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CDS scenarios and requirements for the clinical decision support tool

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ABSTRACT:

This deliverable starts with the elaboration of the CDS use scenarios that we aim to support, based on the clinical scenarios developed in WP2. It is of utmost importance that the selected user scenarios have to drive the technology development and not vice versa. This gives an indication of what type of information is needed to manage, what decision support services we aim to build, etc. On top of that, of course we need to look at ways to extract and combine the relevant information and to make it targeted to a specific patient.

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[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)

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Contents

1 Executive Summary

This deliverable starts with the elaboration of the CDS use scenarios that we aim to support, based on the clinical scenarios developed in WP2. It is of utmost importance that the selected user scenarios have to drive the technology development and not vice versa. This gives an indication of what type of information is needed to manage, what decision support services we aim to build, etc. On top of that, of course we need to look at ways to extract and combine the relevant information and to make it targeted to a specific patient.

The final main objective is to develop tools able to support the clinicians to efficiently access all relevant data and infer knowledge necessary to reach the most accurate diagnosis and prescribe the most suitable treatment. By making use of the latest medical evidence, CDS solutions will support clinicians to provide personalized treatment and improve patient outcomes. Proper implementation and use of CDS systems is regarded as an important recommendation for reducing the frequency and consequences of errors in medical care.

A second main goal is to support the clinicians to prevent or identify early in the treatment potentially serious side effects to treatments and drugs, and the patients most susceptible to develop serious side effects.

This deliverable will analyze the requirement for a CDS tool from a clinic point of view. This tool will allow users to input biomarker information and using such information the tool will formulate a prediction about how a patient will respond to different treatment regimes. The tool will then suggest the best treatment for an individual patient. Eventually, the tool should be able to combine various inputs; biomarkers, pathological markers, imaging data etc. We envision a tool that can integrate several variables following a multi-dimensional approach.

In fact, the tool should be able to integrate data and information stemming from three dimensions, namely, clinical information, genomic information and psychological information.

This will form the basis for a multi-dimensional analysis of a patient's predictive outcome to clinical trials.

Furthermore, the variables in the multi-dimensional (or multi-parameter) analysis of the predictive patient outcome needs to be defined and weighted

This document will therefore analyze the scenarios developed by WP2, extract requirements relevant for decision support and define relevant scenarios for the decision support tools developed in this WP.

2 Introduction and Background

A Clinical Decision Support System (CDSS or CDS) is an interactive computer software system designed to assist physicians and other health professionals with decision making tasks, as determining diagnosis of patient data. CDS systems have the potential to minimize practice variation and improve patient care and have begun to surface throughout the healthcare industry.

The widespread adoption of clinical IT, including CDS systems, depends on having the right organization and individual financial incentives in place. Although CDS systems and clinical IT in general are powerful tools that can be used to support the practice of medicine, they alone cannot redefine the workflow or process within the profession. Healthcare managers counting on technology to restructure or monitor clinicians' work patterns are likely to encounter substantial resistance to CDS systems, even those that generate valuable information. While the pace of implementing IT systems in healthcare has lagged behind that of other industries, many of the obstacles are gradually diminishing. However, several factors continue to inhibit their widespread diffusion, including the organizational turmoil created by large numbers of mergers and acquisitions, and the lack of uniform data standards.

A decision tool is an active knowledge resource that uses patient data to generate case-specific advice which supports decision making about individual patients by health professionals, the patients themselves or others concerned about them.

The following are some of the characteristics of a decision tool:

- The target decision maker: the tool is designed to aid a health professional and/or a patient in the clinical decision making process.
- The target decision: the decisions concerned to an individual patient.
- The knowledge component: the tool uses patient data and knowledge to generate an interpretation that aids clinical decision making.
- Timing: the tool is used before the health professional or a patient takes the relevant decision.

As stated previously, a CDS serves physicians' needs to improve decision efficacy through the use of electronic systems. However, there is the need to create a link between this two area and cognitive psychology, actually, may contribute to give rise to more practical and effective decision tools, by improving human actors' (physicians, technicians, nurses and so on) trust in these systems. This goal can be obtained through the following steps:

- Using the actual cognitive theories of decision-making processes will accomplish a schematic architecture of an ideal decision support tool. This architecture will be adapted to the clinical context and tested for face and construct validity thanks to a panel of experts, privileged testimonials, and a beta testing phase. The conceptual structure will use tree graphs representations.
- Implementation of the tool in electronic format (off-line). Once implemented the feasibility of the instrument will be tested by a sample of physicians belonging to different specializations and IT tools experiences.
- Testing the tool in a restricted sample for efficacy and user satisfaction.
- An extensive survey about physician attitudes toward CDS will be performed in order to understand the actual context. Trust concerns will be particularly handled.

This step finally will be useful to investigate and appreciate physician' needs, fears and practical difficulties when approaching CDS. The final goal is to define a potential standard of decision-makers education in health.

