# ICT-2011-288048

# EURECA

# Enabling information re-Use by linking clinical Research and CAre

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# 0 DOCUMENT INFO

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# Table of Contents

# 1 Introduction

## 1.1 Purpose and structure of the deliverable

EURECA goal is to enable a seamless, secure and consistent link between clinical research and clinical care systems. Such a link would enable for example the healthcare professionals to extract, in the context of each patient's case, the relevant data out of the overwhelmingly large amounts of heterogeneous patient data and treatment information. On the other end, it would help a more effective and efficient execution of clinical research, early detection of patient safety issues, faster transfer of new research findings and guidelines to the clinical setting (from bench-to-bedside).

EURECA plan to achieve this by implementing a set of loosely-coupled software services and tools which will be deployed in the context of pilot demonstrators ("the scenarios"). These scenarios will constitute the basis for tool development; however, a modular approach will be used to ensure re-usability and scalability of the solutions.

A core element of EURECA is to develop such solutions whilst fulfilling the data protection and security needs and the legal, ethical and regulatory requirements related to linking research and EHR data and allowing the extraction of data based on relevance and its contextualization to the patient case.

The above key aims and components of EURECA will be reflected in the solutions suggested for the data-mining and the purpose of this deliverable is to describe the data-mining requirements to support the EURECA scenarios. The deliverable has a specific focus on knowledge discovery scenarios, and these scenarios will be expanded and developed further here.

General key-points of the EURECA project are re-usability, compatibility and standardization of all components. In this context, we will try to build upon several previously defined concepts and methodologies whenever this is possible and point out areas for further methodological work.

The structure of this deliverable is as follows. A high-level illustration of the deliverable reviews the findings and the scenarios described in deliverable D1.1 "User needs and specification for the EURECA environment and software services" in chapter 2. These needs set up the landscape for a more in-depth requirements analysis for data-mining, which is the subject of chapter 3. Chapter 4 focuses and expand on the knowledge discovery scenarios.

# 2 Data-mining in EURECA

EURECA wants to deliver measurable benefit to various communities ranging from the patients them-selves, to the clinical professional, research and industry.

As stated in to the DoW the main objectives are:

1. **Support more effective and efficient execution of clinical research** by:
    a. Allowing faster eligible patient identification and enrolment in clinical trials,
    b. Providing access – in a legally compliant and secure manner – to the large amounts of patient data collected in the EHR systems to be re-used in clinical research, for new hypotheses building and testing (e.g. to benefit rare diseases), study feasibility, as well as for epidemiology studies,
    c. Enabling long term follow up of patients, beyond the end of a clinical trial,
    d. Avoid the current need for multiple data entry in the various clinical care and research systems during the execution of a study.
2. **Allow data mining of longitudinal EHR data for early detection of patient safety issues** related to therapies and drugs that would not become manifest in a clinical trial either due to limited sample size or to limited trial duration, and eliminate duplicate reporting (in care and research) of identified serious side effects,
3. **Allow for faster transfer of new research findings and guidelines** to the clinical setting (from bench-to-bedside),
4. **Enable the healthcare professionals to extract, in the context of each patient's case, the relevant data** out of the overwhelmingly large amounts of heterogeneous patient data and treatment information.

Thus, the basic requirement is an approach that focuses on specific and realistic clinical questions, or scenarios, initially, whilst adopting a moth modular, standard-based and scalable approach that could be easily generalized at a later stage.

The following section aims at extracting the data-mining requirements from concrete scenarios and clinical questions. The further section will expand on and describe some of the identified areas of data mining.

## 2.1 Scenario based requirements

The first task of EURECA clinical partners has been to develop general and modular scenarios that cover the above aims and define their specific application. Such scenarios have been described in a previous document; the "User needs and specifications for the EURECA environment and software services" deliverable D1.1, chapter 3.

### 2.1.1 The EURECA scenarios

A general classification was suggested in deliverable D1.1 that sees the EURECA scenarios classified into three categories:

- **Knowledge discovery**
  - Selection of best trials for a patient
  - Trial / protocol feasibility
  - Selection and inclusion of patients into trials
  - Detection and prediction of SAEs / SUSARs
  - Pharmacovigilance – Automatic reporting of SAEs and SUSARs
  - Early detection and prevention of diseases
  - Personal medical information recommender
  - Develop or update guidelines for diseases
  - Data mining of consultations
  - Analyse economic data between different procedures / approaches
  - Build, optimize, validate or update a diagnostic classifier
  - Build predictive models of late morbidity
- **Data curation**
  - Long term follow-up
  - Patient diary (connection between PHR and data management tools)
- **Basic research and clinical trials support**
  - Supporting design of new trials and hypothesis generation
  - Mining of information from EHR and CT to validate research/clinical hypotheses
  - Clinical data reuse
  - Opt-out solution for new research
  - Simulation of datasets to combine
  - Rapid learning
  - High-level genomic meta-analyses in genomic/genetic
  - Association studies

EURECA scenarios are still evolving and are being defined by clinical and technical partners together within the activities of WP1. The above scenarios reflect the activities and discussion within EURECA so far. A general schema for most of these scenarios is already available and presented in Chapter 3 of the D1.1 deliverable; others will be discussed in this document.
In the next section we will discuss the requirements and implications of these scenarios from a data-mining perspective.

## 2.1.2 Dissecting the scenarios data-mining components

In the following sections we try to extract and discussed the main data-mining requirements and challenges of the EURECA scenarios.
A summary table is also provided at the end of this section (Table 2.1).

#### 2.1.2.1 Knowledge discovery

### *Selection of trials for patient enrolment*

Brief description

The goal of this scenario is to find the optimal trial that fits the needs of the patient the best. The schema is presented in D1.1 figure 3.4.

Data-mining components

The following components are needed:

1) Mining of PHR or HER is needed to get the specific data of the patient

2) mining of the relevant trial databases and identification of a trial for the specific patient

3) mining of the literature and identification of suitable trials that have been completed

Requirements and Methods

Similarity learning: discovery of similar datasets and similar trials

Frequent pattern mining: discovery of frequently occurring patterns to summarize datasets and to aid similarity learning

Text mining of unstructured databases

Time-dependent data mining methods that effectively address the continuously changing landscape in trial databases, literature, public databases.

Change detection to effectively detect changes in data, annotation and structure of databases

Multi-dimensional data mining

Dimensionality reduction of high-throughput and imaging data

Challenges

- complex structured and non-structured data: both patient and trial data can include EHR/PHR data, imaging data, pathology data, genomic and genetic data
- Representation of semantic similarity in such a complex data space is challenging
- Time dependency
- Data are not anonymous: privacy issues needs to be addressed, possibly by performing the data-mining at the hospital site

## *Trial / Protocol feasibility*

Brief description

This scenario describes if a new clinical trial is feasible to start according to the estimation of recruitment potential. Two versions of this scenario are possible:

1. Based on EHR/PHR/HIS data
2. Based on other data sources

or a combination of these two; for more details see D1.1 figure 3.5.

