Deliverable No. D13.3

Selection and annotation of the CDS training and evaluation datasets

Grant Agreement No.:	270089
Deliverable No.:	D13.3
Deliverable Name:	Selection and annotation of the CDS training and evaluation datasets
Contractual Submission Date:	
Actual Submission Date:	17/8/2012

Dissemination Level		
PU	Public	
PP	Restricted to other programme participants (including the Commission Services)	
RE	Restricted to a group specified by the consortium (including the Commission	

	Services)	
CO	Confidential, only for members of the consortium (including the Commission Services)	

COVER AND CONTROL PAGE OF DOCUMENT	
Project Acronym:	***p-medicine***
Project Full Name:	From data sharing and integration via VPH models to personalized medicine
Deliverable No.:	D13.3
Document name:	Selection and annotation of the CDS training and evaluation datasets
Nature (R, P, D, O)[1]	R
Dissemination Level (PU, PP, RE, CO)[2]	PU
Version:	3
Actual Submission Date:	17/8/2012
Editor: Institution: E-Mail:	

ABSTRACT:

The aim of this deliverable is to describe the datasets used in the building of the clinical decision support system (CDS). This includes the description of the documents that serve as an input to the treatment recommendation module and the datasets used for data mining activities which would optimally lead to creating models that will also be used in the CDS application. It is important to note that this deliverable is about the data currently available or in the progress of obtaining while more data resources might be obtained during the course of the project.

KEYWORD LIST: Datasets, Clinical decision support, data mining, annotation, scenario

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement n^{o} 270089.

MODIFICATION CONTROL

[1] **R**=Report, **P**=Prototype, **D**=Demonstrator, **O**=Other

[2] **PU**=Public, **PP**=Restricted to other programme participants (including the Commission Services), **RE**=Restricted to a group specified by the consortium (including the Commission Services), **CO**=Confidential, only for members of the consortium (including the Commission Services)

Version	Date	Status	Author
1.0	15/7/2012	Draft	Philips
2.0	1/8/2012	Draft	Philips
3.0	10/8/2012	Draft	Philips

List of contributors

- Anca Bucur, Philips
- Aisan Maghsoudi, Philips
- Martin Stanula, UKSH
- Antje Torg, UKSH
- Norbert Graf, USAAR
- Stefan Ruping, FHG-IAIS
- Elisabetta Munzone, IEO
- Laura Adamoli, IEO

Table of Contents

1. Executive Summary

This deliverable describes the data resources to be used in the development of clinical decision support (CDS) application. The data resources include the datasets used for building and evaluation of models which will be integrated in the application as well other types of data resources such as evidences and protocols which will serve as the knowledge backbone. The integration of patient data, the evidences and knowledge sources, and the predictive models into the CDS system that generates patient-specific treatment, follow-up and monitoring advice, supports the concept of personalized evidence-based decision support at the point of care.

The data and knowledge resources needed for the envisioned scenarios of the CDS are related to the three main oncology domains: breast cancer, nephroblastoma, and childhood leukemia. Ideally, access to the data sets of quality patient data containing the diagnosis, treatment, adverse events, and follow-up as well as the protocols, knowledge sources used for treatment recommendation for all three domains is required. However, all of these datasets were not yet available at the time of writing this deliverable.

This deliverable provides an overview of the data resources available or becoming available for the CDS application at this point of time while the number of resources might be extended in the future as more datasets might become available and used in developing parts of the system throughout the project.

2. Introduction

A Clinical Decision Support System (CDSS or CDS) is software application designed to help clinicians making the correct decisions at the point of care. This can be achieved by bringing the data and information necessary for making a decision to the clinician at the time of decision making. It has been shown that CDS can improve patient care and reduce the deviations from best practices if they are integrated in the workflow of the clinicians in a seamless and efficient way.

