Distributed Knowledge Modeling and Integration of Model-Based Beliefs into the Clinical Decision-Making Process

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Referat

Die vorliegende Arbeit untersucht Methoden zur computergestützten Zusammenführung von fragmentierten Wissensbausteinen zu übergeordneten medizinischen Wissensbasen in Form von kausalen Bayes-Netzen sowie Möglichkeiten zu deren Anwendung in der klinischen Praxis. Unterschiedliche individuelle Ansichten zu einem identischen Entscheidungsproblem werden dabei durch einen neu entwickelten Fusions-Algorithmus kombiniert, um automatisiert umfassende Wissensmodelle zu spezifischen klinischen Fragestellungen zu erzeugen. Hierbei wird sichgestellt, dass das resultierende Modell stets ein valides Bayes-Netz ist und somit im Rahmen von modellbasierter klinischer Entscheidungsunterstützung verwendet werden kann. Neben der Erläuterung der hierfür erforderlichen Grundlagen werden im Rahmen der Arbeit drei praxisnahe Systeme vorgestellt, welche auf diesen methodischen Ansatz Bezug nehmen. Dies umfasst eine auf einem Blockchain Datenspeicher aufbauende Plattform zur Erhebung und Sammlung von Wissensbausteinen, ein System zur personalisierten Evaluation von klinischen Laborbefunden sowie ein Assistenzsystem zur kollaborativen Entscheidungsfindung im Tumor Board.

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Chapter 1

Introduction

> *The image of the world around us, which we carry in our head, is just a model. Nobody in his head imagines all the world, government or country. He has only selected concepts, and relationships between them, and uses those to represent the real system.*
>
> *Jay Wright Forrester, 1971*

The process of digitalization within the healthcare domain comprises an extensive dispute between the human and a computer. On the one hand, the computer aims to assist humans by providing a set of functionalities rooted in a rule-based foundation defined within the systems' code. On the other hand, the human is aware of the utter diversity among individual patients and the fact that rules might not be suitable enough for a complex system like the human body [1]. Although this fundamental difference seems insurmountable from a current perspective, computer systems have proven to be helpful for the clinical routine in a variety of ways, including diagnostics (e.g., image processing in radiology) [2], medical order management [3] or summarized digital case management in general. Nowadays, the preference of digital medical data compared to its analog and foremost paper-based predecessors have also become a crucial optimization factor as the need for cost-effective, up-to-date quality healthcare faces a growing population with more elderly patients, a higher number of chronic diseases, and thus more complex cases [1]. Nonetheless, the aim to provide a tailored treatment for each patient, often referred to as *precision medicine*, has become an overarching goal for patients, healthcare providers, policymakers, and the healthcare industry [4]. The approach features the consideration of specific patient characteristics (e.g., the genetic profile, biomarkers, phenotype, or psychosocial status) for the respective treatment selection to achieve higher efficiency and better outcomes [4]. While the elicitation of this data requires very specialized and precise examinations, technological advancements and extensive cost reductions in genomics or Next-generation Sequencing (NGS) allow for easier integration into the clinical routine [5]. Nonetheless, those comprehensive diagnostic methods come along with an increase in data volume and case complexity for physicians. To catch up with the progression in granularity from a diagnostic view, treatment-related information from clinical studies or a Clinical Practice Guideline (CPG) is now easier to find online through dedicated internet search services such as PubMed or other clinical publication databases. The consolidation of both perspectives generated the need for specific tools that make the contained information easily processable for physicians [5].

A Clinical Decision Support System (CDSS) aims to address those issues by enabling automatic data assessment based on actual clinical knowledge, i.e., by highlighting pathological laboratory findings or providing situation-aware warnings in the case of possible drug-drug interactions each time a medical subscription is made [6]. The respective systems can provide those assistance functions because they are equipped with formalized clinical knowledge. This knowledge needs to be integrated to define a respective set of rules that allows for the clinically relevant processing of incoming data. Sources of information include individual knowledge from domain experts, CPGs, study and research results, or data analysis from the respective use case [7].

1.1 Motivation and Clinical Setting

The diagnosis and treatment of complex or chronic diseases involve the participation of various clinical disciplines and departments. Each actor contributes with his or her individual knowledge to dedicated segments of the overall process, which might have derived from personal experience or external evidences such as research publications or clinical studies. In oncology, some process steps require synchronization of individual findings to confirm a certain condition (diagnostics), plan the next step (therapy decision), estimate therapy-related risk factors (risk stratification), or provide the best possible outcome (therapy planning). Interdisciplinary expert meetings, so-called *tumor boards*, are a way to ensure that all relevant medical contributors have evaluated a respective case, that information has been synchronized throughout all actors, and that decision-making is based on collaborative consent. Due to the rapid increase of individual disease-specific data, the urge of implementing precision medicine, and thus a high case complexity, physicians are facing a variety of cognitive strain while considering the necessary information from relevant CPGs, medical studies, or state-of-the-art research in their field [8].

The application of Clinical Decision Support (CDS) can assist physicians in their decision-making by providing a model-based representation of the actual medical modality and techniques to match individual patient data with a broader medical knowledge base. Those features allow a CDSS to offer suggestions for choosing the most suitable option. However, such systems heavily rely on the quality of their inherent knowledge base to provide valid assessments and thus, clinical significance [9, 7, 10]. Knowledge integration into a CDSS requires implementing a knowledge engineering process, which usually involves the collaboration of a knowledge engineer and (at least) one specialized domain expert [11]. In the most simple scenario, the system's internal logic would derive from one single domain expert's assessment. However, even if formally and technically correct, those assessments might not represent the actual use case universally. Especially in oncology, which involves the participation of different departments and thus diverging specialized expertise for subsets of the overall modality (including current developments, novel therapeutic concepts and targets).

Another problem in the knowledge engineering process derives from the contradiction of providing a preferably detailed representation of the problem while still keeping the overall formal complexity at a stage that makes it efficiently processable by current computer systems. Furthermore, a knowledge base for the clinical domain is often subject to change when new and relevant evidence becomes available (e.g., results from clinical studies or CPG updates). Those updates can cause extensive maintenance since some impacts might be substantial enough to result in invasive structural changes of the knowledge base. Efficient knowledge engineering thus needs to be performed by multiple institutions or participants to decrease the risk of outdated information, and missing resources for maintenance [9].

Apart from the expert-based way, methods for generating knowledge from available data sources (patient data, public health databases) have been established. This process, also referred to as *data mining*, can be used to analyze large sets of data to find contained patterns and relationships from which a causal structure can be derived [12]. However, given the use case of clinical oncology or other complex medical use cases, an automatic process of knowledge-generation is constrained by various aspects like the heterogeneity and quality of data sources, the complexity of terminology and content as well as potential bias captured in the considered data [13, 14]. Reviewing those constraints reveals the current limitations in automatic knowledge engineering. Thus, domain experts still have a significant role in the process of building a Knowledge-based System (KBS). However, to avoid the problems resulting from implementing a potentially subjective or non-representative knowledge engineering process (e.g., caused by limited consideration of evidence or professional viewpoints), a collaborative and distributed way of knowledge aggregation and management becomes inevitable. To achieve this, both methodologically and technologically, various aspects must be considered. Above all, these include the possibility of formalizing both evidence and individual experience (resulting from the expertise of the individual medical experts). Furthermore, it is necessary to effectively manage and combine these individual viewpoints to enable a holistic view of the respective medical modality (represented as a knowledge model). To utilize the resulting knowledge bases in the context of CDS, it must also be ensured that the respective models are compatible with the requirements of CDSSs in order to be able to assist in clinical practice.

Apart from the problems resulting from the creation of the actual knowledge base, there are also various issues related to the application of this formalized knowledge in the context of CDS. Five major deficiencies common in establishing KBS (specifically expert systems) have been identified by Luger [15]. Those undermine the more general differences between problem-solving through humans and computers.

1. **The lack of deep knowledge** - the fact that a system is (to this date) not able to fully understand the real function or meaning beyond the represented information entities (e.g., the physiological function of the heart or the technical operation of a computer tomograph) introduces a certain narrowness to the actual system. Although the granularity of a knowledge base is the subject of the detail provided, several aspects might not be possible to formalize or introduce unnecessary computational complexity.

2. **The lack of robustness and flexibility** - in a CDSS, the knowledge base is instantiated with a set of patient data to calculate a result and provide a suggestion to the actual decision problem. If this result is somehow affected by unfavorable conditions (e.g., contradictions, inconsistencies, or missing data), the system might produce uncertain assumptions, consequently leading to potentially wrong decisions. While a human can examine the initial problem, the system is not able to properly question itself.

3. **The inability to provide deep explanations** - although KBS might utilize a graph-based representation (see section 3.2.3) of a decision problem, which allows for tracing of the actual decision-making pathway, a system will not be able to answer the question of why a certain path has been taken. This is also due to the lack of deep knowledge integration.

4. **Difficulties in verification** - in most cases, establishing a knowledge base that derives mainly from expert assessments assumes that the input provided has general applicability to a variety of individual cases (e.g., patient cases). This assumption might be tough to achieve, and thus to verify, because of the heterogeneous subject (human) and the respective resources (e.g., large amounts of prepared patient data) necessary. Furthermore, some decision problems might not even be subject to existing gold standards, which hinders establishing a fundamental truth for those cases.

5. **Little learning from ground truth** - establishing significant knowledge bases requires the frequent consideration of updated information whenever new evidence becomes available (e.g., CPG updates, new therapeutic options, or diagnostic procedures). Adapting to those changes is a crucial technical issue about how the knowledge base is generated. It requires the implementation of mechanisms for automated adjustment based on previous results or other structural updates.

Both aspects *the lack of deep knowledge* and *the inability to provide deep explanations* are due to fundamental differences in reasoning between humans and computers and are not further considered in the course of this thesis. In contrast, *the lack of robustness and flexibility*, addresses essential factors of quality assurance in the development of a CDSS as well as the need to comply with formal requirements in the underlying data management (knowledge base as well as patient data). By using a Bayesian Network (BN) as the methodological basis of the knowledge models (see section 3.4), those requirements can be determined by the structure of the model itself based on the definition of information modalities and causality. Furthermore, the implementation of a Knowledge Fusion (KF) process (see sections 3.6 and 4.2) allows for the resolution of conflicts resulting from different perspectives on a specific problem. Finally, the approach of a distributed knowledge modeling platform (see section 5.1), addresses the two aspects *difficulties in verification* and *little learning from ground truth* by enabling collective intelligence to model a single decision problem by considering multiple viewpoints. This approach enables the formalized representation of knowledge that exists outside of CPGs.

1.2 Objectives

This thesis's main objective is to establish a distributed way to capture personalized viewpoints (beliefs) on medical modalities based on BNs through a range of medical experts and to combine them in a valid KF process to generate collaborative knowledge bases. The solution will allow for a decentralized knowledge engineering process to gather the necessary assessments and store them in a structured way to enable further CDS-related processing. In the context of this thesis, applications in the field of oncology, and in particular head and neck oncology, are considered, whereby an interdisciplinary approach for the evaluation of clinical cases is required. The proposed method is aimed to represent an intuitive way for medical experts to contribute to the development of medical knowledge bases through their professional experience and expertise. The platform then gathers and composes those fragmented beliefs and fuses them algorithmically into a single resulting BN. Based on the amount of integrated beliefs on a certain modality, those will then be independent of stationary factors such as institutions, countries, and thus the respective healthcare system. This shall contribute to the development and provision of universal knowledge bases to overcome institutional and individual bias.

To illustrate the methodological aspects of collaborative knowledge modeling, KF and the generation of CDS-compatible knowledge bases, this thesis describes the development of a distributed knowledge modeling process and associated IT platform whose managed knowledge models are applicable to CDSS to support clinial decision-making processes. This proposal is fragmented into four different objectives, which are to be fulfilled in the course of this work.

Objective 1: Structured Belief Aggregation

To allow for an efficient way of contributing belief to a broader knowledge base, domain experts should be able to assess distinct modalities within their field of expertise that will then be placed into a higher-level medical context. To do so, medical experts should be provided with a Human Computer Interface (HCI) that assists them during belief integration. This includes functionality for structured data input, including verification, and the reduction of complexity in every reasonable way. This objective further aims to develop a software component that allows for intuitive information retrieval while also ensuring technical conformity to associated processes, e.g., CDS.

Objective 2: Development of a Method to Handle Opposing Beliefs

Since belief is a subjective assessment, it is a very natural process that there might be different views on the same modality. While this is in no way a disadvantage, it becomes a relevant issue if the captured knowledge is used for certain processes that rely on the provided information's unambiguity, e.g., CDS. In those cases, mechanisms that resolve potential conflicts are required.

Objective 3: Ensuring Long-Term Integrity

Providing an universal and up-to-date representation of medical knowledge requires an open platform provided and maintained through a professional community. Since the significance of a knowledge base depends on the quality and integrity of its integrated beliefs, the contained information thus has to be protected against malicious behavior.

Objective 4: Identification of Suitable Medical Applications

Examples of clinical use cases that can benefit from the distributed generation of medical knowledge bases should be introduced and discussed. Those should be based on identifying and evaluating relevant clinical needs through proper scientific practice to ensure relevance for the clinical domain.

1.3 Thesis Outline

This thesis is separated into three main parts which cover the current state of methodological and practical factors, the thematic introduction of key concepts as well as the documentation of methodological and practical implementations of systems in the context of CDS. The three areas are composed so that the concepts discussed build on each other and a clear focus of the covered topics becomes apparent.

Chapter 2 introduces the background information on medical knowledge modeling, KF and CDS as the essential thematic aspects of this thesis. Those will be introduced and discussed from a state of the art perspective, provding additional information about relevant research to complement an initial definition of the respective topic. In the course of this work, a special focus is on the utilization of knowledge-based methods and BN for the structured representation of medical information.

Chapter 3 provides relevant concepts and insights which are required for the proper understanding of the methodological and technical developments of this work. This primarily includes the topics of knowledge formalization and BNs as the fundamental components of the practical system implementations in chapter 5.

Chapter 4 contains the derivation of solutions regarding the formal representation of medical knowledge as structured data in the form of valid BNs. Furthermore, a KF algorithm, developed as a novel concept of generating medical knowledge bases from fragmented beliefs, is introduced and discussed in further detail. Finally, the utilization of blockchain technology for storing and managing knowledge fragments is presented.

In chapter 5, three separate proprietary systems in the context of CDS are presented. They were all developed as part of my original research at the Innovation Center Computer Assisted Surgery (ICCAS). For each of the presented works, the corresponding requirements, selected methods, and results are explained in further detail. Subsequently, each section concludes with a discussion that highlights identified problems and limitations as well as the potential for further research on the respective topic.

In a general discussion and conclusion on all topics covered in this thesis (chapter 6), further challenges and limitations for CDS in clinical practice are discussed. Finally, as part of the conclusion, the fulfillment of the initial four objectives (see section 1.2) will be evaluated, followed by a subjective interpretation of the research and development achievements of this work.

Chapter 2

State of the Art

In this chapter, initial definitions and characteristics in medical knowledge modeling and KF are introduced. For both fields, relevant related works providing methodological insights are presented. Based on this thesis' focus on knowledge-based CDS provided through BNs, only approaches relevant for BN-based CDSS are considered. Furthermore, the fundamental aspects of CDSS are introduced in more detail, complemented with a status quo concerning their clinical application. Finally, the concept of a dashboard as a way to effectively support clinical decision-making is presented, complemented by relevant works that evaluate their implementation as the visual component of a CDSS in clinical practice.

2.1 Medical Knowledge Modeling

In general, the process of knowledge modeling includes the formalization of already existing knowledge into a way that a computer system can process [16]. This includes the consideration of individual resources (pieces of information like the age of a person) and the relations between them [16]. Thus, a model can be seen as a formal representation of a real-world modality, including its relevant entities and the causality on how those entities interact with each other. This also assumes a prior understanding of the actual system before the modeling process [17]. Since modeling is an unbound and subjective practice, guidelines that facilitate consistency and interoperability need to be applied [18]. This good modeling practice presupposes the adherence to conceptual integrity. According to Lankhorst et al. *»Conceptual integrity is the degree to which a model can be understood by a single human mind, despite its complexity.«* [18]. Thus, a good model can be assessed intuitively by others, even if they only have limited knowledge about it. However, this assessment especially depends on the respective domain of the model itself. In medicine, certain concepts or relations do not allow for abstraction for the sake of general intuitiveness since that might decrease clarity and, thus, the significance of the model itself. Furthermore, the appraisal of quality for a model is primarily determined by the relevant stakeholders [18]. Thus, it is arguable that even throughout the different medical fields, there is an overall consensus about certain modalities. Due to comprehensive medical education, there is also a high level of wide-ranging domain knowledge in general.

Considering the implementation of knowledge models into actual practical applications, KBSs build on top of ontologies and domain models have gained considerable acceptance throughout a wide range of use cases [16]. In this case, ontologies represent a prior set of application-specific terms and relations bound to a respective domain (e.g., medicine). Gruber has defined the term itself as *»[...] a formal, explicit specification of a shared conceptualization.«* [19]. More specifically, *»[...] an ontology defines the basic terms and relations comprising the vocabulary of a topic area as well as the rules for combining terms and relations to define extensions to the vocabulary.«* [20]. Focusing on the medical domain, relevant ontologies include the Systematized Nomenclature of Medicine (SNOMED) or Logical Observation Identifiers Names and Codes (LOINC) amongst others. However, each of those ontologies only represents a specific subset of common concepts in the respective area of interest. Since the modeling of medical use cases might include concepts from other areas (e.g., environmental or societal factors), different preexisting ontologies need to be combined, or new ones need to be established to address the intended applications properly.

Generating a model-based representation of a real-world use case includes the provision of an abstract view on a specific subject as well as the identification and assessment of all relevant entities and relations. In sophisticated domains such as medicine, this will require a collaboration of multiple experts who will individually contribute with their individual expertise. Thus, the associated process is carried out not only to develop the actual model but also for the integration of individual knowledge representation. This includes the communication, discussion, and agreement to provide a consensual formalization [18]. According to Lankhorst et al., the overall process of knowledge modeling can be fragmented into the following segments [18].

1. **Establishing the purpose, scope, and focus** - while the purpose of a model within a CDS context is set to assist in a decision-making scenario, the actual scope and focus heavily rely on the respective use case. This is because the consideration of information entities and the availability of actual measurable evidence might differ based on the decision problem. Furthermore, it has to be determined if the model will be used to represent a present (e.g., therapeutic decision support) or a future (e.g., risk assessments for certain medical conditions) scenario.

2. **Selecting one or more viewpoints** - in medicine, the application of models can be beneficial for many different disciplines (e.g., the physician, the patient, or the hospital management). A different view accompanies each role in the actual decision problem. While a physician might be focused on finding the treatment option with the highest impact on the respective medical condition, the patient might be interested in the most non-invasive procedure to prevent severe side-effects. Each viewpoint introduces a different assessment of the same modality, resulting in the need to provide different model views for a single problem.

3. **Creating and structuring the model** - while building the actual model, different sources of information need to be assessed and put into context. For the medical domain, this might include the integration of CPGs first to offer adherence to clinical routine and a later refinement of the given in-

formation entities, relationships and possible extensions to the status-quo. This part of the process also involves discussion throughout the contributors to agree upon the model structure and inherent causality. Through structuring the model (e.g., in a visual representation), it can be assured that the result is easily understandable. In this way, inconsistencies or redundancies are also easier to identify. When modeling a complex decision problem, structuring might be performed by building logical information groups or sub-models which are visually separated (e.g., based on the medical field or the therapeutic pathway).

4. **Visualizing the model** - visualization can be a great tool to better understand or assess a certain model since it decreases the inherent abstraction by using graphical representations (e.g., diagrams). Applied to the clinical use case, proper visualization of a decision model might allow effective discussions about various aspects of the model between different medical experts without the need to understand the formal characteristics of model-based knowledge representation itself.

5. **Using the model** - the process of evaluation and validation is an important step in developing model-based solutions, regardless of whether the model is intended for knowledge representation or actual decision-support. Defining the value of a model is primarily based on its suitability and validity for the intended use case. Thus, a CDS model will be measured on its precision to give the right suggestions to become significant for clinical practice [21].

6. **Maintaining the model** - the maintenance of knowledge models in the medical domain (especially CDS models) is crucial to preserve their relevance for the respective application. This is based on the fact that medical knowledge is subject to change whenever new evidence becomes available. Thus, update mechanisms to allow for integrating those changes need to be considered in the development process.

2.2 Knowledge Fusion

As a general methodology, KF was defined by Zhang et al. in the following way: *»Knowledge fusion (KF) which supports knowledge discovery, extraction, organisation and representation is developed to tackle the challenging problems of extracting and integrating knowledge from heterogeneous data sources.«* [22]. Applied to the scope of CDS, various aspects of medical knowledge management are thus combined under the single banner of KF when multiple sources of information are available and considered:

1. **knowledge discovery** can be assisted through techniques related to the optimization of information search and retrieval (e.g., publications or published medical study results),
2. **knowledge extraction** needs to be addressed through solutions that enable intuitive ways on how to capture knowledge in a way that is compliant to subsequent processes (e.g., the computer-assisted generation of medical knowledge bases),
3. **knowledge organisation** requires ways that allow for persistent storage of knowledge or knowledge fragments as well as solutions to provide their integrity in the long-term,
4. **knowledge representation** is required to enable CDS application in clinical routine, thus also considering traceability of CDS-based decisions to ensure proper quality management.