3 Overview of the desired characteristics of CDS tools

CDSs include tools and technologies used within clinical information systems (CIS) to improve patient care quality, safety, efficiency and effectiveness. If developed and deployed effectively, CDSs deliver:

- The right information: CDSs offer timely, accurate evidence-based information that complements the clinician's action and situation.
- To the right person: CDSs involve every member of the care team – physicians, nurses, pharmacists, allied health professionals and patients.
- In the right CDS format: CDSs rely on alerts, order sets and medical references to answer clinicians' questions.
- Through the right channel: The outcome of a CDS is disseminated via a clinical information system (CIS) such as an electronic health record (EHR), personal health record (PHR), the Internet or a mobile device such as a smartphone.
- At the right point in the clinical workflow: CDS offers evidence-based content and guidance at the precise moment, when the clinician must make diagnostic and treatment decisions.

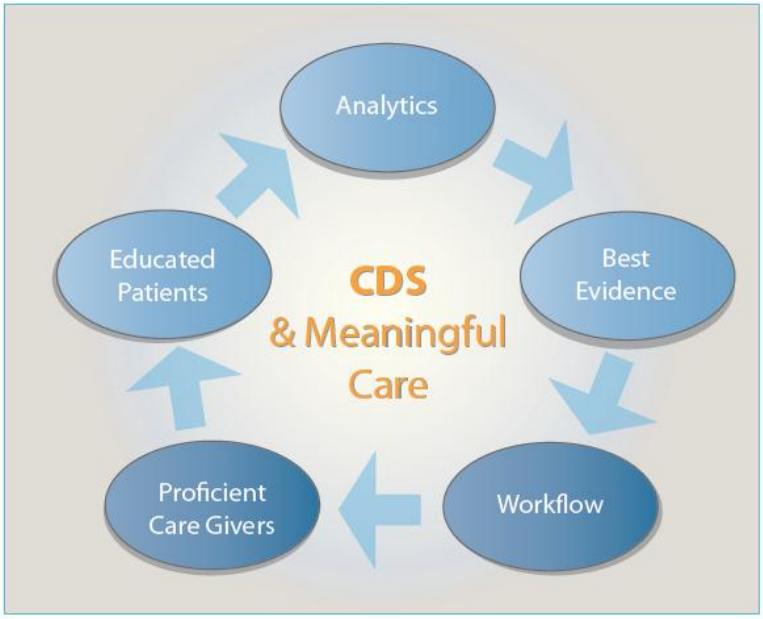
CDS impacts patient care at every phase of the care process— from information gathering and care plan development, diagnosis and drug therapy administration to discharge and consults. When integrated throughout the care process, CDS can significantly improve the quality, safety, efficiency and cost effectiveness of patient care:

- Reduce medical errors, adverse drug events and clinical risk
- Control lengths of stay
- Improved care of specific diseases
- Minimize legal and liability exposure
- Foster adherence to quality guidelines
- Improve referrals, test ordering and admissions.
- Increase patient satisfaction
- Deliver cost effective care

Successful CDS adoption, implementation and use demands that hospitals, health systems and medical groups take a systematic approach and incorporate these elements:

- **Analytics**: CDS should predict the financial and clinical opportunity of adopting best evidence and best practices and then measure and evaluate the benefits.

- **Best-Available Evidence**: CDS should rely on medical references based on the most current research and applied to the patient's unique condition and situation.
- **Best-Practice Workflow**: CDS should integrate best evidence into the clinical workflow using alerts, reminders, drug reference and decision support, multi-disciplinary care plans and order sets.
- **Trained Clinicians**: CDS should ensure that clinical staff receive proper training and demonstrate the highest level of proficiency on best evidence and best practices.
- **Educated and Empowered Patients**: CDS should focus on transferring information from clinicians to patients so patients understand how to best recover from or better manage their conditions



CDS & Meaningful Care Loop

4 Analysis of scenarios developed in WP2

Structure of the Deliverable

This deliverable will analyze the scenarios developed by WP2, extract requirements relevant for decision support and define relevant scenarios for the decision support tools developed in this WP.

Depending on the scenario users are able to execute models with the p-medicine Oncosimulator or they can use the Decision Support System (DSS). In both cases results will lead to personalized medicine via decision support.

In the p-medicine project, requirements will be recorded in the form of use cases/scenario and if it would be applicable in the form of process specifications

Clinical scenarios are central to the project. ALL, Breast Cancer and Nephroblastoma will serve as test cases for the p-medicine platform. The tools developed will be disease specific but they will be built in a way that they can easily be transferred to other cancer types and even to other domains.

4.1.1 Nephroblastoma

Nephroblastoma is the most common kidney cancer in childhood. Dramatic improvements in survival have occurred over the last 40 years. Today treatments are based on several multicenter trials and studies conducted by the SIOP in Europe and COG in North America. Main objectives of these trials and studies are to treat patients according to well-defined risk groups in order to achieve highest cure rates, to decrease the frequency and intensity of acute and late toxicities and to minimize the cost of therapy. In that way the SIOP trials and studies largely focus on the issue of preoperative therapy. The concept of neoadjuvant chemotherapy plays an important role in the treatment for most paediatric solid tumours today. The complete surgical removal of a shrunken tumour is facilitated, mutilation caused by surgical procedures is minimized or avoided and micrometastases, not visible at diagnosis, are treated as early as possible. Besides that, response to treatment can be measured individually by tumour volume reduction and / or percentage of therapy induced necrosis in the histological specimen.

