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# KALIS – An eHealth System for Biomedical Risk Analysis of Drugs

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**Abstract.** Background: In Germany, adverse drug reactions and events cause hospitalizations, which lead to numerous thousands of deaths and several million Euros in additional health costs annually. Objectives: Approximately one in two deaths could be avoided by an appropriate system for risk analysis of drugs. Methods: The integration and storage of several data sources from life sciences are an ongoing need to address various questions with respect to drug therapy. A software architecture for data integration was implemented in order to build up a new data warehouse named KALIS-DWH, which includes pharmacological, biomolecular and patient-related data. Results: Based on this comprehensive KALIS-DWH, an eHealth system named KALIS for biomedical risk analysis of drugs was implemented. The task-specific modules of KALIS offer efficient algorithms for analyzing medication and supporting decision-making in drug therapy. Conclusion: KALIS is meant to be a web-based information system for health professionals and researchers. KALIS provides comprehensive knowledge and modules for risk analysis of drugs, which can contribute to minimizing prescribing errors.

**Keywords.** Information Systems, eHealth, Medication errors, Drug Interactions, Drug Side Effects, Adverse Drug Reaction, Computer-Assisted Drug Therapy

## 1. Introduction

The prevalence of multimorbidity will rise with the predicted global demographic change and the associated aging of the population. Multimorbid patients are treated with complex polypharmacy, which is commonly defined as permanent intake of more than five drugs [1]. Polypharmacy increases the risk of drug-related problems (DRP), including inadequate prescribing (IP), medication errors, and adverse drug reactions and events (ADR, ADE), which in turn are frequent causes of hospitalization and death [2]. In Germany, several studies [3,4] reported a hospitalization rate of 3-7% due to ADE, which led to more than 16,000 drug-related deaths [5] and more than 400 million Euros in additional health costs [6] annually. Additionally, 340,000 to 720,000 patients suffer consequential damages on account of ADE [5]. Up to 50% of all ADE-related hospitalizations are judged to be preventable by avoiding prescribing errors [7]. The causes of prescribing errors in patients are multifaceted and complex, including prescribers lack of medication-related information or insufficient knowledge of geriatric pharmacotherapy. Furthermore, the pharmacotherapy is frequently not perceived as a

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risk process and thus, potential drug-drug interactions (DDI) and drug-disease interactions remain undetected, which are associated with a significantly increased risk for ADE. On the other hand, most the therapeutic guidelines advise prescribing of each drug individually and do not consider multiple diseases to discuss the applicability of their recommendations. Therefore, the evidence is increasing that polypharmacy resulting from recommendations of different therapeutic guidelines can potentially cause more damage than benefit in multimorbid patients.

A variety of commercial or scientific approaches brought up numerous drug-related databases and systems. These available databases such as ifap index®KLINIK [8], DRUG-REAX® [9], Lexi-Interact® [10] and Drug Interaction Facts® [11] have shown to contribute substantially to minimizing prescribing errors, but also have revealed a large discrepancy in number and clinical relevance of detected DDI [12]. Accordingly, at least two drug-related databases are needed to meet the high medical-pharmacological requirements of a reliable analysis of drugs for treatment in patients. Moreover, optimizing polypharmacy without using additional biomolecular information remains still complicated. A comprehensive and patient-specific analysis needs to include biomolecular data for gaining a better understanding of the underlying mechanism of drug action and the potential impact on the disease. Especially in the case of dose adjustment of psychotropic drugs, information on pharmacogenetic interactions is essential to health professionals trying to improve the individual response and thus, to reduce side effects.

For this purpose, we have developed an eHealth system named KALIS for biomedical risk analysis of drugs. The underlying data warehouse named KALIS-DWH integrates drug-related pharmacological, biomolecular, and patient-related databases. This data warehouse enables KALIS to provide task-specific modules for analysis and visualization of drug risks.

## 2. Methods

### *2.1. Architecture of the system*

KALIS was implemented as a web-based information system for health professionals and researchers. It is platform independent and available via the internet by an extended client/server architecture (Figure 1). The client/server architecture ensures a dividing into four functional layers:

- Request and presentation layer, the clients
- Application layer, the web server
- Data storage layer, the database system and the interface
- Data integration layer, the software infrastructure for data integration

An arbitrary set of user inputs is sent via an asynchronous HTTP(S)-request to the Apache web server. On the server side, a database system and PHP scripts were used to generate static HTML pages for visualizing the results of the analysis on basis of the data warehouse KALIS-DWH and/or the external data warehouse system DAWIS-M.D [13].

