h_da
HOCHSCHULE DARMSTADT
UNIVERSITY OF APPLIED SCIENCES
fbi
FACHBEREICH INFORMATIK

Hochschule Darmstadt
Fachbereich Informatik

Evidence-Based Medical Recommendations for Personalized Medicine

---

Abschlussarbeit zur Erlangung des akademischen Grades
Master of Science (M. Sc.)

vorgelegt von
Tino Landmann (742750)

Referent(in):	Prof. Dr. Bernhard G. Humm
Korreferent(in):	Prof. Dr. Uta Störl

Ausgabedatum:	09. Januar 2017
Abgabedatum:	09. Juli 2017

Erklärung

Ich versichere hiermit, dass ich die vorliegende Arbeit selbständig verfasst und keine anderen als die im Literaturverzeichnis angegebenen Quellen benutzt habe. Alle Stellen, die wörtlich oder sinngemäß aus veröffentlichten oder noch nicht veröffentlichten Quellen entnommen sind, sind als solche kenntlich gemacht. Die Zeichnungen oder Abbildungen in dieser Arbeit sind von mir selbst erstellt worden oder mit einem entsprechenden Quellennachweis versehen. Diese Arbeit ist in gleicher oder ähnlicher Form noch bei keiner anderen Prüfungsbehörde eingereicht worden.

Darmstadt, 09. Juli 2017 _____

Tino Landmann

Abstract

Mit der rasanten Entwicklung von medizinischen Behandlungsmethoden und dem stetig wachsende medizinischen Wissen, werden Ärzte heutzutage vor zusätzliche Probleme gestellt. Neben dem Thema Patientensicherheit und personalisierter Medizin, stehen sie vor der Herausforderung auf dem aktuellen Stand der Forschung und ihren Behandlungsmethoden zu bleiben. Um Ärzte dabei zu unterstützen werden von Netzwerken, bestehend aus medizinischen Experten, sogenannte evidenz-basierte medizinische Richtlinien entwickelt. Diese bieten die nötige Expertise, sind jedoch meistens zu umfangreich oder stellenweise irritierend geschrieben. Dieser Umstand und zeitliche Beschränkungen, erschweren es den Ärzten diese Richtlinien sinnvoll in ihrem Arbeitsalltag zu verwenden, da es zu viel Zeit benötigt sich mit diesen auseinander zu setzen. Damit diese Richtlinien besser in den Arbeitsblauf integriert werden können, wird in dieser Thesis ein Empfehlungsservice für evidenz-basierte medizinische Richtlinien in der personalisierten Medizin vorgestellt. Er versucht anhand von Daten, basierend auf einer elektronischen Patientenakte (EHR), die gewünschten Informationen aus einer Richtlinie zu extrahieren und dem Arzt vorzuschlagen.

Der vorgestellte Service ist in ein klinisches Informationssystem für personalisierte Medizin, basierend auf einer EHR-Applikation, integriert. Der Service und das System beschränken sich dabei auf die Behandlung von Melanoma Hautkrebs.

Der Fokus wurde dabei auf die Nutzerfreundlichkeit des Empfehlungsservice gelegt, damit Ärzte in ihrem Arbeitsfluss, so weit möglich, nicht unterbrochen werden und schnell und gezielt die Informationen erhalten, die sie benötigen. Das selbe gilt für die Wartung dieses Service. Da Informationen und Richtlinien sich schnell ändern oder veralten, sollte es möglich sein die anzuzeigenden Informationen möglichst einfach und schnell anzupassen.

Abstract

Due to the rapid development of medical treatments and the continuous growth of medical knowledge, consultants face additional problems today. Besides patient safety and personalized medicine, they face the challenge to remain on the current state of research and their treatment methods. To support consultants, networks of medical experts develop so-called evidence-based medical guidelines. These guidelines provide the necessary expertise, but they are usually too extensive and in some cases written in an irritating way. Due to this condition and time constraints in daily routine, it is difficult for the consultants to integrate these guidelines into their working hours, because it takes too much time to set them apart. This thesis presents a recommendation service for evidence-based medical guidelines in personalized medicine, so that these guidelines can be better integrated into the workflow. It satisfies information needs of consultants, by extracting desired information from the guideline and suggests them to the consultant. The extraction is based on data from the patient's Electronic Health Record (EHR).

The service provided is integrated into a Clinical Decision Support System (CDSS) for personalized medicine. This system is based on an EHR application. The service and the system are limited to the treatment of melanoma cancer.

Particular focus has been on the usability of the recommendation service, so that consultants are not interrupted in their work flow as much as possible. Furthermore they shall receive the information they need, quickly and specific. The same applies to the maintenance of this service. Because medical information and guidelines change quickly or become obsolete, it shall be possible to change the information to be displayed as easily as possible.

Contents

List of Figures

List of Tables

Abbreviations

API ..... Application Programming Interface

BRC ..... Business Rule Composer

BRE ..... Business Rule Engine

CDSS ..... Clinical Decision Support System

CIS ..... Clinical Information System

EBM ..... Evidence-Based Medicine

EHR ..... Electronic Health Record

GAC ..... Global Assembly Cache

GUI ..... Graphical User Interface

HRS ..... Health Recommender System

HTML ..... Hypertext Markup Language

IFrame ..... Inline Frame

NCCN ..... National Comprehensive Cancer Network

ORM ..... Object Relational Mapper

PDF ..... Portable Document Format

RCT ..... Random Control Trial

REST ..... Representational State Transfer

SAGE ..... SemAntically integrating Genomics with EHR

Chapter 1

Introduction

Evidence-based medicine is one of the most important developments of the last decades in the clinical use of information. It changes the way clinicians work and makes the work more efficient. (Puustjärvi et al. 2015) Various studies and surveys have seen that the support by EBM leads to a faster and general overview of diagnoses and treatments. This allows treatments to be started more quickly, which results in lower waiting times for patients and is cost-saving. These are just a few of the advantages of this development for clinicians. For students, EBM can be used as an excellent source of information as well. (Obst et al. 2013) In developing countries, where they have a higher patients-per-physicians ratio, it is used to develop new healthcare models, which integrates EBM. (Puustjärvi et al. 2015) This is finally the focus of evidence-based medicine, the support of health personnel with the required information at the right time.

1.1 Motivation

Over the past decades, medical consultants face increasing challenges in keeping up-to-date with the rapid development of new treatments and medications. Particularly in the field of personalized medicine and cancer treatment, new methods and insights are continuously being added. In this process EBM supports physicians to make the right and necessary medical decisions. The main goal is the health of the individual patient. This goal is to be made possible by fast, effective, but also safe treatments. This shows

how important the EBM is for the clinical sector.

However, the EBM has not achieved its goal yet and is still in development, despite its good feedback. This becomes clear in tests and surveys, as in the case of the web-based EBM system "UpToDate". Occurring criticisms are for example, that there is no pdf file for better readability, it is difficult to find a way to get specific answers or, in clinical practice, there is often not enough time to use these systems. (Obst et al. 2013) It has been recognized though that treatment with EBM usually leads to a real benefit, if it is used in the context with a patient. (Green et al. 2003)

To support consultants to make better medical decisions, this thesis presents a concept and prototypical implementation of a evidence-based medical recommendation service for personalized medicine. With the use of EBM guidelines and individual patient data, it tries to present required information to physicians, quickly and specifically. This is intended to make the use of EBM easier and more accessible to consultants. The concrete patient data is derived from an EHR, which paves the way to personalized medicine. The EBM recommendation service is integrated into a clinical decision support system (CDSS), which is based on an EHR application for melanoma skin cancer.

1.2 Project Environment

This thesis is part of the SAGE-CARE project (SemAntically integrating Genomics with Electronic health records for Cancer CARE). The project is funded by the European Commission, Horizon 2020 Marie Skłodowska-Curie Research and Innovation Staff Exchange, under grant no. 644186. In addition to this project, an EHR application to assist physicians in the treatment of melanoma skin cancer is currently being developed. (Humm et al. 2015)

In the context of SAGE-CARE, a concept and prototypicaly implementation of a clinical decision support system for personalized medicine has been developed in a master thesis. (Idelhauser 2016) The idea of the system is to support consultants with information they need at the point of care, by integrating secondary medical resources based on a concrete patient's Electronic Health Record. Besides this concept, two conceptional services have

been prototypicaly implemented. One is a literature service, which examines relevant and useful medical papers that fit to the patient's disease. The other is a drug information service, which is a drug interaction checker and clinical trial service, which searches for potentially beneficial trials in the country. (Idelhauser 2016) In his thesis, he also presents a concept for evidence-based medical recommendations as a service which displays medical recommendations in a textual way based on patient data. This thesis uses the concept of the EBM recommendations service as a basis idea. It modifies and extends the concept and implements a prototypical version into the EHR application of the SAGE-CARE project.

1.3 Outline

The following parts of this thesis are structured as follows. Chapter 2 includes the statement of the problem as well as functional- and non-functional requirements. Chapter 3 describes all relevant background information. Information sources which are needed to understand interactions and following decisions are in Chapter 4. Chapter 5 explains the software architecture of the EBM recommendations service while Chapter 6 includes the implementation. Chapter 7 evaluates the implemented EBM recommendations service by comparing it with the defined requirements. In Chapter 8, the concept approach is compared to related works. The Chapter 9 finishes with the conclusion and future work of this thesis and its approach.

Chapter 2

Requirements

The defined goal of this thesis is to develop a EBM recommendations service to present clinicians recommended information for individual patients and support them to make the right decision. Based on the requirements of the SAGE-CARE project which consulted physicians, who are involved in the treatment of melanoma skin cancer, the following requirements have been identified:

1. **Functional Requirements**
    1.1. *EBM recommendations:* The consultant shall get evidenced-based medical recommendations for treating cancer patients.
    1.2. *Personalized:* The information provided shall be tailored to the medical condition of a particular patient.
    1.3. *Pro-active:* The EBM recommendations shall offer information pro-actively without additional data entry by the user.
    1.4. *Easily comprehensible:* shall provide a quick overview of all information available as well as the possibility to easily acquire more detailed information when needed.
    1.5. *Non-interfering:* The EBM recommendations shall not interfere with the consultant's EHR workflow.
2. **Non-Functional Requirements**
    2.1. *Usability:* The EBM recommendations shall be intuitive to use and self-explanatory.

2.2. *Performance:* The response time for all interactions with the EBM recommendations shall be less than 5s.

2.3. *Maintenance:* The maintenance of the EBM recommendations shall be easy and quick.

2.4. *Extensibility:* The ongoing extension of the EBM recommendations with new information sources shall be facilitated with moderate implementation effort.

Chapter 3

Background

This chapter contains important definitions and background information on the contents of this thesis. First, basic terms such as Personalized Medicine (Section 3.1), Electonic Health Record (Section 3.2) and Clinical Decision Support System (Section 3.3) are explained. Afterwards, the main topic of this thesis is explained with the sections Medical Recommendations (Section 3.4) and Evidence-Based Medicine (Section 3.5). Finally, the concept of the Business Rule Engine is described in Section 3.6.

3.1 Personalized Medicine

There is no official definition of personalized medicine, rather it describes a concept that is made up of different medical practices/concepts. (Jain 2015) It refers to a medical model, which uses phenotypes and genotypes of individual patients. This includes among other things molecular profiling, medical imaging or lifestyle data. It is used to provide the right treatment strategy for the right person at the right time. But also to determine diseases and/or provide timely and targeted prevention. (Nimmesgern et al. 2017)

Some of these practices are for example genomic medicine, customized drug therapy and stratified medicine. An increasingly important approach is the genomic medicine. It includes the sequencing of the human genome and also makes it possible to identify subtypes of some diseases. This knowledge about the genetics can help clarify why patients with certain subtypes of diseases, respond to a drug more than others. (Redekop et al. 2013) With this,

genomics medicine helps to recognize and treat various diseases.
Furthermore, these genomics play an important role in stratified medicine, another part of the personalized medicine. This medicine is considered as a key approach in the diagnosis, as well as treatment of diseases and depends decisively on such information like genomics. For this purpose, existing data must be integrated into a comprehensive electronic health record and new data, such as genotypes and phenotypes, are generated and added.
Based on these genetic profiles, customized drug therapies can be used and therefore a better match of drugs for the patient can be achieved.