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[3].

A new SIOP trial for Wilms tumour is in a developing process. It will be a randomized prospective multicentre GCP trial running in Europe, Brazil and further centres around the world under the umbrella of the International Society of Paediatric Oncology (SIOP). This trial serves as a clinical trial employing the newly developed and validated tools of *p-medicine*. UDUS on behalf of ECRIN will be involved in the planning and management of this trial. ObTiMA and TOB will be used to serve as CDMS for this trial. As the start of the next Wilms tumour trial is proposed with the beginning of 2014 in the meantime ObTiMA and DoctorEye will be further developed, evaluated and validated. The use of ObTiMA will also allow DICOM transfer of imaging studies, SAE and SUSAR Reporting and will include a tool for consultation.

[3] 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

Today more than 90% of patients with Wilms tumour can be cured[4]. Clinical trials for Wilms tumour continue to seek risk factors for further stratifying and individualizing treatment. This will improve the cure rates for high risk patients by intensifying therapy and the quality of life for children with more favourable prognosis by lowering therapy to the minimum required, both leading to more personalized medicine.

Questions in the future have to address molecular genetic findings for a better understanding of Wilms´ tumour, hopefully influencing treatment and outcome.

The challenges and the main motivation for deploying the nephroblastoma trial in *p-medicine* are:

i. **The distributed nature of the participating clinical sites:** There are at least 100 hospitals treating children with nephroblastoma (different standards, clinical information input, etc.) within Europe, Brazil and other centres around the world according to the SIOP protocol. There is a clear need to seamlessly integrate data related to the treatment used, the type of surgery, histological examinations, as well as reports related to side effects toxicity and relapse. To date, such data is sent by mail and transferred manually to a central database. The same is true for the imaging studies, for pathology and so on. It is noticeable that data related to molecular findings are not integrated into the databases today.

ii. **The fact that research data from molecular biology is still not included in the SIOP nephroblastoma trial.** There is a need to integrate clinico-genomic data in order to investigate prognostic factors and assess the potential of individualized therapy. An integrated clinico-genomic environment that will involve as many sites as possible and will seamlessly cross-validate markers for improving therapy and survival rates is of utmost importance to ultimately enable individualized clinical decision making for nephroblastoma patients. *P-medicine* will promote this integration and provide the necessary analysis tools and standards for clinical trials.

iii. **Use of data to run, evaluate and validate VPH models for decision support.** Data collected are clinical data, images of the tumour during treatment, information about the type of surgery, reports on biopsies, any cytotoxic effects and information about relapse, and hopefully for a majority of patients molecular biological data will be prospectively collected. It is the purpose of *p-medicine* to store these data in the data warehouse described in WP7. *P-medicine* will promote the integration of all these information, facilitate further molecular analysis, access to tissue banks, provide the necessary analysis tools and allow basic scientists to build VPH and decision making tools that can be used by clinicians to efficiently treat patients according to their individual risk.

iv. **Existing biobanks for nephroblastoma.** Within SIOP nephroblastoma trials biobanks storing tumour material and other biomaterial as serum or normal tissue are build at different places throughout Europe. There is no linkage between these biobanks nor is centrally information available on what is stored in these biobanks. As Nephroblastoma is a rare disease the access to information of stored biomaterial will help to avoid unnecessary double analysis and gives the opportunity to share biomaterial between different research groups to coordinate research in nephroblastoma in a more efficient way. Access to biobanks as well as sharing of data and biomaterial will be done in a secure way that will be developed in the legal and ethical work package. WP10 will address the access to biobanks. The SIOP Renal Tumour Study Group (SIOP-RTSG)

[4] de Kraker J, Graf N et al.: Reduction of postoperative chemotherapy in children with stage I intermediate risk and anaplasia Wilms'Tumour. The SIOP 93-01 randomised trial. Lancet 364:1229-1235, 2004

has an urgent need to solve the problem of access to information about distributed biobanks[5]. Together with WP10 the nephroblastoma trial will address the access to biobanks throughout Europe.

All these challenges will be addressed in p-medicine and are a prerequisite for decision support services. The oncosimulator scenario is described in D2.2 as well as the ObTiMA, DoctorEye and Biobank scenarios. In this deliverable another scenario will be described that should predict venous occlusive disease (VOD) in a patient as a severe adverse event after actinomycin treatment for nephroblastoma. Up to know such a prediction is not possible to give in advance of the treatment of this drug. The side effect itself can be life threatening making this scenario very important.