This development approach uses the concept of modularity and scalability to provide a flexible and location independent access to the information services offered by KALIS to a high number of users. In turn, the modularity covers the maintainability and extensibility with regard to the steadily increasing requirements.

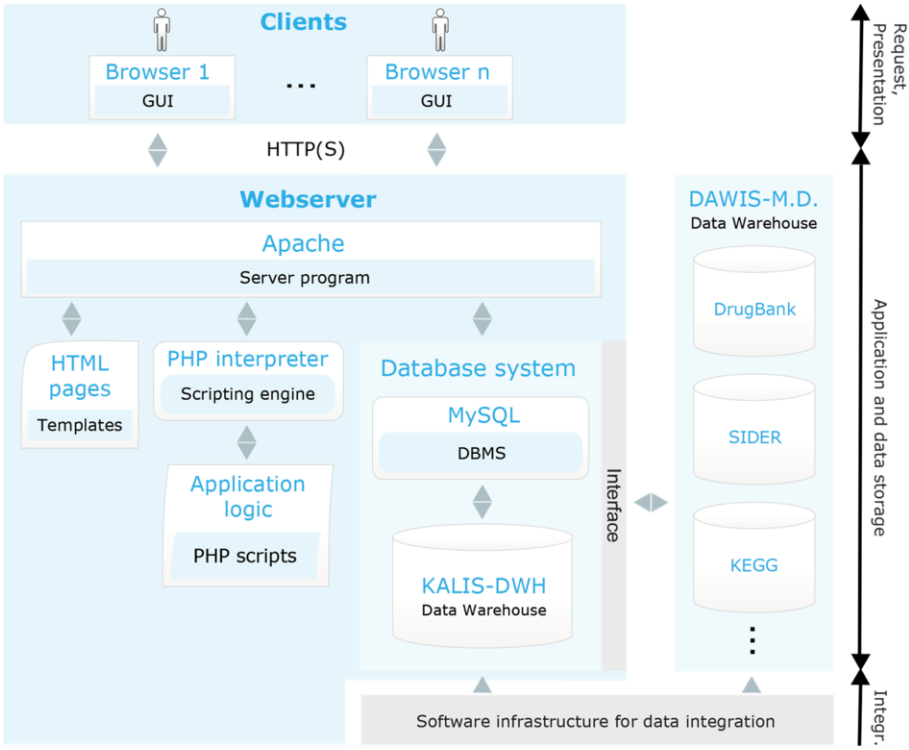


**Figure 1.** Client/Server architecture of the system KALIS.

## *2.2. Data storage and integration*

The growing specialization of distributed and heterogeneous data sources with corresponding different formats represent a major challenge in the integration. For this reason, a software infrastructure for data integration was developed. As summarized in Figure 2, the architecture is divided into integration, conception and merging layer. Applying this integration infrastructure, a consistent data warehouse named KALIS-DWH was created, which has a uniform data structure and provides comprehensive information to deal with various questions regarding drug therapy. The data warehouse KALIS-DWH includes eight different data sources from life sciences:

- three pharmacological databases (grey): ABDAMED [14], ROTE LISTE® [15], and GELBE LISTE® [16];
- three international databases with patient-related case reports of ADE (red): FAERS [17], ARD [18] and DPD [19];
- two newly developed databases (green): CYP-P450 and PRISCUS-Liste. The databases CYP-P450 and PRISCUS-Liste are based on information sources from scientific literature such as publications about pharmacogenetic interactions [20] or inappropriate drugs [21].

Due to different exchange formats (XML, ASCII, CSV, MDB) and license models, specific SAX[2]-Parser were implemented in Java for each data source. These parsers were

[2] SAX is the Simple API for XML. SAX was the first widely adopted API for XML in Java.

performed to extract the datasets, transform the data into the respective MySQL database and to load it efficiently into KALIS-DWH. Furthermore, relevant metadata for user management and data analysis is stored in a separate database.

The pharmacological databases of KALIS-DWH were fused with the biomolecular databases such as DrugBank [22], SIDER [23] or KEGG [24] via the interface to DAWIS-M.D. This biomolecular data can be used for knowledge discovery of the underlying mechanism of drug action or the potential impact on the disease. The integration of the biomolecular data sources into DAWIS-M.D. was performed by implementing SAX-Parser in Java and using the software kit BioDWH [25]. National and international standards were used for coding, mapping and assignment of medical information such as drugs, therapeutic indications, diseases and side effects. These standards include medical-pharmacological classifications and terminologies such as ATC [26], ICD-10 [27] or MedDRA [28]. In this way, the homogeneous data warehouses KALIS-DWH and DAWIS-M.D. provide pharmacological and biomolecular information for efficient and goal-oriented risk analysis of drugs. The standardized codes support the accuracy of data inputs and processing as well as a simple data exchange and uniform communication between KALIS and end user.