This is only a part of the medical approaches, which are related to the personalized medicine. However, it shows how the personalized medicine is composed as an overall concept of different cooperative and partly independent medical areas.

3.2 Electronic Health Record

The International Organization for Standardization (ISO) defines the concept of Electonic Health Record as a "repository of information regarding the health status of a subject of care, in computer processable form, stored and transmitted securely and accessible by multiple authorized users" and its "primary purpose is the support of continuing, efficient and quality integrated healthcare". (*Health informatics — Electronic health record — Definition* 2005)

The idea behind such a system is to share the health record of a patient across organisations. Through the comprehensive sharing of information, it is possible to gain a better overview of the health condition. In the case of planned treatments, for example, health prehistory or secondary diseases can play an important role, which would otherwise have been ignored. However, physicians and hospitals usually store and own the patient data and this makes it more diffcult to exchange the data. EHR systems are designed to solve this problem. (Goth 2008)

For this reason, many countries and companies have started pilot projects on this subject. For example, in a long process, the government of Austria adopted the law for the development and engineering of a nationwide EHR system. (Steininger et al. 2014) This is to enable the storage, use and exchange

of patient data, across citizens and organisations. But also companies such as Google and Microsoft are developing, together with hospitals, on their own EHR systems, independent from the government. The systems follow different approaches, while Google Health is a front-end application, Microsoft's HealthVault tries to represent a database. But both of them have the goal, that patients can collect their clinical data and, if desired, synchronize them with authorized persons or institutions. (Goth 2008)

The concept and the implementation in this thesis refer to an EHR application, as the data storing environment for patients. In this context, the EHR system is also used as a reference for concrete patient data.

3.3 Clinical Decision Support System

Clinical decision support systems "provide clinicians, staff, patients, and other individuals with knowledge and person-specific information, intelligently filtered and presented at appropriate times, to enhance health and healthcare." (Berner 2009)

Such a system has various goals. On the one hand, patient data can be better evaluated and decision-making is improved. On the other hand, the problem-solving process and the way of behaving with diagnoses and treatments are optimized. Lastly, it provides necessary knowledge to make correct decisions and prevent the occurrence of medical errors. (Sanchez 2014)

CDSS can contain a wide range of different tools. This can be, for example, computerized alerts or reminders, clinical guidelines, patient data reports and dashboards, documentation and literature templates, drug information or clinical workflow tools. (Sanchez 2014)

The development of the CDSS has shown that the trend is going away from the stand-alone system in the direction of service model architecture. For that, the clinical information system and the clinical decisions support system components of an integrated decision support system are seperated and recombined by the use of a standard application programming interface (API). One of the first projects with this approach was the SAGE project. The advantage of this approach is, that it solves the so-called vocabulary problem. The problem is, that the "virtual medical record specifies the vocabularies that will be used to access and process the medical record, and to the extent

that a clinical system uses different terminologies, it is required to provide a suitable mapping." (Wright et al. 2008)

The EBM recommendation service, developed in this thesis, is part of such a clinical decisions support system, which is also based on a service-based architecture. (Idelhauser 2016)

3.4 Evidence-Based Medicine

Evidence-Based Medicine (EBM) is a medicine based on clinical research. It uses the best external scientific evidence for decisions in the medical treatment of individual patients. In practice, this means integrating individual clinical expertise with external evidence from systematic research. (Antes 1998)

The evidence required can come from external medical literature and practice-based expertise. The literature sources can come from: (West et al. 2002)

- randomized-controlled trials (RCT)
- systematic reviews
- clinical guidelines
- cohort studies
- quasi-experimental studies
- descriptive studies
- expert opinions

On the other hand, practice-based evidence is collected primarily from day-to-day routine data in the treatment of patients in hospitals (EHR). They also may contain additional data such as claims, insurance or administrative hospital data. (El-Gayar et al. 2014)

The process of evidence-based medicine takes place in seven steps, these are as follows: (El-Gayar et al. 2014)

1. Identifying the Patient's Condition

2. Formulating EBM Question
3. Evidence Gathering
4. Evidence Evaluation
5. Convert the Critically Appraised Evidence into Consumable Unit (practicable to use at the point of care)
6. Evidence Presentation and Use
7. Evaluate the Result of Putting Evidence into Practice

3.5 Medical Recommendations

Medical recommendations are systematically developed statements that assist clinicians as medical decision-making for certain medical conditions. However, they are not a substitute for a medical judgment, but rather support the judgment and the decision-making. Most of the recommendations are based on literature reviews and research publications created by panels, which consist of many medical experts. (AACE - American Association of Clinical Endocrinologists 2017)

Medical recommentations usually reflect the current medicine at the time of the publication. (AACE - American Association of Clinical Endocrinologists 2017) Since the medicine can change rapidly in a short time, the recommendations have to be reviewed and revised continually. However, medical recommendations are less an independent concept, much more they are a main component or important factor in certain medical areas, such as evidence-based medicine.

For evidence-based information and recommendations, grading systems exist to classify them according to their strengths. There are grading systems for the various fields of medicine like prognostic studies and therapeutic studies (Burns et al. 2011), but also for evidence-based guidelines, there are special grading systems. (Harbour et al. 2001) To determine the strength of the recommendation, the level of the evidence must be determined. This is possible via a corresponding grading system. (Appendix A) Using the evidence level, it is then possible to classify how strongly a recommendation is. (Table 3.1)

Grade	Description
A	At least one meta-analysis, systematic review or RCT rated as 1++ and directly applicable to the target population or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+

Table 3.1: Grading system for EBM guideline recommendations (et al. Harbour)

3.6 EBM Guidelines

EBM guidelines are a collection of clinical guidelines based on the best availabe evidence. They are easy to use for primary as well as ambulatory care. These guidelines are continually updated and follow the current state of clinical medicine, thus bringing evidence into practice. (Wiley 2014)

Over the years, EBM guidelines have become a very important tool that has developed rapidly. It improves patient care quality, clinical outcomes and reduces unwanted variation in treatment methods between institutions and geographic regions. It also reduces the costs associated with healthcare. (Linskey et al. 2009)

Because of the exponential rise in medical literature and the time pressure in clinical practice, it has become impossible for the clinician to keep up-to-date on the latest research, even in their special area. EBM guidelines can help to solve this problem by providing a starting point from which the guideline

systematically leads, through evidence, to a practical recommendation. By that, it becomes the best-evident-to-date, formulated by a panel of specialized experts. The advantage of such guidelines lies in the fact that they are based not only on the opinion of an expert or any random clinical trials. The existing expertise has been systematically developed by several experts and is therefore more generalizable for routine practice situations. (Linskey et al. 2009)

The construction of guidelines consists of two steps. First step is the systematic identification of evidence and classifications according to the strength or quality of the study as evidence. In the second step, the panel agrees on the strength of recommendations linked to the previous analysis. (Linskey et al. 2009) The validity and usefulness of a guideline depends on three factors:

1. Composition of the panel and the process
2. Identification and synthesis of the evidence
3. Construction of the guideline

The composition of the panel plays an important role in the acceptance of a guideline by the practicing physicians, as well as critical influences in the construction of the guideline. (Grimshaw et al. 1995) This is due to the fact that the recommendations of the board members can differ, even if they analyze the same data. (Woolf 1992)

There are three levels of quality in the methodology for guidelines: informal consensus guidelines, formal consensus guidelines and evidence-linked construction. (Linskey et al. 2009) The first is most commonly used for guidelines of patient support. They often consist of treatment algorithms without systematic evidence testing and the recommendations are usually not classified by strength. (IRSA - International RadioSurgery Association 2008) The second can be evidence-based, in the sense that a literature search is performed, but the proofs can not or are not classified in evidence tables. Moreover, the strength of the resulting recommendation is not limited by the strength of the evidence. Therefore the evidence tables used in the construction of the guidelines are often not presented, which would allow independent verification of the evidence and recommendation strengths. Evidence-linked constructions have the highest quality because they are the only guidelines with independent evidence status for EBM recommendations.

They contain evidence tables for independent review of the literature and classification of the strength of evidence. It is important that the strength of an evidence always has a higher priority than the strength of a recommendation. Because these properties maximize the chance that the guideline is accepted and applied by clinicians. (Linskey et al. 2009)

Since the evidence-linked constructions method is a more complex and new method, it has been used less frequently. Instead, formal census guidelines (level two) are the common method for developing guidelines. (Linskey et al. 2009)

There are two approaches to the use of EBM guidelines. The first is a web-based / database approach, in which clinicians can search for information directly and receive appropriate results. This approach provides initially very quick results, but is in the disadvantage if additional or more detailed information is needed. These usually have to be searched additionally, which costs more time and the results are under certain circumstances only superficial. Current examples of this approach are the web applications "UpToDate" or "EBM Guidelines Database". (Obst et al. 2013; Wiley 2014)
The second approach is limited to guidelines as a document format. A search can be more complex here, since these documents are usually very extensive. However, they provide a good overview of the information sought and are directly linked to additional and detailed information. Organizations such as the *National Comprehensive Cancer Network* (NCCN) have specialized in this approach, they are developing EBM guidelines in the form of PDF documents.

3.7 Business Rule Engines

A business rule engine (BRE) is a software that performs one or more business rules in a runtime production environment. The rules can be set freely and individually by the user and a set of rules is stored as a so-called *policy*. These policies can define processes in a company or they are defined for a special system. An example of such a rule could be *"All customers who spend more than 100 € on one of our products receive 10 percent discount"*. A BRE allows that these policies and other operational decisions to be defined, tested and executed. These policies are seperately managed from the application code. (Taylor et al. 2007)

Rule Engine supports besides rules also scores, mutual exclusion, conditions and other functions. In an IT-application, business rules usually change more often than the rest of the application code and therefore, rule engines are a seperated pluggable software component. (Taylor et al. 2007) Thus, it is possible for the user to change rules without having specific IT knowledge and without changing the application code. A system can become more adaptable and dynamic through a BRE.

However, you can distinguish BRE 's from different types. These usually differ in how the execution of the rules is planned. Most rule engines use the so-called *forward chaining*, which can be separated into two classes. First class treats production rules, which represent behavioral patterns according to the pattern "if condition, then action". The other class processes response/event condition action rules. They recognize and respond to incoming events and handle certain process event patterns. With such a rule engine the user can be notified, for example, when a certain product is no longer in stock. (Taylor et al. 2007) The biggest difference between these types is that production rule behaves when a user or application calls them, but the reactive rule engine responds automatically when an event occurs. In addition, some BRE's support *backward chaining*, where the rule engine tries to solve the facts to achieve a specific goal. Therefore, it is referred to as goal-driven because it attempts to determine whether something exists by existing information. (Taylor et al. 2007) The third class is the deterministic engine. It renounces both forward and backward chaining and instead uses a domain-specific language to describe the policy better.. This has the advantage that it is often easier to implement and maintain and provides a better performance. But a domain-specific language must first be developed or agreed upon. (Taylor et al. 2007)

The BRE used for the prototypical implementation in this thesis uses the forward chaining described above with the typical "if condition, then action" behavioral pattern of production rules.