Data-mining components

The following components are needed:

1) mining of EHR or other databases to select the cohort of patients that fits recruitment criteria best

2) discovery of similar patients based on eligibility criteria

3) discovery of similar trials or similar datasets

Requirements and Methods

Privacy preserving data mining if based on EHR

Distributed data learning as a possible solution to the ethical, legal and practical problem in transferring data to central repository

Similarity learning: discovery of similar patients and similar trials

Frequent pattern mining: discovery of frequently occurring patterns to summarize datasets and to aid similarity learning

Text mining of unstructured databases

Time-dependent data mining methods that effectively address the continuously changing landscape in EHR, trial databases, literature, public databases.

Change detection to effectively detect changes in data, annotation and structure

Multi-dimensional data mining

Dimensionality reduction if high-throughput and imaging data needs to be considered

Challenges

- complex structured and non-structured data: both patient and trial data can include EHR/PHR data, imaging data, pathology data, genomic and genetic data

- representation of semantic similarity in such a complex data space is challenging

- Data are not anonymous: privacy issues needs to be addressed, possibly by performing the data-mining at the hospital site

## *Selection and inclusion of patients into trials*

Brief description

This scenario describes how patients can be selected for a specific trial. The initiator could be a pharmaceutical company, a research or a clinical institution. The specific requirements for implementation will change partially depending on the initiator. There is a relation to the scenario KD15 (Personal medical information recommender). The schema is presented in D1.1 figure 3.6.

Data mining components

The following steps are needed (see figure 3.6):

1. mining of EHR or other databases to select the cohort of patients that fits inclusion criteria of the trial

2. discovery of similar patients based on eligibility criteria

3. discovery of similar trials or similar datasets

Requirements and Methods

Privacy preserving data mining if based on EHR/PHR

Distributed data learning as a possible solution to the ethical, legal and practical problem in transferring data to central repository

Similarity learning: discovery of similar patients and similar trials

Frequent pattern mining: discovery of frequently occurring patterns to summarize datasets and to aid similarity learning

Text mining of unstructured databases

Time-dependent data mining methods that effectively address the continuously changing landscape in EHR, trial databases, literature, public databases.

Change detection to effectively detect changes in data, annotation and structure

Multi-dimensional data mining

Dimensionality reduction if high-throughput and imaging data needs to be considered

Challenges

- complex structured and non-structured data: both patient and trial data can include EHR/PHR data, imaging data, pathology data, genomic and genetic data

- representation of semantic similarity in such a complex data space is challenging

## *Detection and prediction of SAEs and SUSARs*

Brief description

This scenario describes how SAEs and SUSARs can be detected and predicted before a treatment is given to a patient (see D1.1, figure 3.7).

Data mining components

1. Data mining in databases of EMA for SAEs and literature mining to find association between a specific profile and SAEs

2. Assign patient to a risk group based on the molecular analysis of the pharmacogenomics in the blood of the patient

Requirements and Methods

Frequent pattern mining: discovery of frequently occurring patterns to summarize datasets and to aid similarity learning

Similarity learning to discover similar SAEs profiles

Classification rules to assign patient to risk group

Text mining of unstructured databases

Association rule mining

Time-dependent data mining methods that effectively address the continuously changing landscape in SAEs, literature and other databases, with a view to extend to data stream mining in the future

Change detection to effectively detect changes in data, annotation and structure

Multi-dimensional data mining

Dimensionality reduction if high-throughput and/or imaging data need to be considered

Challenges

- Complex structured data

- Time dependent data

## *Pharmacovigilance – Automatic reporting of SAEs and SUSARs*

Brief description

This scenario describes how SAEs and SUSARs are detected in specific patients and will be reported automatically to regulatory bodies. Details and scenario schema can be found in D1.1, figure 3.8.

Data mining components

1. At regular time points query databases, e.g. HIS/EHR/PHR, for SAEs and SUSARs and generate automatic report.

Requirements and Methods

Text mining if unstructured databases are considered

Challenges

- Complex structured data
- Time dependent data

## *Early detection of cancer / individual risk / prevention*

Brief description

According to the patient's personal life style data (social networks), his genetic data and clinical data (EHR, PHR, HIS, etc.) the personal risks for diseases can be listed. This might help to detect cancer earlier by starting a screening program for the patient or advice the patient to change his/her lifestyle to prevent cancer, if such a program exists. The scenario is outlined in D1.1, figure 3.9.

Data mining components

1. Data Mining of literature to find risks for diseases (Cancer)
2. Data mining of social networks to describe the lifestyle of a patient
3. Prediction of the individual cancer risk

Requirements and Methods

Text mining of unstructured databases

Privacy preserving data mining

Frequent pattern mining to identify frequent patterns in different datasets

Rule discovery to identify and predict risk for disease

Classification rules to assign patient to risk group

Time-dependent data mining methods that effectively address the continuously changing landscape in SAEs, literature and other databases, with a view to extend to data stream mining

Change detection to effectively detect changes in data, annotation and structure

Multi-dimensional data mining

Challenges

- complex structured and non-structured data: both patient and trial data can include EHR/PHR data, imaging data, pathology data, genomic and genetic data
- Representation of semantic similarity in such a complex data space is challenging
- Large amount of time-dependent data, time-dependent data-mining with a view to methods used in data stream mining
- Data are not anonymous: privacy issues needs to be addressed. If complex scenarios involving tool such as social networks are executed privacy preserving data-mining methods need to be developed and implemented.

## *Personal medical information recommender*

Brief description

This scenario describes how people can obtain objective information about trials, treatments etc. about their specific disease. It defines the condition of a patient and does data mining in all available data sources (see D1.1, figure 3.10):

Data mining components

1. Data mining of literature and trial databases to identify and extract information about the disease and possible trials
2. Summary analysis of information and reporting
3. Analysis and summarization of patient data

Requirements and Methods

Text mining of unstructured databases

Frequent pattern mining to identify frequent patterns in different datasets

Association rule mining

Classification rules to assign patient to risk group

Time-dependent data mining methods that effectively address the continuously changing landscape in SAEs, literature and other databases, with a view to extend to data stream mining

Change detection to effectively detect changes in data, annotation and structure

Multi-dimensional data mining

Dimensionality reduction if high-throughput or imaging data are considered

Challenges

- complex structured and non-structured data: both patient and trial data can include EHR/PHR data, imaging data, pathology data, genomic and genetic data
- Representation of semantic similarity in such a complex data space is challenging
- Time dependency

## *Develop or update of guidelines from clinical trial data and literature mining*

Brief description

This scenario describes how guidelines can be developed and regularly updated from data mining of clinical trials and literature; details and schema re presented in D1.1, see figure 3.11.