An important concept for KF is also represented in the way compromises are made. For example, opposing beliefs of multiple experts about the same modality can either be discussed before building a knowledge model (prior compromise), or they can be solved after individual models have been built (posterior compromise) [23]. A good example of prior compromise is the way CPGs are established. While the actual CPG can be considered a knowledge base, its development process is based on integrating recommendations that are then discussed and evaluated by an interdisciplinary group of experts before the actual document is generated. However, this thesis will only address posterior compromise, as this aspect introduces new challenges to KF, which can be addressed algorithmically.

For the scope of BN-based KF, relevant groundwork was published in 1992 by Matzkevich and Abramson. In their paper *»The Topological Fusion of Bayes Nets«* [24], the authors present an approach to allow for topological fusion of two independent BN, formalized in their *FUSE_DAGS* algorithm. It considers that those two BNs are already finalized regarding the knowledge or use case they represent. This means that there are already several layers of node-based relations formalized into the graph structures. For the fusion of a consolidated Conditional Probability Table (CPT) (see section 3.4), Matzkevich and Abramson introduce the utilization of the weighted average, which has proven to be a reliable, yet simple, way of expressing multi-user consensus. This argument is based on the prior work by Ng and Abramson, who investigated the problem of calculating and numerically expressing consensus in their study *»Consensus Diagnosis: A Simulation Study«* [25]. While comparing the performance of four different aggregation functions: linear opinion pool (weighted average), logarithmic opinion pool [1], conjugate method [26], and an approach proposed by Bordley [27], the study showed that rather simple operations, especially the weighted average, provided the most intuitive and robust performance.

Santos et al. [28] introduce a mathematical concept of enabling the fusion of multiple knowledge sources, referred to as *»Bayesian Knowledge Fragments (BKF)«* into a Bayesian knowledge base. The presented method includes the formalization of individual beliefs of a person into a BN. Furthermore, this person is assigned a reliability index, which denotes the respective influence that this belief has in the fusion process. Thus, in case of a contradiction between two (or

[1] The logarithmic opinion pool method is similar to a weighted average but uses the weighted product of all given statements and not their sum.

more) beliefs about the same modality, higher reliability will ensure a greater impact on the result. However, while this approach is intended to provide a metric that can be used to solve methodological conflicts that might hinder the KF process, e.g., when one belief notes that information B depends on information A and another one states that A depends on B and thus, creates a cycle which violates the formalism of a Directed Acyclic Graph (DAG) (see section 3.4), the authors do not provide a concept about how this might be achieved in practice. Since the focus of the work is on the construction of Bayesian knowledge bases, which do not necessarily align to the formal rules of BNs, those possible conflicts are tolerated.

Another approach to KF was presented by Jiang et al. [29]. The authors introduce a four-step process when combining different BN models (referred to as candidate models in the paper). This process is based on re-organization of the candidate models by using chain rule factorization and applying arc-reversal[2] (see section 3.6) to prevent cycles in the DAG (see section 3.4). Based on those operations, CPT fusion can be performed very easily since no formal conflicts should be present anymore, e.g., every permutation of integrated dependencies in CPT of model A either completely or partially matches the structure of every other CPT other than A. As an extension, the authors also discuss the possibility of integrating weight factors while merging the CPTs. This could, for example, be performed on the reliability index introduced by Santos et al. [28].

In general, Jiang et al.'s proposed four-step process introduces a methodological concept that focuses primarily on optimization of the calculatory KF process rather than the preservation of the initially integrated information. This is mostly due to the consideration or arc reversal and thus, the manipulation of causal directions in the result BN.

[2] In an arc reversal operation, the direction of an edge between two dependent nodes (i.e., X and Y) is reversed. In this way, the initial parents of X become the new parents of Y and vice versa.

2.3 Clinical Decision Support Systems

Due to the continuously increasing demand for quality improvement within the healthcare sector, technical solutions that aim to assist the medical staff during their work routines have been developed [30]. Those systems are trying to tackle the issues raised by information overload (derived from examination data and overall clinical knowledge), the associated cognitive strain, and the higher claims towards individualized treatment and precision medicine [31]. One major example of the application of such systems are CDSS, which aim to deliver the right and evidence-based information to the right people in the right format through the right channels at the right time (also known as the *five rights*) [32]. CDS, as an inherent methodology of a CDSS, has been defined as *»[...] a process for enhancing health-related decisions and actions with pertinent, organized clinical knowledge, and patient information to improve health and health care delivery.«* [33]. Thus, CDS relies upon a clinical knowledge base and individual patient information to ponder the respective case's available options. In a broader context, the system aims to find the best available solution for the patient based on the available data. This also causes the dependency on the quality and granularity of the available knowledge base and the integrity of the considered patient data.

The early development of knowledge-based systems in the medical domain was driven by expert system research and the idea to simulate the way physicians think and make decisions [6]. Their decision-support functionality was implemented through a set of rules in the form of if-then-statements (see Listing 2.1), which were then matched against incoming patient data [34].

```
if {
  the patient is younger than 12 months and has a body temperature above 38.5
    degrees (celsius)
} then {
  conclude that the patient has a mild fever
}
```

Listing 2.1: Example for an if-then-statement rule for CDS

Later, CDSS systems started to address diagnostic problems (e.g., the INTERNIST I system) and switched their focus to assisting the physician in the decision-making process rather than trying to simulate it [35]. This was managed by providing mechanisms of information gathering and filtering to enhance the way that the respective case and all the associated information is presented to the user [6]. Through the following years, several CDSSs for a variety of medical use cases, ranging from drug prescription support [36] to digital benchmarking [37], have found their way into hospitals. Since those systems require the electronic availability of medical data, installments were almost exclusive to facilities that have developed and integrated their own Hospital Information System (HIS) [38]. Thanks to the advent of the Electronic Health Record (EHR) and the establishment of data representation standards (e.g., HL7), information access for current and future systems can become much easier. Nonetheless, problems associated with the lack of standardized terminology or ontologies for the healthcare domain persist. This hinders the flawless exchange of information [39] and thus an efficient implementation of CDS. However, fragmented but robust standards for medical data segments, e.g., LOINC for laboratory terms, the International Classification of Diseases (ICD-9-CM/10), the SNOMED or the Current Procedural Terminology, might be used to provide a proper level of terminological consistency [38].

Pawlowski et al. [40] performed a structured review of publications associated with the implementation of CDSS in clinical oncology. The findings included solutions related to medical prescriptions and pharmaceutical workflows [41, 42, 43, 44, 45, 46, 47, 48, 49], Patient-reported Outcome (PRO) [50, 51, 52], prescriber alerts [53], and systems for diagnosis- or therapy-related CDS[54, 55]. While the scope of the decision points varies, all identified solutions were based on the methodological utilization of CPGs as the integrated knowledge base, which shows that the consideration of CDS derived from non-CPG-based knowledge bases is still in an experimental, research-centric state.

A CDSS for therapy decision-making for Laryngeal cancer based on BNs was proposed by Cypko et al. [56, 57]. Their system relies on an expert-based modeling process to (1) construct the knowledge model's causal structure, and (2) determine the CPT based on individual experience. In their paper *»Web-tool to Support Medical Experts in Probabilistic Modeling Using Large Bayesian Networks With an Example of Rhinosinusitis«* [58], Cypko et al. furthermore introduce an approach to optimize the process of expert-based information gathering through a web-based application. This is based on the previous work by van der Gaag et al. [59]. In this approach, the individual probabilities for each node's CPT are verbalized into easy to understand questions, e.g., *»What is the probability of a flu, when the patient has an increased body temperature and a sore throat?«*. In this way, a medical expert can better understand the context of the probability measure. Based on the prior development of the Laryngeal cancer network, its actual CDS-related value has been evaluated by calculating the TNM tumor classification for 66 individual patients through the model, which resulted in prediction accuracy of 76% before making adjustments based on corrections of false data and the model itself.

The successful implementation of CDS also relies on the benefits noticeable for the users. Kawamoto et al. investigated the implementation of 70 different CDSSs into clinical practice through their respective case studies. They derived a set of 15 features of those systems that had a positive or negative impact on the system's corresponding success rate. The study yielded the following aspects to be most significant [60] (features were chosen due to a stated success rate of more than 75 percent):

1. provision of computer-generated decision support
2. integration into the clinical workflow
3. enabling the need to document deviations from the CDSS suggestions
4. representation of calculation results through noting agreements
5. provision of an actual recommendation rather than pure data assessment
6. integration of research evidence and reasoning for result justification
7. dedicated result presentation to clinicians as well as patients

While most of the reported findings are rather obvious in the context of CDS, the aspect of integrating research evidence and reasoning for result justification represents an interesting contradiction to the fact that nearly all of the identified CDS systems by Pawlowski et al. [40] were purely based on CPG knowledge rather than the current state of research or even practice-based reasoning (see section 3.1.2).

2.4 Clinical Information Access

Although the management of medical case data is increasingly being handled through digital solutions [61], e.g., EHRs, a significant amount of information communication is still paper-based and requires the gathering of case-related information from a variety of clinical subsystems [62, 63]. Especially in situations where a clear and holistic availability of information is required, the use of ways for effective information access becomes necessary. A common tool that adresses this issue is a dashboard, which provides a condensed overview of single or multiple modalities and is intended to minimize the number of actions required to obtain the requested information. In the medical domain, their installation has become a popular way to measure and improve various aspects of the clinical routine [64].

In their work, *»Development and initial evaluation of a treatment decision dashboard«*, Dolan et al. [65] present a dashboard-based solution focused on clustering information to support decision-making for non-opioid pain medication for patients with osteoarthritis. The implemented dashboard features a wide range of information, including possible side-effects, drug-drug interactions, and the simulated prognosis of therapeutic effectiveness on a single display. The clinical benefits are based on the hypothesis that considering the advantages and disadvantages of the respective treatment options will enable more effective decision-making through the physicians. Through an evaluation study, including 25 volunteers, positive results regarding an increase in effectiveness and uncertainty reduction during decision-making are shown.

Another solution to patient data management in the field of head and neck oncology was developed by Meier et al. In their paper *»Design and evaluation of a multimedia electronic patient record "oncoflow" with clinical workflow assistance for head and neck tumor therapy«* [66], the authors present their solution *oncoflow*, which is a custom HIS that was specifically tailored for the use case of head and neck oncology. The system features a dedicated EHR limited to information entities relevant to the documentation and monitoring of head and neck patients. Furthermore, *oncoflow* aims at enabling primarily structured information rather than plain text, which is still very common in clinical documentation. Based on the structured EHR, several services were implemented, e.g., a clinical workflow tracker, which deduces the respective state in the treatment process based on the provided documents and information entities. While the application also features a dashboard view for big-screen presentation in a tumor board setting, its corresponding user interface was not designed for an integrated case overview. It only features a limited subset of the available case data, focusing mainly on the representation of endoscopic imaging.

Chapter 3

Fundamentals

In this chapter, fundamental concepts and methods for the context of this work are introduced. Those include the general principles of Evidence-based Medicine (EBM) (section 3.1) and the principles of how knowledge can be formally represented (section 3.2) as the crucial foundations of knowledge-based CDSS (section 3.3). Due to the focus on BN-based methods for CDS in this work, the principles of conditional probability and BNs (section 3.4) as well as methods of reasoning in the context of CDS (section 3.5) are provided in further detail. Finally, the process of fusing individual BNs in a KF process is explained in section 3.6, providing the necessary methodological prerequisites of the solutions presented in the following chapters 4 and 5.

3.1 Evidence-Based Medicine

Making decisions in the medical domain comprises a complex regime of individual considerations. The respective knowledge necessary to act in the patient's favor derives from various sources of information. While some assessments are possible due to the individual knowledge, training, and experience of the physician, verifiable results from significant medical studies or clinical trials represent another layer of certainty due to the containment of demonstrated clinical evidence. This evidence also acts as a baseline in establishing CPGs provided by medical associations (e.g., the National Comprehensive Cancer Network (NCCN)), which represent a crucial foundation in clinical decision-making [6]. EBM has been defined by Rosenberg et al. as *»[...] the process of* *systematically finding, appraising, and using contemporaneous research findings as the basis for clinical decisions.«* [67]. Thus, a decision-making process based on EBM integrates medical science and research, evaluates the given information based on its significance and outcome for the present scenario, and takes it to choose the respective option. The needed evidence for EBM might derive from one of the following sources.

3.1.1 Literature-Based Evidence

The medical literature, from reference books to research articles, is a prevalent information source. Nonetheless, it carries serious flaws associated with the relatively small amount of therapeutic interventions covered with significant evidence of efficacy. Furthermore, problems related to the published materials' qualitative measures, i.e., study design and reporting problems, limit the number of relevant sources to be considered [68, 69, 70]. Due to the time constraints in clinical practice, an efficient quality assessment process is hard to implement, which calls upon technical support functionality (e.g., automatic quality assessment) that might better assist this process in the future [7].

3.1.2 Practice-Based Evidence

Practice-based evidence is an important way to adapt general medical facts (provided through literature) to local facilities since major differences in equipment, patient characteristics, or relevant policies might greatly impact the respective decision-making process. It is also a source of very granular knowledge that is truly valuable for the refinement or adjustment of CPGs. However, constraints caused by the lack of terminological standardization in the medical domain or institutional and individual data privacy regulations interfere with an efficient and broadly accessible knowledge integration [7].

3.1.3 Patient-Directed Evidence

Modern technologies have drastically improved how patients can access medical information, even though this has also led to an increase of misinterpretation or misinformation. Nonetheless, patients can now get more involved in the decision-making process (shared decision-making) and provide more valuable feedback about their conditions. This proactive way of reporting is also a crucial component towards precision medicine, and thus, the possible improvement of the individual clinical outcome [7]. Although EBM is now acting as a best practice for clinical decision-making, its implementation into the clinical routine is a comprehensive endeavor. This is because the methodology's focus is on the generation and assessment of research results, which requires guidance for the physicians to ensure the significance of the integrated evidence [71]. Furthermore, technical requirements regarding an effective EBM integration into the clinical workflow and IT infrastructure need to be considered, e.g., the effectiveness of searching and gathering relevant information [67]. IT systems are thus able to contribute to a successful adoption if they can provide sufficient support. Examples include specialized search or metasearch engines, data mining systems for automated information retrieval, or CDSS.

3.2 Knowledge Representation Formats

The urge for knowledge representation mechanisms is closely tied to the development of Artificial Intelligence (AI). This is because human intelligence has a knowledge-based foundation and requires a prior understanding of general and specific real-world modalities [72]. For example, deciding upon the best-suited therapy for a cancer patient does require general knowledge about possible treatment strategies and their characteristics and precise information about the patient and the associated disease [1, 2]. Processing both of those information clusters in a decision-making context then relates to the performance of intelligent behavior. While several ways facilitate the formal representation of knowledge so that IT systems can perform constitutive processes (e.g., machine-based reasoning or learning), those can be classified into the following categories [11].

3.2.1 Logic-Based Representation

Ideas for the utilization of formal logic as a way to represent human knowledge for IT systems date back to the year of 1968 [73]. Since then, various concepts for applying logic to provide formalisms (e.g., description or non-monotonic logics) have been established. One specific way in this context is the utilization of the core concepts of predicate logic to allow for the determination of real-world modalities as predicates and the objects it interacts with [11]. For example, given a subset of present knowledge about possible influential factors of a human's body temperature as well as associated effects for the affected person, those relations can be formally described as:

```
body temperature (increased, fever)
body temperature (decreased, hypothermia)
```

Listing 3.1: Example for a logic-based representation for assessing body temperature

This formal representation can now be used to answer some particular questions like *»What happens to the body temperature if a patient has a fever?«* or *»The patient has a decreased body temperature, what might be a possible reason for this?«*. However, based on the declarative nature of logic-based representations, only boolean (true or false) statements are possible, and performing inference is limited to the mechanisms of logic itself, which is a crucial limitation for complex applications that often feature uncertain conditions, e.g., CDS.

3.2.2 Procedural Representation

In contrast to logic-based representations, the procedural approach enables the integration of process statements, which are then used to formulate processing rules that represent knowledge fragments. Thus, a system utilizing this method comprises a rule engine that processes incoming data and offers suggestions that are based on the accordance to the underlying rule base. Applied to the example for body temperature, the procedural representation would be noted as:

```
IF body temperature is increased
THEN conclude fever

IF body temperature is decreased
THEN conclude hypothermia
```

Listing 3.2: Example of a procedural representation for assessing body temperature

Rule-based systems that rely on the principles of procedural knowledge representation have been used for a wide range of expert systems within the medical domain (as well as other professional fields) [11]. However, the methodology still only offers a very abstract way of knowledge modeling due to the missing concepts towards the consideration of uncertainty. Furthermore, systems might become overwhelmingly complicated if the rule-base extends over time. This might also introduce problems to the knowledge base, such as contradictory rules for the same modality.

3.2.3 Network or Graph-Based Representation

A network or graph comprises the integration of nodes as a way to represent different modalities as well as arcs (also referred to as *edges*) that connect those nodes to form the actual network [11]. Popular types of networks include decision trees, artificial neural networks, or BN (see section 3.4). CDS systems based on BN have proven to offer valuable assistance in a broad range of applications, e.g., the prediction of cancer recurrence [74] or diagnostics [75].

3.3 Knowledge-Based Clinical Decision Support

The initial definition of CDS does not include a specific methodology; neither does it contain a distinct technology that should be used for implementation. In practice, this generosity allows for different approaches in developing a CDSS, which can be classified as knowledge-based and nonknowledge-based systems. However, although both classes are distinguished in their respective methodology, this does not prevent different combinations between them [76].

In Maier's definition *»Knowledge comprises all cognitive expectancies — observations that have been meaningfully organized, accumulated and embedded in a context through experience, communication, or inference [...]«* [16]. Thus, knowledge derives from various sources of information that need to be aggregated, processed, and put into a specific context. While this process serves as one of the foundations of individual human behavior, utilizing effective knowledge-management in an organizational context requires tools that enable the acquisition, storage, and management of knowledge. This led to the establishment of Knowledge Management Systems (KMS). According to Maier, a KMS is *»[...] an Information and Communications Technology (ICT) system in the sense of an application system or an ICT platform that combines and integrates functions for the contextualized handling of both, explicit and tacit knowledge, throughout the organization or that part of the organization that is targeted by a Knowledge Management initiative. A KMS offers integrated services to deploy KM instruments for networks of participants, i.e., active knowledge workers, in knowledge-intensive business processes along the entire knowledge life cycle [...]«* [16]. In this way, a KMS is an IT system that integrates tacit (knowledge derived from the human brain) and explicit (knowledge derived from all other sources than the human brain) knowledge. It offers a set of functionalities to enable effective knowledge management and sharing for multiple users. Although general definitions of KMS or KBS address primarily business-oriented applications, their suitability for the clinical domain and application for CDS purposes has already been utilized by various systems [76]. However, an adaptation of KBS for CDS in the medical domain requires the consideration of domain-specific characteristics, e.g., the complexity and unpredictability of the subject (human body), the differences in quality concerning the available evidence, the fact that some processes and relations boast high uncertainty, as well as the amount of available data [77].

From a technical view, a knowledge-based CDSS comprises three core components [78]:

1. **Knowledge-Base** - the implementation of a KMS or similar forms of knowledge aggregation techniques allow for gathering individual assessments about a certain modality. The formal way of how those assessments are structurally represented depends on the methodology used for the CDSS implementation [79], e.g., BNs or decision trees.
2. **Inference Engine** - the general purpose of an inference engine in a CDSS context is the combination of input and other data through applying a logical scheme that determines an output [79]. In the clinical scenario, this might relate to matching patient measures and findings with the knowledge base to generate an assessment about the most reasonable choice within a set of multiple options. Again, the kind of engine or mathematical formalism used for those calculations is based on the respective CDSS's methodology.
3. **Human Computer Interface** - the HCI handles the result presentation of the calculations carried out by the inference engine. It usually presents the set of available options for the respective decision problem and ranks them based on a given criterion, e.g., the probability [79]. Based on the methodology, a HCI can also visualize the way of decision-making through the CDSS to allow traceability of the user's results.

While in the case of a KBS, assessments that represent the system's knowledge have to be integrated by domain experts, Nonknowledge-based Systems (NKBS), also referred to as Intelligent Computing Methods (ICM) [76], derive their inherent information from an automatic learning process [79]. This approach, also known as Machine Learning (ML), takes a set of given data, analyses it through specialized algorithms to find regularities, and finally constructs a model based upon those findings, which can then be applied to new cases [80]. Those automatic learning techniques can be further classified into *unsupervised* and *supervised* learning. The main difference between those two methods is how the data is being prepared in advance. In unsupervised learning, no further input than the data itself is provided to the learning process, which is a common way to analyze unlabeled datasets or data from use cases without lots of prior knowledge at all [80]. The main goal of this approach is to find patterns within the data to use for further classification, and thus knowledge generation [81]. In supervised learning, the algorithm is presented with data that has already been labeled (e.g., through a domain expert) beforehand, which shifts the resulting model's main focus to optimizing a classification problem [80].

Although the application of ML in CDS has many benefits (e.g., potential savings in time and personnel resources or the ability to generate dynamic models that adapt whenever new data becomes available), its utilization also faces serious problems like:

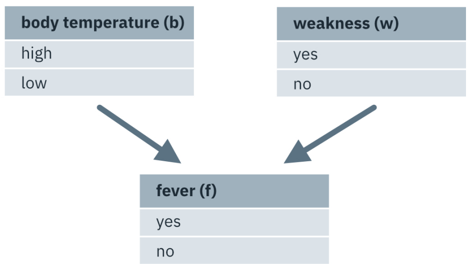
- the challenge of dealing with the heterogeneous and unstructured data that is still very present in the medical domain,
- the uncertainty that the methodological approaches used for finding the relevant patterns in the given data are appropriate for the medical domain,
- the fact that the ML-process's raw results might be hard to evaluate for a domain expert [80].