3.8 Requirement for Information

The most important question in developing a recommendation service is what information clinicians need at the point of care and how they are presented. There are already some studies on this question. One was concerned

by the observations and interviews of clinicians with how often and which information clinicians search for. The result was that clinicians are looking frequently for information in their working hours and the most information needed, requires the synthesis of patient data and medical knowledge, which is often difficult to obtain. (Osheroff et al. 1991)
In a further publication on the implementation of a clinical information system (CIS), ten so-called *commandments* were developed, which is important for clinicians in an information system (Fig. 4.1). With these ten commandments it becomes clear that the most important points are the speed / time with which the information is delivered or retrieved. And that the search fits in the workflow without long processes having to be executed. In addition, the autonomy of the clinician should always be maintained. (Shabot 2004)

Table. Ten commandments for clinical information systems

1. Speed is everything.
2. Realize that doctors won't wait for the computer's pearls.
3. Deliver "just-in-time" information.
4. Fit into the user's workflow.
5. Respect physicians' sense of autonomy.
6. Monitor implementation in real time and respond "right now."
7. Beware of unintended consequences.
8. Be wary of uncovering long-standing process flaws.
9. Don't disrupt "magic nursing glue."
10. Speed is everything.

Figure 3.1: Ten commandments for CIS

Obst et al. (2013) surveyed clinicians, students, scientists and medical professionals to use and evaluate the evidence-based resource UpToDate for clinical decision support in a multicenter study at four german universities. A frequently mentioned advantage, in the use of the system, was that the treatments were started more quickly and treatment methods can be checked. Clinicians quickly get a general overview of diseases and can thus make better diagnoses. This makes the choice of treatment more reliable, which improves patient healthcare and saves money through a reduced stationary stay. However, there were also some negative aspects of criticism and suggestions for improvement. A common aspect was that there is not enough time in the clinic to use UpToDate or there were difficulties in finding the

right information. The information received was then rather confusing and long-written. In general, some clinicians would have preferred a PDF file for better legibility. It has been singled out that sometimes detailed guidelines already exist in hospitals and the access to the UpToDate system is a hindrance.

Based on the results of these studies one can summarize the most important points when it comes to the information requirements of physicians and clinicians, as well as the presentation of the information. The most valuable information is the one that relates to individual patient data and very specifically at the point-of-need. When presenting the information, it is important that it does not interfere with the physician's workflow, as well as that it can be quickly retrieved and is easily comprehensive.

Chapter 4

Information Architecture

This chapter describes the information architecture. Section 4.1 deals with the requirements of the physicians and clinicians for information sources, with regard to the point of care. The user interaction concept, which is to meet the requirements, is described in Section 4.2. The potential and relevant information sources, identified for this, are listed in Section 4.3.

4.1 User Interaction Concept

To meet the previously identified requirements of information, various services are offered that are integrated within the EHR application into a clinical decision support system. Besides the EBM recommendation service developed in this thesis, this is a literature service and a drug interaction service. Each of these services tries to satisfy the various information needs of the physicians. The EBM recommendation services provides information on recommended treatments depending on the individual issue data of the patient.

If the physician interacts with the EHR system, there are initially superordinate functions available. On the patient's edit page, current patient data can be edited and modified and the patient's discussion page provides a detailed overview of the condition of a patient. The CDSS panel including the EBM recommendation service is integrated on these two sites. The clinical decision support services are organized in panels and the physician can configure them as they want, depending on which service should be

displayed. (Idelhauser 2016) So the physician can autonomously decide if and which information they need and integrate it into their workflow within the EHR application.

4.1.1 EBM Guidelines

The consultant works with the EHR system during their daily routine. There they treat a melanoma patient with the following values. See Figure 4.2 for a more detailed view.

- Clinical Stage: IB
- Breslow Thickness: 0.76 mm
- Drugs (Medications): Ipilimumab, Interferon
- Procedure Type: Surgery
- Biopsy Type: Biopsy

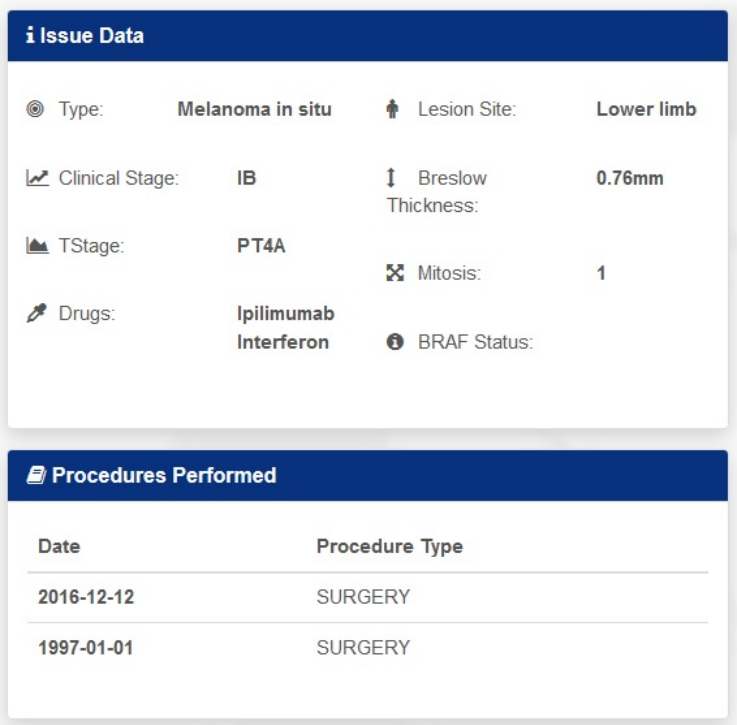


Figure 4.1: Patient-related issue data

While the physician examines the patient's electronic health records, they automatically get the EBM guideline displayed. They can use it when they need it, but it does not interrupt them in their workflow. As in Figure 4.3 can be seen, they get the required NCCN page, which matches with the patient's EHR data. In this case, this is the recommendation page for the treatment of melanoma skin cancer in clinical stage IB with a breslow thickness greater than 0.75 mm. In addition, the terms *Interferon* and *Biopsy* are highlighted, which indicates that this patient is receiving this drug and that a biopsy has already been performed. The NCCN guideline therefore provides an evidence-based and proven information source which is always kept up-to-date by the NCCN.

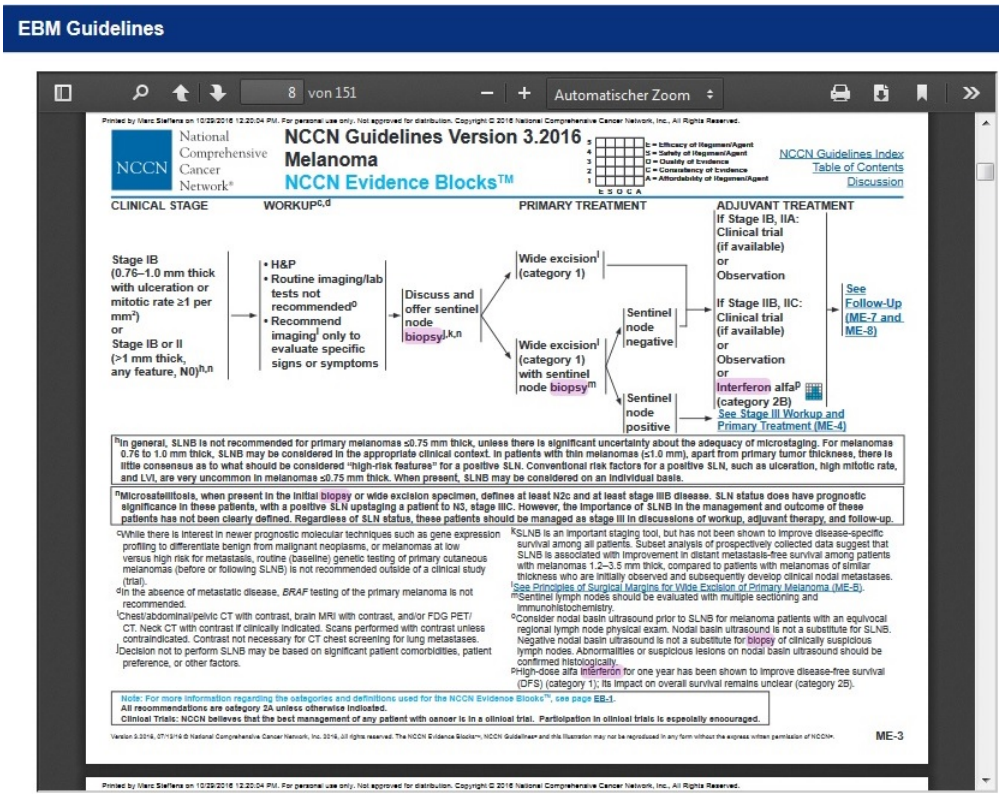


Figure 4.2: EBM recommendation

NCCN guidelines contain detailed instructions on specific algorithms/decision paths which support decision-making step-by-step. In discussion texts and additional information the data is summarized on which the recommendations are based. That provides the consultant with detailed information about the instructions. (National Comprehensive Cancer Network 2017)

Within this information texts mostly are hyperlinks to other guideline sections. (Fig. 4.4) By using these hyperlinks, the user can easily jump to the detailed instructions. (Appendix A) The same applies to follow-up treatments, but different from the detailed information, these are found at the end of a decision path and lead to further treatment that is based on the current treatment plan.

If no matching page to the existing EHR data of the patient can be found, then the default page for the diagnosis and classification of melanoma skin cancer is displayed.

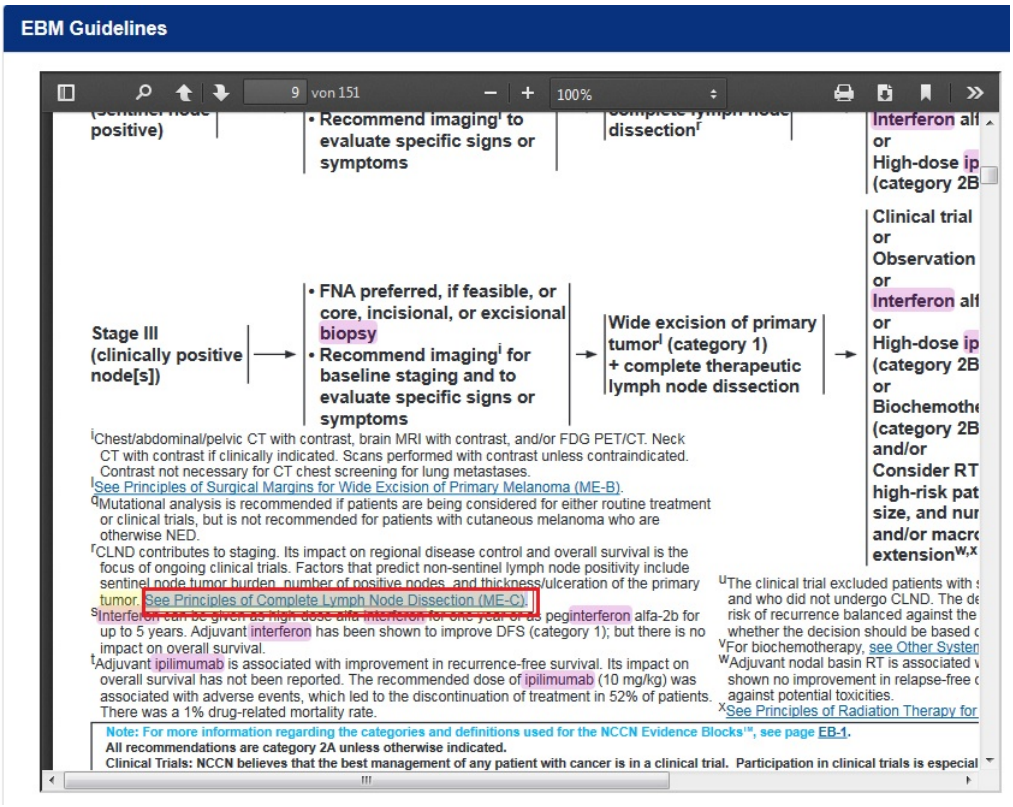


Figure 4.3: Hyperlink for detailed information

4.1.2 EBM Guideline Management

The EHR mapping for determining which guideline page is displayed on the basis of certain EHR values is managed by a medical admin using the BRE. For this they use the Business Rule Composer (BRC), an external application with various tools to manage business rules. Thus, the rules can be managed

independently of the application code and no programming skills are needed.