Data mining components

1. Data mining in CT/HIS, Literature and trial databases
2. Limit the data-mining to data published after the date of the most recent guideline
3. Generate automatic listing of the updated items

Requirements and Methods

Text mining of free text databases and literature

Association rule mining

Frequent pattern mining to understand data structure and aid association rule mining

Time-dependent data mining methods that effectively address the continuously changing landscape in SAEs, literature and other databases, with a view to extend to data stream mining

Change detection to effectively detect changes in data, annotation and structure

Multi-dimensional data mining

Dimensionality reduction if high-throughput or imaging data are considered

Challenges

- complex structured and non-structured data: both patient and trial data can include EHR/PHR data, imaging data, pathology data, genomic and genetic data
- Representation of semantic similarity in such a complex data space is challenging
- Time dependency

## *Data mining of consultations*

Brief description

In prospective clinical trials many consultations are performed. A part of the questions of such consultations are repeatedly asked. This scenario generates an automatic answer to questions asked during consultations. Details and schema are in D1.1, figure 3.12.

Data-mining components

1. Data-mining of structured documentation from consultation
2. Data-mining of free text from consultation or data-mining of structured information extracted from the free text
3. Selection and analysis of answers to the same consultation question
4. Literature mining to validate results

Requirements and Methods

Text mining

Association rule mining

Frequent pattern mining to understand data structure and aid association rule mining

Time-dependent data mining methods that effectively address the continuously changing landscape in SAEs, literature and other databases

Privacy preserving data mining

Challenges

- Representation of semantic similarity in such a complex data space is challenging
- Text data from consultations can be non-anonymous; this needs to be addressed either by anonymization tools used before the mining or by using privacy preserving data-mining techniques

## *Analyse economic data between different procedures (for funding reasons) compared to outcome and quality of life / data of hospital stays, expected side effects, etc.*

Brief description

By joining data from EHR, clinical trials, literature and open databases economic aspects of different procedures (diagnostic and/or therapeutic) can be analysed in respect to outcome and quality of life in an individual patient. The relevant steps for this scenario are described in D1.1, figure 3.13.

Data-mining components

1. Data-mining of literature
2. and data-mining of open source databases: identify best diagnostic and treatment procedures for patients
3. Data mining of economic databases

Requirements and Methods

Text mining of literature

Association rule mining

Frequent pattern mining to aid association rule mining

Time-dependent data-mining with a view to methods used in data stream mining

Challenges

- complex structured and non-structured data: both patient and trial data can include EHR/PHR data, imaging data, pathology data, genomic and genetic data
- Representation of semantic similarity in such a complex data space is challenging

- Large amount of time-dependent data, time-dependent data-mining with a view to methods used in data stream mining

- Data are not anonymous: privacy issues needs to be addressed. If complex scenarios involving tool such as social networks are executed privacy preserving data-mining methods need to be developed and implemented.

## *Build, optimize, validate or update a diagnostic classifier*

Brief description

By analyzing data from literature together with patient data produced using high-throughput assays, imaging, pathology, information from clinical trials and EHR databases, build a diagnostic classifier or update existing ones. The relevant steps for this scenario are described in D1.1.

Data-mining components

1. Data-mining of literature
2. and data-mining of open source databases
3. Analysis of data from high-throughput assays, imaging, pathology, EHR/PHR and clinical trials to build a diagnostic classifier
4. Classify new patients
5. Validate classification using data from different clinical centres

Requirements and Methods

Text mining

Association rule mining

Frequent pattern mining to aid association rule mining

Time-dependent data-mining

Distributed learning: data from different centres can be merged without having to transfer data to central repository

Classification

Challenges

- complex structured and non-structured data: both patient and trial data can include EHR/PHR data, imaging data, pathology data, genomic and genetic data

- Data are not anonymous: privacy issues needs to be addressed. Distributed learning could provide a solution.

### *Build and validate predictive models of late toxicity*

Brief description

By analyzing data from literature together with patient data including imaging, pathology, information from clinical trials and EHR databases, build a mathematical model of late toxicity or update existing ones. The relevant steps for this scenario are described in D1.1.

Data-mining components

1. Data-mining of relevant literature
2. Data-mining of relevant clinical trials
3. Analysis of data from imaging, pathology, EHR/PHR and clinical trials together with long-term follow-up to build models of late toxicity
4. Mining of clinical trials and other databases to find datasets for validation of models
5. Predict late toxicity risk

Requirements and Methods

Text mining

Association rule mining

Frequent pattern mining to aid association rule mining

Time-dependent data-mining

Distributed learning: data from different centres can be merged without having to transfer data to central repository

Classification

Challenges

- complex structured and non-structured data: both patient and trial data can include EHR/PHR data, imaging data, pathology data, genomic and genetic data

- Data are not anonymous: privacy issues needs to be addressed. Distributed learning could provide an alternative solution to anonymization and storage of data in a central repository.

#### 2.1.2.2 Data curation

### *Long-term follow-up*

Brief description

This scenario deals with the curation of data in long-term follow-up including also survival follow-up, primary and secondary outcome measures follow-up, safety reporting for adverse reactions are study treatment completion. The relevant steps for this scenario are provided in D1.1, figure 3.14.

Data mining components

1. Data mining of HIS/EHR/PHR
2. Data mining of National registries

Requirements and Methods

Text mining

Time-dependent data mining

Privacy preserving data mining

Challenges

- Data might be not anonymous: privacy issues needs to be addressed.

### *Patient Diary*

Brief description

This scenario deals with the possibilities of a patient diary. Such a diary can be used in clinical trials; the details are provided in D1.1, figure 3.15.

Data-mining components

1. No specific data-mining component specified

#### 2.1.2.3 Basic research and clinical trials support

### *Supporting design of new trials and hypothesis generation*

Brief description

Clinical trials are often generated to test a research question; analysing all available data from previous trials, guidelines, literature and others, can support the generation of research hypotheses such as to identify potential biomarkers. Some of the key steps involved in this scenario are identified in D1.1, figure 3.16.

Data-mining components

1. Data mining of CT
2. Data-mining of literature

3. Data-mining of other databases

Requirements and methods

Similarity learning to find similar clinical trials and/or datasets

Association rule mining

Frequent pattern leaning to aid association rule mining

Rule discovery

Text mining of literature

Time-dependent data-mining

Multi-dimensional data mining

Dimensionality reduction if data from high-throughput assays and imaging are considered

Challenges

- complex structured and non-structured data: data can include EHR/PHR-like data, imaging data, pathology data, genomic and genetic data
- Large amount of time-dependent data, time-dependent data-mining with a view to methods used in data stream mining

## *Clinical data reuse*

Brief description

Re-use the clinical data into the trial eCRF systems to avoid double data entry.