In the field of oncology, like other domains of medicine the amount of knowledge generated each year is enormous and it is impossible for the clinicians to be able to keep up with the fast growing newly introduced technologies, medications, studies and knowledge in order to incorporate them in practical use. This knowledge-practice gap can be attended through an intervention system such as CDS which provides evidence-based recommendations, alerts taking into consideration the specific patient condition by being integrated to the electronic health record (EHR) system.

Despite the various efforts for the implementation of CDS systems, a comprehensive CDS which covers all decision points of the clinicians from diagnosis and treatment to follow-up and monitoring is not yet available for the field of oncology. A successful CDS should not only provide advice and necessary information to the right people at the right time -which is often at the point of care-, but also should be integrated seamlessly with the EHR in order to fetch the patient conditions, test results and all other needed input data automatically and employ them in the CDS modules in an efficient manner fast enough to be adopted by the clinicians.

It is clear that in order to create the functionalities of such a CDS a collection medical knowledge and patient data is needed and as they say in data mining: “the only good data is more data.” The amount of data is important for having more precise models and for validation and evaluation. However, rather than the amount of data, the quality of data used for building the models is of utmost importance along with the privacy issues. The data received for building the models should be properly anonymized , consistent, validated and accurate.

In section 3, the knowledge sources currently available for use in the CDS and their role in the development of CDS are discussed. Section 4, contains the description of dataset(s) followed by the CDS scenarios related to the models created from mining the data.

3. Domain knowledge resources

In this section the knowledge sources from the three main cancer domain namely, breast cancer, Acute lymphoblastic leukemia (ALL) and nephroblastoma that will be used in the development of some of CDS modules such as treatment recommendation are listed. The CDS scenarios relevant to the knowledge sources will be discussed in section 3.4.

3.1. ALL-BFM treatment protocol

The term Leukemia comes from the Greek for white blood. It is the cancer of the blood forming or hematopoietic tissue and is a result of uncontrolled proliferation of abnormal, immature blood cells (blasts). Leukemia occurs when normal hematopoiesis is disrupted and cells fail to divide and mature normally. Leukemic cells are found in the bone marrow, and may be found in extramedullary sites such as the liver, spleen, testes, or the CNS.

Childhood leukemia classification includes:

- Acute lymphoblastic leukemia (ALL)
- Acute myeloid leukemia
- Chronic myeloid leukemia,
- myelodysplastic syndrome and others

ALL is the most common type of malignancy in children with 3.3 cases per 100,000 inhabitants under 15 years of age. Approximately 600 new cases of ALL is reported each year in Germany.

ALL-BFM study group

Since the 1970s, the ALL-BFM Study Group conducts nationwide multicenter cooperative clinical trials on the treatment of childhood acute lymphoblastic leukemia (ALL). The ALL-BFM Study Group Clinical Trial Center is involved in the design, conduction, analysis, and interpretation of clinical trials in childhood ALL . A growing number of participating national study groups from more than 30 countries world-wide collaborates in committees and associated working groups addressing important aspects of clinical and basic research in the field of leukemia and lymphoma occurring during childhood and adolescence. The ALL related trials completed by BFM study group are as follows:

-IDH (1991-1995): SR ALL
-Pulses (1995-2000): MR ALL
-HSCT in VHR ALL (1995-2000)
-AIEOP-BFM ALL (2000-2006): ALL
-Interfant-99 (1999-2006): ALL below the age of one year (ALL<1y)
-EsPhALL (2004-2009): ALL positive for the t(9;22) translocation

The ongoing trials are:

-ALLIC-BFM 2002 (2002-2009): Randomized clinical protocol for ALL in countries with limited resources
-Interfant-06: Randomized clinical trial for ALL under 1y
-ALL-SCT BFM 2003: HSCT in VHR ALL
-AIEOP-BFM ALL 2009: Randomized clinical trial for ALL (age 1-18y)
-EsPhALL"bridge"study