In the Policy Explorer of the BRC, the medical admin sets a policy, which is a collection of rules that applies to the EBM recommendation service. (yellow field Fig. 4.5) In the green field (Fig. 4.5) the condition of a rule will be defined, which is determined by what values a rule is triggered. In the field below (blue field 4.5), the corresponding action is then defined, in this case the NCCN page is to be displayed. Optionally, medical terms can also be specified, which are additionally highlighted later. The corresponding values and functions to define the conditions and actions of the rules are taken from the Facts Explorer by the medical admin. (orange field Fig. 4.5)

If a set of rules has been defined, the policy will be published and provided. By that, the rules are active and are used by the EBM recommendation service.

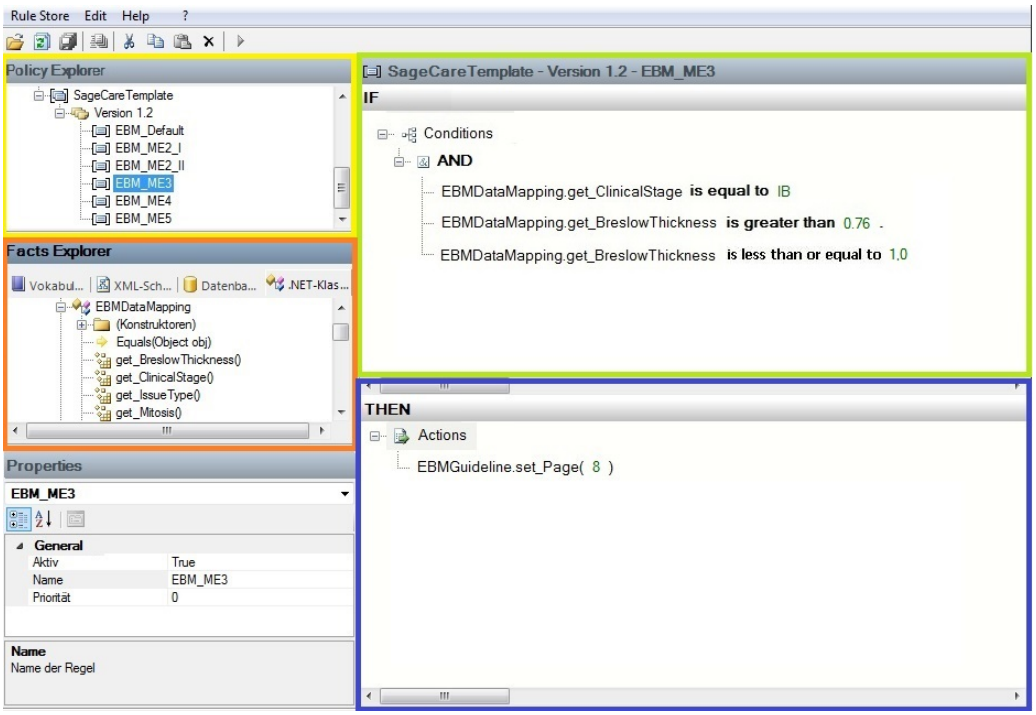


Figure 4.4: Business Rule Engine (Rule Composer)

4.2 Information Sources

In order to make the EBM recommendation service available, potential sources of information were identified.The right choice of the information source is an essential part of a recommendation service, since physicians must trust the source, because the health of the patient can depend on the correctness and quality of this information.
EBM information sources are often a combination of primary medical knowledge and a collection of clinical guidelines and reviews. They should be designed in such a way that they are comprehensive, accessible and up-to-date. (Kwag et al. 2016) Evidence-based information should also be written by medical experts to ensure the reliability and quality of the information. Most information sources require subscriptions or commercial licenses, which is why only a few free resources could be found within this thesis. This section contains a collection of identified sources of information that are relevant and shows how they differ. (Appendix C)

The identified sources of information can be distinguished firstly into oversubscriptions or commercial licenses accessible and freely accessible. Commercial licenses have the advantage that they usually also offer an API, through which the information source can be integrated into other applications. Freely accessible information sources, that were found, didn't offer an additional API.

In a study from 2016, the resources *UpToDate*, *DynamitPlus* and *BMJ Best Practice*, which were identified commercially, were partly among the most highly rated in terms of scope, quality and evidence. For those who were identified as free-to-access, only *Medscape* was part of this study and also appeared in the higher-rated. (Kwag et al. 2016) This shows that the freely accessible resources are not necessarily inferior to commercial ones, but commercial ones are quite reliable in terms of quality and extent.

Through a free registration, services such as *Physician Data Query (PDA)*, *NCCN* and MedScape provide easier access to their medical knowledge-base, which is especially good for normal clinicians and patients. With regard to the scope of information, services such as Medscape have a similar volume as commercial. Services such as NCCN or PDA, however, have specialized in certain medical areas such as the cancer domain, offering a correspondingly smaller but specified scope.

In the case of the evidence of information, these are predominantly found in commercial information sources, except for the freely accessible ones is the NCCN guidelines.

In structure and content, information sources differ independent from their access. While services like BMJ Best Practice and NCCN provide step-by-step guidelines on treatments and diagnosis, other sources such as UpToDate and Medscape focus on overviews and general information. DynmadPlus offers the advantage of providing both overviews and guidelines.

The NCCN guide was chosen as the information source for the EBM recommendation service. Since the concept developed in this thesis is intended to assist physicians in the treatment, an information source with step-by-step guidelines is a great advantage. Since, it is developed as a part of an EHR application for the treatment of melanoma skin cancer, the NCCN guidelines specialization on cancer treatment, is a benefit. With the free registration, one gets easy access to the needed documents. The information available as a document was also a criterion, since a more reliable and confidential presentation of the recommendations is possible and physicians can search autonomous the document for further information. Since NCCN guidelines are updated several times a year by a panel of medical experts and the evidence-based information sources can be viewed within the document, the NCCN guide also has the necessary quality for the recommendation service. Furthermore, according to current knowledge, none of the other identified sources offers the possibility of matching conditions like "breslow thickness greater 0.75", which is a relevant criterion for the concept.

4.3 NCCN Guidelines

The National Comprehensive Cancer Network (NCCN) is a federation of 27 of the world's leading cancer centers. They develop together treatment guidelines for most cancer types to improve cancer care. In addition to the guidelines, they offer further programs and knowledge to assist clinicians in decision-making. The guideline is developed and updated by 48 individual panels, consisting of 1,150 experts. These experts are mostly clinicians and researchers at the same time and are specialized in a disease. Each guideline is subjected to an annual institutional review in which it is disseminated among all NCCN member organizations. (National Comprehensive Cancer

Network 2017)

NCCN guidelines consist a comprehensive set of detailed guidelines for the sequencing, making of decisions and interventions in the treatment of 97 percent of all current cancer types. In addition, guideline offers recommendations for the topic of cancer prevention and screening. These recommendations are based on the best possible evidence at any time. For this, the guidelines are continually updated, as new data is constantly being published and these can have an impact on the standards of practice. (National Comprehensive Cancer Network 2017)

The NCCN guidelines consist of several core components. (National Comprehensive Cancer Network 2017)

- Algorithms and decision paths / trees which support the physician in the decision-making process step for step.
- In discussion texts and additional information the data is summarized on which the recommendations are based and which had to be taken into account in the development of the algorithms.
- Sources used to provide the appropriate evidence for recommendations are referenced and listed.
- Potential conflicts of interest of panel members and NCCN members are disclosed.

To determine the level of evidence and thus strength of the recommendations, the NCCN uses its own categorization. According to (National Comprehensive Cancer Network 2017), the level of evidence depends on the *extent* of data, ie, the number and size of trials and clinical observations, the *consistency* of data, ie, whether there are conflicts between studies and observations, and the *quality* of the data on how the trials are designed (RCT's, meta-analysis, systematic reviews etc.). On the basis of these criteria, the panel agrees how high the level of evidence is. The percentage of panel votes then determines the consensus of the recommendation. To classify the recommendations, the NCCN has designed its own categories (Table 4.1). According to National Comprehensive Cancer Network (2017), most of the recommendations in the NCCN guides correspond to category 2A, which is also known as default designation for recommendations.

Category	Description
1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

Table 4.1: Categories for strength of recommendations.

Chapter 5

Software Architecture

This section describes the prototypical implementation of the EBM recommendation service and the integration into the existing EHR application, as described in the introduction (1.2). Section 5.1 provides a general overview of the system architecture and integration into the EHR application architecture. After that, in 5.2 the EBM recommendation service from Section 4.2 is implemented. Section 5.3 explains the **Decision Support Controller**, which controls the communication between business logic and client. Finally, the user interface architecture is described in Section 5.4.

5.1 System Overview

The application is built in a three layer architecture. Each of these layers contains components which logically encapsulate separate units. The EBM recommendation service is a subcomponent of the main decision support service module (Fig. 5.1). Already existing components are surrounded by a dashed line, while newly added components have a solid line.

For the recommendation service to communicate with the client EBM recommandation GUI, an additional controller is used which has been added to the existing API module. (Idelhauser 2016) The information source at the right side is not part of the system, but a third party information data source. Required data is loaded from the existing *EHR Store* by the EBM recommendation service. This allows EHR to store data in a standardized format and to reach the data with an object relational mapper (ORM) tool. (Humm et al.

2015)

Different then in the business logic layer, the EBM recommendation service is implemented alongside the EHR GUI and CDSS GUI, which encapsulates the recommendation service logic on the client. This has the advantage that it can be displayed independently of the CDSS at any point in the EHR GUI.

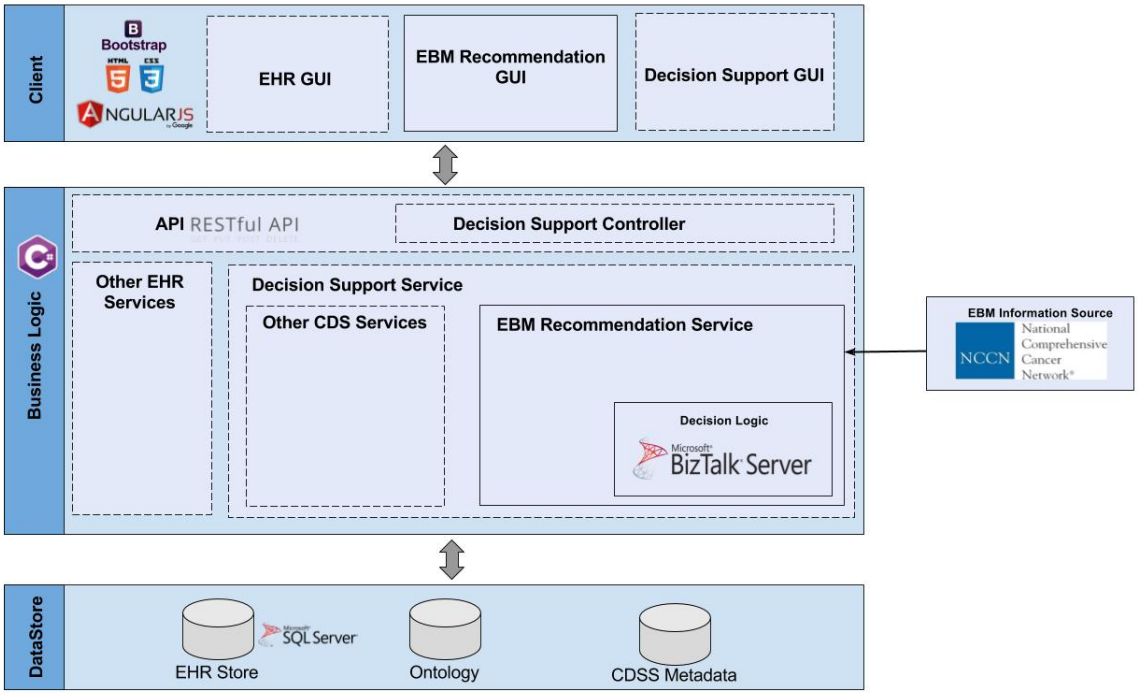


Figure 5.1: System architecture

5.2 EBM Recommendation Service

This section describes the architecture and business logic of the EBM recommendation service in detail. For this purpose, the individual components, which are essential for the functionality of the recommendation service, are explained in the following sections. For a better understanding, figure 5.2 shows the detailed architecture of the service and its components.

