PSIP

A European Project on Patient Safety

www.psip-project.eu
Patient Safety through Intelligent Procedures in medication

Régis Beuscart, Lille (Coordinator)
And the PSIP Consortium
PROJECT PARTNERS

1. University Hospital of Lille and University of Lille2 (F)
2. University Hospital of Rouen (F)
3. Denain General Hospital (F)
4. 10 hospitals from the « Capital Region of Copenhagen » (DK)

5. Oracle (Europe)
6. IBM Denmark – division ACURE (DK)
7. Medasys (F)
8. Vidal SA (F)
9. KITE solutions (I)
10. Ideea Advertising (Romania)

11. Aristotle Thessaloniki University (Greece)
12. Aalborg University (DK)
13. UMIT – Innsbruck University (A)
Scientific goals

– **Identification** of ADEs
  • « To get a better knowledge of the prevalence of Adverse Drug Events (ADEs) and of their characteristics per Hospital, per Region, per Country »

– **Prevention** of ADEs
  • « To develop concepts and methods to achieve the contextualization of CDSS (alerting) functions »
Scientific goals

– **Identification** of ADEs

First Question: “*Is it possible to detect and identify Adverse Drug Events by mining medical databases?*”

– **Prevention** of ADEs

Second Question: “*Is it possible to prevent these Adverse drug Events through IT methods?*”
Scope of PSIP
Adverse Drug Events

- “Any injury occurring during the patient’s drug therapy and resulting either from appropriate care, or from unsuitable or suboptimal care”*

ADEs / ADRs / medication errors

**Taxonomy of medication errors**

- **NCCMERP:**
  - Dose omission
  - Improper dose
  - Wrong strength / concentration
  - Wrong drug
  - Wrong dosage form
  - Wrong technique
  - Wrong route of administration
  - Wrong rate
  - Wrong duration
  - Wrong time
  - Wrong patient
  - **Monitoring error**

Opportunistic errors: not identified by systematic mining / screening of EHR databases

**PSIP target**
Medication monitoring errors

• NCCMERP taxonomy:
  - Drug-drug interaction
  - Drug-food / nutrient interaction
  - Drug - documented allergy interaction
  - Drug-disease interaction
  - Deteriorated drug (out of PSIP scope)
  - Other

• Adapted PSIP taxonomy
  - Drug-drug interaction
  - Drug-food / nutrient interaction
  - Drug-documentated allergy interaction
  - Drug-disease interaction
  - Drug-patient's characteristics interaction
  - Drug-lab value monitoring
Identification of ADEs

Identification of ADEs

First Question: “Is it possible to detect and identify Adverse Drug Events by mining medical databases?”
Step1: Obtaining Data
Flowchart for ADEs identification in PSIP

Common Data Model

Export

Common data warehouse

Data mining – Multivariate analysis, non linear techniques
Semantic mining (discharge summaries)

Groups of atypical stays
Association rules

Cross-Validation
Expert review
This model is freely available and usable
With complete definition of the items and scripts

Common Data Model

ITEMS
RELATIONSHIPS

1- Stays
1-1-keys
1-2-patient
1-3-resuscitation
1-4-medical unit
1-5-dates, duration
1-6-misc

2- Steps of the stay
2-1-keys
2-2-medical unit
2-3-misc

3- Diagnosis
3-1-keys
3-2-diagnosis

4-Acts
4-1-keys
4-2-acts

5-Drug prescriptions
5-1-keys
5-2-drug

6-Biology
6-1-keys
6-2-biology

7-Reports
7-1-keys
7-2-reports

Physical files
Step 2: Data Mining
Data Mining

Common Data Model

Export

Common data warehouse

Data mining – Multivariate analysis, non linear techniques
Semantic mining (discharge summaries)

Groups of atypical stays
Association rules

Cross-Validation
Expert review

Hosp 1  Hosp 2  Hosp 3  Hosp n
Data Mining Methods

• Multiple Correspondence analysis:
  – identification of risk factors, groups of patients at risk.
  – Some Rules, but too general, not as precise as expected