3.4 Conditional Probability and Bayesian Networks

A BN is a probabilistic graph-based model that represents the conditional dependencies of a set of variables in the form of a DAG [82, 83]. It comprises nodes (representing information entities) and edges (representing relationships). Each node can be further specified through an unlimited amount of states to integrate different expressions of that specific information. For example, a node representing the presence of a symptom that a patient might have can feature the individual states: *observed, not observed* as well as *unknown*. The connection of two individual nodes through an edge denotes a conditional dependence, e.g., the diagnosis A depends on the presence of symptom B. To satisfy the DAG specification, only directed (unidirectional) connections between the nodes are allowed, and no cycles (loops) may arise from connections throughout the network. Those cycles may either be caused by direct conflicts (e.g. if nodes A and B share an equal dependency of one another) or indirect conflicts (e.g if node A has indirect influence on node B through another node C [29].

When two nodes are dependent, they form a CPT, which includes the probabilistic values for each permutation derived from the set of states of both nodes (see Figure 3.1). This behavior results in exponential complexity for each CPT depending on the number of dependent nodes (parent nodes). While the structure (or topology) of a BN is considered the qualitative part of the network, the conditional probabilities represent its quantitative component [82].

The development of a BN as a tool to utilize CDS can be implemented in multiple ways. The simplest way is to perform a knowledge engineering process. Here a domain expert manually creates the structure of the BN by formalizing the required knowledge. Then, either by the same or other experts, the network's CPTs are filled with probabilities. In recent years, the application of ML as a suitable method for the automatic learning of BNs has also been extensively investigated. ML can be used to create the BN structure and to determine probabilities [84]. Depending on the quality and objectivity of the underlying data, this approach offers a way to reduce the subjectivity of expert-based processes based on only a small number of individual opinions. However, as with the expert-based approach, it needs to be considered that the underlying data of an ML process might also contain extensive bias (e.g., due to prior selection and filtering), and steps to overcome this issue need to be implemented to ensure objectivity.



	$b_{high}\,w_{yes}$	$b_{low}\,w_{yes}$	$b_{high}\,w_{no}$	$b_{low}\,w_{no}$
f_{yes}	0.99	0.30	0.85	0.01
f_{no}	0.01	0.70	0.15	0.99

Figure 3.1: Example of a CPT for a node (fever) based on two dependent parent nodes (body temperature and weakness) with binary states. The corresponding cells in the CPT can be read as »The probability of fever is 0.99 (equal to 99%), if body temperature is high and weakness is yes. The probabilistic values for each permutation of parent's states (represented through the columns in the CPT) always sum up to 1.0 to express a valid probability distribution.

A major advantage of BNs is the possibility to consider uncertain conditions [85]. This is a crucial feature for the medical domain since many domain-specific modalities (e.g., diagnosis, interpretation of test results) do not offer absolute certainty in most cases [86]. Thus, it is challenging, if not impossible, to make definitive statements about certain events or conditions. This is mainly because the information that has to be taken into account in a decision-making process is subject to numerous uncertainties [87]. These include:

- the available information about the patient,
- the medical history of the patient, which in most cases can only be communicated subjectively,
- the uncertainty of the physical examination, which in most cases only allows a vague separation of normal and pathological conditions,

- the not fully calculable factors influencing laboratory findings (e.g., caused by medication or other patient-related factors),
- the subjective assessment of the patient's individual health status and his or her respective symptoms [87].

These information-related problems become clear, for example, when making a diagnosis. If a physician considers a patient's symptoms, these must first be viewed with a certain degree of uncertainty. Furthermore, even objective findings usually do not only allow a specific conclusion to be drawn but rather a set of potential outcomes. Thus, a close examination of multiple factors, which are rarely absolute, is required to finally make a decision. In a strictly rule-based system, which only allows for states to be either true or false, a diagnosis would only be insufficiently possible since the individual information's value is often somewhere in between. The specific concept of mapping uncertainty in modeling information is referred to as *fuzzy logic*. It represents the inclusion of uncertainty in the classification of information and is an essential component in the CDS context. Torres et al. refer to the concept of fuzzy logic as a *»[...] qualitative computational approach [...]«* [88], since a significantly more realistic representation of real-world modalities in computer systems can be achieved.

From a technical view, the integration of fuzzy logic can be achieved in multiple ways. One possibility is the implementation of dedicated software components for the preprocessing of information, which take into account one or more factors in addition to the actual characteristic of the modality. Gaebel et al. introduced, for example, the temporal aspect of information in the context of the *diagnostic delay* [89]. In this specific case, radiological findings of a CDSS for laryngeal carcinomas by Cypko et al. [57] are considered, by which specific characteristics of a tumor (e.g., tumor size) were determined. Given the definitive point in time when this information is obtained and the medical subject's dynamic behavior (tumor growth), the information's value is thus subject to a time dependency. If a previously defined temporal threshold is exceeded, the individual information impact is automatically decreased, as the system evaluates it as no longer relevant enough for full consideration.

3.5 Clinical Reasoning

In 1959, Ledley et al. first introduced a logical concept for clinical reasoning and CDS based on logical conclusion and conditional probability in their article *»Reasoning Foundations of Medical Diagnosis«* [90]. The mathematical basis for this was Bayes' theorem. The authors separated the reasoning process into three components:

1. the medical knowledge about the link between symptoms and diagnoses,
2. the reported or identified symptoms of the patient,
3. the final diagnosis resulting from the correlation of (1) and (2).

According to Ledley et al., this results in a two-stage process, whereby the available information must first be pre-processed. This refers to the logical combination of findings to either completely include or exclude a certain diagnosis in advance [90]. This step is also useful in a practical context to reduce the complexity of the considerations and keep the necessary computing effort as low as possible. In a more general manner, Steinhilber et al. describe the term clinical reasoning as *»[...] the process of gathering information as well as generating and testing hypotheses to develop a diagnosis and treatment plan.«* [91]. Thus, the term can rather be understood as a process in which the information necessary for decision-making is correlated with the available knowledge to generate a result. In essence, clinical reasoning as a concept thus acts as a synonym for CDS, whereby the reference to an IT system's application is initially excluded.

3.5.1 Deterministic Reasoning

The process of deterministic reasoning is based on the known interrelationships between causes and effects and, thus, is highly correlated to rule-based decision-making, as it utilizes decision rules (e.g., implemented in the form of if-then-statements) to generate conclusions. According to Jenders, those rules *»[...] map the circumstances of a particular situation, such as the case of an ill patient for whom a diagnosis must be chosen, to a particular choice, whether that be a diagnosis, a treatment plan or an inferred observation that, in turn, may lead to another decision.«* [92]. As a technological implementation of this approach, the Arden Syntax was developed in the 1980s [93]. As an independent and abstract expression language, it allows for a relatively simple formalization of medical facts in the form of dedicated rules (see Listing 3.3).

```
IF body_temperature IS MORE THAN 37.4 DEGREES THEN
CONCLUDE classification := 'fever';
ENDIF;
```

Listing 3.3: Arden Syntax implementation of a decision-rule for the diagnosis of fever

3.5.2 Probabilistic Reasoning

Another perspective on the derivation of possible results in the CDS context is the use of probabilistic systems. These systems are based on the formal principles of conditional probabilities (see section 3.4) and consider the probability of occurrence of certain events under specific conditions. An essential feature of probability theory is the use of numerical values to express specific characteristics, which, depending on the approach, may be considered as positive or negative. Positive concerning the possibility of expressing knowledge that is very difficult to fit into individual categories, the possibility of merging different views on the same facts, or handling uncertainties (e.g., through consideration of fuzzy logic). Negative concerning the fact that many modalities might sometimes be very difficult to express numerically and humans tend to struggle in making precise numerical estimations [83].

3.6 Knowledge Fusion of Bayesian Networks

When fusing individual knowledge fragments in the form of valid BNs during posterior compromise, two separate processes need to be performed. The first one is the topological fusion of the BN graph structures to generate a result BN that also satisfies the DAG criteria. For this operation, a first step to perform is graph union, which generates the union of the node sets and the arc sets (edges) [24] (see Figure 3.2). During this process, it might be the case that the plain union introduces violations to the DAG criteria, e.g., by introducing cycles in the resulting structure. One possible way to overcome this issue is the utilization of the arc-reversal operation, which reverses the respective arc causing the cycle. While this process is described to preserve information [94, 95] since a flow of information is valid in both directions [24], it also impacts the causal directions and thus, the generation of CPTs in the resulting network. Given the scope of utilizing BNs for modeling medical knowledge or, more specific, medical decision problems, causality is given by the underlying nature of the process and how information is observed [96]. Therefore, the initial causality of a BN considered for KF needs to be preserved in the case of a CDS application.

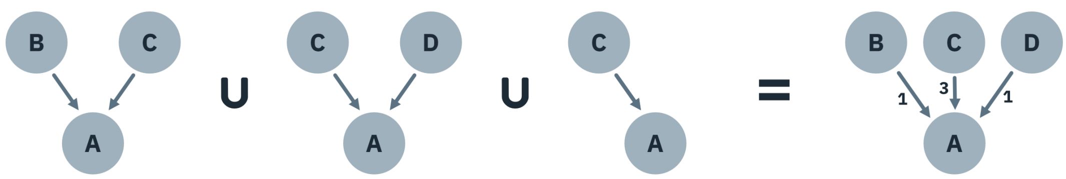


Figure 3.2: Illustration of graph union with three input BN. The number next to each edge denotes its total number of occurrence.

Another way is to resolve potential structural conflicts through the determination of rules or factors that are considered by an algorithm, e.g., weight factors for the provided nodes and edges. In this way, each component of the BN is assigned an additional numerical weight which represents its respective impact in case of conflict resolution (see Figure 3.2). If a violation of a DAG criteria arises, e.g., a loop between two nodes A and B, the edge with the lower weight is automatically removed in the KF process to ensure a valid output. If more than two BNs are fused, this procedure becomes an iterative process, utilizing continuous checks if new arcs introduce new cycles and apply prevention methods.

The second step is the fusion of CPTs. Since each knowledge fragment inherits its own CPT and the represented probabilities are specifically adjusted to the respective BN structure, the KF process introduces specific challenges that need to be addressed. Those are the handling of: (1) numerically merging the stated probabilities in general, (2) contrary belief about the same modality and, (3) new permutations which are generated by the KF process and were not considered in the prior knowledge fragments.

Chapter 4

Block-Based Collaborative Knowledge Modeling

An essential aspect in the provision of CDS is the continuous maintenance and update of the underlying knowledge base [15] since it acts as the foundation and, thus, a primary quality measure of each CDSS. The generation and continuous evaluation of the integrated information, as well as its structuring in a form that can be used by the system, is therefore particularly relevant. Conversely, however, it is also this aspect that presents itself as particularly demanding in practice. As already described in detail in section 3.1, there are different sources for the procurement or derivation of application-relevant evidence. Different advantages and disadvantages must be considered depending on the type.

Although modern informatics methods such as ML represent an auspicious approach for the generation and consideration of data-based evidence in the CDS context; there are still several hurdles that hamper the development of ML-based CDSS. This is due not least to the most important ingredient of these methods - the underlying data. The biggest dispute in this context is because, despite progressive digitization, much of the information on clinical cases continue to be recorded on paper and stored only as finished documents in the EHR. In addition to technical difficulties in processing these files, this also creates problems with content since the relevant clinical information contained therein is primarily stored in free text and thus not structured. Furthermore, this text information often has individual, non-standardized abbreviations, which can be interpreted by a human being due to the underlying context, but cause great problems for automated extraction. This also applies to the designation of technical terms, which do not necessarily have to be used identically in a multicentric context [97]. Although Natural Language Processing (NLP) methods can be used to extract structured and relevant information from unstructured documents, this step adds a further source of error to the overall process of creating a valid medical knowledge base.

Yet another problem arises when considering the surrounding clinical circumstances. Methods such as ML are relevant for CDS because they can take a data-driven view of the situation and thus theoretically do not introduce personal bias into their assessments [98]. However, this feature is only given if the data used are not inherently subject to bias. In the clinical context, this would be the case if the treatment of patients or patient groups always follows an existing regime. However, suitable alternatives are available but are not considered for reasons such as cost coverage by insurance companies, general approval for a specific therapy or medication, individual preference, or other institutional guidelines.

Last but not least, it must be considered that, depending on the complexity and weight of a clinical decision problem, a very high number of variables might have to be taken into account. A prominent example is the HEPAR-II model for the diagnosis of liver disorders by Wasyluk et al. [99], which contains and processes about 70 information entities to generate a diagnostic decision. The model's structure was first created manually by a medical expert in the form of a BN. Then, the conditional probabilities were learned from a processed clinical data set to populate the CPTs. The process can thus be described as a hybrid approach since manual and automatic methods were combined. However, the aspect of automatic learning of the conditional probabilities goes hand in hand with the requirement that the underlying data set also contains information about every conceivable permutation of the incoming data in the context of the respective decision problem. Thus, for each application of CDS for a new medical case, the available learning data must also contain at least one, or even better, a large number of known precedents available to the system to make calculations based on actual evidence. However, this circumstance is sometimes not realistic for every clinical application or, depending on the complexity of the model, even impossible to implement, which introduces uncertainties into the learning process. This becomes particularly clear in use cases that show a high degree of variance regarding the influencing factors, e.g., a high number of possible characteristics per information entity, in particularly rare medical cases or in clinical pathways for which there is hardly any significant evidence at all.

Although these problems primarily address the use of ML to create clinical knowledge bases, they can also be transferred to manual, expert-based creation. While information extraction, in this case, only has a minor role, the factor of bias gains much more importance. This is mainly because expert-based modeling of knowledge bases is a subjective process reflecting individual views, experiences, and interpretations of available evidence (e.g., literature- or practice-based evidence). Viewed on its own, the resulting model is thus a formal reflection of an individual viewpoint that is subject to numerous variables, such as the individual selection of information sources, own preferences, or the respective experience in a particular field. The hypothesis underlying this circumstance is, therefore, that the application of an expert-based approach to creating medical knowledge bases is only significant if the following factors are taken into account[1]:

1. The generation of the medical knowledge base must support different views about the same modality. This requires capturing separate data structures for each view, which can be assigned to a superordinate context by integrating identification features.
2. For the actual CDS application of the knowledge base (implemented as

[1]This list adapts to the overall objectives for this thesis mentioned in section 1.2

a BN), each node and edge may only exist once. However, they may be present in the system multiple times due to the different views on a certain modality. Thus, a KF process of the different instances is required. This must be carried out transparently and based on comprehensible criteria.

3. The individual contribution to the knowledge base must be supported by an intuitive process through the software so that a user without prior modeling competence can contribute to the system with their individual view.

In addition to these factors, formal criteria must also be taken into account, resulting from the application of BNs as the methodological foundation for the CDSS. This includes the topology of the underlying graph, which strictly requires a DAG structure of the contained nodes and edges. Furthermore, automatic completion of CPTs is required when, due to the fusion of individual views, certain conditional probabilities are not available and therefore have to be generated synthetically.

4.1 Data Model

In order to meet these challenges adequately, a system was developed that enables the collection of individual views of a decision problem in the form of a data structure referred to as a *belief block*. This specific data structure contains:

- the structural representation of a decision consisting of a decision problem X and all influencing factors (parents) $X \mid n_i$
- the numerical evaluation of all conditional probabilities $P(X \mid n_i)$
- information for block identification, the date of creation as well as information on its affiliation (assignment to one or more specific knowledge bases)
- information about the respective belief block author

The data structure is implemented in JavaScript Object Notation (JSON) format. It follows the conventions of the JSON Graph Format (JGF) specification[2] which offers a solid framework for all relevant entities of a graph. It has freely definable areas (e.g., for metadata), which allows for an adaptation of the specific requirements of a BN.

4.1.1 Belief Structure

The data structure of a belief block is represented by two main areas (nodes and edges). First, the information entities (nodes) involved in the later decision are defined (see Listing 4.1).

```
"nodes": [
  {
    "id": "0001",
    "label": "surgery",
    "type": "calculated",
    "metadata": {
      "node_states": [ "compatible", "not_compatible" ],
      "pimary_performer": "radiological_oncology"
    }
  }
]
```

Listing 4.1: Definition of a node in a belief block

Each `node` object has a number of different attributes, which are utilized in further process steps, e.g. in the fusion of different blocks. The following attributes are provided in the belief block data schema:

[2]Further information about the specification can be found at `http://jsongraphformat.info/`.

- `id` - assigns a unique ID to each node within the block
- `label` - the name of the respective node
- `type` - specification if the underlying information of the node can be either calculated or measured
- `metadata.node_states` - contains a list of possible states of the respective node
- `metadata.primary_performer` - contains the information to which medical competence area the respective information primarily belongs

An important aspect is the specification of the `type` for the respective node. While the *calculated* attribute indicates that the respective information depends on further parent nodes within a network, *measured* indicates that it can be derived directly from the patient, e.g., by carrying out medical tests or asking him or her about the respective facts. From the list of measurable nodes, a patient profile can be derived for the later utilization of CDS, i.e., the number of information entities that must be collected before the CDSS can be instantiated with patient data.

After all relevant nodes are defined, the causal structure is mapped through the integration of edges. Each `edge` object has the following attributes:

- `source` - identifies the source node of the respective edge
- `target` - identifies the decision target node of the respective edge
- `relation` - defines the relationship (in the present case always an edge relationship)
- `directed` - defines if the edge is directed or not (since BNs are used, this always has to be true)
- `metadata.references` - contains an array of references that can be attached as a source of corresponding evidence to the respective edge

A special feature of edges within a belief block is the ability to add references. This gives the possibility to note the source of structural knowledge. Each reference is represented by a set of structured attributes: publication type, authors, title, year, DOI, and a URL (see Listing 4.2). These attributes can be used, for example, by external processes to check the validity or significance of the evidence introduced. The respective return value can then modify the attribute `valid` to indicate whether the source should be considered or not in other related processes (e.g., during block fusion). This feature also provides an important component in CDS quality assurance since the creation of the knowledge base can be dependent on specific factors in the context of verifiability or significance.

```
"edges": [
  {
    "source": "0001",
    "target": "0004",
    "relation": "edge relationship",
    "directed": true,
    "metadata": {
      "references": [
        {
          "valid": true,
          "type":"article",
          "authors":"Oeser A.",
          "title": "Belief Blocks for CDS",
          "year": "2021",
          "doi": "123456789",
          "url": "https://iccas.de"
        }
      ]
    }
  }
]
```

Listing 4.2: Definition of an edge in a belief block

4.1.2 Conditional Probabilities

Since the JGF convention is not explicitly adapted to the requirements of a BN; the basic structure does not provide any preceding attributes for mapping CPTs. For this reason, the freely definable `metadata` attribute within the `graph` object is used for their integration (see Listing 4.3).

```
"conditionalProbabilities": [
  {
    "source": "0001",
    "sourceState": "yes",
    "targets": [
      {
        "targetNode": "0004",
        "targetState": "suitable"
      }
    ],
    "probability": "0.70",
    "certainty": "0.85",
    "metadata": {
      "references": []
    }
  }
]
```

Listing 4.3: Definition of a CPT in a belief block

The contents of the CPT are stored in the `conditionalProbabilities` array, whereby the following attributes are used to map the contained information:

- `source` - identifies the source node of the respective edge
- `sourceState` - identifies the respective state of the source node

- `targets` - contains an array of nodes (and corresponding states) that represent the affected entities of the source node
- `targets.targetNode` - identifies a specific decision target node
- `targets.targetState` - identifies a specific state in the decision target node
- `probability` - stores the numeric value of the conditional probability
- `certainty` - stores a numeric value that represents the self-assessed certainty about the integrated conditional probability
- `metadata.references` - contains an optional array of unique references that can be attached to the respective edge as a source of corresponding evidence

Just as with the structural information of the respective belief, any number of references can be attached to the conditional probabilities as well. This is particularly useful if the evaluation of the respective numeric values is not based on individual expertise or professional knowledge but actual published evidence (e.g., the result of a clinical study).

Another additional value that is not directly part of the necessary information for mapping a BN is `certainty`. The numerical value stored in this attribute is a parameter that can be self-determined by the user. As the name suggests, it acts as a numerical measure for the individual certainty of the corresponding probability evaluation.

4.1.3 Metadata

In addition to the structural and CPT information of the BN, certain general information is also stored in the belief block, which uniquely identifies both the data block (belief) and the associated author (see Listing 4.4). The following attributes represent this block-specific metadata:

- `block_id` - sets an unique id for each individual belief block
- `model_id` - denotes the id of the actual model to which this block contributes
- `creation_date` - stores the timestamp at which the block was created (using Unix timestamp)
- `belief_type` - represents the way of how the integrated knowledge was obtained through the system (in the present case, this is always through a guided survey; however, other ways of determining the probability values are also imaginable, e.g., through ML or data mining on already available evidence)
- `author.id` - stores an individual id for each author
- `author.medical_field` - stores the individual medical field the author is specialized in (e.g. oncology, surgery)
- `author.job_title` - contains the medical job title of the user, i.e. chief resident
- `author.years_of_experience` - stores the number of years that the author is active in the medical domain
- `author.facility` - stores the name of the facility the author is affiliated with

```
"metadata": {
  "block_id": "1234",
  "model_id": "1234",
  "creation_date": 1075128200,
  "belief_type": "survey",
  "author": {
    "id": "author-001",
    "medical_field": "hematology",
    "job_title": "chief resident",
    "years_of_expertise": 12,
```

```
    "facility": "University Hospital Leipzig"
  }
}
```

Listing 4.4: Metadata section of a belief block

The attribute `author.medical_field` is used in the KF process to determine a comparison between the author's primary expertise and the assignment of the respective information entity (further explained in section 4.2). The other author-specific attributes `author.job_title`, `author.years_of_expertise` and `author.facility` are provided as options to filter the selection of belief blocks to be considered in the KF process, e.g., to only consider blocks where the author has at least 5 years of expertise or whose facility is located in a specific country or continent.