Data-mining components

1. No specific data-mining component specified

## *Opt-out solution for further research*

Brief description

Provide a platform where patients can select which research they do not like to do with their data or biomaterial. Such a scenario is based on the fact that every patient agrees to share his data to any research project and that he can disagree to specific research projects at any time by using the above described website. The relevant steps for this scenario are described in D1.1, figure 3.17.

Data-mining components

1. Data-mining on anonymized data to select patients to answer specific research question

Requirements and methods

Text mining. No other specific requirements, data-mining will depend on specific realization of this scenario and research questions.

Challenges

Maintenance of a website where the patient has access to disagree with the research project
Further challenges will depend on the specific research questions

## *Similarity of datasets to combine*

Brief description

Detection and identification of similar datasets to use in meta-analyses or combined analyse. This scenario is further described in D1.1.

Data-mining components

1. Data mining of CT databases, EHR, literature

Requirements and methods

Similarity learning to find similar clinical trials and/or datasets

Frequent pattern leaning to aid similarity learning

Text mining

Time-dependent data-mining

Multi-dimensional data mining

Dimensionality reduction if data from high-throughput assays and imaging are considered

Challenges

- complex structured and non-structured data: data can include EHR/PHR-like data, imaging data, pathology data, genomic and genetic data
- Large amount of time-dependent data, time-dependent data-mining with a view to methods used in data stream mining

### 2.1.3 Summary

The above analysis of all scenarios identified some key areas that need to be considered for EURECA data-mining. These are still general as the specific implementation or methods will need to be tailored to the specific scenarios, also in accordance with the EURECA environment and with the choices for semantic interoperability. Table 2.1 summarize the results so far for all scenarios described either in the previous paragraph of this section, or in the last section of this document (EURECA knowledge discovery) or in WP2 deliverable 2.1.

| | | **Data mining requirements** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Scenario** | **Similarity learning** | **Frequent pattern mining** | **Association rule discovery** | **Classification** | **Text mining** | **Time-dependent data mining** | **Change detection** | **Multi-dimentional datamining** | **Dimensionality reducton** | **Data stream mining** | **Privacy preserving data mining** | **Distributed data learning** |
| **Knowledge discovery** | Selection of best trials for a patient | x | x | | | x | X | x | x | x | | | |
| | Trial / protocol feasibility | x | x | | | x | X | x | x | x | | x | x |
| | Selection and inclusion of patients into trials | x | x | | | x | x | x | x | x | | x | x |
| | Detection and prediction of SAEs / SUSARs | | x | x | x | x | x | x | x | x | x | | |
| | Pharmacovigilance | | | | x | x | | | | | | | |
| | Early detection and prevention of diseases | | x | x | x | x | x | x | x | | x | x | |
| | Personal medical information recommender | | | x | | x | x | | x | x | x | | |
| | Develop or update guidelines for diseases | | x | x | | x | x | | x | x | x | | |
| | Data mining of consultations | | x | x | | x | x | | | | | x | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Analyse economic data between different procedures / approaches | | x | x | | x | x | | | | x | | |
| | Build, optimize, validate or update a diagnostic classifier | | x | x | x | | x | | x | x | | x | x |
| | Build predictive models of late morbidity | | x | x | x | x | x | | | | | | x |
| **Data curation** | Long term follow-up | | | | | x | x | | | | | x | |
| | Patient diary (connection between PHR and data management tools) | | | | | | | | | | | | |
| **Basic research and clinical trials support** | Supporting design of new trials and hypothesis generation | x | x | x | | x | x | | x | x | | | |
| | Mining of information from EHR and CT to validate research/clinical hypotheses | x | x | x | | x | x | | x | x | | | |
| | Clinical data reuse | | | | | | | | | | | | |
| | Opt-out solution for new research | | | | | x | | | | | | | |
| | Similarity of datasets to combine | x | x | | | x | x | | x | x | | | |
| | Rapid learning | | | x | | x | x | | x | x | x | | |
| | High-level genomic meta-analyses in genomic/genetic | | x | x | | x | x | | x | x | | | |
| | Association studies | | x | x | | x | x | | x | x | | | |

## 2.2 User needs based requirements

At the start of the project a survey was performed that was aimed at gathering opinions about the projects, the possible applications, and about the methods and the datasets which could be available.

### 2.2.1 Results from user need questionnaires

The description of the survey and an in-depth analysis of results can be found in a previous document D1.1 “User needs and specifications for the EURECA environment and software services”.

In brief five main points were highlighted there:

1. The described clinical scenarios are important as they cover the needs of the participants of the survey.

2. Tools need to be developed build out of use cases as open source tools and stored in the VPH toolkit.

3. Legal issues need to be solved to share data if the data producer wants to share and not only use EURECA tools to work on his own data.

4. Some of the answer highlighted that data should not leave the centre, thus distributed data analysis/mining should be considered

5. Need for standardization

### 2.2.2 Implication for data-mining requirements

The implication of the above points for data-mining are:

1. The need to base the specific requirements on the scenarios

2. The need to develop open source tools

3. The need to investigate and test privacy preserving data mining

4. The need to investigate distributed learning

5. Modular approach needed

# 3 Data-mining approaches and methods

The previous sections analyzed the scenarios and user need questionnaire to lay the main components and requirements for the data-mining. Below we will define and describe the main data mining areas mentioned in the previous section. This is an extremely brief overview and it is provided here exclusively with the purpose of aiding the interpretation of the previous requirement analysis and related discussion. A more in depth description and further discussion on the existing application and limitations of the specific methods in each of these data mining areas will be found in deliverable D5.2. This deliverable will focus on a state-of-art review of existing data-mining methods.

## 3.1.1 Data mining techniques in EURECA

### *Data pre-processing: dimensionality reduction*

New clinical trials include techniques such as high-throughput assays and imaging techniques which produce a very large amount of data points/variables. Thus, data pre-processing has become a very important step in data analysis.

Many of the variables (e.g. gene) in these datasets are correlated and not independent. Methods such as dimensionality reduction help to reduces the number of such variables to some smaller set of independent variables. This helps gaining statistical power in analyses where usually the number of variables is much higher than the number of cases.

Dimensionality reduction approaches can be applied before the analysis or, for example in classification problems, whilst building the classifier.

### *Similarity Learning*

Similarity Learning consists of classification on pairwise similarities. In contrast to traditional machine learning, similarity learning does not assume that objects are well represented in a Euclidean feature space. This is useful for problems in bioinformatics, information retrieval and many other areas with diverse object representations.

In EURECA for example we want to find similar clinical trials. Since clinical trials more frequently now include pathology, genomic and imaging data, the representation of semantic similarity will need to be defined in extremely complex data space.

### *Association Rule Discovery*

Association rule mining considers the problem of discovering association rules between items in a large databases; it has been applied extensively for example to databases of sales transactions but less so to the clinical or medical sciences.