4.1.1.1 Knowledge about VOD (venous occlusive disease)

The high cure rate of patients with Wilms Tumor (WT) emphasizes the interest in treatment-related toxicity. One example is hepatic veno-occlusive disease (VOD). This is an important reason of liver toxicity associated with conventional and high-dose chemotherapy in children with hematologic malignancies and certain solid tumours, like nephroblastoma[6]. Based on clinical parameters, VOD has been reported in up to 8% of the patients treated for WT[7],[8]. There are two different clinical definitions used worldwide for the diagnosis of VOD; those by McDonald et al.[9] and by Jones et al.[10]. The criteria are known as the Seattle and the Baltimore criteria, respectively. Although these criteria are only validated for the BMT setting, they are generally accepted to be used when VOD is suspected in solid tumours. These two sets of criteria are very much alike and are based on clinical findings, which may arise at an advanced stage of VOD[11]. Clinically, patients present with jaundice, painful hepatomegaly, and fluid retention, which may evolve into multi-organ failure, a hallmark of severe disease. The pathogenesis is complex and not completely understood, but the damage to sinusoidal endothelium, typically caused by toxic metabolites released from antineoplastic drugs, is thought to play a crucial role, together with cytokine activation, immune deregulation, and coagulopathy[12].

Diagnosis is based on clinical criteria supported by characteristic ultrasound findings, with the gold standard investigation being hepatic-venous pressure gradient measurement and biopsy. VOD has been associated with abnormalities of several parameters of coagulation

[5] 7th International Meeting on the Biology of Childhood Renal Tumors. Banff; 1st – 3rd of March 2010

[6] Cefalo, Maria Giuseppina; Maurizi, Palma; Arlotta, Annalisa; Scalzone, Maria; Attinà, Giorgio; Ruggiero, Antonio; Riccardi, Riccardo: Hepatic Veno-Occlusive Disease: A Chemotherapy-Related Toxicity in Children with Malignancies. Pediatric Drugs 12:77-284

[7] Bisogno G, de KJ, Weirich A, et al. Veno-occlusive disease of the liver in children treated for Wilms tumor. Med Pediatr Oncol 1997;29:245–251

[8] Green DM, Norkool P, Breslow NE. Severe hepatic toxicity after treatment with vincristine and dactinomycin using single-dose or divided-dose schedules: A report of the National Wilms Tumor Study. J Clin Oncol 1990;8:1525–1530.

[9] Mc Donald GB, Sharma P, Matthews DE. Veno-Occlusive disease of the liver after bone marrow transplantation. Diagnosis, incidence and factors. Hepatology 1984;4:112–116.

[10] Jones RJ, Lee KS, Beschorner WE, et al. Venoocclusive disease of the liver following bone marrow transplantation. Transplantation 1987;44:778–783

[11] Carreras E, Granena A, Navasa M, et al. On the reliability of clinical criteria for the diagnosis of hepatic veno-occlusive disease. Ann Hematol 1993;66:77–80

[12] Charissa T. Jagt, Michelle Zuckermann, Fibo Ten Kate, Jan A.J.M. Taminiau, Marcel G.W. Dijkgraaf, Hugo Heij, Jan De Kraker, Arnauld C. Verschuur: Veno-Occlusive Disease in Pediatric Patients Affected by Wilms Tumor. Pediatr Blood Cancer 2009;53:1211–1215

and fibrinolytic cascade. The increase in the plasminogen activator inhibitor type 1 (PAI-1) levels in adult patients undergoing HSCT was an independent predictor of VOD and was associated with disease severity and response to defibrotide treatment[13]. Several treatment options have been tested; the most convincing approach to date is the use of defibrotide, a novel oligonucleotide with antithrombotic and antiplatelet aggregating properties, as well as endothelial-stabilizing effects. This agent, together with other specific forms of supportive care, has shown efficacy in the treatment of established VOD and promising results in the prevention of VOD in paediatric patients receiving chemotherapy[6],[12].

4.1.1.2 Prediction of VOD scenario

The prediction of VOD before the use of actinomycin-D in a child with WT would have great impact in the avoidance of severe side effects. Such a decision support service would be of utmost importance for patients with WT and could serve as a test for DSS for the prediction of other SAEs or SUSARs.

The following data are needed to be used:

1. individual patient's data including
    a. clinical data (age, body weight, heigh, etc.)
    b. laboratory data, including clotting parameters (like PAI-1)
    c. imaging data of the liver, if available
    d. tumour specific data (size, site, location, etc.)
    e. family history of clotting disorders
    f. molecular markers of the tumour, if available
2. data mining of
    a. clinical trials reporting of VOD in WT to find risk factors
    b. literature on VOD to find biomarkers predicting VOD
    c. pharmacogenomics of actinomycin to find biomarkers predicting VOD

All these data should be used to predict an individual risk in a specific patient to develop VOD. This scenario should include a learning part. The more patients are checked for the risk and validated by the clinical course the better the tool should predict the risk of VOD.

4.1.1.3 Knowledge about cardiotoxicity

Anthracyclines are widely used anticancer agents that cause a dose-related cardiotoxicity, often aggravated by nonanthracycline chemotherapeutics, radiation and new generation targeted drugs. Anthracycline cardiotoxicity may occur anytime in the life of cancer survivors. Understanding the molecular mechanisms and clinical correlates of cardiotoxicity is necessary to avoid this SAE .