4.2 Constraint-Based Automatic Knowledge Fusion

The main goal of the presented approach is to merge different BN-based beliefs into a consolidated network that can be used in a CDS context. This results in special requirements that affect the methodological process:

1. it must be possible to merge any number of beliefs on the same subject
2. discrepancies must be resolved by the algorithm
3. the causal relationship should stay intact
4. the result of the KF process must be a valid BN

Concerning these requirements, it is clear that none of the solutions presented in section 2.2 is directly applicable, since they either allow the utilization of arc reversal operations [24, 29] or do not provide valid DAG as a result [28]. Thus, a novel methodological approach is required.

The presented solution is based on the principles of DAG constraints and the consideration of weight attributes used to satisfy those in specific cases. It considers the specific attributes relating to (1) the integrated knowledge and (2) the corresponding author to determine various weight factors, which are then appended to the respective nodes and edges during KF. Based on those weights, the fusion algorithm can objectively reason which operation needs to be performed to preserve the DAG-related constraints.

The calculation of those weights is based on specific rules determined before the fusion process. Each rule is intended to consider several attributes provided by the belief block objects, e.g., information about the author or the belief itself. Since the focus of this thesis is on developing and evaluating a methodical approach to KF in the context of CDS, only simplified and purely subjective rules were integrated to verify the requirements. An exact and objective definition of the value of specific information of a person (e.g., based on years of experience) or the respective supply (e.g., the reputation of a given source) does not occur. The formalization of the integrated rule set for this proof of concept approach consists of the following assumptions:

1. a belief author with a higher number of `years_of_experience` has more impact than an author with a lower number
2. a match between the `medical_field` attribute of the belief author and the `primary_performer` attribute of a node is more valuable than a mismatch
3. an edge with one or more provided sources is more valuable than an edge without sources
4. consensus between two or more beliefs (either in terms of a node or an edge) increases the weight of that information
5. a statement with a higher certainty has more impact than one with a lower certainty

For the sake of clarity, the structural and CPT fusion process are explained separately in the following two sections 4.2.1 and 4.2.2. To further provide a better notational distinction of the presented BN-related modalities, the representation of structural information about a BN-based belief block will be noted in the form of $(A \mid B, C, D)$ which refers to the fact that node A is dependent on nodes B, C and D. This simplified form is introduced because the regular notation of a BN (represented as a directed graph), i.e., $\Pr(A, B, C) = \Pr(A \mid B, C) \Pr(B \mid C) \Pr(C)$ is not required for a belief block since only direct parents of the target node can be modeled and further edges between parents may only result from the subsequent KF process. Each time a probabilistic value is presented, it is noted in the form of $P(A \mid B, C, D)$ which refers to the numerically expressed probability (in a range between 0 and 1) of A given B, C and D.

4.2.1 Fusion of the Bayesian Network Structures

The solutions presented by Matzkevich et al. [24], Jiang et al. [29] and Santos et al. [28] are based on iterative fusion, which takes two input BN, fuses them into a result BN and uses this result for further iterations. In the presented case, this approach is not appropriate since valuable information might get lost along the way due to the utilization of weights as the primary factor of resolution in case of formal conflicts.

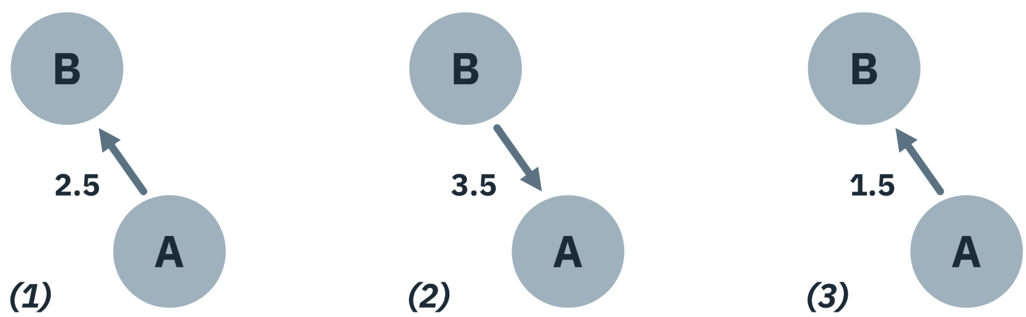


Figure 4.1: Three input BN with different views on the causal relationship between two nodes

As an example, three simple BN are aimed to be fused (see Figure 4.1). Each one contains an individual view on the nodes A and B and their causal dependency. In an iterative approach, (1) and (2) would be fused in a dedicated step, which will result in $(A \mid B)$ due to the larger weight of (2). In a second step, the result $(A \mid B)$ is fused with (3), which will also result in $(A \mid B)$ because of the higher weight of (2). However, when the process of fusion would be processed in parallel rather than sequentially, the result would be $(B \mid A)$ since there is a larger joint weight resulting from the consensus of (1) and (3).

To overcome those issues, the presented approach introduces the utilization of an intermediate graph for temporarily storing the original BN structures of each belief before processing them in parallel to form a result BN (see Listing 4.5). In contrast to the result BN, the intermediate graph does not need to satisfy the DAG criteria. In two independent loops, the algorithm gathers the individual beliefs and assigns edge weights according to the previously formalized rules. It will then sort the resulting blocks based on their respective edge weight. In a second loop, the algorithm initiates the KF process by performing a graph union operation with all blocks in a temporary graph structure. After every iteration, a dedicated function will check if the union process has caused a cycle in the temporary graph structure. If this is the case, the function will investigate the respective situation and will erase the problematic edge with the lower edge weight.

```
intermediateGraph = {}

for block of blocks {
  for edge of block.edges {
    add edge or increment edge weight in intermediateGraph
  }
}

sort blocks by their edge weight in intermediateGraph

```

```
finalGraph = {}

for block of blocks {
  tmpGraph = finalGraph

  add block edges to tmpGraph

  if tmpGraph is not cyclic {
    finalGraph = tmpGraph
  }
}
```

Listing 4.5: Pseudocode for the block fusion and structural graph building algorithm

To form a result BN, the algorithm will first fuse all available belief blocks for a certain decision problem X. Based on the `label` attribute, it will then check if other belief blocks are available that contain information about a parent node of X, thus providing the information about the modalities the parent of X is dependent on. Through this iterative process, all dependencies for a decision problem can be considered in the final BN model.

4.2.2 Fusion of the Conditional Probability Tables

For the fusion of the CPTs, all blocks representing the same knowledge modality are first gathered through their respective `label` attribute and are then temporarily stored in the array `blocksByNode`. In a second step, the algorithm generates a result CPT by considering all possible permutations derived from the states of the influenced node and all its parents. If overlaps for certain permutations are detected in the KF process, the respective values are merged by calculating a weighted average. If the fusion process introduces new permutations that were not initially considered in the input BN, synthetic probabilities need to be generated. As an example, three individual input BNs, which model the causal dependencies for a node A are considered (see Figure 3.1). In this example, each node features the two individual states 1 and 2. The structural fusion

	$B_1C_1D_1$	$B_1C_1D_2$	$B_1C_2D_1$	$B_1C_2D_2$	$B_2C_1D_1$	$B_2C_1D_2$	$B_2C_2D_1$	$B_2C_2D_2$
A_1	0.4	0.2	0.7	0.5	0.8	0.6	0.1	0.5
A_2	0.6	0.8	0.3	0.5	0.2	0.4	0.9	0.5

Table 4.1: Result CPT after the structural KF process

of the three BN $(A \mid B, C)$, $(A \mid C, D)$ and $(A \mid C)$ result in a final BN $(A \mid B, C, D)$ and its own newly formed CPT (see Table 4.1). Due to multiple occurrences of the $(A \mid C)$ dependency, it can be concluded that there is a much higher consent regarding this particular causality than there is for $(A \mid B)$ or $(A \mid D)$.

As shown in Table 4.1, the original CPTs of each single input BN cannot be directly integrated into the result since they might feature the consideration of one or two dependent nodes on A but never the whole set of (B, C, D). In this case, the algorithm needs to process those missing values programmatically, generating a synthetic probability for the respective constellation based on partial knowledge from the other modalities. For the presented example, two separate processes apply. For the CPT fusion of $(A \mid B, C)$ and $(A \mid C, D)$, one previously known and one new dependency are introduced. To integrate the contained information in the result CPT, all dependent factors need to be considered separately. Methodically, an arithmetic mean is used to estimate the influence of a single factor on the respective decision point. In the example case, this is achieved by first extracting B and its respective states B_1 and B_2 from the CPT of $(A \mid B, C)$ and C and its respective states C_1 and C_2 from both CPTs $(A \mid B, C)$ and $(A \mid C, D)$.

$$P(B_1) = \frac{1}{2}(P(B_1C_1) + P(B_1C_2)) \tag{4.1}$$

$$P(B_2) = \frac{1}{2}(P(B_2C_1) + P(B_2C_2)) \tag{4.2}$$

$$P(C_1) = \frac{\frac{1}{2}(P(B_1C_1) + P(B_2C_1)) + \frac{1}{2}(P(C_1D_1) + P(C_1D_2))}{2} \tag{4.3}$$

$$P(C_2) = \frac{\frac{1}{2}(P(B_1C_2) + P(B_2C_2)) + \frac{1}{2}(P(C_2D_1) + P(C_2D_2))}{2} \tag{4.4}$$

This process results in a dedicated view of every single factor's individual impacts on the respective states of A. Without the consideration of D as a further dependency on A, C_1 and C_2 are now representing the joint impact of both beliefs and can again be fused with B_1 and B_2 to result in a final CPT for $P(A \mid B, C)$.

$$P(A_1 \mid B_1C_1) = \frac{1}{2}(P(B_1) + P(C_1)) \tag{4.5}$$

However, in the given example, a new dependency D is introduced to the fusion process. Based on the separation of individual factors, the respective probabilistic values for the corresponding states of D and can be fused into the CPT for $P(A|B, C, D)$ in the following way.

$$P(A_1 \mid B_1C_1D_1) = \frac{1}{3}(P(B_1) + P(C_1) + P(D_1)) \tag{4.6}$$

To address the implications caused by the higher consent towards the dependency of C on A and the previously introduced factors to quantify belief impact (e.g., appended sources or certainty), those formulas can be extended by respective weight factors w_i to numerically express individual impact in the resulting probabilistic values more precisely.

$$P(A_1 \mid B_1C_1D_1) = \frac{1}{3}(w_1 \cdot P(B_1) + w_2 \cdot P(C_1) + w_3 \cdot P(D_1)) \tag{4.7}$$

From an algorithmic viewpoint, this procedure needs to be handled by different functions triggered individually based on the structure of the BNs that need to be fused. In general, three scenarios need to be considered:

1. One or multiple new and previously unknown dependencies are added, i.e., $(A \mid B, C) \cup (A \mid D)$ - this is handled by fusing the additional dependency into the existing CPT (see equations 4.6 and 4.7).
2. One or multiple previously known dependencies are added, i.e., $(A \mid B, C) \cup (A \mid B)$ - this is handled by separating the individual factors before fusion and reintegration into the CPT (see equations 4.1 - 4.5).
3. One or more dependencies are excluded from the BN topology due to structural issues - this is handled by separation of the factors that still need to be considered before KF and reintegration into the CPT.

Since the fusion of individual states of the decision target node might introduce formal errors to the resulting probability distribution (i.e., when the sum of all states is larger than 1), normalization needs to be applied (see Listing 4.6). This necessary step ensures formal validity while preserving the respective ratios of the fused output distribution.

```
finalCptsByNode = {}
blocksByNode = sort blocks by characterizing node

for node of blocksByNode {
  blocks = blocks of node
  mergedPermutations = {}

  for block of blocks {
    if all block permutations are previously known to the graph structure {
      calculate and apply weight factors
      merge permutations of block into mergedPermutations
      apply normalization to the resulting probability distribution
```

```
    }

    if there are block permutations previously unknown to the graph structure {
      separate the individual factors
      calculate and apply weight factors
      merge permutations of block into mergedPermutations
      apply normalization to the resulting probability distribution
    }

    if block permutations can only be considered partially {
      separate the individual factors
      calculate and apply weight factors
      merge permutations of block into mergedPermutations
      apply normalization to the resulting probability distribution
    }
  }

  finalCptsByNode[node] = mergedPermutations
}
```

Listing 4.6: Pseudocode for the CPT fusion algorithm

4.3 Blockchain-Based Belief Storage and Retrieval

An essential component of the presented system is the storage and administration of the individual belief blocks. These represent self-contained data structures, which are processed only in the KF process (further explained in section 4.2), but otherwise must be held in a persistent form. Considering the system's actual use case as a tool to provide extensive support in clinical decision-making and thus the associated requirements towards security, immutability, and trustworthiness of the underlying information, specific challenges arise for the technical conception and implementation.

The most common approach to store the captured information is using a centralized database, which stores and manages all captured information entities in a structured way, regardless of the utilized technology. This database acts as a central component and must be managed and maintained by a corresponding trustworthy institution (see Figure 4.2). The responsibility for ensuring the integrity and quality of the information depends on this single actor, which also creates a single point of failure [97]. This means that a potential attack on the system's infrastructure might allow for the modification or even deletion of the stored data. This would then inevitably lead to damage or even termination of the system, which might cause serious consequences for the medical users and, in turn, also the affected patients (e.g., through the consideration of tampered beliefs).

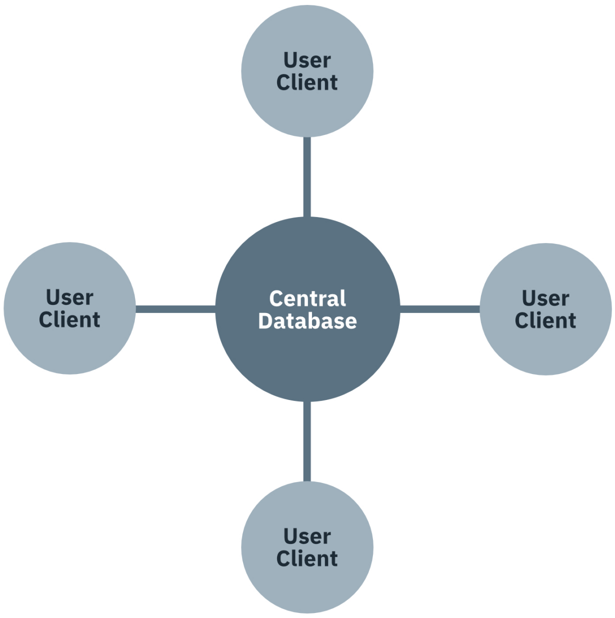


Figure 4.2: Illustration of a centralized system infrastructure. All data is managed on a central database, and each client is sending and receiving data by directly connecting to this instance. In case of a failure, all data-driven operations of the system become unavailable for the clients.

One way of preventing this situation to a large extent is to implement the system based on a decentralized technical infrastructure (see Figure 4.3) which does not organize the location of data storage at a single site but distributes it over several nodes within a network [98]. In this case, control of the data collected is not assigned to a single actor, but different components that are managed by different instances [100]. Popular systems that utilize this approach and have contributed significantly to its popularity are the BitTorrent [101], and Tor [102] networks and the digital currency Bitcoin [103]. The latter represents the use of blockchain technology, which has gained rapid popularity in recent years and now addresses a broad landscape of different industries (e.g., finance, manufacturing, e-commerce) and use cases through specific system solutions.

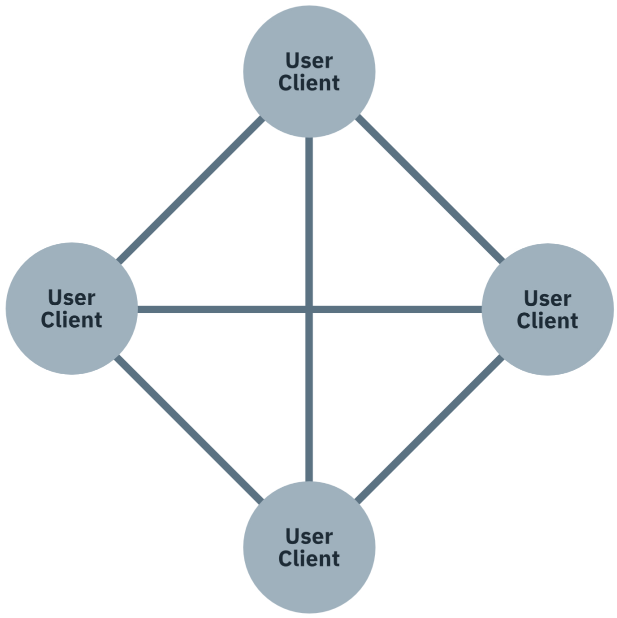


Figure 4.3: Illustration of a decentralized system infrastructure without a centralized component. Copies of the system data (database) are available to multiple clients at the same time. In case of a single or multiple clients' failure, data can still be transferred by requesting it from another instance in the network.

4.3.1 Blockchain Characteristics

According to Crosby et al. a blockchain can be described as a »*[...] distributed database of records or public ledger of all transactions or digital events that have been* *executed and shared among participating parties.«* [104]. In a more generic sense, the actual construction of a blockchain is based on several entities (blocks), which contain specific data and are linked to each other (chain). A copy of this data structure (also known as a *ledger*) is then shared among all participating parties through a network, a mechanism also known as *distributed ledger*.

The initial motivation to develop this technology results from the so-called *double-spending problem* of decentralized system structures [97]. The problem describes that in the context of a digital transaction, it is particularly difficult to ensure that it is executed only once with the exact same parameters since a single digital asset (represented and stored as a plain data object) can theoretically be easily reproduced infinitely. An associated transfer (transaction) could therefore be executed as often as desired, which in the real world is equivalent to making a copy of an actual banknote and using those copies to buy a variety of goods or services. In a centralized system (e.g., in financial accounting), the bank ensures a verified transfer of assets (in this case, the respective amount of money from account A to account B). However, in a decentralized system without a dedicated authority to continuously check the integrity of transactions, this verification process is far more complex. In the case of Bitcoin, the problem is addressed through adopting the *hash-chain* principle by Lamport et al. [105]. While each block contains a set of specific data entries (e.g., transaction records including a sender, a receiver, and a respective transaction amount), it is also given a unique identifier (represented as a hash value[3]) by the underlying system. Since one single block can only store a finite number of transactions, new blocks are generated continuously through a process called *mining*. Each new block inherits the id of its predecessor in addition to its own. Thus, a sequence of data blocks is generated in which every valid successor can be easily identified by comparing both of those id values. This matching process can also be described as an automatic verification step to ensure the blockchain's integrity. Since a copy of the whole ledger (including all of the generated blocks

[3] A hash value is the output of a hash function. A hash function takes an input string of data and converts it into an output string with a fixed size [106].

to date) is stored in redundancy throughout the network, this verification step is carried out by comparing those copies and performing a majority vote before a new block is integrated into the chain. This procedure is also referred to as *consensus*. Technically, this can be achieved through various computational mechanisms that differ in individual scalability and performance. This mechanism also enables extensive integrity of the underlying data storage since it would take a potential attacker to tamper with the majority vote, which is equivalent to intruding more than 50% of the network (also known as a *51% attack*). Thus, the amount of participants who maintain a copy of the current ledger also defines the system's inherent vulnerability.

4.3.2 Relevance for Belief Management

Although most blockchain applications (i.e., Bitcoin) are focused on implementing a digital currency, their core concepts can be used for a variety of applications and domains. Since the type of data storage within the blocks is technically not restricted, every imageable digital asset can be stored and managed using a blockchain system. However, a characteristic that applies to every blockchain is the focus on data integrity due to its practical immutability. Once a piece of data is integrated into the chain, it can technically not be removed or deleted[4]. However, it can be updated with a newer version of the same asset.

Technically, the introduced system does not fully rely on the characteristics offered through a blockchain and could also be adapted to more traditional database systems. However, the addressed use case of medical knowledge management features some relevant perspectives that appeal to that methodological decision. Since knowledge is a variable modality that might be state-of-the-art at some point but might need revision at a later stage, the initial record of how it evolved remains relevant. Thus, the possibility to interrupt this continuous record through deletion or modification is not required and rather obstructive.

[4]It is considered in this work, that the integrated data is stored persistent and unchangeable, although, in a real-world scenario, there are multiple ways to technically disprove this characteristic if the applied resources are powerful enough [107].

This also complements the provision of intensive audit trailing within the application as the course of the integrated knowledge is fully traceable by design. Furthermore, as the system's main task is to provide CDS at some point, the requirements for the integrity of the considered information are exceptionally high, and ensuring the best possible ways to prevent malicious activities at the data-level is intended and also necessary.

On the other hand, the prevention of information removed from the data storage has lately introduced some discussion. Especially through regulations such as the European General Data Protection Regulation (GDPR) and the associated rights for data removal according to Article 17, paragraph 1 (*right to be forgotten*). While it is not within this thesis's scope to discuss the consequences of this regulation in terms of CDS or knowledge management in general, the respective interests would need to be considered if the presented system would leave its prototype state.