AIEOP-BFM ALL 2009 (International Collaborative Treatment Protocol for Children and Adolescents with Acute Lymphoblastic Leukemia)

AIEOP-BFM ALL 2009 is a collaborative prospective randomized clinical trial for the treatment of children and adolescents (age ≥ 1 and < 18 years) with newly diagnosed ALL. Therapy is conducted in a risk-adapted manner stratifying patients according to biological and response criteria. Three randomized studies are scheduled with the aim to (1) reduce treatment-related morbidity and mortality in well-responding patient subgroups (Randomization R1), (2) to improve the outcome of medium and high-risk patients by treatment intensification (Randomizations R2 and RHR).

More than 95% of the cases are treated in cooperative clinical trials. Nearly 80% of the German population incidents are treated on ALL-BFM protocols.

The treatment of ALL takes 2-3 years of chemotherapy including:

- Induction therapy: multiagent and intensive with the goal of achieving complete remission or CR (no visible leukemia)
- Intensification / consolidation
- CNS-directed therapy: IT med‘s, XRT
- Maintenance: Low intensity, outpatient

The ALL-BFM protocol is an extended document addressing the step by step actions needed to be taken in different time points of treatment for the possible patient conditions. This document is an evidence-based knowledge source containing classified information about different aspects of ALL treatment including the management of adverse events that can be referred to by the clinicians.

However, in practice this document is not effectively used due to the complexity of the text and difficulty of searching for an answer due to multiple conditions that should be correctly considered. Therefore, as discussed with the clinicians, and as a scenario for the clinical decision support (CDS), it has been envisioned to make the protocol document electronically browse-able by structuring the free-text of the document in a semi-electronic approach that can be adopted in other cancer domains with some modification. Having provided such a visualization, it can be linked to the patient data so that the recommended action(s) for a specific patient condition at a certain time point can be retrieved automatically and shown to clinicians. This document will be used as a source of treatment recommendation and follow up actions in the CDS.

The ALL BFM protocol document is partly in German. Discussions have been going on to receive an English version of this document in order to avoid multi-language processing complications.

3.2. The International Society of Paediatric Oncology (SIOP) nephroblastoma study

A Wilms tumour (also known as a nephroblastoma) is a malignant paediatric renal tumour. It is the most common paediatric renal mass, accounting for over 85% of cases [1,2] and

accounting for 6% of all childhood cancers [3]. It typically occurs in early childhood (1 - 11 years) with peak incidence between 3 and 4 years of age. Approximately 80% of these tumours are found before the age of 5 years.

The International Society of Paediatric Oncology (SIOP) enrolled children with Wilms tumour into 6 studies up to now (SIOP 1, SIOP 2, SIOP 5, SIOP 6, SIOP 9, SIOP 93-01). Graf et al give a review of these studies [4].

SIOP WT 2001

The SIOP WT 2001 clinical trial and study aimed to answer certain questions concerning the nephroblastoma domain. Results of the previous SIOP nephroblastoma studies have been used to plan therapy for the risk groups defined. The SIOP WT 2001 document includes pre-treatment investigations, the pathology protocol, the pre and post operative treatment plans for localized or metastatic disease, chemotherapy and radiotherapy administration, as well as surgical techniques and recommendations.

3.3. Breast cancer studies

Breast cancer is the most common cancer in women worldwide, comprising 16% of all female cancers. Implementing and monitoring cost-effective approaches for the early detection of breast cancer is a direction adopted internationally. Thus, early breast cancer detection is of high importance and should be addressed in the p-medicine platform. Breast cancer treatment; prognosis and survival rate varies greatly depending on cancer type and staging.

Breast cancer trial protocols

The following treatment protocols are currently available for use in the CDS:

1.Phase II randomized study of intravenous bevacizumab with sequential versus concurrent oral vinorelbine plus capecitabine in patients with locally advanced or recurrent breast cancer with lymphangitic spread to the chest wall.