5.2.1 Overview

The EBM recommendation service starts automatically as soon as a user opens a patient's EHR in the client. Then, a request is sent to the appropriate API controller, which fetches required patient information from the EHR Store and transfers it to the *EBM Guideline Service*. This is the entry point in the EBM recommendation service.

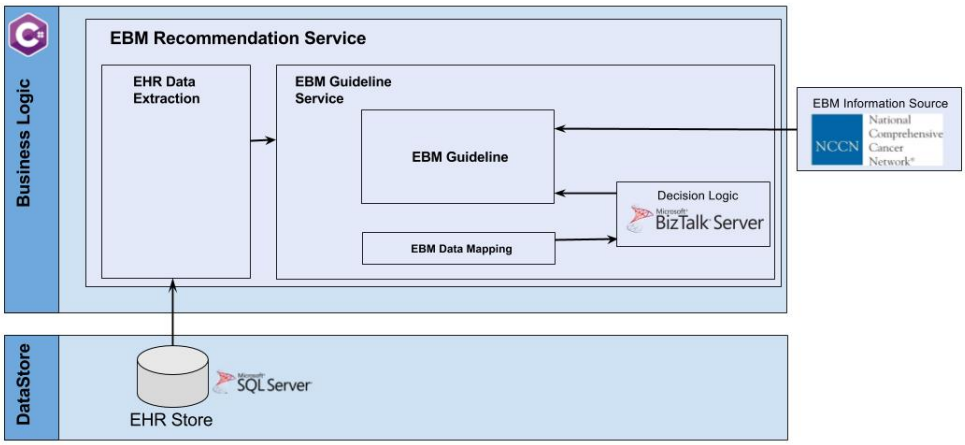


Figure 5.2: EBM recommendation service architecture

The EBM guideline service uses this data to generate an **EBMDataMapping** object. (Fig. 5.4) The EBMDataMapping object contains all the necessary EHR data of the patient needed for the decision-making. The decision logic, for determining the recommendation, is located in the business rule engine. The business rule engine receives the EBMDataMapping object with the required EHR data and an **EBMGuideline** object for processing and return. The EBMGuideline object contains attributes for the recommendation to be displayed, which can be set by the BRE. These are attributes such as the EBM information source, pages to be displayed and medical terms for highlighting. (Fig. 5.3) After processing, the EBMGuideline object is then returned by the EBM guideline service.

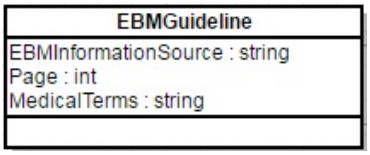


Figure 5.3: EBMGuideline Class

5.2.2 EHR Data Extraction

Since every EHR service has its own API controller, the decision support service also has its own decision support controller. This is responsible for the handling of requests, which are sent by the client and invokes the corresponding business logic and the responsible decision support service, with the required parameters. (Idelhauser 2016) In addition to three other endpoints, such as the drug information service, user feedback service and literature service, the EBM recommendation service (*SearchEBMGuideline*) is also handled by the controller.

SearchEBMGuideline: To find the right EBM guideline for a specific patient, an appropriate EHR identifier must be sent with the request. This is the melanoma issue id. With these, the Decision Support Controller can fetch the correct EHR data from the EHR Store, which is the melanoma issue data and the medication of the patient. The fetched EHR data is then passed to the EBM guideline service and the result is sent back to the client.

5.2.3 EHR Mapping

To prepare the EHR data for the use in a business rule engine, they are mapped to an internal recommendation service representation. Of all the attributes stored in the EHR Store, only a few are needed for the recommendations to a specific patient. Therefore, many are omitted or some attributes, such as the clinical stage are modified for the mapping to fit them for use in the BRE. Modifying and mapping the EHR attributes is done by converting the values to an EBMDataMapping object. (Fig. 5.4)

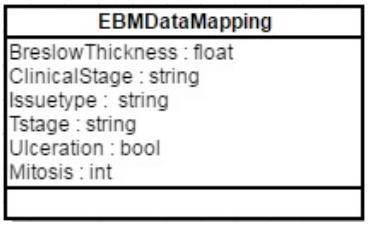


Figure 5.4: EBMDataMapping Class

The EBM Data Mapping object contains values such as the breslow thickness, which indicates the size of a tumor, and the clinical stage, that indicates the patient's cancer stage. The issue type contains the cancer type and ulceration whether ulcers occur in the patient. Mitosis involves the rate at which metastases form. An example of the mapping is the clinical stage. This is stored in the EHR as enumeration and contains roman numerals such as "II" (for example clinical stage "IIB"). The BRE can not use the enumeration in this way, which is why the clinical stage is mapped to a string value.

The conversion of EHR data to an EBM data mapping object always occurs when the EBM guideline service is invoked, via a **EbmMapper** object. The EbmMapper provides a method with which an EBMDataMapping object is generated and the required values from the EHR are mapped to the corresponding attributes. The EBMDataMapping object is then stored until the EBM recommendation service is invoked again.

5.2.4 Decision Logic

The decision logic for determining the recommendations is done in a business rule engine. For this, a so-called **policy** object exists, which is provided by the BRE and serves as a interface between BRE and project. It contains appropriate methods so that the BRE can be used and executed. With this policy object, the BRE receives, as described in 5.2.1, an EBMDataMapping and an EBMGuideline object. From the EBMDataMapping object, it receives the required EHR data, which is used to query and trigger the rules defined by the medical admin. In these rules, for example, a certain value, such as the breslow thickness or clinical stage, is queried. If the value is the same as the rule pretends, the rule is triggered. If a rule is triggered, the values defined by the medical admin are mapped to the corresponding attributes of the EBMGuideline object. The EBMGuideline object finally contains all the

information needed to display the correct recommendation and is returned by the BRE to the EBM guideline service.

5.2.5 GUI Architecture

While in the business layer, the EBM recommendation service is a subcomponent of the CDSS. It represents a separate component in the client, decoupled from the decision support GUI. This has the advantage that the EBM recommendation service can be displayed at any point in the EHR and is independent of the CDSS GUI. The EBM recommendation service has its own controller and view, so it is responsible for communication with the correct API endpoint in the business layer. The recommendation service GUI could also easily be integrated into the CDSS GUI module but could then only be displayed together with the decision support GUI.

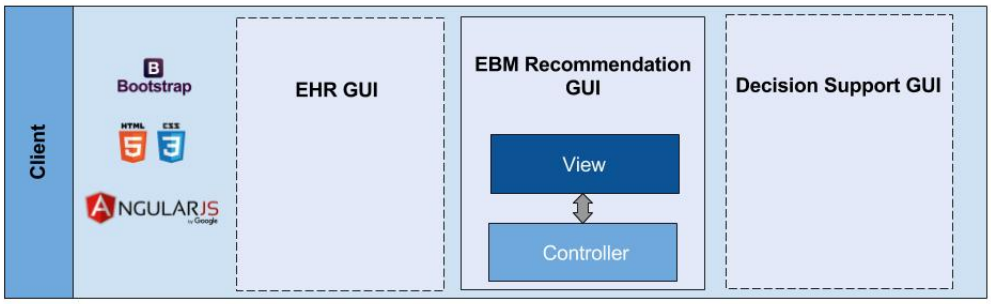


Figure 5.5: EBM recommendation service GUI architecture

Chapter 6

Implementation

This chapter describes how the EBM recommendation service was implemented. Section 6.1 addresses the preparation of the data before it is passed to the decision logic. The implementation to the decision logic is explained in the following section, 6.2. Finally, Section 6.3 describes how the view components of the recommendation service are implemented.

The application was implemented in C using .NET and a MS SQL Server on the server side. On the client side, it was decided to use HTML5, JavaScript and CSS with the appropriate frameworks Bootstrap and AngularJS. Since these technologies have been used in the development of the EHR application, they are also used in the development of the EBM recommendaton service.

6.1 Data Preparation

The data preparation describes the implementation steps which are required before the decision logic and data is processed. This starts with the extraction of the data required by decision logic and the EBM Mapping, in which the data is prepared for later use. And finally, the EBM Class Library, which tells the decision logic which data to be expected and in which form it will receive or has to process it.

6.1.1 Fetching EHR Data

The EBM recommendation service is first called by the REST API controller. To do this, the corresponding **MelanomaIssue** and the **Medication** object from the EHR store are loaded, as described in Section 5.2.2 by means of an issue id, and passed to the EBM guideline service by calling the **SearchEbmGuideline** method. (Appendix D) This uses the data foremost to get the patient's procedures. Thus, the EBM guideline service keeps all the data needed for the recommendations. The EBM guideline service now prepares or processes this data accordingly.

6.1.2 EBM Mapping

In order for the data to be processed from the BRE, it is processed by EbmMapper as described in Section 5.2.3. For this purpose, an **EbmMapper** object is created, which generates a corresponding **EBMDataMapping** object via createMapping and maps the EHR data to make it easier to handle it in subsequent decision logic process steps. (Fig. 6.1)

```
public EBMDataMapping CreateMapping(MelanomaIssue issue)
{

    EBMDataMapping mapping = new EBMDataMapping();

    mapping.ClinicalStage = GetDescriptionFromEnum(issue.ClinicalStage);
    mapping.Mitosis = issue.Mitosis;
    mapping.BreslowThickness = issue.BreslowThickness;
    mapping.Tstage = GetDescriptionFromEnum(issue.TStage);
    mapping.IssueType = issue.Type.Definition;

    if (issue.Ulceration == ExtendedBoolean.TRUE ||
        issue.Ulceration == ExtendedBoolean.UNKNOWN)
    {
        mapping.Ulceration = true;
    }

    return mapping;
```

Figure 6.1: Function for EHR data mapping

6.1.3 Creation of EBM Class Library

Before BRE rules can be defined and processed, the BRE must be informed of the data interface used. For this purpose, an EBM class library, ie *SAGECARE-EBMService_Class_Library.dll*, is created. This contains the interfaces

of the **EBMDataMapping** and **EBMGuideline** class. It thus serves as a mapping between the project and the BRE. For this library to be used, it must be added to the Global Assembly Cache (GAC). Before this can be done, the library must be signed. Therefore, a self-signed certificate named SAGE_CARE.snk is created and referenced in the corresponding **AssemblyInfo** class of the project. Only then can the library be added to the GAC of the system and be found and used by the BRE. This process only needs to be performed once, for example, if the data interface of the **EBMDataMapping** or **EBMGuideline** class changes.