Algorithms have been proposed and tested mainly for categorical data and less so for numerical data (1-5).

### *Classification*

Classification is a mining technique based on machine learning; it is used to classify each item in a set of data into one of predefined sets of classes or groups.

The data classification process involves a learning phase and classification phase. In the learning phase a set of training data are analyzed by classification algorithm; then in the classification phase data are used to estimate the accuracy of the classification rules. If the accuracy is acceptable the rules can be applied to the new data tuples. The classifier-training algorithm uses these pre-classified examples to determine the set of parameters required for proper discrimination. The algorithm then encodes these parameters into a model called a classifier.

Methods applied to classification problems vary from linear models, to decision trees, Bayesian Classification, Neural Networks, Support Vector Machines (SVM). Depending on the specific realization of the EURECA scenarios different classification methods will be used.

### *Clustering*

Clustering is a data mining technique that defines groups of objects that have similar characteristic. Contrarily to classification where objects are assigned into predefined classes, clustering both defines the classes and assigns objects to them.

By using clustering techniques we can identify particular regions in object space and can discover overall distribution pattern and the correlations among data attributes. Classification approach can also be used for identifying groups or classes of object but it becomes costly;

Types of clustering methods include partitioning methods, hierarchical agglomerative methods, density based methods, grid-based methods, model-based methods.

### *Prediction*

Prediction is a data mining techniques that attempts to discover the relationship between independent variables and relationship between dependent and independent variables. Regression techniques can be applied to predication. Regression analysis can be used to model the relationship between one or more independent variables and dependent variables. In data mining independent variables are attributes already known and response variables are what we want to predict.

### *Frequent pattern mining*

Frequent pattern mining is a core data mining technique that focuses on identifying and extracting frequently occurring patterns from different types of datasets, including unstructured ones. By doing this, frequent pattern mining, can summarize effectively very complex datasets.

Frequent pattern mining is also used as a tool in combination with other data-mining techniques such as association rule mining and classification.

### *Text mining*

Text Mining is a branch of data mining that refers to learning by using automatic extraction of information from free text. Information from different text documents and/or resources is extracted and then linked to generate new rules or hypotheses. These are typically organized and explored with other data-mining methods.

In text mining the data patterns are extracted from natural language text rather than from structured databases; such automated processing of natural language is challenging and methods to perform such a task are still limited. Typically, it requires dividing text mining in specific relatively small tasks that can be performed automatically.

An example of application to genomics is the study of co-occurrences of words in publications to infer related function of genes or proteins, or generate hypotheses that can then be tested in further studies.

### *Time-dependent and data stream mining*

In many modern scientific and medical research domains, new knowledge and data are stored and recorded in large data streams of transactional data that rapidly and continuously grow over time. Not all scenarios described above present all the data stream characteristics but several of them present the challenge of being data that change over time and a large amount of data to be processed.

These types of data require a different data mining approach with respect to the ones used for classical static databases; both as the data change in time but also because the dimension of the data does not allow the classical re-sampling and training approaches often used in the machine learning and data mining community. For example, several classification algorithms require a recursive processing of the data.

Methods for analysis of such data have been described and a recent collection has been published, edited by Aggarwal, which describes many of the advances in the area (6).

## 3.1.2 Modularity and standardization

One key aspect central to EURECA is a modular approach where tools can be developed for specific scenarios but then be easily re-used and extended to different or larger scale scenarios.

In this context, the aim is to build upon several previously defined concepts and methodologies whenever this is possible and point out areas for further methodological work.

One area where we would like to re-utilize previous concepts is the high-level generation and handling of workflows.

For example, we will take on the concept of data-mining process patterns previously described in the p-medicine project (deliverable 11.1) and we will bring this concept to the EURECA application domain.

Briefly, the concept of data mining process patterns extend the classical data mining workflows to a more general process description which also include a representation of the manual work that needs to be done in order to successfully apply a workflow to a specific problem.

### 3.1.3 Distributed data learning

For some of the EURECA scenarios, and also as one of the requirements in the survey, was highlighted the need of analyzing the data locally at the hospital site and then merging results or further mine external public databases.

The field of distributed data mining study and addresses the problem of analyzing data residing at different locations, or nodes, without necessarily having to collect them at a central site, for a recent review see (7). In this case, the challenge is to solve learning problems with minimal exchange of information between nodes; thus the algorithms used need to use and summarize the limited amount of exchanged information very efficiently.

Several methods have been applied to distribute data mining including machine learning methods and Bayesian Network Learning (6, 8) In the last section of this document we will discuss specific scenarios where a distributed data approach mining is chosen and we will discuss specific methods. Furthermore, we will focus on the main different solutions available and their applicability to EURECA in a following state-of-art review on data-mining methods.

### 3.1.4 Privacy preserving data-mining

One of EURECA key goals is to deliver an environment that fulfils the data protection and security needs and the legal, ethical and regulatory requirements related to linking research and EHR data. In addition, several conflicting interests of different stakeholders must be taken into account to ensure the practicability of data mining solutions. The main problem are conflicting interests on which information should be protected, and which information should be freely available, in particular when considering information that should be made public outside of the EURECA contractual framework, e.g. in the form of scientific publications or open models for decision support.

The most relevant of the aforementioned stakeholders and interests are

- Patients require their personal information to be kept private. On the other hand, many patients are willing to freely share at least part of their information on public websites such as Facebook or Patientslikeme. This can become problematic when considering backgroung knowledge attacks on released information. In addition, patients may also profit from their information being released, as new treatments can be found. Hence, it is not clear where to best draw the line between privacy and data publication.
- Trial chairmen (and the general public) are ultimately interested in finding new scientific knowledge that may help their patients, and publishing it in scientic journals.

Rules of good scientific practice may require them to make available a large part of the data that is the basis of their findings.

- Data protection officers are responsible for following all applicable legal and regulatory requirements.
- Hospital and pharma companies, being economic entities, also have to consider patient data as an economic asset, and may not be willing to freely share data with other entities, as long as questions of intellectual property rights and financial compensation have not been cleared.

Vast research on methods for privacy-preserving data mining exists. The main directions of privacy-preserving data mining can be described as follows:

**Privacy-preserving data publishing** deals with the question of releasing data in such a way that all sensitive information is removed. The released data can then be processed with standard data mining methods. Approaches include randomization, k-anonymity (9), l-diversity (10) and t-closeness (11).
In EURECA, however, this approach does not seem promising. The problem is that once relevant information is removed, it cannot be recovered. Hence, it may be that clinically important information cannot be found, which clearly violates the interests of trial chairmen and the general public. The key point is here that under the applicable privacy law it is still possible to go back to patients and ask them for additional consent for their data to be processed and made public once it is known that an important discovery is made.