2. Phase II study of metronomic oral Vinorelbine (Navelbine®) plus Bevacizumab (Avastin®) as first line treatment for metastatic breast cancer patients

3. Phase II study of cisplatin plus cyclophospamide for patients with previously treated, advanced, triple receptor negative breast cancer

4. A phase II study of metronomic oral chemotherapy with cyclophosphamide plus capecitabine and vinorelbine in metastatic breast cancer patients -VEX STUDY

3.4. CDS scenarios related to knowledge resources

The CDS scenarios related to the use of knowledge sources aim to support more efficient execution of the trial protocols, patient stratification with respect to risk of relapse and adverse events, and early detection and management of serious adverse events. These scenarios are important for patients treated both in clinical trials and in standard care and are also relevant for other cancers and can be extended.

3.4.1. Computer-interpretable clinical treatment protocols as the basis for treatment recommendation in clinical decision support (CDS):

Treatment protocols are constructed with the aim of assisting clinicians in decision making, reducing costs and variability in practice, and improving patient outcomes. Despite the enormous effort put into creation of protocols and the studies showing the positive effects of using such documents, their overall impact on the clinical practice has not lived up to expectations [5],[6].

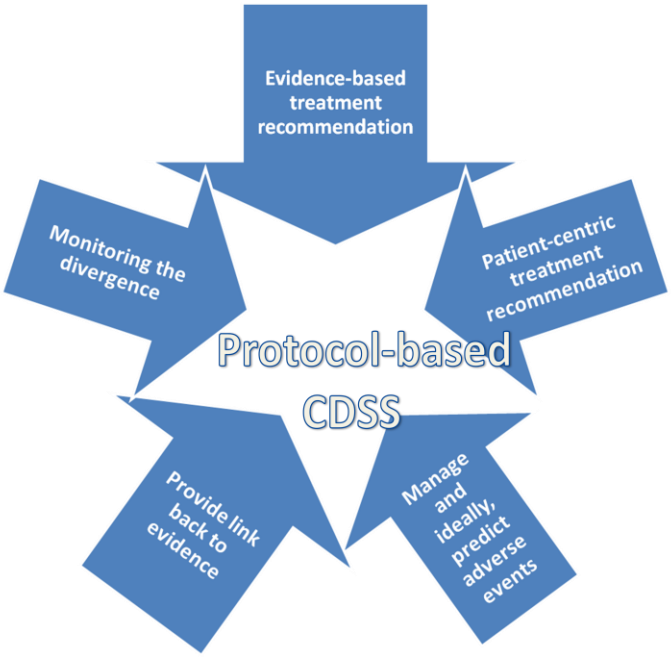

Figure 1: Protocol-based CDS

Systematic reviews have shown that mere existence of protocols and guidelines does not necessarily lead to improvement in practice [7],[8].Treatment protocols are often large documents in narrative form which is complex, ambiguous and sometimes structure-wise inconsistent. For instance, the information related to a certain topic is not necessarily found under its related heading and the expression of recommendations or criteria fitting with a recommendation are sometimes implicit. Searching such documents for specific information is cumbersome and time-consuming for clinicians at today's clinical environment.

Studies have shown that delivering patient-specific advice to clinicians is most effective if delivered automatically at the point of care [9]. It can be imagined that clinicians in their busy workdays need answers fast and would not attempt to use a system less convenient or fast than their normal approach. Thus, the recommendations from the protocols should be provided for the clinicians in an efficient way and seamlessly integrated in their workflow.

In order to build such a system, the treatment protocol document needs to be translated from natural language into a computer-interpretable form. A structure should be found that most effectively models the document for example by capturing the hidden and implicit rules, conditions, decision points and plans contained in the protocol document. This structure can be the basis for the treatment recommendation part of the clinical decision support application. Ideally, the preconditions satisfying protocol recommendation rules should be

derived automatically from the EHR –if available-so that the recommendations in the protocol most suitable for a specific patient can be presented to the clinician with minimum effort from his side. However, having a good EHR is an issue since some centers still preserve their data in paper format or have only a portion of patient data. It should be considered that some parts of patient's data might not be available for automatic retrieval and might need to be entered manually.