Up to now the following items are under discussion to get a better understanding of cardiotoxicity after anthracycline treatment in cancer patients :

- the molecular mechanisms underlying anthracycline-induced cardiotoxicity;
- the role of cytosolic NADPH-dependent reductases in anthracycline metabolism;
- the influence of genetic polymorphisms on cardiotoxicity outcome;
- the perspectives on the most promising strategies for limiting or preventing anthracycline-induced cardiotoxicity, focusing on controversial aspects and on recent

[13] Salat C, Holler E, Hans-Jochem K, et al. Plasminogen activator inhibitor-1confirmsthe diagnosis of hepatic veno-occlusivedisease in patients with hyperbilirubinemia after bone marrow transplant. Blood 1997;89:2184–2188

data regarding analogues of the natural compounds, tumor-targeted formulations and cardioprotective agents.

The developed tool for DSS should help to predict in individual patients the risk to develop cardiotoxicity.

4.1.1.4 Scenario for prediction of cardiotoxicity

The prediction of cardiotoxicity before the use of anthracyclines in patients would have great impact in the avoidance of severe side effects. Such a decision support service would be of utmost importance and could serve as a test for DSS for the prediction of other SAEs or SUSARs.

The following data are needed to be used:

1. individual patient's data including
    a. clinical data (age, body weight, heigh, etc.)
    b. laboratory data
    c. imaging data of the heart (ultrasound)
    d. tumour specific data (size, site, location, etc.)
    e. family history of cardiac diseases
    f. molecular markers of the tumour, if available
2. data mining of
    a. clinical trials reporting of cardiotoxicity in different cancers to find risk factors
    b. literature on cardiotoxicity to find biomarkers predicting cardiotoxicity
    c. pharmacogenomics of anthracyclines to find biomarkers predicting cardiotoxicity

All these data should be used to predict an individual risk in a specific patient to develop VOD. This scenario should include a learning part. The more patients are checked for the risk and validated by the clinical course the better the tool should predict the risk of cardiotoxicity.

4.1.2 ALL

The CDS scenarios for ALL 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.

4.1.2.1 Computer-interpretable treatment protocols as a basis for 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[14], [15].

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.

Systematic reviews have shown that mere existence of protocols and guidelines does not necessarily lead to improvement in practice[16] [17]. Studies have shown that delivering patient-specific advice to clinicians is most effective if delivered automatically at the point of care[18]. 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.

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.

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.

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

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[14] 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.

[15] 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.

[16] 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;321:1306–11.

[17] Greco PJ, Eisenberg JM. Changing physicians' practices. NEngl J Med. 1993;329:1271–3.

[18] Grimshaw J, Russell I. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. Lancet 1993;342:1317-22.

of time of the experts, who are currently often asked by less experienced colleagues to provide information that is already covered by the protocol.

4.1.2.2 Prediction, detection and management of severe adverse events

For the best patient outcome, a successful treatment needs to reach the right balance between efficacy and side effects. Keeping side effects to a low level is also relevant to ensure compliance. Therefore, it would be relevant to be able to predict the severity of adverse events for a patient for each potential treatment. When AEs cannot be predicted, an early detection can reduce patient suffering, improve outcomes and reduce costs. Next to that, support for the management of the adverse events that have occurred would also be beneficial.

In the case of leukaemia, in a population of over 11000 patients, over 20% have developed a severe adverse event. Among those infections, fever, VOD and secondary malignancies are very important. Secondary malignancies as late effect of treatment are particularly difficult to predict. Some known genetic factors provide an increased risk of treatment toxicity. For example the Down syndrome brings both an increased risk of ALL and for developing toxicities to treatments. For these patients the treatment phases need to be spaced out compared to the standard.

Clinical decision support systems can contribute to stratification of patients, to early detection of events and to the management of events that have occurred.

In our research we will address the following severe adverse events:

- Febrile neutropenia which is a common and very serious adverse event. The management of this adverse event is known with several guidelines being available. In this case early detection and treatment is essential.
- Venous occlusive disease is a rare and complex adverse events and its management is not yet fully understood
- Cardiotoxicity, for example as a complication of anthracyclines causing severe cardiomyopathy that can even lead to heart transplantation

Building risk models for adverse events

Patient stratification concerns determining the risk of a patient for developing a particular adverse event

- Given the patient context (its history, and current status) and available data about prior cases, what is the risk of an event?
- What are adequate prevention measures for a patient of this type?
- Can we distinguish different approaches for high and low risk patients?

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.

Beside 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.

CDS for treatment selection that integrates risk models for toxicity

Knowing the potential adverse events of treatments can affect the very choice of treatment in the beginning or the course of the therapy. For example, once the clinician knows a certain SAE such as infection has a high chance for a specific patient he can consider giving antibiotics to the patient from certain point of time.

In the clinical decision support application this information can be linked to the recommended treatments after automatically matching the patient data to the pre-conditions for the potential adverse events of the recommended treatment. An alert can be displayed beside treatment recommendation if a high fit has occurred. Some of these potential adverse events related to treatments for patients can be extracted from the protocol itself if mentioned in the document. Co-morbidities, drug-drug interactions and genetic factors could be among some of the known factors increasing the risk for severe adverse events for some patients after being given certain treatments.

For some well studied adverse events that occur often, risk models have already been developed, e.g. the MASCC index for Febrile Neutropenia. Such models can be directly integrated in a CDS tool.

Early detection of potential adverse events

Because of the time pressure involved it is highly important that cases developing severe adverse events are detected as early as possible. This is complicated by the fact that patients undergoing chemotherapy are typically at home during the treatment.