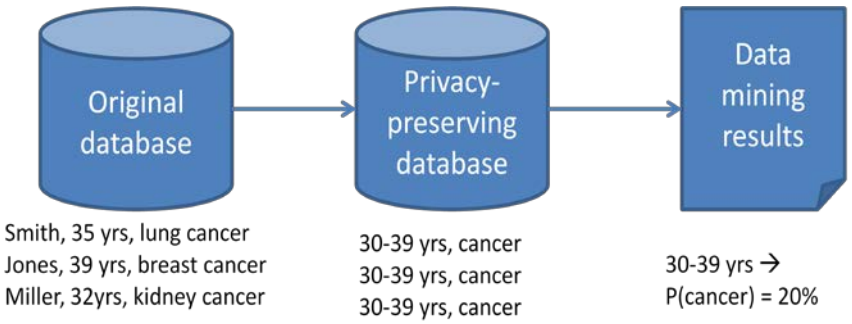



Figure 3.1.1 Privacy-preserving data publishing schema

**Secure distributed computation** removes the need for a central database in which data mining takes place. Instead, models are computed in a distributed way, such that it is guaranteed that the content of the individual, distributed databases are kept private except for what can be learned from the global results. Several approaches, based on techniques like the solution of the Millionaire's problem or the secure sum algorithm exist.

In EURECA, this approach will be interesting because it matches the EURECA distributed architecture (seeing hospitals as the local databases). In particular, it will help to cover the interests of hospitals and pharma companies, which most likely will object to the transfer of their data to a central database. The implementation of this approach consists of putting a computational endpoint at every hospital, which execute the local data mining queries and gives information back according to the privacy-preserving protocol to a central instance which coordinated the computation and assembles the final result.

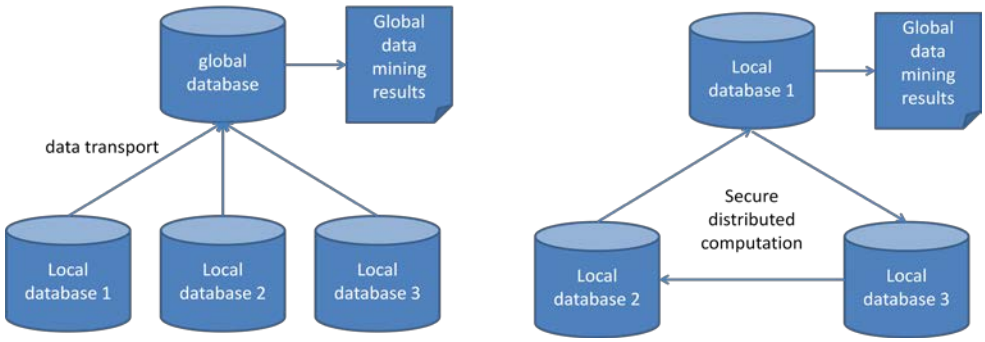



Figure 3.1.2 Secure distributed computation schema

**Privacy-preserving model publishing** deals with the question of quantifying the information that is contained in a released piece of knowledge such as a statistic, or a data mining model such as a complete decision tree (12-14).

An example of this scenario could be a neighbor, who knows that the patient regularly goes to the university hospital of the city to get treated for cancer. The neighbor might then look up running clinical studies of the university hospital on the internet, look for the latest publications of these studies, and try to see if he can use the published results to infer knowledge about the patient from his public data.

For EURECA, this is a central problem, as it addresses the problem of exporting valuable knowledge outside of the contractual framework. The problem is that while collaborating parties (such as the project consortium) can be bound by be legal contracts to observe all legal and ethical constraints, the ultimate goal of medical research is to generate new medical knowledge and make it available to the general public. Hence, it must be possible to weigh the scientific importance of a new discovery against the privacy implications, so that an adequate decision can be made.

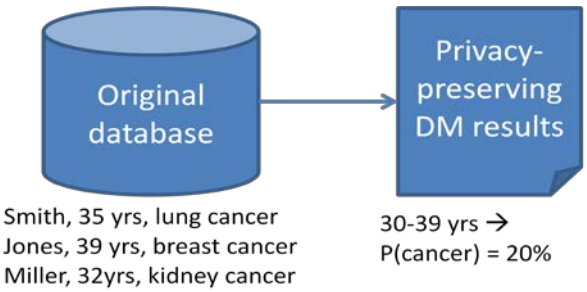



Figure 3.1.3 Privacy preserving model publishing

To give a closer idea of privacy preserving data-mining, a recent example that has been successfully applied to this area is micro-clustering, for a review see e.g. (6). Micro-clustering is a technique based on condensed representation of the data which show k-anonymity; these representations act as pseudo-points that can be used in the data-mining as a surrogate of the actual points. These and other methods will be reviewed in a following deliverable focusing on a state-of-the art review of current data-mining methods which could find an application in EURECA.

In the context of EURECA the privacy-preserving requirement are different depending on the specific application. In D1.1, chapter 4, the legal and privacy requirements for the EURECA scenarios have been discussed. In this respect, the following categorization was adopted:

- **Research domain**

  In the research domain, in most cases the data can be anonymized before the data-mining occurs, thus privacy preserving data-mining techniques are not required and there will be tools in EURECA to guarantee anonymisation is compliant with European regulations.

  The following scenarios were classified as research domains:

  - Develop or update guidelines for diseases
  - Data mining of consultations
  - Analyse economic data between different procedures / approaches
  - Opt-out solution for new research

- **Care domain**

  In the care domain personal data are always needed; thus data-mining algorithms applied to this area will need to address the privacy problem either by applying specific privacy-preserving data-mining technique or by working in combination with other EURECA tools and algorithms to create privacy-preserving workflows.

  The following scenarios were classified care domain:

  - Detection and prediction of SAEs / SUSARs

- Early detection and prevention of diseases
- Personal medical information recommender
- Long term follow-up
- Patient diary (connection between PHR and data management tools)
- Clinical data reuse

- **Trial support and execution**

  In the trial support and execution setting the situation can be more complex, and some scenarios do need access to personal data, others do not.

  The following scenarios were classified as trial support and execution:

  - Selection of best trials for a patient
  - Trial / protocol feasibility
  - Selection and inclusion of patients into trials
  - Pharmacovigilance – Automatic reporting of SAEs and SUSARs
  - Supporting design of new trials and hypothesis generation
  - Similarity of datasets to combine
  - Rapid learning

This “legal” categorization is maintained throughout this document; whilst a more detailed discussion on specific data-mining requirements and related available algorithms will be provided in a following document.

The main goal of research of privacy-preserving data mining in EURECA will be to find an approach with strict guarantees on data privacy that addresses the practical needs in the scenarios that are described in this document. A main criterion will be to find clear, understandable descriptions of privacy problems (e.g. which information of which patient might be at risk, or which part of a set of information to be published is problematic) such that productive discussion between all relevant stakeholders is possible, and privacy problems can be easily detected and solved.