6.2 Decision Logic

Since the establishment of a business rule engine requires a certain configuration effort, as well as possibly additional licenses and because a BRE only applies to many different rules, a primitive structure was also implemented, in addition to the BRE approach. The implementation of these two approaches is described below. In order to use one of these approaches, an activateBRE variable must be set, which is passed to the EBM guideline service. If it is set to true, the BRE approach is used. If it is set to false, then the approach with a primitive structure is used. By default, it is set to false so that the EBM recommendation service can also be presented on external computers, without previously installing a BRE.

6.2.1 Using BRE

For the BRE approach, Microsoft BizTalk Business Rule Engine was chosen. (Microsoft Biztalk 2017) Since the project is developed with .NET technologies, the MS BRE was very well integrated into the project environment and it only needed a few lines of code, therefore little development effort.

Before the data is sent to the BRE, it is mapped as described in Section 6.1.2. Then the so-called **Policy** object is created. This is part of the Microsoft RuleEngine API and serves as an interface between project and BRE. (Appendix E) The **Policy** object must be given the unique name of the BRE policy which is to be used for the recommendation. (Fig. 6.2) The execution method of the policy object is used to initiate the BRE and the recommendation pro-

cess. To do this, the execute method receives the EBMDataMapping and the EBMGuideline object.

```
public EBMGuideline SearchGuidelines(MelanomaIssue issue, ICollection<Medication> medications, bool activateBRE)
{
    EBMGuideline guideline = new EBMGuideline();
    var procedures = issue.Procedures;
    var medicalTerms = "";

    if (activateBRE)
    {
        EbmMapper mapper = new EbmMapper();
        EBMDataMapping mappingInput = mapper.CreateMapping(issue);

        try
        {
            Policy policy = new Policy("SageCare");
            policy.Execute(mappingInput, guideline);

        }
        catch (Exception)
        {
            return guideline;
        }
```

Figure 6.2: Decision logic with BRE

If the EBM Class library has been correctly integrated into the GAC, the appropriate rules for the recommendations can be defined with the help of the interfaces of the EBMDataMapping and EBMGuideline class. This is done in the Business Rule Composer (BRC), a tool of the Biztalk BRE, to manage business rules. In the rules, a medical admin defines which values must be given in the attributes, such as the clinical stage or breslow thickness, to trigger certain rules. Various functions are available in the BRC to create a corresponding query structure. At the same time, the medical admin defines in the BRC which values are required for the recommendation. To do this, they set the attributes of the EBMGuideline object by using the given set of methods.

If the BRE is triggered by the policy object, the corresponding rule is triggered using the EHR data in the EBMDataMapping object (Fig. 6.3.) and the defined values are automatically set for the EBMGuideline object and will be returned. If none of the defined rules are triggered, a default rule exists, which in this case is always triggered and contains values for a default recommendation.

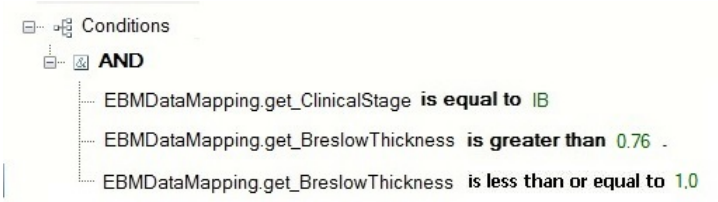


Figure 6.3: Defined condition to trigger a specific rule

6.2.2 Using Primitive Structure

In the primitive approach, the functioning of the BRE was mapped using a primitive if-else structure. For each existing rule in the BRE, there is an if-branch which checks the EHR data instead and sets the values of the EBMGuideline object accordingly. (Fig. 6.4)

```
} else
{
    var guidelinePage = 0;

    // Sets the page to be displayed by specific medical data's
    // like clinical stage or breslow thickness.
    if (issue.ClinicalStage == ClinicalStage._0)
    {
        guidelinePage = 7;
    }
    else if (issue.ClinicalStage == ClinicalStage.IA
            || (issue.ClinicalStage == ClinicalStage.IB
             && issue.BreslowThickness <= 0.75))
    {
        guidelinePage = 7;
    }
    else if ((issue.ClinicalStage == ClinicalStage.IB
             && issue.BreslowThickness > 0.75)
            || (issue.ClinicalStage >= ClinicalStage.IIA
                && issue.ClinicalStage <= ClinicalStage.IIC))
    {
        guidelinePage = 8;
    }
```

Figure 6.4: Decision logic with primitive structure

6.3 EBM Recommendation View Component

To implement the EBM recommendation service interface, JavaScript and HTML were used. The view component consists of a controller and a view. After an EHR page is loaded, a request is automatically sent to the CDSS API, and the response is used to display the correct NCCN guideline page with highlightings. If no recommendation information is found, the default NCCN page is displayed for the diagnosis of melanoma skin cancer.

Sending the request and receiving the response takes the **EbmGuideli-**

nesController. (Fig. 6.5) It is initially responsible for loading the patient's issue id, so that it can be passed to the controller API. Also the activateBRE variable is set at this point and thus configured to whether the BRE should be used or not. The activateBRE is set in the EbmGuidelinesController so that it can be changed during the runtime, by which it is possible to switch between BRE and primitive structure without restarting.

```
// Set activateBRE true to use the business rule engine, otherwise the ebmguideline will be generated
// by the SearchGuildeline class.
var activateBRE = false;

$scope.$watch('issueId', function (issueId) {
    if (!_.isUndefined(issueId)) {
        vm.loadGuideLines(issueId, activateBRE);
    }
});

// Gets EBMGuideline from the business rule engine for the given issueID (if activateBRE = true).
// Otherwise gets EBMGuideline by issueid and patientId from SearchEBMGuide-Class.
vm.loadGuideLines = function (issueId, activateBRE) {
    // retrieves the MelanomaIssue of that MdtDiscussion
    if (activateBRE) { console.log("BRE activated"); }
    else { console.log("BRE deactivated"); }

    vm.ebmGuideLines = ebmGuideLineService.getCurrentGuidelines(issueId, activateBRE).then(function (response) {
        var ebmGuideline = "";
        var ebmGuidelinePage = null;
        var medicalTerms = "";

        if (response.data.EBMInformationSource) { ebmGuideline = response.data.EBMInformationSource; }
        if (response.data.Page) { ebmGuidelinePage = response.data.Page; }
        if (response.data.MedicalTerms) { medicalTerms = response.data.MedicalTerms }

        if (medicalTerms != null && ebmGuidelinePage != null) {
            document.getElementById("pdfViewer").src = (ebmGuideline + "#search=" + medicalTerms);
            setTimeout(function () {
                document.getElementById("pdfViewer").src = (ebmGuideline + "#page=" + ebmGuidelinePage);
            }, 7000);
        } else {
            document.getElementById("pdfViewer").src = (ebmGuideline);
```

Figure 6.5: EbmGuidelinesController class

The Ebmguidelines.html is responsible for the view and thus the displaying of the recommendation.. To control the view, AngularJS was used and happens via the *ng-controller* function. (Fig. 6.6) With this the view is assigned to the **EbmGuidelinesController**. Since the recommendation of the NCCN guideline, which is available in the form of a PDF document, was chosen, the HTML inline frame (iframe) was used. In this the NCCN guideline is embedded and offers a wide range of features to interact with the PDF document.

```
<div ng-controller="EbmguidelinesController" class="container-fluid">
    <!--------------------------THE PDF VIEWER DIRECTIVE------------------------>

    <iframe id="pdfViewer" src="" frameborder="1" height="600" width="800"></iframe>

    <!--------------------------THE PDF VIEWER DIRECTIVE------------------------>
</div>
```

Figure 6.6: EbmGuidelineHTML class with AngularJS integration.

To display the recommendation with the iframe, the required data is fetched from the response. The representation of the page and the highlighting are executed via the *search* and *page* functions, which are called with the domain. An API does not exist for these functions. Because the search function is used for the highlighting, which, depending on the number of words to be highlighted, can take several milliseconds or seconds, a timeout of 4 seconds was inserted between the calls of the search function and the call of the page. Otherwise, there may be side effects, if several medical terms are highlighted. It can happen that the desired page is not called or not all words are highlighted correctly.

Chapter 7

Evaluation

In this chapter, the EBM recommendation service is evaluated by comparing the concept and the implemented prototype with the requirements from Chapter 2. The requirements 1.1 (EBM recommendations), 1.2 (Personalized) and 1.3 (Pro-active) are obviously achieved since the clinician automatically receives evidence-based recommendations and additional information using the NCCN guideline and the recommendations are made by using the individual EHR data. Since the clinician does not have to enter additional information for the recommendations, they are not interrupted in their EHR workflow (1.5 Non-interfering). NCCN guidelines provide a quick overview of the information needed. The structure of the guides in the form of decision trees helps to make the recommendations intuitive and self-explanatory. This makes the recommendation service easily comprehensible (1.4) and promotes usability (2.1).

7.1 Response Time

When the patient's EHR page is opened, the initial loading of the recommendation can take up to 15 seconds, depending on the system. Since the recommendation data as well as the other CDSS data is loaded asynchronously, the consultant can nevertheless work with the EHR and are not interrupted in their EHR workflow. (Idelhauser 2016) With each additional loading of the same EHR, the loading time is reduced to under 5 seconds.

If the recommendation data is loaded, any interaction with the service re-

quires an average of less than 1 second (200 - 400 ms). (Fig. 7.1) However, in exceptional cases, as in the search for terms, which are often to be found in the document, it may occur that more than 1 second is required, but never longer than 4 seconds. So the system fulfills the requirement 2.2 (Performance).

Gesamtzeit	Gesamtkost...	Eigenzeit	Eigenkosten	Einträge	Funktion
16.857,03 ms	52,96%	16.857,03 ms	52,96%	16226	GC
10.698,49 ms	33,61%	10.698,49 ms	33,61%	10298	Gecko
3.277,70 ms	10,30%	3.277,70 ms	10,30%	3155	Grafiken
292,97 ms	0,92%	292,97 ms	0,92%	282	Werkzeuge
278,42 ms	0,87%	278,42 ms	0,87%	268	Stile
193,23 ms	0,61%	193,23 ms	0,61%	186	Eingabe & Ereignisse
139,21 ms	0,44%	139,21 ms	0,44%	134	GC
93,50 ms	0,29%	93,50 ms	0,29%	90	JIT

Figure 7.1: Interaction response time from Chrome performance console

7.2 Maintainability

The NCCN guidelines are regularly updated to keep them state of the art. However, it is to be expected that there will be very few changes that affect whole sections of the EBM recommendations and therefore the decision logic rules. If a new version of an NCCN guideline with major changes occurs, it can be quickly integrated into the system by the **EBMInformationSource** variable, as described in Section 6.2.3. Furthermore, the decision logic could be adapted quickly and easily by using the BRC, which means that the maintenance effort is very low (2.3).

7.3 Extensibility

In contrast to maintenance, replacing the EBM information provider with a new information provider, such as UpToDate (2.4 Extensibility), requires a certain amount of implementation. Due to the modular structure of the software architecture, only adapters that link the corresponding API with the interfaces of the recommendation service would have to be implemented. Existing structures and interfaces could be reused. Depending on the API which is to be integrated, the effort can be up to a few hundred lines of code, which can be considered as a moderate effort.

7.4 EBM Recommendation Evaluation

To test the quality of the recommendations, ten test patients were created. Each test patient had individual and different issue data. It was tested whether the displayed recommendation and highlighted medical terms match the issue data.