Based on data in the Electronic Medical Record (EMR), the CDS can provide an early alert when a patient seems to have developed an SAE. Additionally, the CDS can report the confirmed Severe Adverse Event.

CDS for the management of adverse events

For severe adverse events that have occurred, the clinicians need to take the necessary steps to reduce their effects and to treat the patients. Decisions concerning the continuation of the initial treatment that originated the adverse event need to be made. The management of severe adverse events, as it is the case is Febrile Neutropenia, is sometimes covered by treatment guidelines. In such cases a CDS tool can incorporate those recommendations.

4.1.2.3 Integration of evidence pertinent to a specific recommendation

Lack of confidence in the validity of the guidelines has been cited as a reason for poor acceptance[19]. 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

[19] Weingarten S. Practice guidelines and prediction rules should be subject to careful clinical testing. JAMA. 1997;277:1977–8.

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[20].

4.1.2.4 Capturing choices of treatments, especially divergence from protocols:

Assessing the clinical impact of using the protocols is considered essential[21] [22]. 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.

4.1.2.5 Prediction of relapse

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.

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[20] R.D. Zielstorff, Online practice guidelines, Journal of the American Medical Informatics Association, 5 (1998) 227-236.

[21] Naditch MP. Practice guidelines and the emperor's new clothes. J Healthcare Resource Manag. 1995;13(12):24–7.

[22] G.O. Barnett, J.J. Cimino, J.A. Hupp, E.P. Hoffer, An Evolving Diagnostic Decision-Support System, Jama, 258 (1987) 67-74.

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.

4.1.2.6 Prediction of MRD level

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 three months 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.

4.1.3 Breast Cancer

Breast cancer is the most common cancer in women worldwide, comprising 16% of all female cancers. It is estimated that 519 000 women died in 2004 due to breast cancer, and although breast cancer is thought to be a disease of the developed world, a majority (69%) of all breast cancer deaths occurs in developing countries. The p-medicine project will specially focus (in close collaboration with project partners) on targeted drugs, pathway and oncosimulator scenarios

Additionally, one of the WHO's proposed actions for member states is the reorientation and strengthening of health systems by implementing and monitoring cost-effective approaches for the early detection of breast cancer. It suggests that the p-medicine platform due to its modular infrastructure and powerful tools could focus as well on early breast cancer detection. It is of high importance especially when one takes into account that breast cancer treatment; prognosis and survival rate varies greatly depending on cancer type and staging.

4.1.3.1 Specific Breast Cancer scenarios

The Breast Cancer scenarios are developed in close collaboration with the p-medicine project partners enrolled in the breast cancer.

One specific scenario suggested for the breast cancer VPH will be to model the response to preoperative therapy using the available trials. This will be done within WP12 in two phases:

- Response to anti-angiogenic treatment

- Response to combined modalities of biological drugs with standard cytotoxic and/or hormonal therapies

The first phases will be the primary aim and will be validated within the duration of the project using the existing Bevacizumab phase II trials (Bevacizumab 1 and 2 trials, please explore WP9 for further information). Both of these trials address the same drug and the data from the trials will be merged in a single meta-entity to be used for tuning and validating the Oncosimulator breast cancer model. Thus, the primary aim would be to have a solid and validated modelling of angiogenesis and response to antiangiogenic drugs. Furthermore, due to the high number of trials in breast cancer, we will explore the possibility of validating further combined therapies models using large-scale data mining of published CTs. This will be done in collaboration with partners responsible for WP 7 and WP 11.

A second specific scenario will deal with the identification of biomarkers as a crucial issue to move forward with individualized therapy.

We will specifically analyze, retrospectively, data from a bevacizumab based trial with concomitant metronomic chemotherapy.

Biological ancillary studies are necessary in order to better understand why a treatment does or does not work for a given patient, and identify predictive biomarkers and surrogate markers of efficacy on a given component of the tumour. Indeed, one should be able to identify which agents or combinations of agents are the most efficacious, in which clinical setting and for which patients to be able to alter the treatment protocol or adjust its dosing and/or schedule of administration. Biomarkers may also help identify how a given tumour may escape from a multitarget treatment and how treatment should be adjusted. The tool will analyze those biomarkers predictive of response to metronomic chemotherapy in metastatic breast cancer patients. By correlation to clinical data of patients, individual biomarkers for a cohort of patients with Breast Cancer will be produced as a result. The tool should be made in a general way such that by describing the databases and the interfaces the tool will become domain-independent.

We will analyze the following biomarkers: VEGF, VEGFr2, TSP1, bFGF , PDGF, IL-6, IL-8, Ang-1, Ang-2, SDF-1 and VCAM-1, circulating endothelial cells (CECs), CEPs ald Lymphangioblast (LBs) mRNA levels of angiogenesis-, vasculogenesis- and lumphangiogenesis-related genes VE-Cadherin, CD133 and VEGFR3;

A dynamic MRI will be performed as well.