In order to make the protocols executable in the clinical environment and contribute to them being adopted in the workflow of clinicians when needed, firstly they should have been represented in a computer-understandable way and secondly, the guideline or protocol model should be able to link to patient data model in order to match the requirements needed to fetch the required piece of information.

The need of a computer-interpretable guidelines and protocols has lead to the development of formalisms and languages to which the guidelines can be translated. These languages tried to come up with the models which are built over the main concepts available in a guideline document, their relations and interactions, the sequence and timeline of actions, decision points, etc. However, most of these models target specific types of documents, users, and environment. Some of these translation languages are ASBRU,EON, GASTON,GEM, GLARE, GLIF, PRODIGY, PROforma, and SAGE.

Multiple environments has been developed implementing the aforementioned languages and facilitating the visualization of the document models, while providing execution platforms. The complexity of these languages demanded for creation of tools and methods to assist the process of translation or formalization of the guideline and protocol documents. Some of these tools are: Arezzo, Protege', GLEAM. Tallis, and GEM cutter.

Although these tools facilitate the translation of documents to the representational models the actual mapping and work is done manually by clinical experts or most of times by knowledge engineers. Obviously this task involves reading and understanding the text, recognizing the concepts and the relations on one hand, and the complexities of the structure of the formalisms being adopted on the other hand, while involving tremendous effort and time.

The modelling or translation of protocols or guidelines not always takes place while generating the document and most often it is done after selecting the protocol to be adopted in the clinical environment. The translation process should often be repeated for new versions as change management is not foreseen in the formalisms. Moreover, the resulting model can be inconsistent or not accurate due to the fact that the people responsible for translating them might not have enough domain knowledge or simply that a piece of text may not sometimes have a unique modelling when done by different people.

The gap that exists between the acquisition of a computer-interpretable model for protocol documents creates a barrier to adopting protocol execution interventions which could be of extreme benefit for the quality of care. Despite the fact that the value and necessity of guideline and protocol documents has been known, few successful instances of integrating them with workflow have been reported.

In order to bridge this gap, we plan to come up with a methodology for (semi-)automatically representing the protocols documents that we have and mapping them to a formalism that is applicable to our domains including the aspects needed for realization of the CDS scenarios. This way the final representation model will be created with less effort and as a result the CDS can benefit from integrating sources of knowledge, which also comprise the evidences for treatment recommendation.