The evaluation showed that the correct recommendation, in the form of the correct NCCN page, was displayed in all test cases. Furthermore, the medical terms such as medications or procedures performed were correctly highlighted, if these were included in the NCCN guide. For the test patient, which contained issue data for which no suitable recommendation can be found, the default page for the diagnosis and classification of melanoma skin cancer was displayed as expected.

Strength of Recommendations

As described in Chapter 4.1, most of the recommendations in the NCCN guide correspond to category 2A, which means that the recommendation is "based on lower-level evidence, there is a uniform NCCN consensus that the intervention is appropriate" (National Comprehensive Cancer Network 2017). When this category is transferred to the general system for determining the level of evidence, the evidence is approximately between level 1+ and 2+. (Appendix A) On the basis of this assessment, the strength of the recommendations in the NCCN guide and thus also the strengths of the recommendations of the EBM recommendation service presented in this thesis, can be evaluated with the grade **B**. (Table 3.1) Recommendations of grade B can be classified as good/strong and are therefore a reliable and consistent source for consultants.

Chapter 8

Related Work

In this chapter, concepts are described which also deal with the field of EBM recommendation and how these differ from the concept in this thesis. Section 8.1 refers primarily to publications and research activities which have arisen in recent years. A comparison to current systems in use is drawn in Section 8.2.

8.1 Publications

The idea of a recommendation service based on EBM data is not entirely new. There are already publications dealing with the concept of so-called *Health Recommender Systems* (HRS). The described concepts of Pfeifer et al. (2014) or Tarnowska et al. (2017) partly resemble the basic concept described in this thesis. An EHR holds the necessary patient data and a *Health Knowledge Repository* serves as an information source for the corresponding medical information. In a HRS that is enabled as an extension, the data is then merged. The result is the recommendation, which is returned to the EHR. (Fig. 8.1) (Pfeifer et al. 2014)

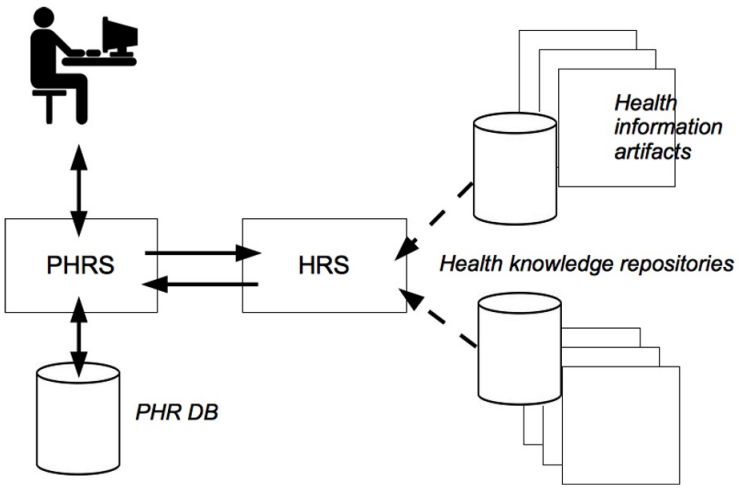


Figure 8.1: Concept of a Personal Health Record (PHR) with HRS extension.

In another concept, developed for telemedicine in Thailand, a consultant provides the patient data to a web-based application to recieve recommendations with the use of the internet and intelligent algorithms data from medical history of patients, experimental studies, as well as case reports and expert opinions. The physician then consults the patient on the basis of the recommendation with a corresponding diagnosis. (Tarnowska et al. 2017)

In addition to the concepts, some approaches already exist for such a HRS. Thus, Morrell et al. (2013) described and implemented the *Personal Health Explorer*, a semantic health recommendation system. This system uses an agent-based framework to find content from web resources such as PubMed or HealthVault to match the EHR data. The system is similar to a semantic search engine and can be used for "further research and consultation". (Morrell et al. 2013) The user specifies his / her data in a form and receives information on diagnoses or treatments, which can be stored and which are taken into account in future searches.

Another approach of Wiesner et al. (2010) integrates a health recommender system into a EHR. For this purpose, existing semantic networks such as *Wikipedia* are used to create a health graph data structure. The data stored in the graphs represent health-related concepts and is used to calculate a semantic distance between such concepts. These health graphs can be used to calculate matches to entries in the EHR. Thus, the EHR user can receive individual health information which may interest him. That Wikipedia is used as a resource, has the advantage that the source is free and always

accessible, but at the same time is a great disadvantage, because it is not an evident and trustful information source.

In general, many recommendation approaches and concepts are similar in their capacity. Most recommender systems work like a medical search engine, in which first active data has to be entered, in order to receive recommendations. Rarely are there approaches where the data of an EHR is automatically used to search for the required information.

8.2 Existing Systems

In addition to the described approaches and publications, some systems of this capacity already exist. In this context, Kwag et al. (2016) evaluated in a study 26 web-based point-of-care information sources. Among the most valuable measured systems in terms of scope, evidence and quality were DynamedPlus, UpToDate and BMJ Best Practice. These resources provide, in large part, evidence-based information as well as fast and efficient search algorithms to assist physicians in decision-making. For this the systems operate in a similar way. In order to obtain the required information, physicians can use a comprehensive full-text search. (EBSCO Health 2017; BMJ Best Practice 2017; UpToDate - Wolters, Kluwer 2017). A condition-based search, as well as semantic matching, are, according to current knowledge, not possible at the moment.

The most advanced and comprehensive system to date is Watson from IBM. Watson is a system of artificial intelligence and is characterized by the fact that it is able to respond to questions entered in the natural language. Watson is used in a wide range of applications, including the medical sector, for example, Watson Health for oncology. (IBM Watson Health 2017) To keep up-to-date, Watson is constantly trained with the latest information. Consultants can use the corpus of knowledge to get relevant information by a detailed search mask. However, there is currently no automatic matching of EHR data with EBM guidelines. (IBM Watson Health 2017)

In conclusion, it can be said that one or the other system or concept is similar to the concept and prototype presented in this thesis, but finally differ in their functionality. The one part of the systems offers fast, high-quality evidence-based information, which however must be called up via entered

information. Other systems can search automatically by patient data for information, but from unreliable sources. Here are the differences to the system presented in this thesis. It is possible to search automatically for information based on individual patient EHR data and the information is at the same time from evidenced and reliable information sources. Thus the system is a hybrid in terms of its functions from the existing systems and approaches. Another function, which clearly differs from the others, is the condition-based matching. So it can find information based on individual and very specific data, such as for example, for a patient in the clinical stage IB with a breslow thickness between 0.76 - 1.0 mm. This is, according to current knowledge, in none of the other systems and approaches at the moment possible.

Chapter 9

Conclusions and Future Work

9.1 Conclusion

In this thesis an EBM recommendation service was presented, which provides physicians with information at the point of care, in the field of personalized medicine. For this purpose, it was analyzed in Chapter 3 what consultants information needs are and how they should be prepared. Based on this information, a user interaction model was presented, which tries to satisfy the identified information needs. After an overview of the possible information sources, which could be considered for the recommendation service, the architecture of the EBM recommendation service in Chapter 5 was described. The focus was on how the data is fetched automatically from the EHR and the most accurate and reliable information can be displayed with the use of the BRE and the NCCN guideline.

In Chapter 6, the implementation of the prototype was described in detail and how the technologies used interacted with each other as well as what had to be considered during the implementation and what difficulties occurred. Finally, the EBM recommendation service in Chapter 7 was evaluated against the requirements of Chapter 2. It could be shown that all the described requirements are met.

The focus was on the usabillity of the recommendation service, in order to allow physicians to get the desired information automatically without being interrupted in their EHR workflow. This is especially relevant for displaying the correct NCCN page and highlighting medical terms, which are related to

the patient.

Personalized medicine offers many options for treatment, diagnosis and decision making of consultants and can significantly improve patient health and safety. A lot of information resources exist, but it is usually difficult to integrate these into everyday medical practice. Therefore clinicians benefit from the fact that such a recommendation service is integrated into an EHR application. With the concept and the prototypical implementation of the EBM recommendation service for personalized medicine presented in this thesis, a contribution could possibly be made in this direction.

9.2 Future Work

It is planned that the EBM recommendation service will be integrated into a commercial EHR application for the treatment of melanoma skin cancer. However, future work is required for this. The most important is a detailed analysis of the recommendation service with consultants to identify potential improvements, followed by a test phase with real patient data in everyday medical practice in order to obtain a realistic feedback.

9.2.1 Advanced Display of Recommendations

The display of the recommendations could be improved and expanded by new approaches. Thus it is conceivable that instead of only the page with the appropriate recommendation, also required information and decision paths are highlighted. This could be done over several pages of the NCCN guide and the consultant could therefore be offered an individual treatment path which fits to the patient's disease. This would be possible by highlighting the text information or with a colored overlay over the corresponding decision path.

9.2.2 More Specific Patient Data

In the context of the extension of the recommendations, a larger quantity and more detailed patient data could lead to better and more accurate recommendations. An example would be the cancer status, which is called

in-transit and appears in the clinical stage III. In order to diagnose this, a more comprehensive tumor stage is required for the EHR data, which is currently not possible. However, it must be taken into account that with a higher quantity and more specific data, the maintenance effort increases as well. Therefore, one would have to first assess in detail how much the effort is and whether it is worthwhile.

9.2.3 Integration of Information Source API's

As already described in the previous chapters, there are besides the NCCN guide more information sources which also partly have APIs. Here it would be useful to see if the recommendation service would benefit from another or an additional information source and how great the resulting maintenance would be.

Appendices

Appendix A

Grading System for Level of Evidence

The following table shows the grading system for the determination of evidence levels according to (Harbour et al. 2001). "Levels of evidence are based on study design and the methodological quality of individual studies" (Harbour et al. 2001). This grading system thus forms the basis for the determination of the strength of the recommendations.

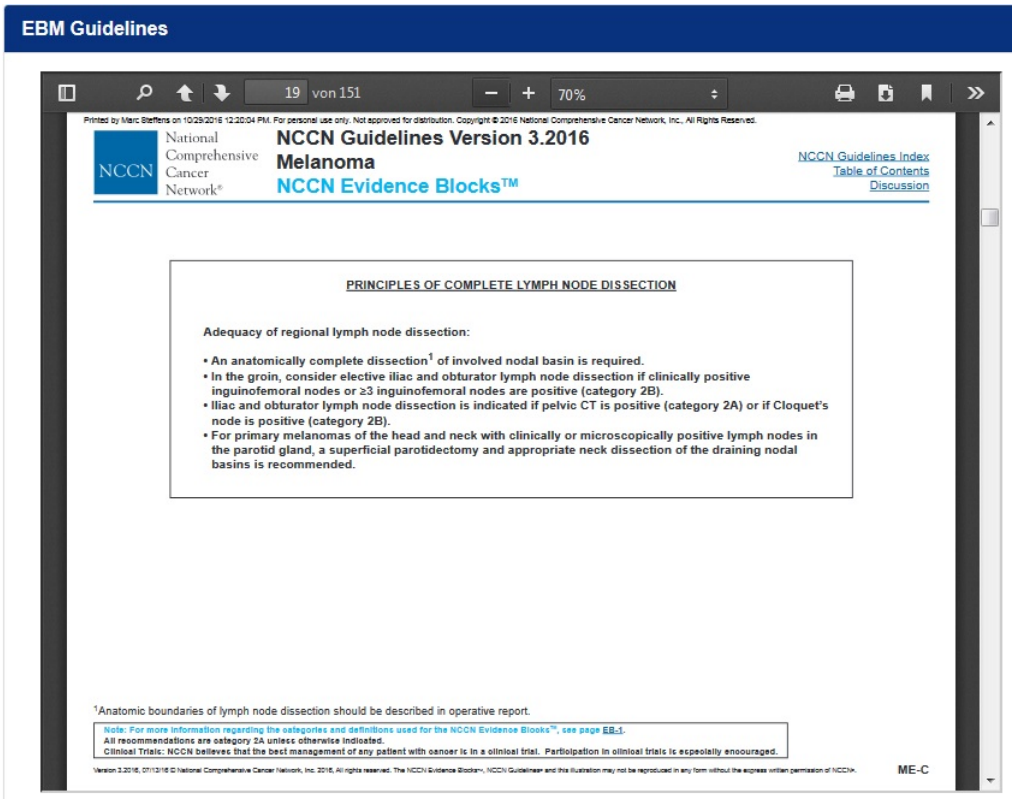
Level	Description
1++	High quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
1-	High quality systematic reviews of case-control or cohort studies or high quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

Level	Description
2-	Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

Appendix B

NCCN Guideline Hyperlink Information

Via the hyperlinks, the consultant gets to NCCN pages with further information and procedures on suggested treatments.