For the benefit of a personalized medicine we expect that in individual patients it will be possible to find predictive biomarkers that will help clinicians to identify sub group of patients potentially responsive to metronomic chemotherapy

4.1.3.2 Patient stratification, treatment selection and long term follow up

An important area for the implementation of CDS is patient stratification for the best treatment: most effective and with the lowest risk of adverse events. There is a strong need for tools for better and more efficient patient stratification in oncology due to the following aspects:

- Cancers are complex diseases that require complex clinical decision process. Increasingly many treatment options exist with large amounts of heterogeneous data collected
- More targeted, individualized treatments are required for better outcomes
- Co-morbidities and risk of adverse events always need to be considered in cancer treatments

- Currently tools for comprehensive stratification are missing
- Many patients receive suboptimal treatments or treatments that do not work, with a large gap between outcomes of patients treated in expert/research sites and those of patients treated in community care
- Severe adverse events may require the treatment to be stopped or cause delays, therefore a focus on prevention and on early detection and management of those events is beneficial.

Currently there are many available treatments, but the best choice not always obvious. To improve effectiveness, there are significant ongoing efforts to replace the ineffective trial-and-error approach with personalized treatments that work. The current focus is on stratification on smaller populations with increased effectiveness and there is a need for more personalized predictive factors of response and to reduce whenever possible the unnecessary treatment-induced suffering in patients. These developments also generated strong needs for tools to efficiently integrate complex models into clinical care. Meaningful CDS tools should enable clinicians to evaluate therapeutic gains versus risks when comparing available treatments and to efficiently select the most effective treatment for a patient.

Additionally, enabling long term follow up of patients (i.e. providing access to all patient data and clinical decisions) will support the accurate evaluation of treatment outcomes, but also enable the early assessment of the response to treatment, and the prevention and early detection of serious adverse events. Moreover, this longitudinal data is a valuable resource for data mining and retrospective studies.

In order to be able to provide recommendations, a CDS system first needs to extract from the relevant sources the needed data and knowledge with semantics. Next, recommendations can be provided based on the available evidence. Links to the clinical evidence that was used (literature, guidelines, protocols, models, knowledge repositories, etc.) need to be provided.

4.1.3.3 Implementation of the St. Gallen stratification for early breast cancer

Since 1978, St. Gallen conferences have developed consensus opinions for managing early breast cancer. These are recognised as the leading European treatment guidelines. Provide the clinician with recommendations developed from the consensus opinions of international experts based on their interpretation of the most recent clinical data. In the US, St. Gallen guidelines are strongly supported by both the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) guidelines.

The 2011 St. Gallen recommendations focus on new patient stratification according to the intrinsic molecular subtypes as defined by genetic array testing. They state that it is no longer tenable to consider breast cancer as a single disease as these subtypes have different epidemiological risk factors, different natural histories and different responses to therapies[23]. They also propose an approximation to the molecular classification that is based on standard immunohistochemistry. This classification should be used by those healthcare organizations that cannot carry out array testing.

[23] Goldhirsch, A, et all. Strategies for subtypes – dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011, Annals of Oncology, doi:10.1093/annonc/mdr304

A CDS inference tool providing patient stratification and treatment selection based on St. Gallen and the translation to the proposed approximation based on standard tests when genetic array testing is not available would facilitate the quick and wide scale adoption of the new St. Gallen stratification.

The tool would require the input of relevant patient data to enable the matching of a patient to the appropriate subtype. The extraction of relevant patient data out of the patient file to allow automatic evaluation of the specific subtype of the patient would also be beneficial. This would require the development of a semantic solution for access to the patient data. Scalability could be achieved by focusing on semantic interoperability based on widely adopted standards and terminologies.

4.1.4 General way to develop the tool for DSS to predict SAEs

Steps:

a) literature mining --> find items that are correlated to the specified SAE (literature needs to include pharmacogenomics)

b) data mining of clinical databases --> find items that are correlated to the specified SAE

c) data mining of SUSAR databases (EMA, NIH) --> find all of the specified SAEs and the corresponding data of patients

d) develop a list of items that from the 3 searches that are correlated with the specified SAE

e) develop CRF(s) in ObTiMA for these items for prospective collection of necessary data

e) collect data in CRFs from HIS and clinical databases for building the model with these data

f) validate the model with prospective data

g) inclusion of a learning loop for optimizing the model --> find the most relevant and least items for he best prediction

h) use the model prospectively

The following clinical databases will be used:

1. SIOP nephroblastoma database (for VOD and cardiotoxicity)
2. ALL database (for cardiotoxicity)
3. Breast cancer databases (for cardiotoxicity)

The output of the DSS:

The output of the DSS needs to be a risk profile of the individual patient that should help the physician in applying the best treatment with fewer side effects to the individual patient.

4.1.5 Oncosimulator scenario for Breast Cancer

It is the intention of the Oncosimulator to predict the most likely response of a given patient to one or more candidate treatment schemes while toxicological limitations are taken into account. At the same time the Oncosimulator is a concept of multi-level integrative cancer biology. It is a biomedical engineering system and clinical tool that implements a complex

algorithm with the aim of supporting the clinician in the process of optimizing cancer treatment in the patient individualized context by conducting experiments in silico i.e. on the computer. Additionally, it is a platform for simulating, investigating, better understanding and exploring the natural phenomenon of cancer, supporting the design and interpretation of clinico-genomic trials and finally training doctors, researchers and interested patients alike.