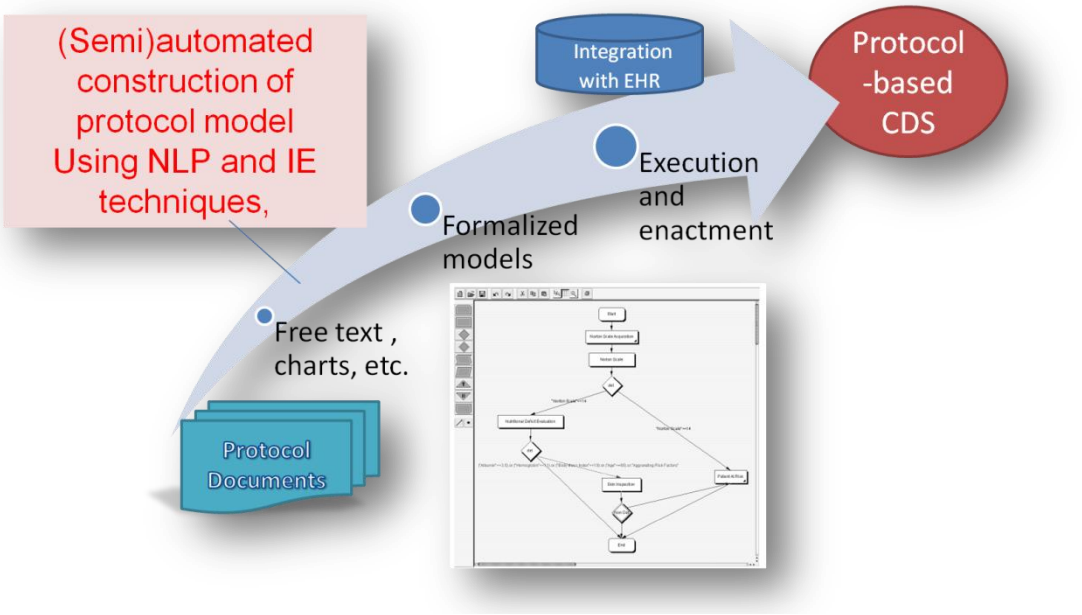

Figure 2: Processes towards realization of protocol-based CDS

The methodology includes extracting information from the natural language text by using advanced natural language processing techniques using entity extractors trained on the domain concept annotated corpus or simply by domain ontology. Multiple views and models of the document would be created at this level of processing such as patient data model, clinical finding model, treatment model, time sequence model, etc. The relation between these models will be established by semantically processing the text looking for relations, hierarchies, patterns, logics, sequences, decision points, conditions, plans, and states of plans.

The focus of this scenario is minimizing the manual and human effort needed for the translation of text into formalized models to be used by other applications or modules of the same application. It is clear that omitting the human labour is not feasible and therefore, the system should show the mapping generated automatically by the system beside the paragraph or chunk of text that has been modelled so that an expert could validate the model while drawing the whole flow chart and extracting all the concepts and relations is not necessary.

Since evidence-based treatment protocols are available in multiple cancer domains, it is beneficial to approach the problem of creating computer-interpretable protocols from narrative documents in a way which can be adopted by different cancer treatment protocols in a minimum labour-intensive way and ideally with limited modifications to a pipeline of processing modules. Moreover, the representation strategy should be designed in a way that supports incorporation of updates and modifications of the protocols in the same cancer domain.

We plan to focus on clinical protocols (research and treatment) that are far more detailed and complex than the guideline documents which are more general. As trial protocols are large and complex, a tool providing integrated protocols that support the clinicians through the course of the treatment and link to the patient data would facilitate compliance with the protocol. If easy to use, such a tool would also save a significant amount of time of the experts, who are currently often asked by less experienced colleagues to provide information that is already covered by the protocol.

3.4.2. Integration of evidence for a specific recommendation

Lack of confidence in the validity of the guidelines has been cited as a reason for poor acceptance [10]. It is only natural that clinicians would like to investigate more the rationale of a certain recommendation. Treatment protocols are consensus based documents which are composed after review, discussion and qualifying the evidences, however, these references are implicit or not directly linked to the content of the document and to each recommendation specifically and their ability to impact the outcome are less explicitly proven. Making this knowledge explicit by providing a direct access link to references and evidences resulting in a recommended procedure or medication can potentially help clinicians to look for more detail or better understand the recommendation context and rationale in order to make more accurate decisions.

The link to references of a certain treatment recommendation can be provided in the clinical decision system after the recommendations suitable for a specific patient have been automatically extracted.

Ideally, the level of evidence, the strength of the recommendation or the quality of study can be shown to the clinician if such information has been provided in the protocols or through some other trustable source. Provision of such functionality can result in higher clinician acceptability and enable better transference to computer-based clinical decision support [11].

3.4.3. Capturing choices of treatments, and divergence from protocols

Assessing the clinical impact of using the protocols is considered essential [12],[13]. The divergence of acting in compliance with treatment protocols can be logged and tracked by asking the clinicians to explain why they chose not to accept the protocol recommendations for example, if the protocol was ambiguous or the literature supporting the recommendation not qualified enough, risk of severe adverse event existed, etc.

