Maojo, V. (2012), “CDAPubMed: a browser extension to retrieve EHR-based biomedical literature”, BMC Medical Informatics and Decision Making, 12, 29.

Peters, L. B., Bahr, N. and Bodenreider, O. (2015), “Evaluating drug-drug interaction information in NDF-RT and DrugBank”, Journal of Biomedical Semantics, 6, 19.

Rahmner, P. B., Eiermann, B., Korkmaz, S., Gustafsson, L. L., Gruvén, M., Maxwell, S., … Vég, A. (2012), “Physicians’ reported needs of drug information at point of care in Sweden”, British Journal of Clinical Pharmacology, 73(1), 115–125.

ScienceDaily (2016). Terms and Conditions of Use. URL: https://www.sciencedaily.com/terms.htm (visited on 11/09/2016).

Soldaini, L., Cohan, A., Yates, A., Goharian, N. and Frieder, O. (2015), “Retrieving medical literature for clinical decision support”, European Conference on Information Retrieval, 538-549, Springer International Publishing.