• Decision Trees (CART)
  – Efficient when applied in a coherent context (one medical department in one hospital)
  – Calculation of confidence and support
  – Identification of cases; definition of rules through the exploitation of the decision trees

• Association Rules:
  – Some improvement. New rules implemented.
Appearance of a too low INR (INR < 2) in patients undergoing anticoagulation
Appearance of a too low INR (INR < 2) in patients undergoing anticoagulation

Normal Subjects: INR < 1.5

Patients undergoing anticoagulation
Treatment: 2 < INR < 3

Hypocoagulation (risk of bleeding): INR > 5

Hypercoagulation (risk of thrombosis) in patients needing anticoagulation: INR < 2
Appearance of a too low INR (risk of thrombosis)

Rule N° 1

Too high INR means Hypocoagulation (risk of bleeding): INR > 5

Interpretation: in 30% of the cases: a too low INR (with a risk of thrombosis) is following a too high INR at entry, probably due to an over-reaction of the prescribers

Outcomes:
0% death
avg duration: 6.4 days
Appearance of a too low INR (risk of thrombosis)

Rule N° 2

Rule enunciation:
Bio(previous too high INR)=1 & MedInfo(age)>78.68
Appearance of a too low INR

Rule characteristics:
Support: 7
Confidence: 58%

12 stays match the conditions, 7 of them present the effect (58%=7/12)

Outcomes:
0% death
avg duration: 9.3 days
**Appearance of a too low INR (risk of thrombosis)**

**Rule N° 2**

Too high INR means Hypocoagulation (risk of bleeding): INR > 5

**Interpretation:** in 30% of the cases: a too low INR is following a too high INR at entry

If patient is more than 78 years old, then the risk of Hypercoagulation is 58%

**Outcomes:**
0% death
avg duration: 9.3 days
Appearance of a too low INR (risk of thrombosis)  
Rule N° 3

Rule enunciation:
- Bio(previous too high INR)=1 
- MedInfo(age)>78.68 
- Bio(previous hypoalbuminemia)=1 
 Appears of a too low INR

Rule characteristics:
Support: 6
Confidence: 86%

7 stays match the conditions, 6 of them present the effect 
(86%=6/7)

Outcomes:
0% death 
avg duration: 13.4 days
Appearance of a too low INR (risk of thrombosis)

Rule N° 3

Too high INR means Hypocoagulation (risk of bleeding): INR > 5

Interpretation: in **30%** of the cases: a too low INR is following a too high INR at entry

If patient is more than 78 years old, and with hypoalbuminemia, then the risk of Hypercoagulation is **86 %**

Outcomes:
0% death
avg duration: 13.4 days

Support: 6
Confidence: 86%
Second Example: Appearance of a thrombocytopenia

Tree from Denain, Fr
(Medicine unit) : 2.08%

Tree from Copenhagen, Dk
(Cardiology unit): 0.37%
Step 3: Knowledge elicitation.
Validation of the Knowledge Rules
### Generation of the corresponding Rule

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>CONCLUSION</th>
<th>CONFIDENCE</th>
<th>SUPPORT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bio (previous too high INR) = 1 &amp; MedInfo (age)&gt;78</td>
<td>Risk of Low INR</td>
<td>56 %</td>
<td>7</td>
</tr>
</tbody>
</table>
### Generation of the corresponding Rule

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>CONCLUSION</th>
<th>CONFIDENCE</th>
<th>SUPPORT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bio (previous too high INR) = 0 &amp; Drug(vitamin K antagonist) = 1 &amp; Drug(prokinetic) = 1</td>
<td>Risk of Low INR</td>
<td>67%</td>
<td>4</td>
</tr>
</tbody>
</table>
Rules Validation

- Currently: 600 Decision Trees
- 250 rules

- Validation of rules is mandatory:
  - Matched against existing Experts rules
  - Or verified against scientific references
  - Or validated by physio-pathologic knowledge
Validation of the association rules

- Confrontation to existing scientific knowledge retrieved from various sources:

<table>
<thead>
<tr>
<th></th>
<th>Pharmacorama</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Automated Data Bank on Drugs (Vidal)</td>
</tr>
<tr>
<td></td>
<td>Theriaque</td>
</tr>
<tr>
<td>If necessary</td>
<td>French Society of Pharmacology and Therapeutic</td>
</tr>
<tr>
<td></td>
<td>Association of Teachers of Pharmacology</td>
</tr>
<tr>
<td></td>
<td>Pubmed</td>
</tr>
<tr>
<td>Classifications</td>
<td>Anatomical Therapeutic Chemical Classification</td>
</tr>
<tr>
<td>and terminology</td>
<td>System</td>
</tr>
<tr>
<td></td>
<td>CISMEF</td>
</tr>
<tr>
<td>Other rules</td>
<td>Vidal Expert</td>
</tr>
<tr>
<td>repositories</td>
<td>Vigilanz</td>
</tr>
</tbody>
</table>
In scientific references

Strong fixation of VKA (90 to 99%) in plasma albumin, only the free form is active.

Many Drug interactions are observed with VKA.

1. Drugs that can potentiate anticoagulants
   - Reducing the synthesis of vitamin K by the intestinal flora (antibiotic) or decreasing its intestinal absorption (paraffin oil);
   - By moving the K antivitamin related to its vector protein (albumin), thus increasing free active fraction (clofibrate-sulfonamide-NSAIDs);

2. Drugs that can inhibit the effect of anticoagulants
   - Reducing their intestinal absorption (antacids, laxatives, Questran);
   - Increasing their metabolism liver enzyme induction (barbiturates, Tegretol, carbamates, griseofulvin, rifampicin);
   - A diet rich in vitamin K (liver, cabbage, spinach ...) reduces the effectiveness of AVK.
Validation of the association rules

- Test of the validity of the rules in other environments (hospital / department)
  - Confidence Coefficient in all environments

<table>
<thead>
<tr>
<th>Effect</th>
<th>Condition(s)</th>
<th>REGIONH</th>
<th>DENAIN MED A</th>
<th>DENAIN MED B</th>
<th>DENAIN CHIR</th>
<th>DENAIN GYN</th>
<th>ROUEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>appearance of low inr[Lab]</td>
<td>Lab(high inr)=1 MedInfo(age)&gt;75 Lab(hypoalbuminemia)=1</td>
<td>7/12=58%</td>
<td>2/2=100%</td>
<td>2/3=66%</td>
<td>2/7=28%</td>
<td>no stay matches the causes</td>
<td>6/8=75%</td>
</tr>
</tbody>
</table>

- To date: over 50 rules validated
• Selection of a sample of 40 normal 40 abnormal stays
• 2 hospitals (region H DK, and Denain, Fr)
• Data available:
  – All the data incorporated in the data model and used for the data mining process
  – Plus the discharge letter
  – Available through the IDEEA viewer system
Ideal results would be:

**Data Mining "normal" stays**

<table>
<thead>
<tr>
<th>Stay ID</th>
<th>Expert A</th>
<th>Expert B</th>
</tr>
</thead>
<tbody>
<tr>
<td>713</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>47</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>2458</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>320</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>1976</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>25</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>1400</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>1850</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>524</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>823</td>
<td>No AE</td>
<td>No AE</td>
</tr>
</tbody>
</table>

**Data Mining "Abnormal" stays**

<table>
<thead>
<tr>
<th>Stay ID</th>
<th>Expert A</th>
<th>Expert B</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>pADE</td>
<td>pADE</td>
</tr>
<tr>
<td>414</td>
<td>pADE</td>
<td>pADE</td>
</tr>
<tr>
<td>1854</td>
<td>pADE</td>
<td>pADE</td>
</tr>
<tr>
<td>913</td>
<td>pADE</td>
<td>pADE</td>
</tr>
<tr>
<td>1031</td>
<td>pADE</td>
<td>pADE</td>
</tr>
<tr>
<td>1724</td>
<td>pADE</td>
<td>pADE</td>
</tr>
<tr>
<td>520</td>
<td>pADE</td>
<td>pADE</td>
</tr>
<tr>
<td>1268</td>
<td>pADE</td>
<td>pADE</td>
</tr>
<tr>
<td>297</td>
<td>AE</td>
<td>pADE</td>
</tr>
<tr>
<td>1339</td>
<td>pADE</td>
<td>pADE</td>
</tr>
</tbody>
</table>
Actual results: DM « normal » stays vs. experts’ judgment