Chapter 5

Selected CDS Applications for Clinical Practice

In general, CDS is a comprehensive term that inherits different complexity levels concerning the information entities to be considered. This might range from rather simple (e.g., diagnosis of obesity based on a calculated BMI score) to very complex modalities (e.g., the selection of treatment strategies for chronic diseases) for the provision of truly personalized medicine. The following sections document the conceptualization and development of a distributed knowledge modeling platform for the gathering and fusion of fragmented beliefs into BN-based knowledge models (section 5.1) as well as two CDSS solutions in the context of head and neck oncology (sections 5.2 and 5.3). All systems were developed as part of the research area *»Digital Patient and Process Model«* at the Innovation Center Computer Assisted Surgery (ICCAS). They represent different, although complementary, clinical use cases and are intended to illustrate a selected subset of possibilities for CDSS in clinical practice. Both systems in sections 5.2 and 5.3 are subject to the peer-reviewed journal publications [108] (personalized laboratory findings) and [109] (tumor board dashboard).

5.1 Distributed Knowledge Modeling Platform

The development of the distributed knowledge modeling platform bundles the methodological solutions presented in chapter 4 and has been developed to integrate the concepts and corresponding algorithms into a practical and usable context. In this way, all necessary components: (1) structured acquisition of knowledge, (2) extraction and fusion of related beliefs, and (3) generation of a valid BN as the output of the KF process, have been implemented in such a way that an overall user evaluation (see section 5.1.3) could be conducted.

5.1.1 Requirement Analysis

The requirements for the platform result from the main objectives of this thesis, initially defined in section 1.2, as well as the need for valuable and up-to-date knowledge bases to provide CDS. Thus, it is first necessary to enable a structured data acquisition, which needs to be based on a proper data model (see section 4.1). In addition to the structural and probabilistic information that differs for each captured belief, structured author information for identifying the information source is required. To make this aspect effective from the user's point of view, registration becomes necessary. In this process, the user's identifying information is recorded only once in the system and can then be used automatically for each following contribution. This also creates a persistent relationship between the individual medical expert and the beliefs he or she has contributed. The system should actively support collecting the information necessary for the BN-based belief blocks. The HCI and how the information is requested from the user thus have a decisive role. If possible, select forms should be used so that errors resulting, for example, from inconsistent designations or spelling mistakes can be avoided. An important aspect, which results from the exponential behavior of BNs (see section 3.4), is the reduction of complexity in knowledge modeling. Accordingly, mechanisms should be provided, which allow more effective integration of the necessary probabilistic values.

Concerning the system output expected by the user, specific requests for the retrieval and model-based provision of the managed knowledge fragments need to be enabled. For this purpose, the user should first be allowed to uniquely determine a specific knowledge model. The system will then collect all the beliefs assigned to this model from the blockchain storage. It will then merge them according to a KF process (see section 4.2) and compose a valid result BN. The user should be able to manually determine the process of selecting the beliefs to be taken into account in order to adapt the result set to the respective preferences. The possible filter mechanisms must be based on the data model of the belief blocks.

5.1.2 System Architecture

The presented system is based on a traditional client-server architecture that utilizes the user's web browser for providing the graphical user interface and all user-specific communication interfaces. The server then handles all incoming requests, e.g., data handling in and out of the blockchain storage, for every connected user device (client). Overall, the system provides three separate components, each with its own HCI and functional tasks. Every component communicates with the blockchain data structure by either adding or extracting data for further processing. Since the blockchain itself manages the accounts of the authors and the integrated knowledge in the form of belief blocks, no further data storage solution is required. For the actual implementation, a BigchainDB instance was used. The technology is based on a MongoDB database for storage but adds the following blockchain-related characteristics:

1. **Decentralization** - multiple instances of the same BigchainDB entity (so-called *nodes*) can be connected to generate a network. Within this network, every node stores a redundant version of the captured data, or more specifically, the actual blockchain itself (decentralized storage). If new data is integrated, e.g., by adding a new block (carrying the hash value of its predecessor in the chain), its respective hash value can be compared with all other versions in the network to make sure that it matches the sequence so that the overall integrity of the chain is preserved [107].
2. **Byzantine Fault Tolerance** - a characteristic that is required in distributed (or decentralized) computing systems. It preserves the overall integrity

and functionality, although some nodes in the network show a malicious or deficient behavior [110].

3. **Immutability** - as previously described, blockchains intend to provide practical immutability by design. This characteristic prohibits modifying or deleting data once it has been integrated [107].

Apart from the server-side blockchain data storage, the system utilizes the SurveyJS JavaScript library for providing the data input forms for the graphical user interfaces. Besides rendering the actual forms, the library also takes care of handling input errors (e.g., missing values) and the provision of conditional input requests, e.g., when selecting a specific option requires further input from the user.

The first functional component of the system is the registration of new authors in the blockchain. For this purpose, the application provides a dedicated form-based dialog in which person-specific properties are entered (see Figure 5.1). The registration focuses on parameters that allow for an objective assessment of the author in the system's context. As described in section 4.2, the KF algorithm currently uses only a subset of information to weight integrated beliefs. Therefore, the remaining aspects are only listed as a precaution and can be used in the future for further analysis to determine the impact of a specific belief.

For the unique identification of each author, an alphanumeric identifier is generated by the blockchain. This identifier is then stored locally in the user's browser and is used to sign each integrated belief block. Based on this signature, the system can consider all the respective author attributes during the fusion process.

With the help of the belief aggregation view, knowledge is gathered in a structured way, transferred to the belief block schema, and processed in a system-compatible manner. For this purpose, the author identifier is first taken from the user's device's local memory. Then, the user needs to determine to which

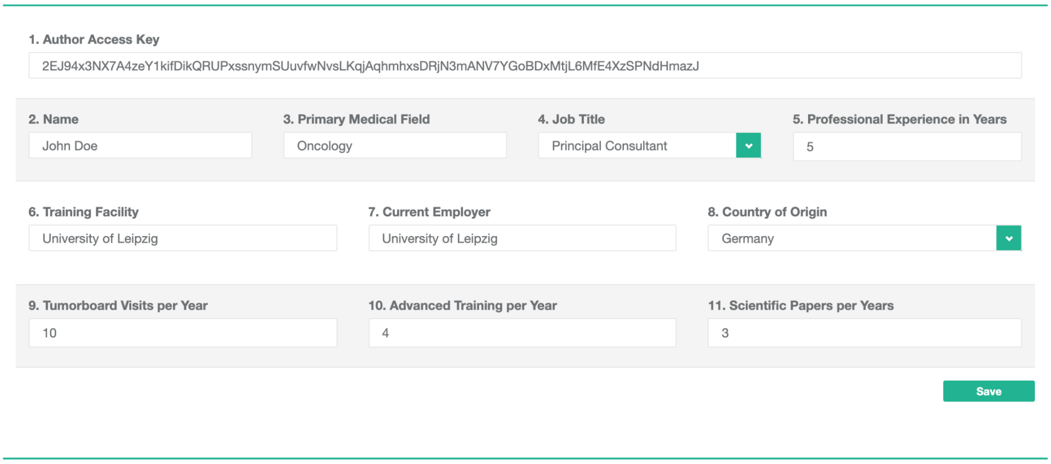


Figure 5.1: User interface for the author registration process

superordinate model the new belief block belongs. An alphanumerical model identifier is requested within the system prototype, which links different belief blocks with a more comprehensive BN model. After this identification process, the user is prompted to provide all information that defines the target node of the BN to be modeled. This includes the name of the respective modality as well as the associated states. The application theoretically allows an infinite number of states per node.

Then, all parent nodes, on which the decision target node is dependent, are modeled in a structured way (see Figure 5.2). Again, there are no restrictions in the system regarding the allowed number of parents. In addition to the information about the node's name and the respective states, it must be specified for each parent node whether the described information is (1) measurable or (2) computable. Thus it is clearly recorded for each node whether information can be directly integrated into a superordinate system context (e.g., a laboratory value from the patient file) or whether the respective information has further dependencies (e.g., medical risk scores or other relevant multi-factor classifications).

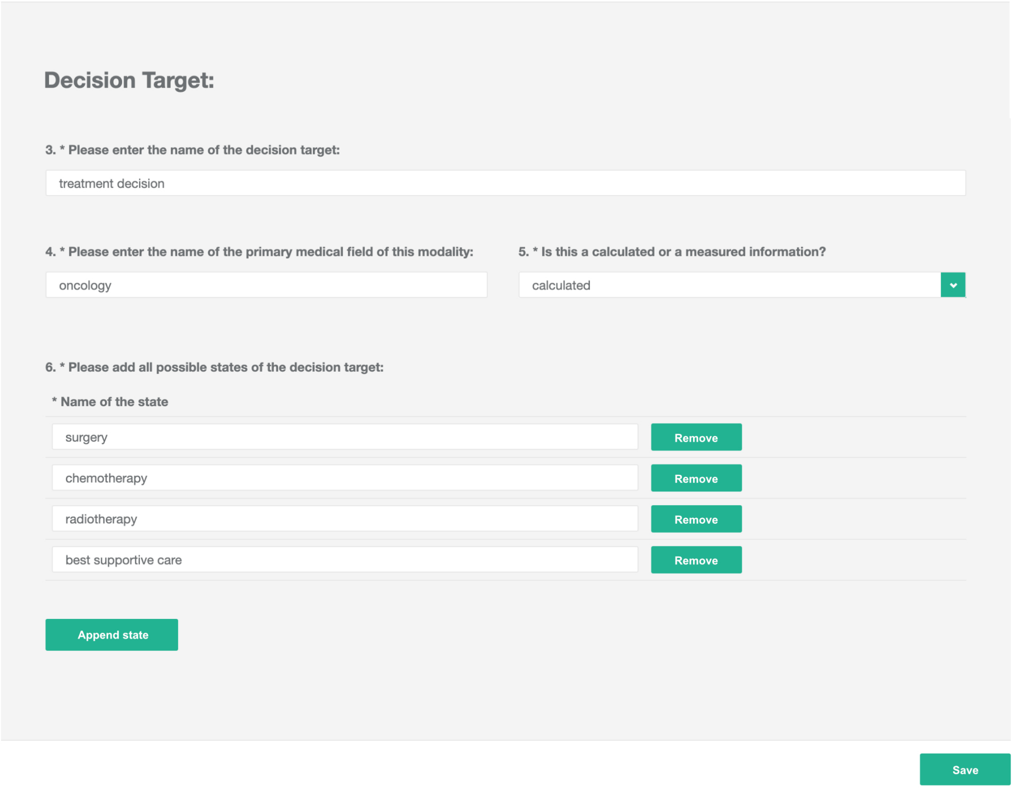


Figure 5.2: User interface for the specification of the decision target node

Since the input of a parent node automatically creates an edge in the resulting BN, which connects the two modeled nodes, a source (e.g., a scientific publication or medical study) can optionally be provided when entering the corresponding modality. This source is then assigned to the edge in the data schema and used to calculate the respective edge weight during the fusion process (see section 4.2).

Based on the previous work by Cypko et al. [58], a matrix from the specified states of the decision target node and the dependent parent nodes was integrated. For each possible correlation of target and parent node states, it can be optionally specified whether an unplausible or dominant relationship exists (see Figure 5.3).

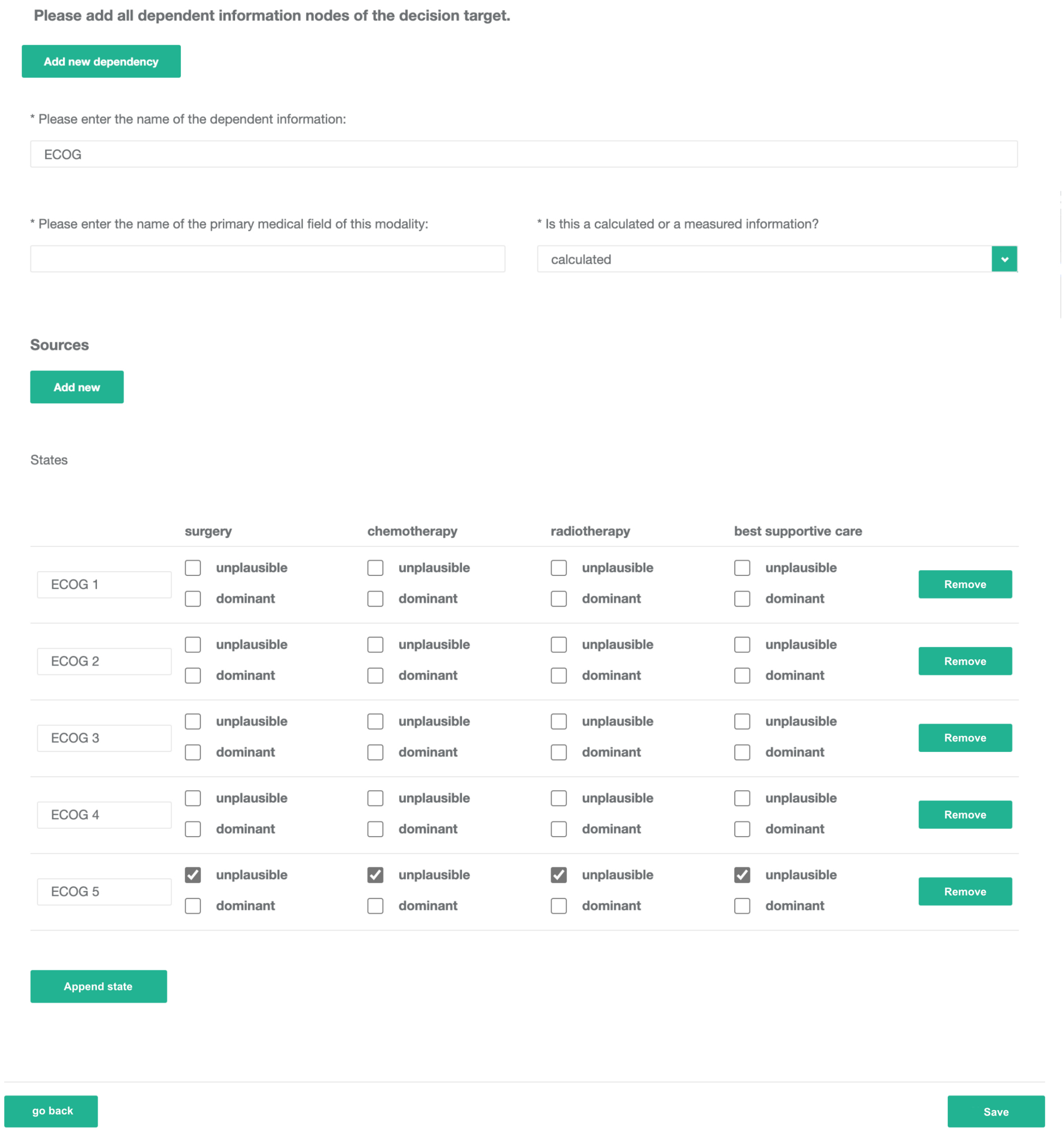


Figure 5.3: User interface for the specification process of all parent nodes

1. **unplaubsible** denotes a relation between states, for which the existence of a property is equivalent to the exclusion of all other states relating to it. In a medical context this would be the case, for example, if the decision target node is *chemotherapy* (i.e., the possibility to give chemotherapy to a patient) with the states *yes* and *no* and the parent node is *ECOG* (a metric for

assessing the general health condition of a patient) with the states *ECOG 0*, *ECOG 1*, *ECOG 2*, *ECOG 3*, *ECOG 4* and *ECOG 5*. In this case, the state *ECOG 5* would be unplausible concerning *yes* regarding the chemotherapy because *ECOG 5* is equivalent to the death of the patient. This constellation would not make any sense, even if other parent nodes tend towards *yes* concerning the possibility of chemotherapy for the respective patient.

2. **dominant** denotes a relation, where a single state is so important for a state in the decision target node that all other states can be safely ignored. In a medical context, this would be the case if the decision target node is *quarantine* (i.e., the decision if a patient has to be quarantined) with the states *yes* and *no* and the parent node is *SARS-CoV-2 infection* (the detection of infection with the SARS-CoV-2 virus) with the states *positive*,and *negative*. In this case, the state *positive* is dominant concerning a *yes* for quarantine, since the detection of the infection is so important for the transfer of the patient into a quarantine that other factors that might have been considered can be ignored in the decision.

Technically, this information is used to automatically set the probabilities in the CPT of the decision target node in the result BN by constructing dominant subsets [58]. While an unplausible relation provides a probabilistic value of 0 for all permutations containing the corresponding state, a dominant relation provides a probabilistic value of 1.

When the belief author has finished the causal modeling process, the probabilistic values need to be captured for the corresponding CPTs. To do so, the method introduced by van Gaag et al. [111] is used. In this case, a natural language formulation of the respective permutation is provided to the user (see Figure 5.4). Authors are prompted to evaluate the respective modality and provide a corresponding probabilistic value that matches their subjective belief. Alongside this assessment, the system also requires a numerical value (on a scale between 0 and 100%) about the individual certainty related to this assessment. To this point, the approach is an adaptation of the solution introduced by Cypko et al. [58]. However, as an extension of the proposed method, the system enables the user to provide further evidence about the assessment in the form of one or multiple sources that allow further traceability of the provided estimates. If statements about unplausible or dominant relations were made, the system would ensure that the respective permutations are not considered in the survey, which also represents an essential factor in reducing complexity for BN modeling [58].

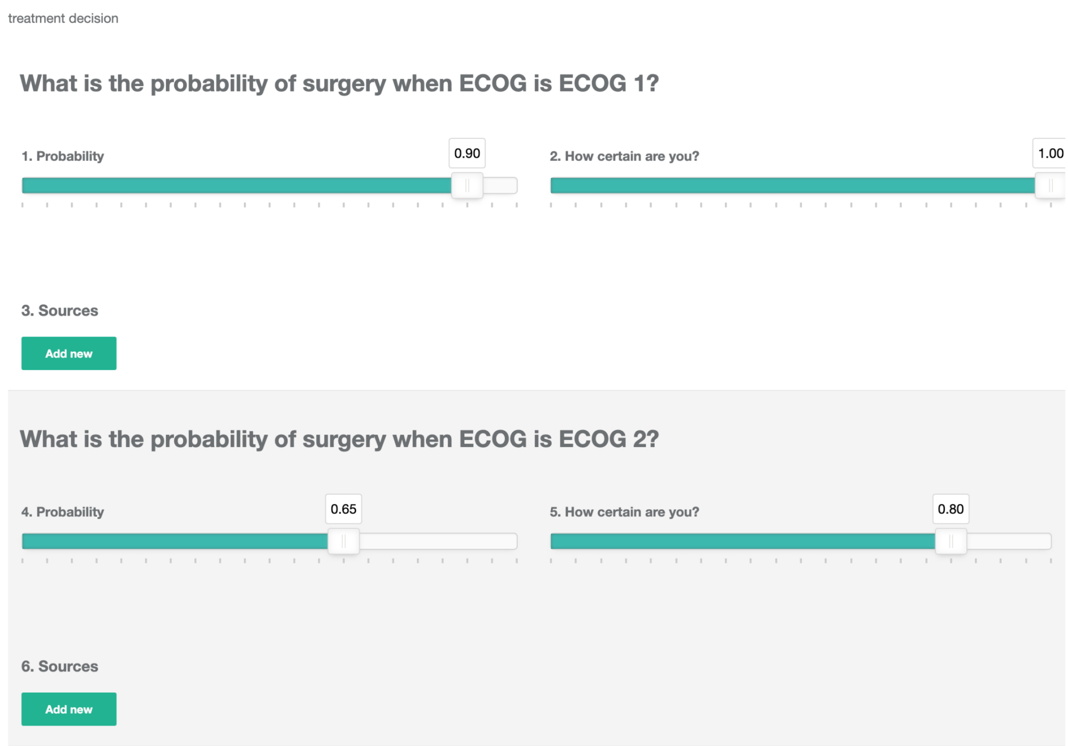


Figure 5.4: User interface for the integration of probabilistic values to each permutation in the CPT

The third view of the system provides the system functionalities related to querying and obtain beliefs from the blockchain storage (see Figure 5.5). Furthermore, it provides the resulting BN after the internal fusion process and allows the export of the BN for further use, e.g., for instantiation with actual patient data for the application of CDS.

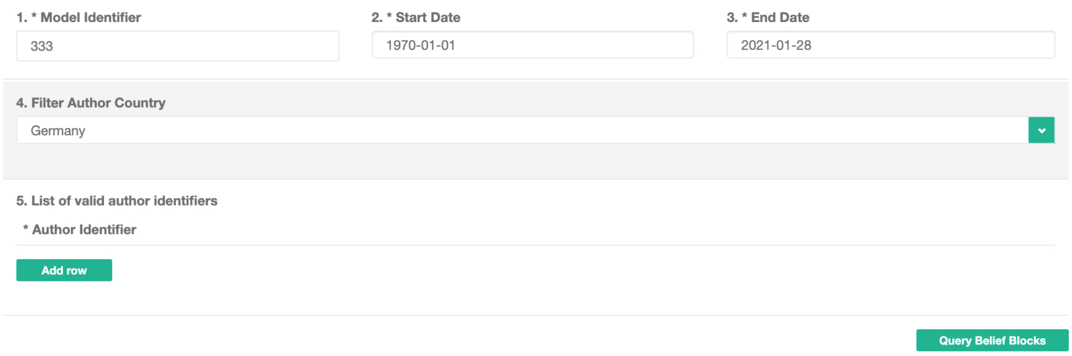


Figure 5.5: User interface for the belief block filter and result BN generation

Using information from the metadata section of the integrated BN, the user can also filter the result set of belief blocks provided to the fusion algorithm based on the following attributes:

- **Model identifier** - this attribute is used to query all integrated belief blocks associated with a superordinate model context (e.g., a specific disease). Setting a valid model identifier is a mandatory input.
- **Start and end dates** - through selecting a start and end date, the user can only query beliefs that were integrated during a specific time period, e.g., to only consider beliefs not older than 5 years from the current date.
- **Country** - as there might be major differences in beliefs based on the residence and work location of a belief author (e.g., caused by the characteristics of the respective healthcare system or differences in patient population), users can choose which countries of origin they want to consider in the KF process.
- **Author identifier** - for an even more restrictive consideration of beliefs, the user can select beliefs by one or more specific authors. In the current state of the system, this requires the specification of authors by their respective ID.