### *2.3. Conception of new databases*

Much of the information on pharmacogenetic interactions and inappropriate medications is spread across literature and the internet. Aggregating of this knowledge into databases and merging it with important therapeutic data makes the risk analysis more efficient. Therefore, two new databases named CYP-P450 and PRISCUS-Liste were created.

#### *2.3.1. CYP-P450*

The most important pharmacokinetic interactions occur at the level of biotransformation. The family of Cytochrome P450 Enzymes (CYP) plays a crucial role in the biotransformation of many substances. The inter-individual variability in the biotransformation of drugs by enzyme induction or inhibition and genetic polymorphisms also indicate a significant issue of drug therapy. Based on these facts, a new database CYP-P450 was designed, which contains information on interactions between substances and CYP enzymes in the liver and kidney. Currently, the database contains 680 substrates, 30 enzymes, 2,661 interactions and 738 references. This data is primarily based on the results of the literature research of Dippl [20].

#### *2.3.2. PRISCUS-Liste*

Due to age-changing pharmacokinetics and pharmacodynamics as well as increasing multimorbidity, numerous drugs are considered as potentially inappropriate in elderly patients (> 65 years). For this purpose, the Priscus List was created as a part of the joint project “PRISCUS” [21], which was funded by the German Federal Ministry of Education and Research (BMBF). The Priscus List includes 83 drugs of 18 drug classes that are adapted to the German drug market. The risk of these drugs for any side effects or age-related complications prevails the medical benefits. Therefore, a new database PRISCUS-Liste was designed, which contains all the information on these 83 potentially inadequate drugs (e.g.: reason, therapy alternatives).

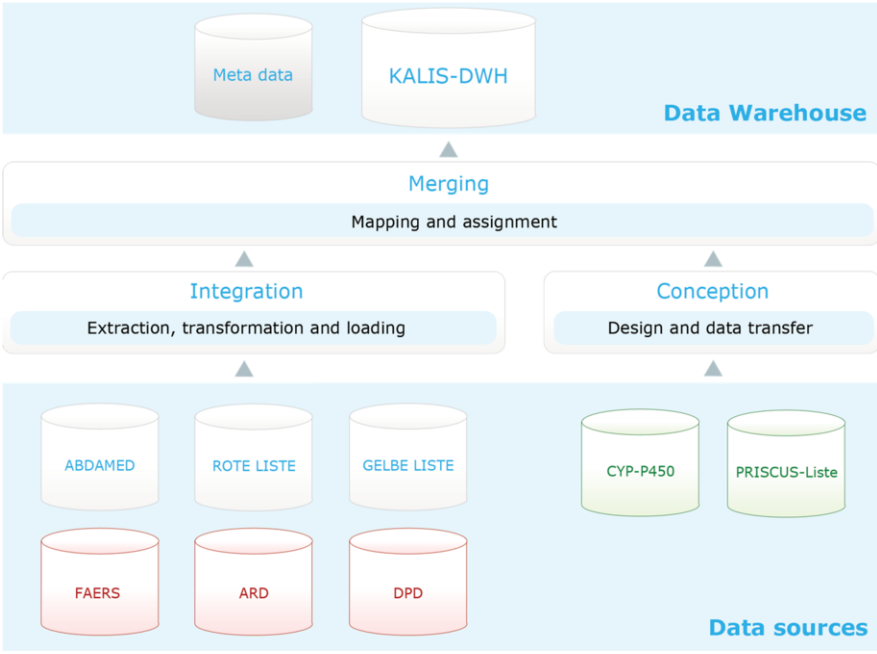


**Figure 2.** Software infrastructure for data integration.

### *2.4. Data analysis*

The server-side application logic is responsible for algorithmic analyzing, processing and visualizing of the data from KALIS-DWH. The focus is on the web-based availability of drug-related information associated with patient-specific risk factors or therapeutic targets. Accordingly, a wide range of task-specific modules for decision support in drug therapy is offered by KALIS. The major modules are described in the following:

1) *Pharmacological risk-check*
   This module enables users to check the patient-related data for drug-drug interactions, contra-indications, side effects, drug allergies, double prescriptions and drug-food interactions. Using two recognized databases, ABDAMED and ROTE LISTE, the quality of interactions data is significantly increased, resulting in a higher rate of detection and clinical relevance of the interactions. For further support and improvement of medication process, alternative therapies are also determined and proposed to the user.
2) *Inadequate medications*
   This module allows users to check the prescription of elderly patients (> 65 years) for potentially inadequate drugs.
3) *Pharmacogenetic drug interactions*
   Many drugs inhibit or induce the activity of CYP, which in turn is important to health professionals trying to give an appropriate dosage of those drugs. These interactions between substrates and the family of Cytochrome P450 Enzymes (CYP) can be predicted by this module.
4) *Adverse drug events*
   Incident reports of ADE can provide new impulses in the identification of potential trigger of side effects if they are not included in medicinal product's

professional information already. This module supports the user search for ADE reports of a drug considering the patient characteristics (age, gender, etc.).

5) *Patient-specific medication assistant in hypertension*
   This module assists in the computing of patient-specific diagnostic scores (PIDS) in hypertension by using evidence-based therapeutic guidelines [29] and individual patient data (age, blood pressure, gender, etc.). The predictive PIDS defines the suitability of the drug for the treatment of hypertension.
6) *Diagnoses-based drugs-check*
   With this module, the corresponding medications of the entered diagnoses can be checked for adverse drug-drug interactions. Due to the preventive identification of interactions and their measures, prescribing errors can be avoided.
7) *Molecular risk-check*
   Besides the pharmacological risk analysis of drugs (1-5), this module gives insight into the underlying biomedical networks where drugs interact at the biomolecular level. It includes various search forms for the analysis of drug-drug interactions, drug-molecule interactions and side effects using additional biomolecular data via an interface to the partner system GraphSAW [30].

These comprehensive modules can contribute to pinpoint risks of drugs at pharmacological and biomolecular level.

## 3. Results

Prescribing errors in patients and the corresponding several thousands of drug-related deaths could be avoided by an appropriate system. There is still a deficiency of consistency and grading of DDI due to the lack of standardization of the terminology used to classify DDI which to base the analysis of the clinical relevance of DDI. Currently, biomolecular information is hardly considered in the decision-making of the prescribing process.

With KALIS we presented a new eHealth system for biomedical risk analysis of drugs. The underlying homogeneous data warehouse KALIS-DWH includes several pharmacological, biomolecular, and patient-related data sources. The developed software infrastructure ensures a flexible integration and merging of different heterogeneous data sources. The large-scale KALIS-DWH enables to address specific and complex questions regarding drug therapy. The task-specific modules of KALIS offer efficient therapeutic algorithms for the analysis of adverse drug reactions. Health professionals can analyze the prescriptions and manage various drug risks: DDI, contra-indications, side effects, drug allergies, double prescriptions, drug-food interactions, IP, and drug-CYP interactions. In addition, the medication assistant in hypertension and the preventive diagnoses-based drugs-check can support the decision-making in order to avoid prescribing errors. Moreover, the molecular risk-check gives insight into the efficacy of the biochemical drug mechanisms for analysis and optimization of polypharmacy.

In conclusion, substantial improvements in prescribing quality can be achieved by using KALIS. Potential risks of drug-related problems of polypharmacy in multimorbid patients can be reduced and thus, consequential damage, deaths and costs can be prevented.

## 4. Discussion

The consistency of the drug-drug interactions and drug side effects among the integrated pharmacological and biomolecular databases was analyzed in a former study [30, 31]. This comparative assessment showed important discrepancies in comprehensiveness and accuracy of DDI and side effects among the databases ABDAMED, DrugBank and SIDER. Apart from that, the data quality increased by merging knowledge of these databases. The study showed that this combination of databases increases the information density of DDI (> 30%) and side effects (> 60%). This results in higher rate of detection and clinical relevance in a risk analysis. In addition, the study indicated that at least one in a hundred of side effects represents a drug-induced disease. However, biomolecular databases are intended for scientific research purposes given the facts of errors and inconsistencies of content. Moreover, the extent of side effects differs in each patient due to several impact factors such as inter-individual genetic diversity, diet or environment. Some of these aspects such as patient's functional level, values, and preferences can be considered appropriately by implementing an interface between KALIS and a computerized physician order entry (CPOE). A CPOE uses established standards, e.g. Health Level 7 (HL7), to provide the patient-related data for the exchange and to address clinical needs in support of prescribing process.

## 5. Availability and requirements

KALIS is available at http://tunicata.techfak.uni-bielefeld.de/kalis/. Access to the system is restricted by the commercial databases and will be enabled by a request to the authors. To fully access all modules of the system, the browser versions such as Internet Explorer 9+ or Mozilla Firefox 23+ should first be installed.

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