- Good inter-experts agreement
- Good DM-Experts agreement

<table>
<thead>
<tr>
<th>Stay ID</th>
<th>Expert A</th>
<th>Expert B</th>
</tr>
</thead>
<tbody>
<tr>
<td>713</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>47</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>2458</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>320</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>1976</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>25</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>823</td>
<td>pADE</td>
<td>pADE</td>
</tr>
<tr>
<td>1850</td>
<td>pADE</td>
<td>pADE</td>
</tr>
<tr>
<td>524</td>
<td>pADE</td>
<td>pADE</td>
</tr>
<tr>
<td>1400</td>
<td>ADE</td>
<td>No AE</td>
</tr>
</tbody>
</table>

ADE BEFORE hospitalization

Region H stays
1 / 6 / 13

Data Mining "Normal" stays

<table>
<thead>
<tr>
<th>Stay ID</th>
<th>Expert A</th>
<th>Expert B</th>
</tr>
</thead>
<tbody>
<tr>
<td>475947</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>481688</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>484325</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>496390</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>531491</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>533792</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>556550</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>576219</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>612356</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>627513</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>634858</td>
<td>No AE</td>
<td>No AE</td>
</tr>
<tr>
<td>454299</td>
<td>No AE</td>
<td>Answ. Imp</td>
</tr>
<tr>
<td>437529</td>
<td>No AE</td>
<td>AE</td>
</tr>
<tr>
<td>509110</td>
<td>ADE</td>
<td>No AE</td>
</tr>
<tr>
<td>439932</td>
<td>ADE</td>
<td>ADE</td>
</tr>
</tbody>
</table>

Denain stays
3 / 30
(1) Moderate inter-experts agreement
(2) Correct to moderate DM-experts agreement
Current status of the Validation process

- Currently: 600 Decision Trees
- Hundreds of rules
- Validation in progress: 250 rules are validated
Scientific goals

– **Identification** of ADEs
  • « To get a better knowledge of the prevalence of Adverse Drug Events (ADEs) and of their characteristics per hospital, per Region, per Country »

– **Prevention** of ADEs
  • « To develop concepts and methods to achieve the contextualization of CDSS (alerting) functions »
Implementation Procedure Followed

Terminology Definition → Intermediate Rules Library Development → Rules Development as Guidelines → Rules Selection for Instantiating the CDSS → CDSS Verification

Potential Refinements/Corrections
Current Results (R) and Expectations (E)

- **R:** A **first release of the PSIP terminology** has been defined
  - **E:** Terminology evolution considering also ADE taxonomies

- **R:** A large **library of intermediate rules** has been developed as well as a **representative portion of rules** originated from data mining via **automated scripts** and **manually** respectively
  - **E:** Support for **fully automated rule implementation**

- **R:** Semi-automated **rule verification mechanism** implemented
  - **E:** Implement **additional knowledge management tools**

- **R:** 1st experiments on KB contextualization
  - **E:** Development of advanced contextualized CDSS

**Final outcome:** Interoperable, manageable and contextualised CDSS for ADE prevention
Research Challenges

- Approaches for **contextualizing** the KB, e.g. profiling, and consequently the decision support functionality
- **Knowledge maintenance**: policies and mechanisms for updating rules, **consistency checking**, **conflict resolution**, etc
- **Prioritization** of rules to avoid **over-alerting** and increase effectiveness
- **CDSS validation** issues
- Encoding **human factors** originated **knowledge**
- **Knowledge interoperability**: KB encoding and accessibility issues
- **Reusability**: Encoding of rules in RuleML, R2ML, etc
- **Interfacing** the healthcare IT infrastructure with the CDSS
Conclusion

• Promising results
• From data mining to CDSS
• Importance of the contextualization
• Importance of Human and organisational factors (avoid over-alerting)

• Time is short
• Legal constraints
• Integration in a more global quality insurance process