After choices for possible filters have been set, the KF process is initiated on the server. After the system has generated a final BN, the output is presented in a dedicated section using the JGF (see Figure 5.6). Based on this neutral data representation, the result BN can then be converted into other formats to meet the data representation of different CDS tools' formal requirements. In the case of the proposed system, an XSDL converter was integrated, which allows further usage of the BN through the GeNIe software application by BayesFusion [1].

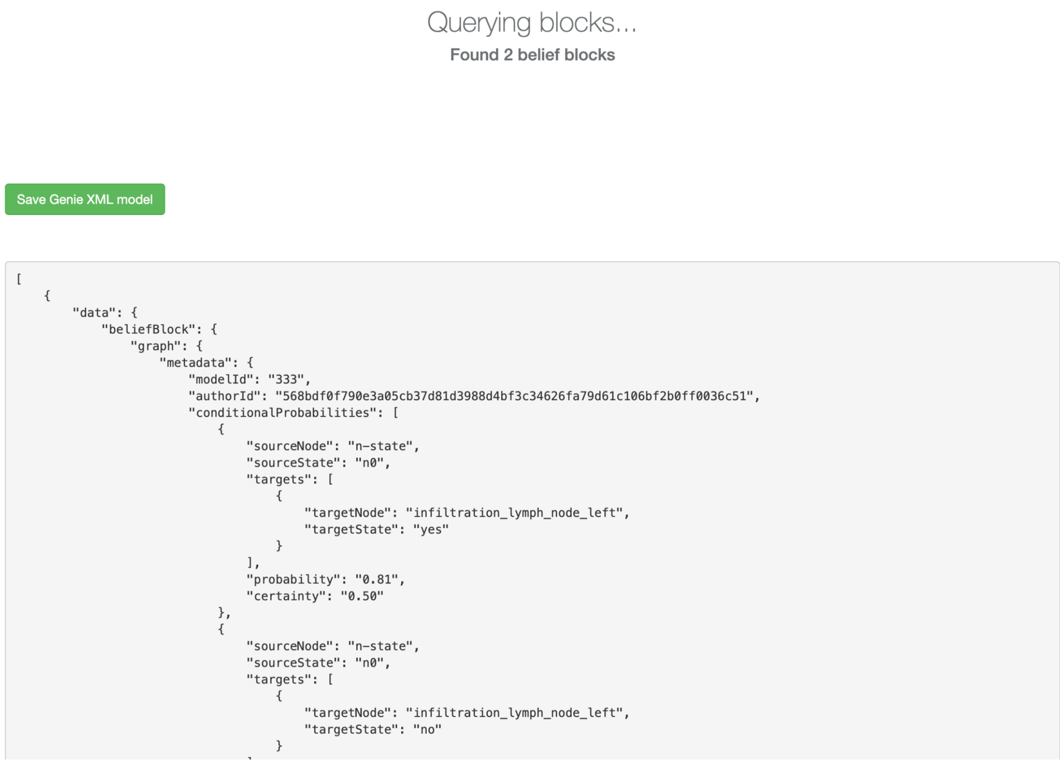


Figure 5.6: User interface showing the output of an example query in the form of a valid BN represented in JGF

5.1.3 System Evaluation

To evaluate the overall system concerning the initially defined objectives, a user study was carried out based on the ISONORM 9241/110-S questionnaire, accord-

[1]BayesFusion GeNIe is a proprietary software application that integrates functionalities related to the graphically assisted development of BNs as well as the integration of structured patient data to perform CDS.

ing to Prümper and Anft [112]. The questionnaire was developed based on the International Standard ISO 9241, Part 110, and serves the qualitative evaluation of factors in the usability of a software system [113]. The questionnaire contains 21 questions, each of which must be answered on a scale with seven options ranging from very bad (1) to very good (7). Those questions are grouped into seven categories: task adequacy, self-descriptiveness, controllability, expectation conformity, error tolerance, customizability, and, learnability, each represented through three dedicated questions. In this way, a software system can be assessed both as a whole and concerning specific properties to detect any potential for improvement in individual areas. A maximum number of 147 points (resulting from a maximum of 7 points for a total of 21 questions) for the overall system and correspondingly 21 points per category can be achieved through a score-based evaluation.

The conducted evaluation study included eleven participants, each with different levels of expertise in their respective professional fields. Of those participants, four had a medical background, four had an informatics background and three others had an informatics background with prior expertise in knowledge engineering and knowledge modeling. During the survey, participants were first given a brief introduction to the system's overall use case and the objective of the evaluation study. Subsequently, a specific task, which was identical for all participants, had to be solved using the system. This task's context was modeling a BN-based belief representing a triage situation, as it is done, i.e., in an emergency room within a hospital. Based on different patient-specific factors, the urgency of the respective case is estimated. By default, the resulting BN comprised one decision target node (urgency) with three states and three parent nodes (respiration, heart rate and neurological status) with two states each.

After the participants generated the BN structure, probabilistic values could be integrated for all resulting permutations using the CPT tool. However, the assessments' medical validity was not subject to the study so no further verifica-

Evalutation Category	**Evaluation Aspect**	**Mean Score**	**Sum**
Task Adequacy	Functional Completeness	6.36	18.45
	Streamlining	5.82	
	Fulfillment of Requirements	6.27	
Self-descriptiveness	Information Content	5.27	13.73
	Potential Support	3.55	
	Contextual Support	4.91	
Controllability	Flexibility	5.18	17.18
	Changeability	5.91	
	Continuity	6.09	
Expectation Conformity	Layout Conformity	6.36	18.18
	Functional Transparency	5.27	
	Operation Conformity	6.55	
Error Tolerance	Error Handling	5.82	17.28
	Correction Ability	5.91	
	Correction Support	5.55	
Customizability	Extensibility	5.09	14.36
	Personalization	4.36	
	Flexibility	4.91	
Learnability	Learnability	6.09	17.72
	Functional Abstraction	6.18	
	Intuitiveness	5.45	
ISONORM Score	**116.90**		

Table 5.1: Evaluation matrix of the ISONORM 9241/110-S questionnaire including eleven participants. The mean score indicates the consolidated assessment score for the respective feature above all participants while the sum represents the combined assessment scores for a evaluation category (maximum score: 21 points). The ISONORM score is the overall sum of all individual categorial scores combined (maximum score: 147 points).

tion steps for the given values were taken. After the respective belief block was generated and added to the blockchain storage, the task was finished. The participants were then asked to complete the ISONORM 9241/110-S questionnaire (see Appendix A) completely to provide a qualitative assessment about the system's usability.

On average, the evaluation showed a positive assessment of the system, with seven aspects rated as very good (between 6 and 7) and ten aspects rated as good (between 5 and 6). Negative outliers of this overall positive result are situation-specific assistance (question 5) and the user interface's adaptability to a user's individual needs (questions 17 and 18). With an overall ISONORM score of 116.90 out of possible 147 points, the presented platform shows a high degree of usability and appropriateness regarding the initial objectives of intuitive and assisted knowledge integration.

5.1.4 Limitations of the Proposed Solution

As a technological proof-of-concept, the current state of the platform has only been deployed as a single node instance, thus does not really take into account the characteristics provided by a decentralized network structure. Since it is not within the scope of this thesis to evaluate the characteristics of a BigchainDB (or other blockchain-based) network, further efforts need to be made to integrate and validate the system's performance and scalability.

Based on the user evaluation study, aspects related to the provision of contextual usage assistance and the system's overall customizability are not satisfactorily enough in the current state. Both aspects form an essential factor in system ergonomics, which were not addressed further in this thesis due to the primary focus on methodological and functional system characteristics. The resulting feedback on those aspects is therefore not surprising but should be considered in further development stages.

5.2 Personalization of Laboratory Findings

The spectrum of HIS ranges from particular applications (e.g., software that accompanies a special hardware device) to pervasive systems (e.g., for clinical documentation or administration), which provide a more ambitious set of features. Current HIS thus offer, for example, the management of a patient's EHR, interfaces to other healthcare applications (e.g., clinical laboratory, Picture Archiving and Communication System (PACS) system) to assist in everyday clinical work. Nevertheless, those systems often offer only insufficient specialization due to their extensive range of functionality and the generalization of clinical use cases. This leads to excessive use of comparatively simple key-value pairs for information display. Especially for the presentation of medical findings, this results in plain and unintuitive representations of the gathered values. This means that their reception entails a high degree of cognitive load for the viewer. Apart from offering a purely numerical representation, current systems also include functions such as color-coding of pathological values or icons which represent the development of values over time. Thus, basic assistance can be provided to allow for a more effective information reception. However, the systemic evaluation of values provided by current systems does not consider the individual patient profile (e.g., disease type, comorbidities, or medication) and its influence on the respective biomedical characteristics. This, therefore, requires a comprehensive evaluation by the treating physician, which is a vulnerable process that can be subject to errors or inefficiencies [114]. These issues are even further aggravated by the increasingly diverse and complex set of available patient data, especially in chronic and long-term treatments. In those cases, laboratory findings act as an essential tool to evaluate the risks and side effects of the respective treatment or treatment combination and the individual response of the patient.

In the case of complex therapies, such as radiochemotherapy in oncology, the allocation of treatment is re-evaluated before each therapy session to monitor tolerability for further doses. During this process, a patient's health status and therapy tolerance is assessed based on the current laboratory findings. Due to this extensive and continuous collection of information, its proper evaluation becomes more complex for the physician. This might lead to problems concerning patient safety, especially in multi-personal care, e.g., through oversights [115]. The use of Health Information Technologies (HIT) for the IT-based support of clinical processes has a high potential for relieving workload. It can thus make a substantial contribution to more effective and better patient treatment. Thompson et al. define HIT as *»[...] the application of information processing in-*

volving both computer hardware and software that deals with the storage, retrieval, sharing, and use of healthcare information, data, and knowledge for communication and decision-making.« [115]. Thus, the systems which utilize HIT, among other things, are intended to assist with automated analysis processes based on presented data. For the radiochemotherapy scenario in oncology, such assistance might be provided through automated value assessment (e.g., by implementing CDS) and intuitive result visualization to enable quick access to the contained evidence. Regarding the consideration of CDS, formalized clinical knowledge needs to be provided to the system to reason valuable assessments of the incoming data [33]. This approach has already shown significant improvements in a variety of clinical applications [36, 37], and laboratory medicine [116]. In regards to the aspect of data visualization, the display of laboratory findings through different types of graphical representations has been the subject of several research studies which showed that their assessment by the user remains a subjective task that heavily relies upon individual taste [117] and the extent of the presented case [118]. Thus, no final statement about an optimal representation format can be made at this point.

The evaluation of laboratory findings through HIS is currently limited to the classification of single values based on fixed evaluation scales. However, those scales might distinguish normal from pathologic states, but they do not consider all influencing factors that impact the individual finding (e.g., disease characteristics, medication, etc.). In oncology, the treatment of a patient is a multi-dimensional problem that requires considering a variety of different patient information simultaneously. Therefore, it is crucial to provide mechanisms that enable the automatic consideration of the multi-factor impact on a single value assessment to provide proper assistance in its patient-centered interpretation.

To tackle the issue of enabling efficient support in the assessment of laboratory findings, a system that supports automatic value interpretation based on CPGs combined with the integration of knowledge-based CDS has been developed. Therefore, the system adapts a BN-based model output which can be generated using the distributed knowledge modeling platform (see section 5.1) to provide the personalized assessments. The application aims to support monitoring long-term treatment procedures while preventing confounding factors such as over-alerting through extended classification of values in regard to their clinical significance for the individual case. Concerning the development process as a proof-of-concept implementation, the system primarily targets the clinical use case of radiochemotherapy in head and neck oncology. However, this focus area does not limit further application in a broader range of clinical use-cases.

5.2.1 Requirement Analysis

To make sure that the initial objective properly addresses medical experts' needs in the respective clinical departments, a Delphi study has been conducted. In this study, the intended IT system's prior requirements and current issues of already existing solutions have been gathered through structured interviews with the relevant stakeholders. The resulting expert group consisted of representatives from the professional fields of medical-, radiological- and head and neck oncology. All participants were situated at the University Hospital Leipzig and had different professional expertise levels based on their respective years of service (see Table 5.2).

Participant	Clinical Department	Years of Expertise
1	Medical Oncology	7
2	Radiation Oncology	24
3	Head and Neck Oncology	6
4	Head and Neck Oncology	7
5	Head and Neck Oncology	13

Table 5.2: Characteristics of the participants in the Delphi study

In each interview, a short presentation about the initial objective of the intended solution was given to determine its significance to the current clinical routine. This allowed ensuring a proper understanding of the relevant technical modalities and associated implications for the future user. According to the characteristics of a Delphi study, this prior introduction was then followed by an extensive feedback cycle that allowed the participant to provide a review of the intended solution and associated topics about possible limitations and issues deriving from the current workflows and procedures of the respective clinical domain. Beginning with the second participant, all gathered feedback from the previous interviews was presented to reveal the previous viewpoints, complaints, and extensions to the concept. After all five interviews had been conducted, a summary of the collected feedback was provided to the whole group of experts to reach an overall consensus.

Information Class	**Information Entities**
hemogram	erythrocytes, hemoglobin, hematocrite, MCH, MCHC, MCV, leucocytes, thrombocytes
differential blood count	leucocytes, lymphocytes, neutrophil granulocytes, eosinophile granulocytes, basophile granulocytes
other laboratory diagnostics	sodium, potassium, chloride, magnesium, creatinine, urea, uric acid, cystatine C, CRP, ALAT, ASAT, AP, gamma-GT, bilirubin, cholinesterase, albumin, total protein, quick, PPT, fibrinogen, TZ, TSH (basal), fT3, fT4
other diagnostics	ECG, transesophageal echo, audiogram, renal scintigraphy
other conditions	presence of PEG tube, surgical extraction (dental)

Table 5.3: Value set of necessary information entities during radiochemotherapy treatment in head and neck oncology

To assess the status-quo on how patient data is collected, processed, and evaluated in the Department of Radiooncology at the University Hospital Leipzig, two individual radiooncologists have been consulted to provide extensive feedback about the characteristics of the current treatment process. This resulted in a series of information entities that need to be considered in clinical routine (e.g., for treatment evaluation, planning, and monitoring). This set of entities (see Table 5.3) then formed the baseline for the system prototype. While most reported entities are defined as numerical values, some are also considered categorical (e.g., ECG, audiogram) and are thus classified by default (e.g., good or bad, present or not present, etc.). This collection of information is equivalent to a required patient profile of measurable entities (see section 4.1.1), which can then be used to instantiate a CDSS.

The Delphi study results showed that the overall objective of providing an automatic knowledge-based laboratory value assessment in combination with intuitive visualization approaches was considered very useful across the group of participants. Furthermore, the study revealed crucial requirements for the intended solution, which needed to be prioritized during development. Those requirements were:

1. The system has to feature a visual prioritization of pathologic values to enhance focus and increase efficiency in reading the laboratory reports. Those visual accentuations should also include warnings to capture the user's attention directly.

2. The deviations from the value-specific reference ranges should feature another layer of visual distinction based on their respective significance for the medical case.

3. The progression of a value over time should be emphasized to better reveal treatment responses.

Those results introduce different levels of technical complexity to be considered for system development. For example, an integration of visual distinctions based on each value's classification (e.g., normal or pathologic) is a comparatively easy to solve problem. It can be addressed by design-related considerations (e.g., color-coding or other visual accentuations). The same applies to integrating views that focus on value progression (e.g., using chart visualizations or timelines). Both of those requirements may also be already addressed through current systems. However, according to the initially stated requirement to enable system-based assistance during the case-specific assessments of the individual findings, the reported need to calculate and integrate value-based significance introduces a more complex problem that requires proper CDS mechanics.

5.2.2 System Architecture

The integral part of providing individualized value assessments is the use of knowledge models that represent the formalized medical evaluation process. To align with the specifications of a BN, the previously determined information entities are first clearly specified through a set of states. For example, a patient's hemoglobin value is defined not only by its actual numerical value but also by previously defined classes, which allow the value to be put into categories (e.g., normal, moderately elevated, significantly elevated, etc.). Using a CPG-based approach, each entity features an initial declaration about when its numerical value classifies it into a specific category. However, this procedure is different when multiple inputs are involved (see Figure 5.7). Hence, the classification is subject to a broader range of dependencies. Due to the utilization of BN-based models, those assessments are made by automatically infering the corresponding output state based on the probability distribution of the decision target node, i.e., hemoglobin (see section 4.2.2).

However, apart from the BN-based classification of the laboratory findings, there are value expressions who carry clinical signifiance by default since they represent severe conditions for the patient and should therefore be treated as warnings by the system. Thus, for the task of providing personalized warnings and

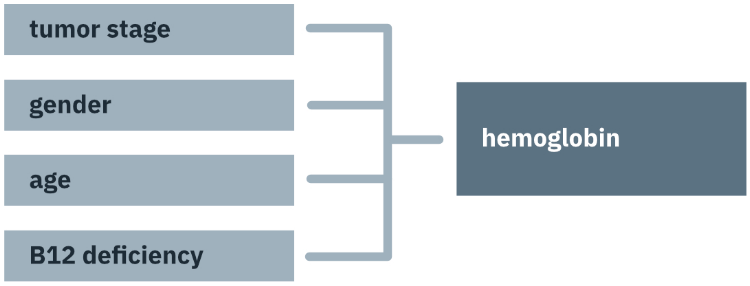


Figure 5.7: Example of a multi-factor classification problem for the medical evaluation of the hemoglobin value of a patient

alerts, the Common Terminology Criteria for Adverse Events (CTCAE) in version 5.0 were considered. Since those classifications represent a CPG, they serve as a determined set of rules which are applied as an addition to the BN-based value assessments on a separate processing pathway.

The actual application comprises two separate components: value assessment and classification based on BN knowledge models (see section 4.1) and the visual display of the corresponding results. Both of them are built on top of the HL7 FHIR specification of CDS services [119]. This enables the technical implementation of the custom evaluation of laboratory values utilizing a FHIR server to retrieve structured and interoperable patient data, and the corresponding handling of CDS results in a consistent way. In this case, the actual FHIR server is provided by a self-hosted instance of Aidbox by Health Samurai [2].

The frontend component is represented as a dashboard view, which allows quick access to relevant data entities of the case file as well as the BN-based assessments (see Figure 5.8). The user interface itself is generated using the VueJS JavaScript framework [3]. This allows for the implementation of rendering conditions for every interface component, e.g., dynamic color-coding or alert handling during runtime. For a more clear separation of concerns, the user interface features three separate sections (see Figure 5.8):

[2]More information about Aidbox is available at `https://www.health-samurai.io/aidbox`.
[3]More information about the VueJS framework is available at `https://vuejs.org/`.

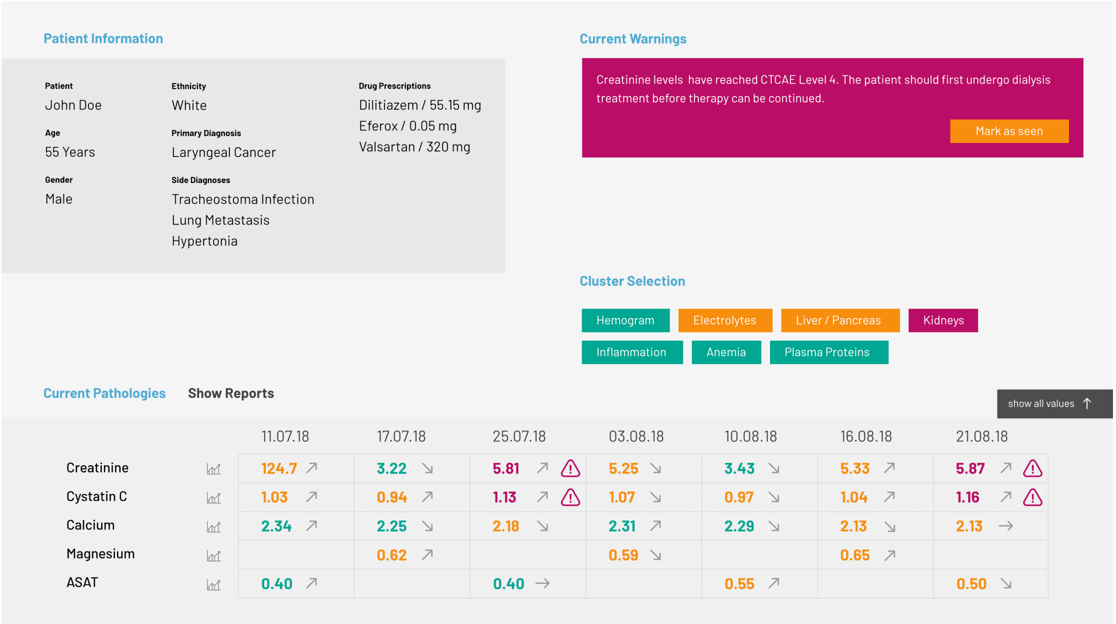


Figure 5.8: The graphical user interface of the dashboard view of the system. Patient characteristics are displayed on the top left, warnings on the top right. The actual laboratory findings are displayed at the bottom. At the initial state, the table-based visualization only shows pathologic values. Through a button (show all values) on the right, the whole laboratory report is revealed.

1. **a patient inspector** which shows patient-based information from the electronic health record,
2. **an alert window** which displays warnings if the evaluation of the values match CTCAE criteria,
3. **the most current laboratory findings report** which uses color-coded highlighting of the evaluation results as well optional line chart visualizations which show the individual progression of a value.