Appendix C

EBM Information Sources

The following table lists the information sources identified as relevant for the EBM recommendation service. The *Access* column describes the type of access to this information source. The term *public* means that the source can be used without costs or registrations, while information sources with *free* access require a free registration. Subscription describes a paid access to the sources.

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
Medscape / eMedicine	Largest clinical knowledge base available for free. Articles updated yearly. Also available as mobile application.	no	free, registration required	~6,800 articles

Name	Description	API	Access	Volume
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
NCCN	Guidelines for treatment of cancer by site offering decision paths. Compiled by panels of medical experts	no	free, registrtion required	~60 documents (for different cancer types)

Appendix D

CDSS Controller

The CDSS Controller represents the interface between the server and the client. It receives the issue ID of the patient displayed in the EHR and returns a suitable recommendation in form of an EBMGuideline object. Using the issue id, the melanoma issue is fetched with the exact disease data and the individual medication of the patient, to determine the right recommendation.

```
[Route("EbmGuidelines/{issueId}/")]
[HttpGet]
– references | 0 changes | 0 authors, 0 changes
public EBMGuideline SearchEBMGuideline(int issueId, [FromUri] bool activateBRE)
{
    var issue = FindMelanomaIssue(issueId);
    var medications = RoleDao.FindPatientById(issue.Patient.Id).Medications;

    return new EBMGuidelineService().SearchGuidelines(issue, medications, activateBRE);
}
```

Appendix E

Microsoft Rule Engine Policy API

The *Policy* class is part of the MicrosoftRuleEngine API and provides a set of functions to enable communication between application and BRE. The focus is on the *Policy* constructor to create a policy object and the *Execute* method to trigger the decision logic process by the BRE.

```
namespace Microsoft.RuleEngine
{
    public sealed class Policy : ISerializable, IDisposable
    {
        public Policy(string policyName);
        public Policy(string policyName, PolicyFetchErrorHandler handleExceptions);
        public Policy(string policyName, int majorRevision, int minorRevision);
        public Policy(string policyName, int majorRevision, int minorRevision, PolicyFetchErrorHandler handleExceptions);

        public int MajorRevision { get; }
        public int MinorRevision { get; }
        public string PolicyName { get; }
        public RuleSetInfo RuleSetInfo { get; }

        public void Clear();
        public void Dispose();
        public void Execute(params object[] facts);
        public void Execute(object facts);
        public void Execute(object[] facts, IRuleSetTrackingInterceptor trackingInterceptor);
        public void Execute(object facts, IRuleSetTrackingInterceptor trackingInterceptor);
        public void GetObjectData(SerializationInfo info, StreamingContext context);
    }
```

Bibliography

AACE - American Association of Clinical Endocrinologists (2017). AACE/ACE CLINICAL PRACTICE GUIDELINES. https://www.aace.com/publications/guidelines.

Antes, G. (1998). Evidence-Based Medicine. Vol. Volume 39. Institut für Medizinische Biometrie und Medizinische Informatik, Klinikum der Albert-Ludwigs-Universität, Freiburg. ISBN: 0020-9554.

Berner, E. S. (2009). "*Clinical Decision Support Systems: State of the Art*". In: *Agency for Healthcare Research and Quality* Publication no. 09-0069-EF, p. 4.

BMJ Best Practice (2017). Clinical Decision Support Tool for Health Professionals. http://bestpractice.bmj.com/info/ (visited 05/2017.

Burns, P. B., R. J. Rohrich, and K. C. Chung (2011). "*The Levels of Evidence and their role in Evidence-Based Medicine*". In: *Plast Reconstr Surg. Author manuscript, PMC* PMCID: PMC3124652, pp. 305–310. DOI: 10.1097/PRS.0b013e318219c171.

EBSCO Health (2017). DynaMed Plus. http://www.dynamed.com/home/ (visited 05/2017).

El-Gayar, O. and P. Timsina (2014). "*Opportunities for Business Intelligence and Big Data Analytics in Evidence Based Medicine*". In: *47th Hawaii International Conference of System Sciences (HICSS)*, pp. 749–757. DOI: 10.1109/HICSS.2014.100.

Goth, G. (2008). "*Power to the Patients*". In: *IEEE Xplore Digital Library* Volume 9. DOI: 10.1109/MDSO.2008.14.

Green, S. C. et al. (2003). "*Clinical practice guidelines: A guide to better practice, not a recipe for uniformity*". In: *Australian Journal of Physiotherapy* Volume 49.PMCID: 12600248, pp. 3–4. DOI: 10.1016/S0004-9514(14)60182-3.

Grimshaw, J., M. Eccles, and I. Russell (1995). "*Developing clinically valid practice guidelines*". In: *US National Library of Medicine National Institutes of Health* PMCID: 9238556, pp. 37–48. DOI: j.1365-2753.1995.tb00006.x.

Harbour, R. and J. Miller (2001). "*A new system for grading recommendations in evidence based guidelines*". In: *British Medical Journal Aug. 11* PMC1120936, pp. 334–336.

Humm, B. G., U. Beez, and P. Walsh (2015). "*Semantic AutoSuggest for Electronic Health Records*". In: *International Conference on Computational Science and Computational Intelligence (CSCI)* Volume 13, pp. 760–765. DOI: 10.1109/CSCI.2015.85.

IBM Watson Health (2017). Watson for Oncology. https://www.ibm.com/watson/health/oncology-and-genomics/oncology/ (visited 05/2017).

Idelhauser, J. (2016). "*A Clinical Decision Support System for Personalised publisher Medicine*". MA thesis. University of Applied Science Darmstadt.

IRSA - International RadioSurgery Association (2008). NGC 006628, May 2008. Stereotactic radiosurgery for patients with metastatic brain tumors.

Health informatics — Electronic health record — Definition (2005). Standard. Geneva, CH: International Organization for Standardization.

Jain, K. K. (2015). Textbook of Personalized Medicine" 2. Edition. Springer, pp. 1–3. ISBN: 978-1-4939-2553-7.

Kwag, K. H. et al. (2016). "*Providing Doctors With High-Quality Information: An Updated Evaluation of Web-Based Point-of-Care Information Summaries*". In: *Journal of Medical Internet Res.* Volume 18.PMCID: PMC4738183. DOI: 10.2196/jmir.5234.

Linskey, M. E. and S. N. Kalkanis (2009). "*Evidence-linked, clinical practice guidelines—getting serious; getting professional*". In: *Journal of Neuro-Oncology* Volume 96.PMCID: PMC2810238, pp. 1–5. DOI: 10.1007/s11060-009-0070-7.

Microsoft Biztalk (2017). Microsoft Biztalk Business Rule Engine. https://msdn.microsoft.com/en-us/library/aa561216.aspx.

Morrell, T.G. and L. Kerschberg (2013). "*Personal Health Explorer: A Semantic Health Recommendation System.*" In: *29th International Conference on Data Engineering Workshops (ICDEW), Brisbane, Australia*, pp. 55–59. DOI: 10.1109/ICDEW.2012.64.

National Comprehensive Cancer Network (2017). National Comprehensive Cancer Network - Evidence-Based Cancer Guidelines. https://www.nccn.org/professionals/default.aspx (visited /04/2017).

Nimmesgern, E., I. Benediktsson, and I. Norstedt (2017). "*Personalized Medicine in Europe*". In: *Clinical and Translational Science Journal*. DOI: 10.1111/cts.12446.

Obst, O. et al. (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*". In: *GMS Med Bibl Inf* Volume 13, p. 26. DOI: 10.3205/mbi000290.

Osheroff, J. A. et al. (1991). "*Physicians' Information Needs: Analysis of Questions Posed during Clinical Teaching*". In: *Annals of Internal Medicine Joural* PMID: 2001091.

Pfeifer, D. and M. Wiesner (2014). "*Health Recommender Systems: Concepts, Requirements, Technical Basics and Challenges*". In: *Int J Environ Res Public Health* Volume 11.PMCID: PMC3968965, pp. 2580–2607. DOI: 10.3390/ijerph110302580.

Puustjärvi, J. and J. Piehl (2015). "*Practicing evidence-based medicine in developing countries*". In: *IST-Africa Conference, 2015*. DOI: 10.1109/ISTAFRICA.2015.7190517.

Redekop, W. K. and D. Mladsi (2013). "*The Faces of Personalized Medicine: A Framework for Understanding Its Meaning and Scope*". In: *Value in Health Journal* Volume 16.PMID: 24034312, pp. 4–9. DOI: 10.1016/j.jval.2013.06.005.

Sanchez, E. (2014). "*Semantically Steered Clinical Decision Support Systems*". In: *Doctoral Thesis*, pp. 37–38.

Shabot, M. (2004). "*Ten commandments for implementing clinical information systems*". In: *US National Library of Medicine*, pp. 265–269. DOI: PMCID: PMC1200662.

Steininger, K., B. Stiglbauer, and B. Baumgartner (2014). "*Factors Explaining Physicians' Acceptance of Electronic Health Records*". In: *System Sciences (HICSS), 2014 47th Hawaii International Conference*, pp. 2768–2777. DOI: 10.1109/HICSS.2014.347.

Tarnowska, K. A., W. R. Zbigniew, and P. J. Jastreboff (2017). Decision Support System for Diagnosis and Treatment of Hearing Disorders: The Case of Tinnitus, pp. 17–19. ISBN: 9783319514635.

Taylor, J. and N. Raden (2007). Smart (Enough) Systems. Prentice Hall. ISBN: 0-13-234796-2.

UpToDate - Wolters, Kluwer (2017). UpToDate - Evidence-Based Clinical Decision Support at the Point of Care. http://www.uptodate.com/de/home (visited 05/2017).

West, S. et al. (2002). "*Systems to Rate the Strength of Scientific Evidence*". In: *Agency for Healthcare Research and Quality*.

Wiesner, M. and D. Pfeifer (2010). "*Adapting recommender systems to the requirements of personal health record systems*". In: *ACM International Health Informatics Symposium* ISBN: 978-1-4503-0030-8, pp. 410–414. DOI: 10.1145/1882992.1883053.

Wiley, J. (2014). EBM Guidelines: Evidence-Based Medicine. ISBN: 9780470057209. DOI: 10.1002/0470057203.

Woolf, SH. (1992). "*Practice guidelines, a new reality in medicine. II. Methods of developing guidelines*". In: *US National Library of Medicine National Institutes of Health* PMID: 1580720, pp. 946–952. DOI: 10.1001/archinte.152.5.946.

Wright, A. and D. F. Sittig (2008). "*A Four-Phase Model of the Evolution of Clinical Decision Support Architectures*". In: *Medical Informatic Journal* Volume 77.PMCID: PMC2627782, pp. 641–649. DOI: 10.1016/j.ijmedinf.2008.01.004.