# 4 EURECA knowledge discovery: focus on initial data mining components

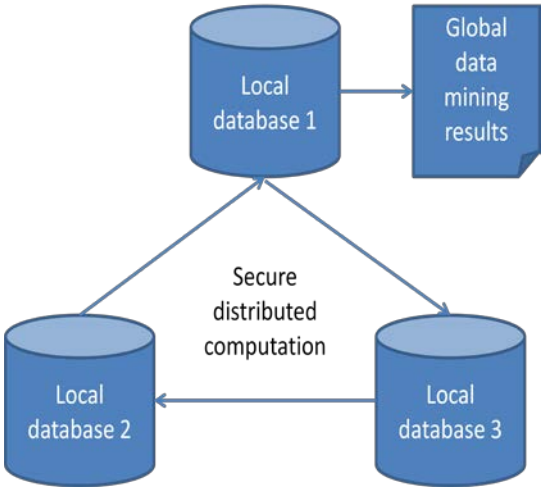
In this section we focus on some scenarios with a large data mining component; these scenarios are described here and will be analyzed further. The requirement analysis above indicated several needs which further specify the needs for the EURECA environment. As not every tool should be built from scratch it is important to dissect the scenarios into use cases of highest granularity. This approach will help to build tools in a modular way and reuse granular tools in different scenarios. This will be described in detail in D1.2 (Definition of relevant user scenarios based on input from the users) and further documents.

## 4.1 Secure distributed data mining

As an example of privacy-preserving data mining, consider a group of hospitals, all with a local database. We assume that all local databases are accessible under a common data schema, and that they all contain information about patients with a certain condition, e.g. patients for which a certain treatment has led to the development of a severe adverse event.

In a realistic setting, hospitals might be willing to cooperate to find an explanation for the occurrence of the severe adverse event, however, as the local databases contain much more information about the patients and their treatment, they might not be willing to export their data to a central database.

In this case, secure distributed data mining can be applied to securely compute all rules in the union of all local databases that are significant to describe the occurrence of the severe adverse event in question, while keeping all other information hidden from the participating parties. In particular, secure distributed rule discovery (15) is of interest to Eureca, on the one hand because decision rules are valuable for the use in Clinical Decision Support system, on the other hand because understandable rules make it easier for the clinician or bioinformatician to check whether the discovered patterns are interesting, and hence to act upon the discovered knowledge. Note that only the global, securely computed result is to be accessed by the investigating scientist, the underlying database and the individual patient data in them are hidden. Hence, the investigating scientist has much less information about the underlying data than in the standard case, which means that he might need to access additional sources of information – scientic publications, general medical knowledge – to interpret and evaluate the data mining results, and might also contact the local database owners for additional information. In this case, an understandable representation of the results that can be communicated to other parties, might be necessary.




The basic idea of the approach is that using the well-known secure sum algorithm, sums of different values can be computed securely over the local databases, which allows to securely execute relevant queries, and built a rule mining algorithms on top of it. It is then guaranteed that the output of the algorithm is identical to the output of the standard algorithm applied on a single global database.

The final choice of the algorithms to be implemented in a secure distributed fashion, however, will depend on the performance of several data mining approaches in a non-distributed prior study.

Privacy-preserving data mining is most relevant in those EURECA scenarios where very detailed, privacy-sensitive data from possibly many hospitals need to be combined for knowledge discovery. Furthermore, distributed data minig can be a solution when complex data mining results need to be exported to third parties (like pharmaceutical companies or regulatory bodies) or the general public (like scientifc publications or open source decision support modules). In particular, these are the following knowledge discovery scenarios:

- Detection and prediction of SAEs and SUSARs
- Pharmacovigilance
- Guidelines development
- Data mining on consultation data
- Diagnostic sarcoma classifier
- Analyse economic data between different procedures

## 4.2 Rapid learning

In rapid learning research we learn outcome prediction models from clinical data using machine learning (see Figure 4.2.1 below). Examples have been discussed in the context of Oncology care and research (16). Typically outcomes are tumour related such as survival, tumour progression, local control, pathological complete response, distant metastasis but also toxicity related outcomes such as quality of life, cosmetic result, shoulder movement, heart toxicity etc. Typically a model consists of prognostic and predictive features extracted from the clinical data, and predicts an outcome for a certain treatment choice. By comparing predicted outcomes for different treatments, an

optimal treatment can be chosen. The exact input, treatment and outcome features are very disease dependent. Examples of models for lung, head and neck and lung cancer can be found at www.predictcancer.org.

The basic requirement for machine learning is that a machine (and thus not a human) can learn from the data. This means that a machine should not only be able to read the data (syntactic interoperability) but also that the machine should be able to understand the data (semantic interoperability). A further requirement is that there should be lots of data to learn from as the accuracy of the model is correlated to the amount of data the machine has seen (a machine learns differently than a human). This means that data from many hospitals needs to be available for learning. In conclusion, rapid learning needs large, semantic and syntactic interoperable datasets from many different hospitals.

It is not a requirement for rapid learning to have the data in one place. Distributed learning approaches are available in which the learning applications work locally on the data and publish the knowledge they have extracted from that dataset. By combining local knowledge a global model can be learned that has used all the data to learn from, without data leaving the hospital.

To fulfil the requirements stated above, a number of tools are proposed

- An ETL (Extract Transform Load) tool that connects to clinical data sources, performs the semantic and syntactic transformation into a common data model and stores the data according to this data model.
- An API that allows access to the stored data including the possibility to query and retrieve the data.
- A standardized application environment including machine learning libraries in which a specific rapid learning application can be deployed.
- A tool that allows access to the outside world to publish the knowledge produces by the rapid learning application.

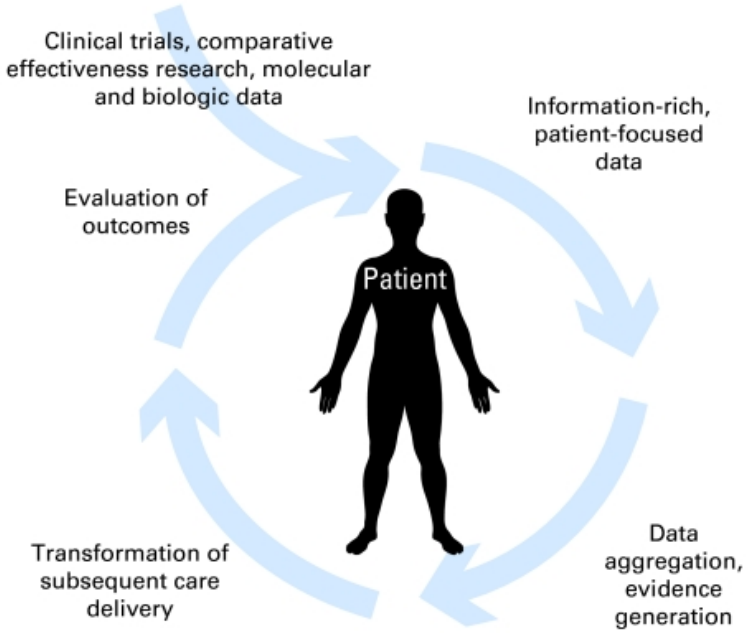


Figure 4.2.1. A representation of Rapid Learning from (16)