When a patient case is invoked through the dashboard, a `patient-view` hook from the underlying FHIR server triggers the custom CDS service for BN-based value assessment. Therefore, the FHIR resources provided by the Aidbox server (featuring patient-based conditions, attributes, and laboratory measures) are inserted through the `pre-fetch-template` parameter (see Listing 5.1).

```
{
  "services": [
    {
      "hook": "patient-view",
      "prefetch": {
        "patient": "Patient/{{context.patientId}}"
      },
      "title": "Laboratory value assessment",
      "description": "Model-based processing of lab values",
      "id": "lab-value-assessment"
    }
  ]
}
```

Listing 5.1: Example of a FHIR pre-fetch-template which provides patient-related data to the CDS service

The CDS service will then calculate the probability distribution of the decision target node, classify the value based on the state with the highest probability, and return the evaluated result as a FHIR `card` object for rendering in the dashboard view (see Listing 5.2). In addition to the structured representation of all CDS-related facts for this process, the respective `card` object also features an evaluation indicator for the individual value, i.e., either *normal*, *pathologic without clinical significance* and *pathologic with clinical significance*. This indicator is then used during rendering of the user interface to provide the correct color-coding for each value expression. If the evaluation results in a critical state of a value, warnings are generated (see Listing 5.2), which will trigger emphasized alerts in the user interface (see Figure 5.8).

```
{
  "cards":[
    {
      "summary": "CTCAE stage 2 warning - transfusion indiated",
      "detail": "the Hemoglobin value is below 8.0 g/dL",
      "indicator": "warning",
      "source": {
        "label": "U.S. Department of Health and Human Services",
        "url": "https://ctep.cancer.gov/"
      },
      "suggestions":[
        {
          "label": "hemoglobin is 7.2 g/dL - transfusion is indicated.",
          "actions": [
            {
              "type": "update",
              "description":"hemoglobin is 7.2 g/dL - transfusion is indicated.",
              "resource": {< name of the FHIR resource to be updated >}
            }
          ]
        }
      ]
    }
  ]
}
```

Listing 5.2: Example of a FHIR card object which provides a warning due to the fulfilment of a critical CTCAE threshold

5.2.3 Limitations of the Proposed Solution

The Delphi study, conducted as a prior evaluation of clinical needs and requirements in the context of assessing laboratory values, revealed an overall consensus about necessary features for IT-based assistance for the intended use case. However, due to the limited amount of participants from only one medical facility, the results have a subjective character that might not be adaptable to other facilities without further adjustments. Furthermore, the developed system's actual value needs to be further evaluated in a prospective scenario to better estimate its potential and associated benefits. This, however, would require multiple precautions related to technical (e.g., integration of the system into already existing clinical and laboratory information systems) and ethical and patient-safety aspects (due to the general risks associated with CDS).

5.3 Dashboard for Collaborative Decision-Making in the Tumor Board

The evaluation of possible treatment options in oncology is a complex decision problem as it involves the participation of multiple clinical modalities and a wide range of information that needs to be considered by the physicians involved in the process. The common way to deal with those issues in the clinical routine is through the conduction of interdisciplinary tumor boards. In those meetings, multiple experts from associated diagnostic- and therapy-related medical fields (depending on the respective oncologic entity) collaboratively discuss each patient case individually.

In addition to the high demands on the cognitive performance of the tumor board members during the consideration of the heterogeneous information fragments, there are also issues related to an effective administration, processing, and communication of the case-related data [66]. As discussed by Gaebel et al., another quality-related problem is introduced by outdated findings that might have a crucial impact on evaluating the patient case [89].

From a process-oriented perspective, each medical case discussed in the tumor board is first introduced through a physician with a profession that matches the patient's oncologic entity, e.g., a head and neck physician if the patient suffers from head and neck cancer. This particular physician is also responsible for providing all necessary information to all other participants who might have never met the patient in person. If further information about the case is available, the corresponding facts are presented through a representative of the respective medical field, e.g., a radiologist or pathologist. In this way, the abstract picture of the individual case, which is presented only through medical facts, needs to provide a precise presentation of the current situation to ensure informed decision-making.

Based on previous analysis of the current situation in the head and neck tumor board meeting at the University Hospital Leipzig (see Figure 5.9), the local conditions consist of two information displays. One is used for the provision of radiological imaging (e.g., CT or MRI scans), and the other one is either used for additional, mostly also imaging-related, information, e.g., from panendoscopy or the EHR of the patient in the hospital's HIS.

Figure 5.9: View of the head and neck tumor board at the University Hospital Leipzig. Several displays are available to review different information modalities from different sources such as radiology, pathology, or endoscopy. However, the patient's presentation and characteristics are still mostly paper-based or presented verbally to the participants.

Considering the complexity of medical case evaluation, the amount of information to consider might as well be overwhelming to some [120]. Based on the works of Halford et al., it was shown that the human mind is only able to process four independent variables simultaneously [121], which emphasizes the need for methods that substantially reduce the sheer complexity of information to effectively prevent overload. One way to achieve this is to utilize visualization, which is a more accessible approach to information communication than raw textual representations [122].

In other professional domains, such as business analytics, the utilization of dashboard views for the presentation of data is a popular tool to provide domain-specific metrics and information for various use cases. If a dashboard is implemented properly, associated benefits include quick information reception even if they need to be gathered from various data sources [123]. Furthermore, they can also provide efficiency for decision-making [124], which can be adapted to the medical domain, and the tumor board scenario, respectively [125]. In this case, the dashboard view might automatically gather all necessary case-related data from the clinical subsystems and utilize different visualization techniques to enable quick and intuitive information access [64].

Due to the hospital being a very time- and error-sensitive environment for information handling in general, the implementation of new systems that might impact decision-making requires extensive planning and conceptualization. Those systems also need to be user-centric to provide valuable assistance in clinical routine. One appropriate way to achieve this by implementing an Information Architecture (IA) process to determine the specific requirements before the actual technical development. This process defines how information is organized in a digital environment or system and provides a dedicated Map of Information (MOI) of all entities that need to considered [126].

To even further reduce the cognitive load of the tumor board participants, CDS can be utilized as a tool to provide data-driven assessments of the respective situation, e.g., by calculating various relevant medical classifications or scores or by making predictions about possible therapeutic outcomes based on simulation.

5.3.1 Requirement Analysis

Based on the works by Pauwels et al. [124], the development of a dashboard is an incremental process implemented in five stages:

1. selection of key-metrics to be featured in the dashboard,
2. population of the view with relevant data,
3. establishing interconnections of the considered information entities,
4. integration of use case scenarios and forecasting methods,
5. connection of the system to surrounding processes and units.

Although the work relates to the development of a dashboard in the business and enterprise domain, e.g. in marketing or strategic management, the universal nature of those five steps can also be adapted for the tumor board scenario, since both use cases feature data-centric and interdisciplinary decision-making [65]. To evaluate the actual clinical need and the requirements derived from clinical routine, a qualitative survey with a focus on steps (1) and (3) was conducted. The limitation of those two steps is based on their relation to an IA process and steps (2), (4) and (5) are related to the actual technical implementation stages of such a system and require an extensive prior analysis of a hospital's IT infrastructure.

The process used to collect the necessary information is based on Understanding Environments and Work Practices (UWP), a concept used to better understand the future application context of a system and thus to develop better products. The implementation of this concept is based on qualitative surveys or the observation of future users and corresponding derivation of quality parameters

Participant	Clinical Department	Years of Expertise
1	Head and Neck Surgery	12
2	Head and Neck Surgery	6
3	Head and Neck Surgery	5
4	Radiology	19
5	Radiation Oncology	23
6	Radiation Oncology	6
7	Medical Oncology	12
8	Pathology	15

Table 5.4: Characteristics of the interdisciplinary medical experts who were selected for the UWP study due to their role in the head and neck tumor board.

[127, 128]. For the implementation of the IA process to develop a dashboard view for the tumor board, an intensive analysis of the status quo was conducted. The focus of this work was on the head and neck tumor board of the University Hospital Leipzig. Based on this analysis, all of the involved systems and processes and necessary participants of the meeting were identified. The characteristics of the participants with regard to the respective clinical department and individual professional experience can be found in Table 5.4.

During the survey, the context of the investigation and the IA process characteristics were explained to each participant. They were then asked to reflect on the tumor board scenario and identify the essential information entities required for decision-making. The assumption was that they had never seen the patient in person and only had to assess the situation based on the available facts. After all entities were gathered, a prioritization was performed to determine the information's hierarchy and importance. For this purpose, the respective values were classified to either have a *high significance* or a *low significance*. Subsequently, it was discussed which specific data can be easily extracted from the EHR and which ones require further pre-processing, e.g., multi-factor classifications or medical scores.

In order to be able to support decision-making in the tumor board with a dashboard, the information to be considered must be put into a relevant context (stage 3 of the IA process). This is the case, for example, when information indicating an effect (e.g., specific risk factors or comorbidities) is linked to the respective causes (e.g., laboratory findings or other test results). To adequately implement this causal link for the head and neck use case, the participants were asked to contribute to the modeling of these relationships. Following the individual interviews, the summarized overall results were presented to all participants to ensure a consensus.

The surveys revealed that the basic installation of a dashboard view in the tumor board could make an important contribution to the meeting's efficiency and quality. In particular, the added value of a uniform overview of all diagnostic findings and the general standardization of the case review for all participants was emphasized. As a result of the IA process, 41 information entities were identified, necessary for a case review in the head and neck tumor board (see Figure 5.10). These entities could then be classified into the following groups: patient metrics (27 entities), disease metrics (11 entities), and process metrics (3 entities). Within these groups, 20 entities have *high signifiance* and 21 have *low signifiance*.

A special feature of the head and neck tumor board is the availability of specific information at different times. If a patient has not received surgery as a first-line therapy, no pathological findings of the tumor can be considered. In this case, some values, such as the classification of the tumor according to TNM [4], are handled differently. In the case of TNM, for example, clinical stages (derived from the radiological image information) and pathological stages (derived from the histological findings of the surgically extracted tumor) are used.

[4]The TNM staging system enables the classification of the tumor (T), lymph node (N) and metastases (M) characteristics for an oncologic entity based on multi-factor measures and assessments [129].

Concerning the causal relationship of the information entities, the survey of the experts revealed a total of 23 relevant information links, which were compiled into a MOI (see Figure 5.10). The underlying structure represents the direction from cause to effect.

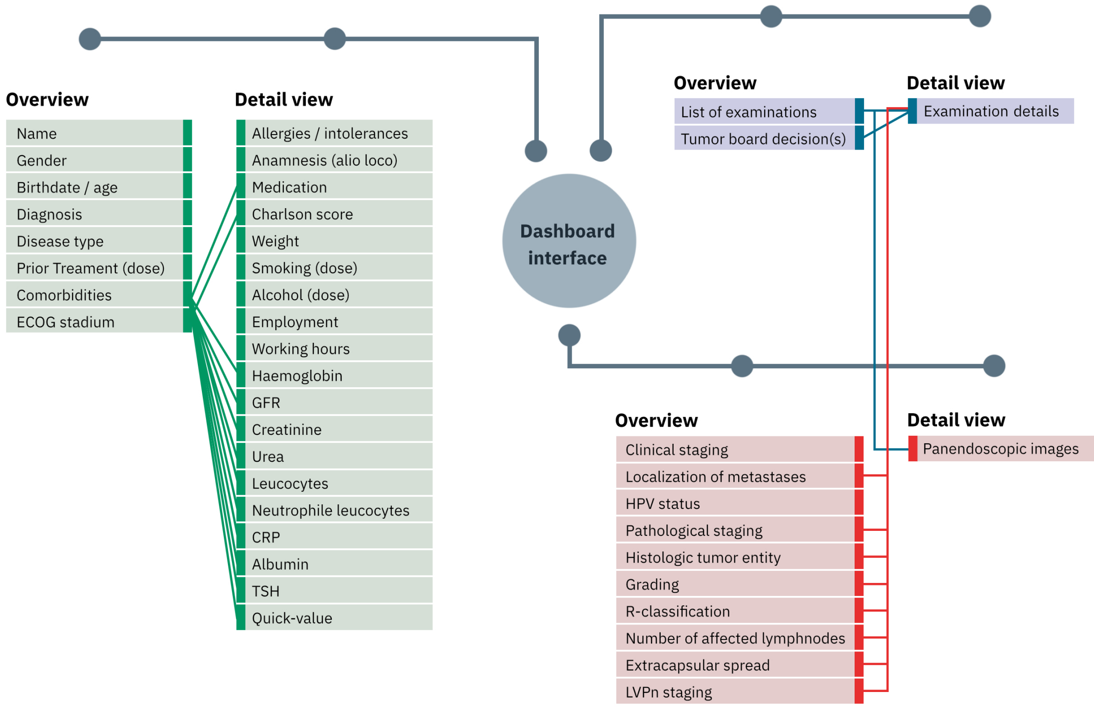


Figure 5.10: MOI for the head and neck tumor board derived from the conducted qualitative survey. The items which were evaluated to have a high signifiance are listed beneath the *Overview* titles and the items with low signifiance are listed beneath the *Detail view* titles.

Based on this dedicated selection of information that needs to be considered in therapy decision-making for head and neck cancer, a patient profile can be generated. This profile contains two different categories of values. On the one hand, deterministic values which represent self-contained evidence, e.g., age, diagnosis, comorbidities or weight. On the other hand, values that depend on multiple factors, e.g., charlson score, laboratory findings (see section 5.2), stagings and medical scores. For the provision of sustainable assistance, the latter category can thus benefit from the application of CDS. Here, analogous to the systems from sections 5.1 and 5.2, the need arises for the integration of knowledge models, e.g., through dedicated BN.

5.3.2 System Architecture

To translate the IA process results into a graphical representation, a dashboard application was developed. It considers the medical experts' gathered feedback (see Figure 5.11). To take into account the hierarchy of information, based on their respective significance, the results were separated into an overview and a detail view. This division is based on the visual information-seeking mantra of Ben Shneiderman *»Overview first, zoom and filter, then details-on-demand.«* [122]. The overview layer is further split into three groups: patient, disease, and process metrics, which act as separate visual components. Based on the created MOI, each of these components also has a dedicated detail view, displaying the corresponding information entities with *low significance*. These detail views can be triggered through items in a sidebar navigation and are displayed in a fullscreen mode to consider the spatial conditions and the distance to the screen in the tumor board setting. Furthermore, a dedicated detail view for laboratory findings was implemented. This view features the presentation of results from the personalized assessment of the laboratory values according to the system introduced in section 5.2.

Regarding the process metrics, a grid-based listing was implemented, displaying the events sorted by the respective finding's timestamp in descending order (see Figure 5.12). Each event is displayed as a single container object that features the examination's name, the corresponding results, and the age of the information concerning the tumor board's date. In this way, the user can easily check if the respective information is up-to-date and should be considered for decision-making [63].

As an extension to the identified metrics, a dedicated view for the instantiated CDS-based therapy selection was generated. For the proof-of-concept imple-

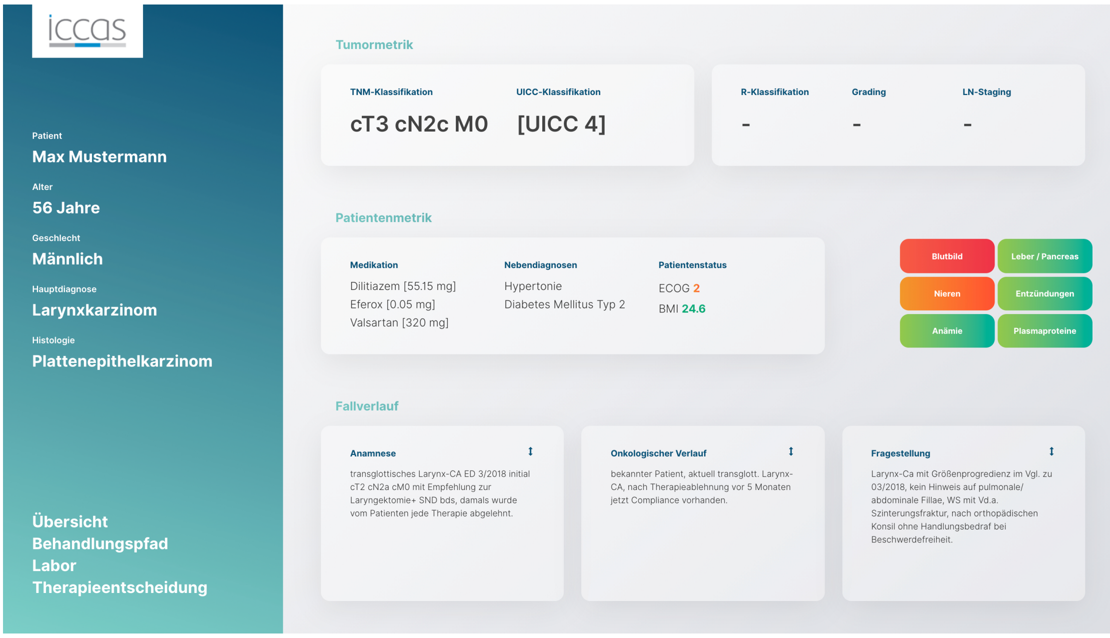


Figure 5.11: Overview of the head and neck tumor board dashboard system. The user interface features separate components that contain information clusters. In this way, a clear and purely data-based image of the patient can be presented to all tumor board participants.

mentation, the TreLynCa therapy decision model by Cypko et al. [57] was considered for the provision of a therapeutic suggestion. The model is based on a BN which evaluates different therapeutic options for patients with laryngeal carcinomas. However, this particular component is interchangeable and might be adapted to other oncologic entities as well, e.g. by using BNs generated from the distributed knowledge modeling platform (see section 5.1). The detail view features the primary and secondary therapy suggestion, which can be derived from a BN in the form text-based representations by selecting the option with the highest and second-highest value from the probability distribution of the decision target node. Furthermore, a visualization of the model-based reasoning results in the form of an icicle plot, according to Kruskal et al. [130], is provided. This visualization allows for assessable traceability of the decision-making pathway through hierarchical clustering (see Figure 5.13).

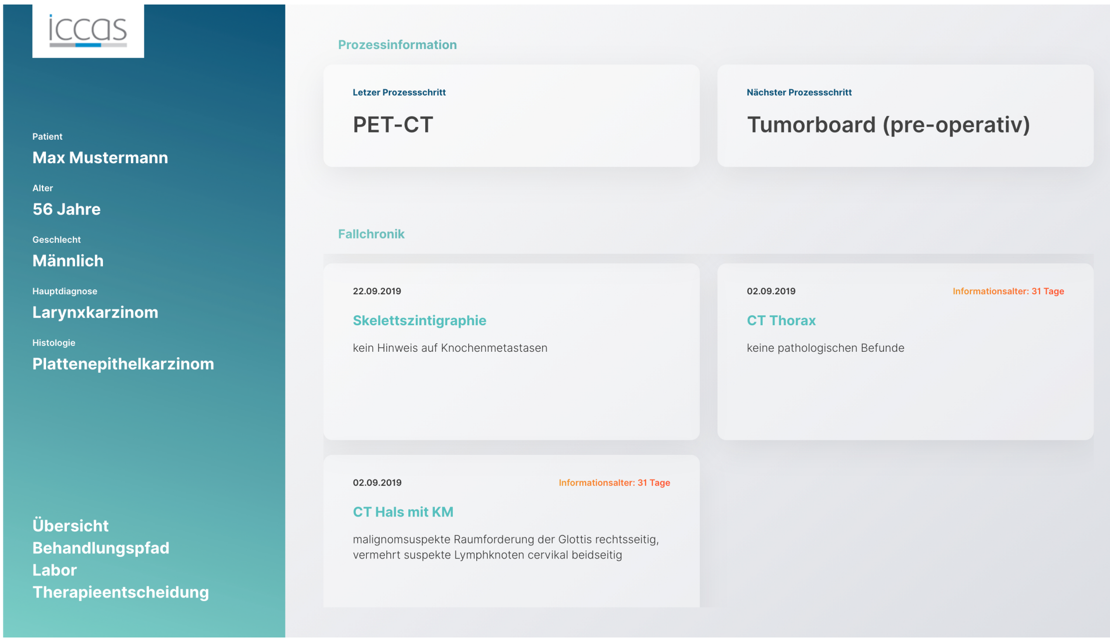


Figure 5.12: Detail view of all available findings for the respective case in a grid-based view. Each entity shows the type of intervention, its respective outcome as well as a warning if the information exceeded a certain age.

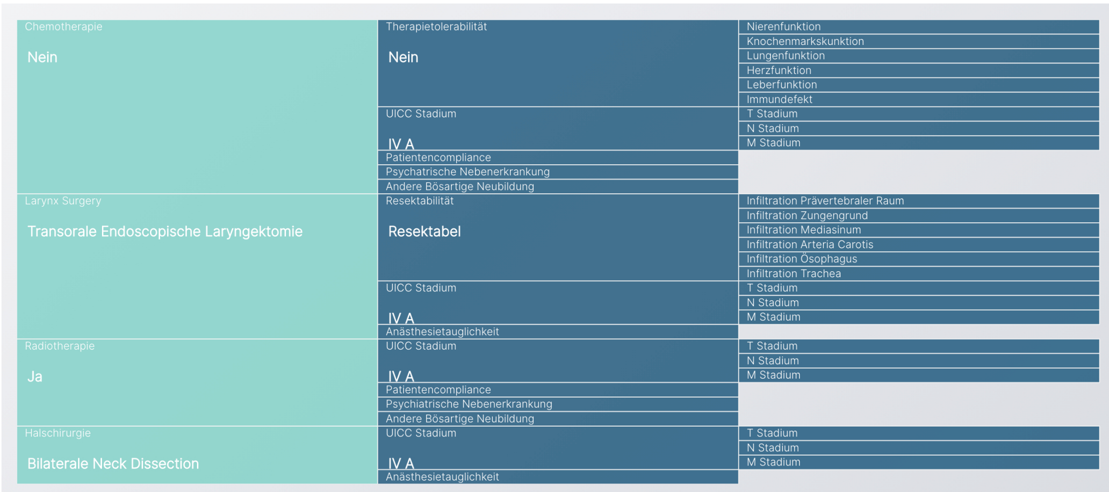


Figure 5.13: Detail view of the head and neck BN decision model based on an icicle plot. On the left, all possible treatment options are shown. By following a cause-to-effect schema, each option is accompanied by its direct dependencies (parent nodes in the BN) and their respective most probable state for the current case.