The computer-interpretable protocols facilitate the divergence documentation. This can have a useful impact on the quality of the protocol itself by communicating the significantly high divergences opted by different clinicians over similar cases to the protocol authoring boards.

Moreover, the clinicians' decisions at different times on a specific decision point can be counted or tracked as an additional source of confidence in the recommendation. For instance, when a clinician is provided with certain patient specific recommendation based on protocol, in addition to the links to evidences for recommending that treatment, the number of times other clinicians have been at that decision point and their reaction to the recommendation can be shown as such data can be insightful for specially the younger clinicians. Multiple types of reports can also e provided from this type of data.

4. Data sets

4.1. ALL

The ALL-BFM Study Group data base encompasses information on more than 11,000 childhood ALL patients and contains information on:

- Patient characteristics (e.g., age, gender)
- Leukemia characteristics (e.g., immunology, genetics)
- Treatment response (e.g., cytomorphologic, molecular)
- Treatment
- Treatment toxicity (incl. SAEs)
- Follow-up / outcome data

Currently, nearly 600 variables per patient are documented.

The data has been anonymized and checked for the consistency and outliers. The adverse events have been recorded for the patients in another database and discussions are in progress in order to obtain this database.

4.2. CDS scenarios related to datasets

The datasets provided for the CDS would be used mainly for creating models for patient stratification with respect to risk of relapse and adverse events, and early detection and management of serious adverse events. The task of patient stratification combines the results of existing research, i.e. explicit knowledge of risk factors in guidelines, with opportunities for mining and extracting knowledge from existing data of prior cases, clinical trial data and publications.

The models generated would help to improve the stratification of patients and therefore, providing more patient-specific and accurate advice. Besides the recommendation of treatments, the associated risks and potential threats, and the measures that are needed to be taken into consideration while opting each treatment action would be presented to the clinician.

The ALL-BFM dataset is going to be used for data mining scenarios including the following:

4.2.1. Prediction of the risk groups based on MRD

Currently, in leukaemia, the stratification of patients is performed during and not before the start of the treatment since the MRD level based on which the stratification is performed can only be measured after a while after starting the treatment and it is only before the second main cycle of treatment that the high risk patients are recognized. There are currently three risk groups: high, intermediate and low risk. The high risk patients receive very intensive treatment (stem cell transplantation) which is very toxic (late effects and treatment related-deaths 10%) and cannot be prescribed to all patients.

A major improvement would be predicting the MRD level at diagnosis and therefore identifying the high risk patients and allowing for accurate and early patient stratification. This way, the high risk patients could get sooner the needed high intensity treatment, while the low risk patients could be spared and could receive a lower intensity treatment when there is a very low risk of relapse.

A model enabling accurate stratification at diagnosis would be highly valuable and could be integrated in a decision support tool as an important source of evidence.

Prediction of MRD level on day 33 of treatment and day 1 of protocol M (~day 75 of treatment) based preferably on information that is available at the time of diagnosis or as early as possible is a major model that can be integrated into the CDS.

4.2.2. Prediction of SAE's

Besides the known factors which put the patient under the risk of facing sever adverse events, recorded sets of patient data containing patient characteristics, diagnosis, given treatment and recorded adverse events can be retrospectively mined for finding relations between other unknown patient characteristics which related to AE's.

After validation this information can be used to build new predictive models which can also be integrated in the clinical decision support systems. While mining of the data is not performed in the CDS application, the results of the data mining –if any relation is found- can be built into a model that is incorporated in the CDS system.

Systematic/invasive fungal infection is most often seen with ALL patients and thus its prediction is highly valuable. The fungal infection events for the induction treatment have been gathered in a database. Fungal infection can be a less severe event for breast cancer but since Leukemia is a disease of the immune system it is more severe and more frequent with ALL patients. Osteonecrosis and fungal infections is a specific SAE and efforts should be targeted to predict the occurrence of such SAEs.