Rapid learning approach will constitute a scenario on its own (see list in the above section; “Basic research and clinical trials support” scenarios) but will also be relevant for the following “knowledge discovery” EURECA scenarios:

- Develop or update guidelines for diseases
- Build, optimize, validate or update a diagnostic classifier (e.g. scenario BR4, Sarcoma diagnostic classifier)
- Build predictive models of late morbidity

and the “Basic research and clinical trials support” EURECA scenarios:

- Supporting design of new trials and hypothesis generation (see also section below)
- Mining of information from EHR and CT to validate research/clinical hypotheses
- Clinical data reuse

## 4.3 Supporting design of new trials and hypothesis generation, and high-level genomic meta-analyses

A clinical trial often starts from the formulation of a clinical research hypothesis. Such a hypothesis generation process is usually a consequence of analysing available data from previous trials, guidelines, literature and others. It can also help to find information related to biomarkers that are relevant for the disease and can be tested during the trial execution (for a review in the area see (17)).

In this context a very much related scenario is the high-level genomic meta-analysis scenario (Table 2.1). High-throughput genomic technologies have brought a revolution in molecular biology and has enabled scientists to study biological systems as a whole, however this technology has not yet delivered the expected benefit to the clinical setting and patient management by producing validated effective biomarkers.

It is now recognized that integrating information of multiple relevant genomic studies in meta-analyses could help this translation process; however this is often challenging due to heterogeneity of data annotation and processing and the integration has been limited to a small amount of genomic and clinical data.

Several tools have been recently suggested that address in part the heterogeneity due to different platforms and different data processing algorithms/workflows, see e.g. (18, 19); however the complexity and potential of a large scale integration of biological and clinical information has not yet been addressed. This does not only require integration of data but also integration of abilities and knowledge domains which often resides with different individuals.

For this reason we introduce here the concept of high-level (distributed) genomic meta-analyses. These can be seen as an extension of existing meta-analysis and

knowledge-based analysis approaches, where information from clinical databases, biological data and the drug and disease knowledge-base are fully integrated in a collaborative analysis that combines data but also human intervention from domain experts.

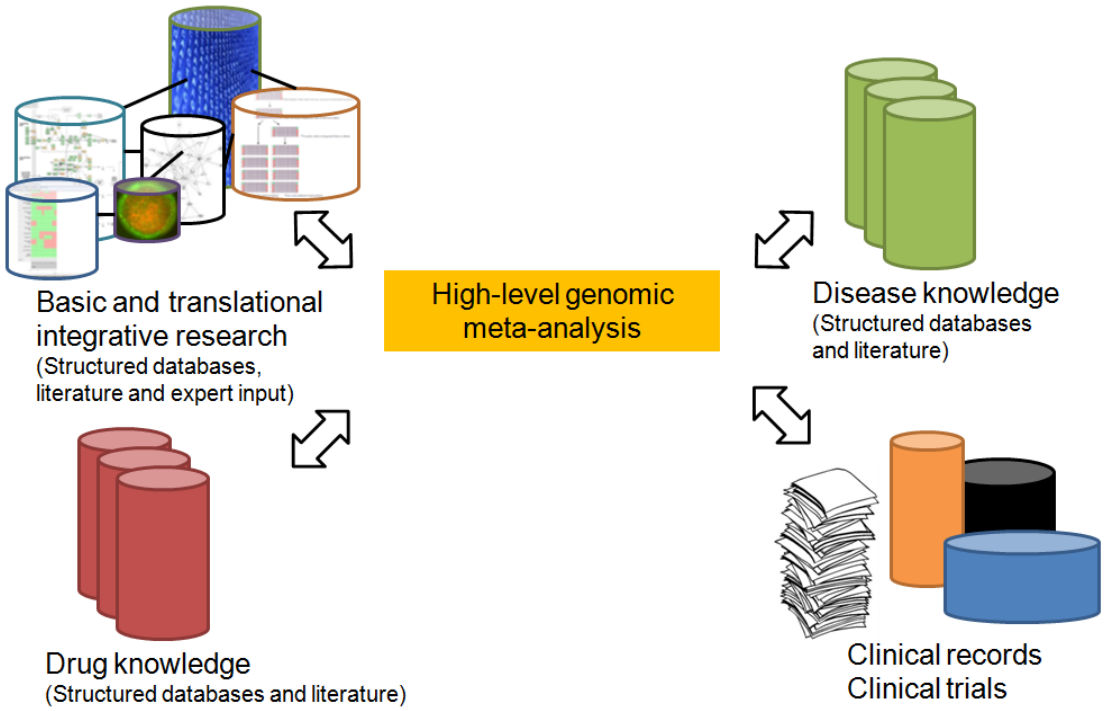



Figure 4.3.1 High-level genomic meta-analysis example schema

Methods such as the above mentioned rapid learning could aid this high-level genomic approach; in fact most of the data mining requirements and tools needed are similar (see previous section, suggested tools list). Furthermore, due to the fast accumulation of scientific, clinical knowledge, and an interactive expertise component, this scenario would benefit from some of the methods used in data stream mining, where mining is performed over continuously and rapidly changing streams of data (see Section 3.1.1, Data stream mining).

One of the basic differences between the present approach and the Rapid Learning approach as described above is that a machine (and thus not a human) can learn from the data but also from the human (expert) intervention, where the latter can be seen as personal communication or actions performed on a machine. This means that a machine should still be able to read the data (syntactic interoperability) and to understand the data (semantic interoperability); but also to rapidly incorporate and integrate knowledge and interpretation from multiple users provided both as structured information and/or for example as free-text.

The point of view of the present approach and related scenario is the use of clinical and biological information, together with human expertise, for both hypothesis generation for future clinical trials and patient management. Distributed data mining is

often necessary in such a context both for practical limitation to transferring large amount of data and for privacy preserving reasons (see Section 4.1).

# 5 SUMMARY

The EURECA environment and the tools to be developed are based on the needs gathered by the questionnaire and scenarios built in WP1. The present requirement analysis was based on the scenarios and questionnaire results described in deliverable D1.1.

Specifically, we have dissected each one of the scenarios and extracted the components relevant for the data mining and highlighted the challenges; this will guarantees that the tools implemented or developed for data mining and the environment will support the user needs.

We have also briefly described the techniques that are available in the area of application; however, a further document will review these methodologies in depth, and understand the needs for validation and development.

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