4.1.6 Biobank scenario

A biobank, also known as a bio-repository, is a place that collects, stores, processes and distributes biological materials and the data associated with those materials. These may include human bio-specimens such as tissue or blood and related clinical information pertaining to the donor of that bio-specimen. Patients will be able to access the biobank data stored on them with the data "translated" into a patient friendly format and language.

4.1.7 Patient empowerment scenario

Personalized medicine includes the analysis of the psychological and cognitive characteristics of each single patient. The analysis of the individual profile of the patient might help physicians to evaluate how to inform the patients and to decide which is the treatment that best fits with the personal profile of each patient. Such an approach will lead to an individualized treatment choice adjusted to the patient's needs.

Patients are typically seen as the recipients of care. An important ideal of personalized medicine is to better enable patients themselves to be participants and guides in their own health care. The role of patients will be strengthened in *p-medicine* by allowing them to decide at any time what kind of research is allowed to be done with their data and their own biomaterial. Patient empowerment is based on information coming from research. Only by using this information to educate patients shared decision support is possible. This will enhance transparency for patients in the healthcare system and will convince patients to use their data for research purposes as shown in figure.

The circuit of patient empowerment from research to decision support and back to research. The green arrow indicates the necessity of tools for patients to provide feedback to enhance clinical research. Adapted from: "The Patients and Consumers Perspective"; eHealth Conference, Barcelona, 15th March 2010.

5. Requirements relevant for CDS

Introduction

Clinical Decision Support is a critical component for organizations seeking to improve the health of the healthcare delivery system. Hospitals, health systems and medical groups already realize that increased patient volume requires more than simply adding staff. It means leveraging technology to improve care quality, access, effectiveness, efficiency and safety, the result of which is better care at lower costs. Many healthcare organizations have implemented CPOE (computerized physician order entry) systems and EHR (electronic health record) systems. Still, challenges remain in system selection, adoption, implementation and use.

5.1 Requirements relevant for CDS tools in Breast Cancer Scenario

- To find biomarkers predictive of response to metronomic chemotherapy
- To make the tool domain independent for usage in other cancer domains
- To find predictive biomarkers that will help clinicians to identify sub group of patients who will have a potential clinical benefit from metronomic chemotherapy
- To implement accurate patient stratification and treatment selection both with respect to effectiveness and lowest risk of severe adverse events
- To provide access to evidence (literature, protocols, guidelines, etc.) for relevant recommendations
- To provide long term follow up

5.2 Requirements relevant for CDS tools in Oncosimulator scenario

- To predict the likely response of a given patient's breast cancer to one or more candidate treatment schemes while toxicological limitations are taken into account.
- To clinically adapt and validate the breast cancer Oncosimulator in such an extent so as to allow its clinical translation.
- Personalization of treatment, optimization of treatment outcome, increase of life expectancy and improvement of the quality of life.

5.3 Requirements relevant for CDS tools in Biobank scenario

- Giving appropriate meaning to the biobank data for patients
- Displaying the information in a way that is suitable for all patients with differing levels of understanding and education.
- Access to each of the biobank repositories

5.4 Requirements relevant for CDS tools in Patient empowerment scenario

- To help physicians to better understand the psychological and cognitive aspects of the patients so that they can find the best therapeutic approach giving them information and treatments personalized on their needs and values finding.
- To increase the power of patients during the therapeutic process.
- To create a fast, easy-to-use tool to collect data from patients that can be easily interpreted by physicians.
- To give patients the possibility to monitor their feelings and quality of life through the use of internet-based questionnaires.
- Obtaining a personal patient's profile will help physicians to better understand the patients and their needs.
- Asking patients to answer the questionnaires will serve to increase their participation and their level of empowerment.

5.5 CDS applications relevant for scenarios for Nephroblastoma and ALL

- Building CDS tools that support the efficient execution of the clinical trial protocols
- Linking to clinical evidence that supports treatment recommendations in a CDS tool (treatment protocols, publications, risk models, guidelines, etc.)
- Development of predictive models concerning the risk of patients to develop different types of severe adverse events
- Development of CDS tools that incorporate risk models for serious adverse events
- Development of CDS functionality for early detection and reporting of severe adverse events
- Providing support for the management of the severe adverse events that have occurred and for long term follow up.

6 Conclusion

In conclusion, improvements in care quality, safety, efficiency, cost and access will occur only when clinicians can make timely, accurate, evidence-based decisions at the point of care.
Medical knowledge in oncology is growing at an unprecedented rate, with the continuous introduction of new treatment options, medication and technologies. At the same time, the domain is burdened by overwhelming amounts of data, information and knowledge that need to be managed, integrated and analyzed, and by a widening evidence-practice gap. The role of clinical decision support is to enable the clinical specialists to efficiently access data and infer knowledge necessary to reach the most accurate decision for the best patient outcome.

Clinical decision support (CDS) tools integrated with the EHR (electronic health record) systems provide a tool set to ensure the right information is available where, when and how clinicians need it and that clinicians follow the proper clinical processes.