4.2.3. Prediction of risk of relapse based on the clinical data

Other useful information that can be integrated in a CDS application is informing the clinicians of the risk of relapse in a specific patient. Risk of relapse for patients is not known when starting the therapy. Knowing the probability of relapse could result in changing therapy for some patients or adjusting the dosage so that the patients do not receive less or more therapy than needed.

As discussed before the prediction of relapse can be calculated in the CDS being provided the factors involved and the model to calculate the probability. This information can be provided by the data mining efforts.

Predicting the probability of relapse is beneficial for different cancer domains and in the CDS application there could be an option to compute this probability and display it beside recommendations once the related factors from patient data are selected and related ranges or any other relation relations and models have been uploaded and provided to calculate the probability.

The ALL-BFM dataset is going to be mined for predictive models of relapse and the resulting models would be used in the CDS treatment recommendation module.

4. Conclusion

The clinical decision support system needs datasets and domain knowledge for the development of its envisioned functionalities. The quality of the CDS and the models created by data mining efforts depends highly on the quality of the datasets provided to support the realization of CDS scenarios. Care should be taken that the data should be verified for errors and inconsistencies as well as being properly anonymized before the start of data mining processes.

The solutions applied to realize the scenarios described for the CDS should be devised and developed with the concepts of modularity and scalability in mind. Therefore, it is foreseen

that the applications should be able to be integrated into clinical environment as efficiently as possible and also be able to be generalized to more cancer domains with minimum modification.

Given the fact that the scalability and modularity is considered in presenting a solution, with minimum customization, applying the same methods to the problems of another domain is possible. Whenever the needed dataset and knowledge source is provided it can be inserted in the pipeline of CDS with reasonable domain-specific modification efforts.

References

1. Guermazi A. Imaging of kidney cancer. Springer Verlag. (2006) ISBN:3540211292.
2. Lowe LH, Isuani BH, Heller RM et-al. Pediatric renal masses: Wilms tumor and beyond. Radiographics. 20 (6): 1585-603.
3. Graham SD, Keane TE. Glenn's Urologic Surgery. Lippincott Williams & Wilkins. (2009) ISBN:0781791413.
4. Graf N, Tournade MF, de Kraker J: The Role of Preoperative Chemotherapy in the Management of Wilms Tumor - The SIOP Studies. Urologic Clinics of North America, 27:443-454, 2000
5. Shea S, DuMouchel W, Bahamonde L. A Meta-analysis of 16 Randomized Controlled Trials to Evaluate Computer-based Clinical Reminder Systems for Preventative Care in the Ambulatory Setting. JAMIA 1996;3(6):399-409.
6. Evans R, Pestotnik S, Classen D, Clemmer T, Weaver L, Orme J, et al. A computer-assisted management program for antibiotics and other antiinfective agents. New England Journal of Medicine 1998;338(4):232-8.
7. Lomas J, Anderson GM, Domnick-Pierre K, et al. Do practice guidelines guide practice? The effect of a consensus statement on the practice of physicians. N Engl J Med. 1989;321:1306–
8. Greco PJ, Eisenberg JM. Changing physicians' practices. NEngl J Med. 1993;329:1271–3.
9. Grimshaw J, Russell I. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. Lancet 1993;342:1317-22.
10. Weingarten S. Practice guidelines and prediction rules should be subject to careful clinical testing. JAMA. 1997;277:1977–8.
11. R.D. Zielstorff, Online practice guidelines, Journal of the American Medical Informatics Association, 5 (1998) 227-236.
12. Naditch MP. Practice guidelines and the emperor's new clothes. J Healthcare Resource Manag. 1995;13(12):24–7.
13. G.O. Barnett, J.J. Cimino, J.A. Hupp, E.P. Hoffer, An Evolving Diagnostic Decision-Support System, Jama, 258 (1987) 67-74.