Due to the utilization of BNs for CDS in this case, result networks derived from the fusion of beliefs related to a specific disease, provided by the distributed knowledge modeling platform introduced in section 5.1 of this thesis, might be used. This would also allow the continuous consideration of current beliefs about the respective disease since each result BN might be generated exclusively for each tumor board session if proper concepts for quality assurance are considered.

5.3.3 Limitations of the Proposed Solution

The conducted survey resulted in an exact IA, which represents the general assessments of all participants involved in the head and neck tumor board. For this reason, the collection has an interdisciplinary relevance, providing a detailed picture of the patient from all necessary medical perspectives of the use case. However, due to the monocentric survey at the University Hospital Leipzig, the results might not be directly transferable to other centers or clinics. This would result in adjustments to the MOI and corresponding changes in the resulting dashboard system. Directly transferable, on the other hand, is the IA process, which can be carried out independently of the respective use case.

Due to the focus on the conceptualization of the dashboard system, no evaluation of the improvement in regards to efficiency and quality in the tumor board was carried out in this thesis. This would first require the final development of the dashboard and its integration into the clinical IT and process landscape to reduce additional data management effort. Based on a production system, performance studies can then be conducted to evaluate the system's intended advantages compared to the current status quo. Furthermore, aspects of information and user interface design gain an increasingly important role in the evaluation of IT systems [127]. Appropriate studies for evaluating usability and user experience of the system are, for example, user feedback evaluation, field observation with additional evaluation questionnaires (see section 5.1.3), and specific usability tests [128].

Chapter 6

Discussion

In general, CDS is a field with various perspectives that need to be discussed. On the one hand, this includes the methodological and technical factors for the provision of CDSS as part of a higher-level clinical IT infrastructure. On the other hand, there is the perspective of the importance of CDS in the patient context and the possible consequences for him or her resulting from this purely rational, data-driven case evaluation.

This thesis has primarily approached the technical aspects of knowledge-based CDS and presented a solution on how knowledge can be captured and represented in a structured way in the form of belief blocks on the methodological foundation of BNs. While the mere storage of knowledge is of great importance in medical knowledge management, further measures are necessary for the development of actual assistance systems, e.g., to implement calculative processes in the context of CDS. Essential here is the compliance with framework conditions, which underlie the mathematical basis of the CDS algorithms. In the case of BNs, this is the assurance of a DAG structure. Derived from the goal to technically enable an unlimited collection of knowledge, adjacent methods must meet these requirements. This includes the fusion of knowledge fragments that address the same modality and integrate algorithmic functions that ensure corresponding compliance with the DAG criteria. Both aspects were presented in the context of this work with corresponding solution proposals (see section 4.2).

Due to the strong focus on the methodological way in which knowledge can be collected, formalized, and ultimately fused in a distributed manner, some aspects related to the practicability of such a system could not be fully considered in this thesis. First and foremost, this includes the consistent provision of interoperability of the modeled facts. For the novel KF algorithm presented in section 4.2, information entities must always be labeled in the same way so that they are considered as equal modalities. The system uses a simple string matching of the provided terms to achieve this in its current state. If two belief blocks model an identical modality, e.g., *chemotherapy*, both decision target nodes need to have the same spelling of the term. This also applies to all states of the respective node. While this aspect is not necessarily a disadvantage, it requires strict terminological control because a belief block with a spelling mistake would currently not be considered. To do justice to this aspect, a more advanced version of the system could also make use of medical ontologies, such as SNOMED-CT for anatomical information and LOINC for the unambiguous assignment of laboratory terms. While the user is entering the respective facts, an automatic comparison with the concept defined in the ontology could be performed. However, due to the system's general and non-restrictive specification, there is also a risk that existing ontologies do not cover certain facts. Especially in the context of medical information, there are large intersections to facts of many contexts, e.g., factors of the social or geographical environment of a patient. Therefore, a valid concept for dealing with these entities must be created to enable an automatic comparison of the modalities.

The use of fragmented beliefs as a foundation for knowledge-based CDS raises questions with regard to ensuring overall validity. Thus, prior to an application in clinical practice, it must first be guaranteed that the assessments captured in the BN-based beliefs are correct and justifiable from a medical viewpoint. Only in this way can it be ensured that the conclusions drawn from the calculated options are valid and thus suitable for significant assistance. This also needs to be adressed through proper mechanisms of quality assurance regarding the users, or more specifically the belief authors, of the considered knowledge. Possible solutions might include peer-reviews or mechanisms of prior authorization to ensure trustworthiness.

Even a decentralized structure, like the platform presented in section 5.1, requires a robust IT governance to validate the system and the managed beliefs. Furthermore, this process must ensure that harmful factors resulting from the compilation of the knowledge base should be effectively prevented. This includes, for example, aspects such as decision bias due to the lack of heterogeneity or number of participating authors, the lack of transparency and comprehensibility of the provided facts (e.g., due to incorrect or non-existent sources), and continuous methodological validation (especially during the KF process) to avoid causal or structural errors.

A major requirement for the provision of personalized medicine, and treatment decision-making as a crucial factor in this context, is the availability of valid and structured data that can be used in an interoperable way. Especially for CDS, which apart from the knowledge base also requires patient data to instantiate the reasoning process, a very granular and expressive data handling procedure is required. Also emphasized by the fact that this data might need to be gathered from various clinical subsystems and documents. Current data specifications, such as HL7 FHIR, already provide extensive concepts for effective clinical data management and sharing. However, there are still only a handful of applications available which support the specification. Even beyond those issues related to availability and compatibility regarding current HIS, a major paradigm shift is needed towards clinical documentation since it currently still heavily relies on heterogeneous information management (both digital and paper-based) and is primarily based on unstructured and narrative texts.

In order to overcome this unfavorable status quo in terms of clinical data management, new systems which allow for automatic gathering, processing, and storing of granular patient information need to be established and implemented into the current hospital IT infrastructures. Although those systems might be tied to a specific use case or clinical department, they need to be interoperable with other information systems in the IT landscape to reduce redundancies and sources of error substantially.

Even if CDSS will become one day largely accepted by medical users due to significant objective improvements in clinical practice, the question remains whether patients share this assessment. Ultimately, a new component, namely the computer, will be integrated into the decision-making process, which was previously carried out either by the physician alone or together with the patient through shared decision-making. While the current trend is towards increasing patient involvement in the therapeutic process [21], it is unclear whether consulting a computer system as a third component in this process will be an advantage or a disadvantage in the long-term.

6.1 Goal Achievements

Initially, four inital objectives were introduced, which were to be addressed through solutions presented during the course of this thesis. For a transparent mapping of those objectives to the corresponding implementations, each one is thus evaluated separately.

Objective 1: Structured Belief Aggregation
To meet the objective of structured belief representation for CDS, a data schema based on JGF was developed and presented in section 4.1. This schema enables the extensive digital representation of beliefs in the form of valid BNs. It is used for the primary capture of causal relationships and for a large amount of meta-information, which can be used in the context of higher-level systems (e.g., source references and information about the author of the respective belief). In order to make the formalization of beliefs intuitive for the user, a dedicated tool for gathering the required information was developed and presented in section 5.1. To validate this approach's quality regarding usability and general suitability, a user study based on an ISONORM 9241/110-S survey was conducted.

Objective 2: Development of a Method to Handle Opposing Beliefs
The developed system allows an unlimited collection of beliefs by different authors and thus also the unhindered modeling of facts according to each author's own interpretation. Since this process can lead to contradictions in the respective facts' causal relationships, a KF algorithm was developed and explained in detail in section 4.2. By utilizing edge weights, which are calculated based on different factors, the resulting conflicts are resolved automatically by the system. A further validation step of the resulting graph structures ensures that the KF process's result is always a valid BN.

Objective 3: Ensuring Long-Term Integrity
To provide long-term integrity of the integrated beliefs, a distributed knowledge modeling platform (see section 5.1) was developed using a blockchain data storage. Due to the characteristics of the blockchain itself (see section 4.3), there are significant advantages concerning the stored information's immutability. Also, a filter mechanism for the individual selection of beliefs from the blockchain storage was developed, enabling the user to set his or her individual qualitative requirements on the beliefs to be considered based on various factors and to use these at his or her own discretion for further processes.

Objective 4: Identification of Suitable Medical Applications
To illustrate the practical application of the methodology described in chapter 4 through practice-oriented approaches, two proprietary systems were presented in sections 5.2 and 5.3, which show knowledge-based CDS in the context of personalized laboratory finding evaluation and collaborative therapy decision-making in the tumor board. Both systems were first conceptualized by qualified methods together with representative user groups and then implemented in the context of a dedicated proof-of-concept.

6.2 Contributions and Conclusion

During the course of this work, mechanisms to capture, gather and process medical knowledge with the goal to enable significant CDS have been presented. This is intended to provide a novel approach to the collaborative exchange and utilization of knowledge and opinions that transcends the boundaries of individuals, departments, institutions and healthcare systems. However, as already discussed in several previous paragraphs, those provided solutions only represent a fraction of the necessary research and development needed to truly enable scalable distributed knowledge generation in healthcare. Apart from tasks related to the robust and intuitive provision of a holistic IT platform for medical experts, solutions regarding quality assurance, standardization, internationalization, deployment and especially integration into existing IT infrastructures still need to be properly adressed.

When in the mid-1980s of the 20th century the first investigations on the applicability of computer systems in the context of CDS were carried out (e.g., the INTERNIST-1 system), one of the main actors of this development, Randolph A. Miller, formulated the following statement *»Limitations in man-machine interfaces, and, more importantly, in automated systems' ability to represent the broad variety of concepts relevant to clinical medicine, will prevent 'human-assisted computer diagnosis' from being feasible for decades, if it is at all possible.«*, which later became known as the so-called *standard view* [131]. Derived from Miller's words, there is a fundamental skepticism about a computer system's ability to take over tasks related to the basic competence of a physician, e.g., making diagnoses, evaluating risks, or deciding on therapeutic measures. However, with the continuous development of IT systems and methodological principles, this assumption had to be largely reconsidered over time. As a result, the question is often no longer whether a computer system can be used for assistance, but rather if it is ethically justifiable and methodologically accurate [21]. As a result, new challenges arise, which are more related to the system's correct use and the resulting interpretation of the provided results.

The development and establishment of algorithms and systems for the comprehensive assistance of clinical processes represent an essential aspect in dealing with the constantly increasing amount of medical data and available information. Nevertheless, the generation of medical evidence still relies on empirical data, which can be derived from single or multiple investigations and studies. The infinite diversity in the way the resulting knowledge is obtained can therefore only have a universal claim if the corresponding results and experiences from different sources are compiled and evaluated to detect and overcome resulting consensus or dissent. International exchange is thus an essential feature for the establishment of holistic knowledge bases on specific disease patterns.

This overarching goal also generates several technical questions, which become clear in the context of the compilation and utilization of the identified evidence. First and foremost, they concern about how knowledge can be mapped in such a way that it can be further used in the context of computer-based systems. At present, the implementation of CDS systems mostly represents a disruptive intervention in clinical practice, as most medical decisions are still based on the physician's cognitive performance for various reasons. Thus, the precise analysis of the respective circumstances becomes crucial to ensure the most holistic assistance possible and achieve the most effective collaboration between humans and machines.

Chapter 7

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Zusammenfassung der Arbeit

Dissertation zur Erlangung des akademischen Grades: Dr. rer. med.

Distributed Knowledge Modeling and Integration of Model-Based Beliefs into the Clinical Decision-Making Process

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Das Treffen komplexer medizinischer Entscheidungen wird durch die stetig steigende Menge an zu berücksichtigenden Informationen zunehmend komplexer. Dieser Umstand ist vor allem auf die Verfügbarkeit von immer präziseren diagnostischen Methoden zur Charakterisierung der Patienten zurückzuführen (z.B. genetische oder molekulare Faktoren). Hiermit einher geht die Entwicklung neuartiger Behandlungsstrategien und Wirkstoffe sowie die damit verbundenen Evidenzen aus klinischen Studien und Leitlinien. Dieser Umstand stellt die behandelnden Ärztinnen und Ärzte vor neuartige Herausforderungen im Hinblick auf die Berücksichtigung aller relevanten Faktoren im Kontext der klinischen Entscheidungsfindung.

Moderne IT-Systeme können einen wesentlichen Beitrag leisten, um die klinischen Experten weitreichend zu unterstützen. Diese Assistenz reicht dabei von Anwendungen zur Vorverarbeitung von Daten für eine Reduktion der damit verbundenen Komplexität bis hin zur systemgestützten Evaluation aller notwendigen Patientendaten für eine therapeutischen Entscheidungsunterstützung. Möglich werden diese Funktionen durch die formale Abbildung von medizinischem Fachwissen in Form einer komplexen Wissensbasis, welche die kognitiven Prozesse im Entscheidungsprozess adaptiert. Entsprechend werden an den Prozess der IT-konformen Wissensabbildung erhöhte Anforderungen bezüglich der Validität und Signifikanz der enthaltenen Informationen gestellt.

In den ersten beiden Kapiteln dieser Arbeit wurden zunächst wichtige methodische Grundlagen im Kontext der strukturierten Abbildung von Wissen sowie dessen Nutzung für die klinische Entscheidungsunterstützung erläutert. Hierbei wurden die inhaltlichen Kernthemen weiterhin im Rahmen eines State of the Art mit bestehenden Ansätzen abgeglichen, um den neuartigen Charakter der vorgestellten Lösungen herauszustellen.

Als innovativer Kern wurde zunächst die Konzeption und Umsetzung eines neuartigen Ansatzes zur Fusion von fragmentierten Wissensbausteinen auf der formalen Grundlage von Bayes-Netzen vorgestellt. Hierfür wurde eine neuartige Datenstruktur unter Verwendung des JSON Graph Formats erarbeitet. Durch die Entwicklung von qualifizierten Methoden zum Umgang mit den formalen Kriterien eines Bayes-Netz wurden weiterhin Lösungen aufgezeigt, welche einen automatischen Fusionsprozess durch einen eigens hierfür entwickelten Algorithmus ermöglichen.

Eine prototypische und funktionale Plattform zur strukturierten und assistierten Integration von Wissen sowie zur Erzeugung valider Bayes-Netze als Resultat der Fusion wurde unter Verwendung eines Blockchain Datenspeichers implementiert und in einer Nutzerstudie gemäß ISONORM 9241/110-S evaluiert. Aufbauend auf dieser technologischen Plattform wurden im Anschluss zwei eigenständige Entscheidungsunterstützungssysteme vorgestellt, welche relevante Anwendungsfälle im Kontext der HNO-Onkologie adressieren. Dies ist zum einen ein System zur personalisierten Bewertung von klinischen Laborwerten im Kontext einer Radiochemotherapie und zum anderen ein in Form eines Dashboard implementiertes Systems zur effektiveren Informationskommunikation innerhalb des Tumor Board. Beide Konzepte wurden hierbei zunächst im Rahmen einer initialen Nutzerstudie auf Relevanz geprüft, um eine nutzerzentrische Umsetzung zu gewährleisten.

Aufgrund des zentralen Fokus dieser Arbeit auf den Bereich der klinischen Entscheidungsunterstützung, werden an zahlreichen Stellen sowohl kritische als auch optimistische Aspekte der damit verbundenen praktischen Lösungen diskutiert.

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Appendix A

ISONORM 9241-110-S questionnaire

	Die Software ...	---	--	-	-/+	+	++	+++	*Die Software ...*
Sw02	bietet nicht alle Funktionen, um die anfallenden Aufgaben effizient zu bewältigen.	❍	❍	❍	❍	❍	❍	❍	bietet alle Funktionen, um die anfallenden Aufgaben effizient zu bewältigen.
Sw04	erfordert überflüssige Eingaben.	❍	❍	❍	❍	❍	❍	❍	erfordert keine überflüssigen Eingaben.
Sw05	ist schlecht auf die Anforderungen der Arbeit zugeschnitten.	❍	❍	❍	❍	❍	❍	❍	ist gut auf die Anforderungen der Arbeit zugeschnitten.
Sw08	liefert in unzureichendem Maße Informationen darüber, welche Eingaben zulässig oder nötig sind.	❍	❍	❍	❍	❍	❍	❍	liefert in zureichendem Maße Informationen darüber, welche Eingaben zulässig oder nötig sind.
Sw09	bietet auf Verlangen keine situationsspezifischen Erklärungen, die konkret weiterhelfen.	❍	❍	❍	❍	❍	❍	❍	bietet auf Verlangen situationsspezifische Erklärungen, die konkret weiterhelfen.
Sw10	bietet von sich aus keine situationsspezifischen Erklärungen, die konkret weiterhelfen.	❍	❍	❍	❍	❍	❍	❍	bietet von sich aus situationsspezifische Erklärungen, die konkret weiterhelfen.
Sw12	erzwingt eine unnötig starre Einhaltung von Bearbeitungsschritten.	❍	❍	❍	❍	❍	❍	❍	erzwingt keine unnötig starre Einhaltung von Bearbeitungsschritten.
Sw13	ermöglicht keinen leichten Wechsel zwischen einzelnen Menüs oder Masken.	❍	❍	❍	❍	❍	❍	❍	ermöglicht einen leichten Wechsel zwischen einzelnen Menüs oder Masken.
Sw15	erzwingt unnötige Unterbrechungen der Arbeit.	❍	❍	❍	❍	❍	❍	❍	erzwingt keine unnötigen Unterbrechungen der Arbeit.
Sw16	erschwert die Orientierung durch eine uneinheitliche Gestaltung.	❍	❍	❍	❍	❍	❍	❍	erleichtert die Orientierung durch eine einheitliche Gestaltung.
Sw18	informiert in unzureichendem Maße über das, was es gerade macht.	❍	❍	❍	❍	❍	❍	❍	informiert in ausreichendem Maße über das, was es gerade macht.
Sw20	lässt sich nicht durchgehend nach einem einheitlichen Prinzip bedienen.	❍	❍	❍	❍	❍	❍	❍	lässt sich durchgehend nach einem einheitlichen Prinzip bedienen.

ISONORM 9241-110-S 2

	Die Software ...	- - -	- -	-	-/+	+	++	+++	*Die Software ...*
Sw23	liefert schlecht verständliche Fehlermeldungen.	❍	❍	❍	❍	❍	❍	❍	liefert gut verständliche Fehlermeldungen.
Sw24	erfordert bei Fehlern im Großen und Ganzen einen hohen Korrekturaufwand.	❍	❍	❍	❍	❍	❍	❍	erfordert bei Fehlern im Großen und Ganzen einen geringen Korrekturaufwand.
Sw25	gibt keine konkreten Hinweise zur Fehlerbehebung.	❍	❍	❍	❍	❍	❍	❍	gibt konkrete Hinweise zur Fehlerbehebung.
Sw26	lässt sich von mir schwer erweitern, wenn für mich neue Aufgaben entstehen.	❍	❍	❍	❍	❍	❍	❍	lässt sich von mir leicht erweitern, wenn für mich neue Aufgaben entstehen.
Sw27	lässt sich von mir schlecht an meine persönliche, individuelle Art der Arbeitserledigung anpassen.	❍	❍	❍	❍	❍	❍	❍	lässt sich von mir gut an meine persönliche, individuelle Art der Arbeitserledigung anpassen.
Sw29	lässt sich - im Rahmen ihres Leistungsumfangs - von mir schlecht für unterschiedliche Aufgaben passend einrichten.	❍	❍	❍	❍	❍	❍	❍	lässt sich – im Rahmen ihres Leistungsumfangs - von mir gut für unterschiedliche Aufgaben passend einrichten.
Sw31	erfordert viel Zeit zum Erlernen.	❍	❍	❍	❍	❍	❍	❍	erfordert wenig Zeit zum Erlernen.
Sw33	erfordert, dass man sich viele Details merken muss.	❍	❍	❍	❍	❍	❍	❍	erfordert nicht, dass man sich viele Details merken muss.
Sw35	ist schlecht ohne fremde Hilfe oder Handbuch erlernbar.	❍	❍	❍	❍	❍	❍	❍	ist gut ohne fremde Hilfe oder Handbuch erlernbar.

Erklärung über die eigenständige Abfassung der Arbeit

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar eine Vergütung oder geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, und dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt wurde. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt an der Entstehung der vorliegenden Arbeit beteiligt waren. Die aktuellen gesetzlichen Vorgaben in Bezug auf die Zulassung der klinischen Studien, die Bestimmungen des Tierschutzgesetzes, die Bestimmungen des Gentechnikgesetzes und die allgemeinen Datenschutzbestimmungen wurden eingehalten. Ich versichere, dass ich die Regelungen der Satzung der Universität Leipzig zur Sicherung guter wissenschaftlicher Praxis kenne und eingehalten habe.

Ort, Datum

M. Eng. Alexander Oeser