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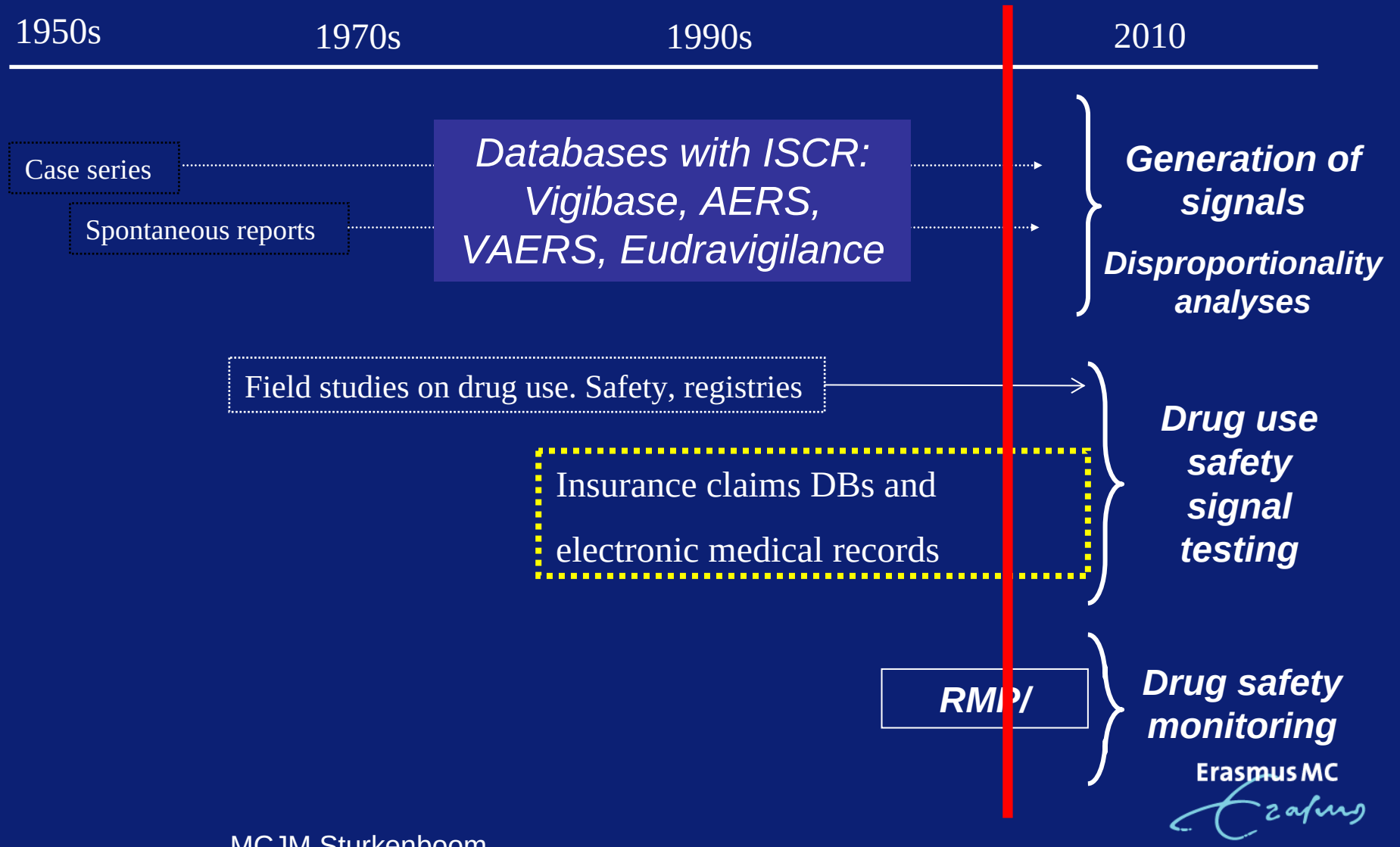
University Medical Center Rotterdam

Detecting Safety issues: will new scientific developments strengthen public health protection?

Developments in the last 10 years for dr. Thomas Lönngren

Prof. dr. Miriam CJM Sturkenboom

Methods/resources for evaluation of drug safety

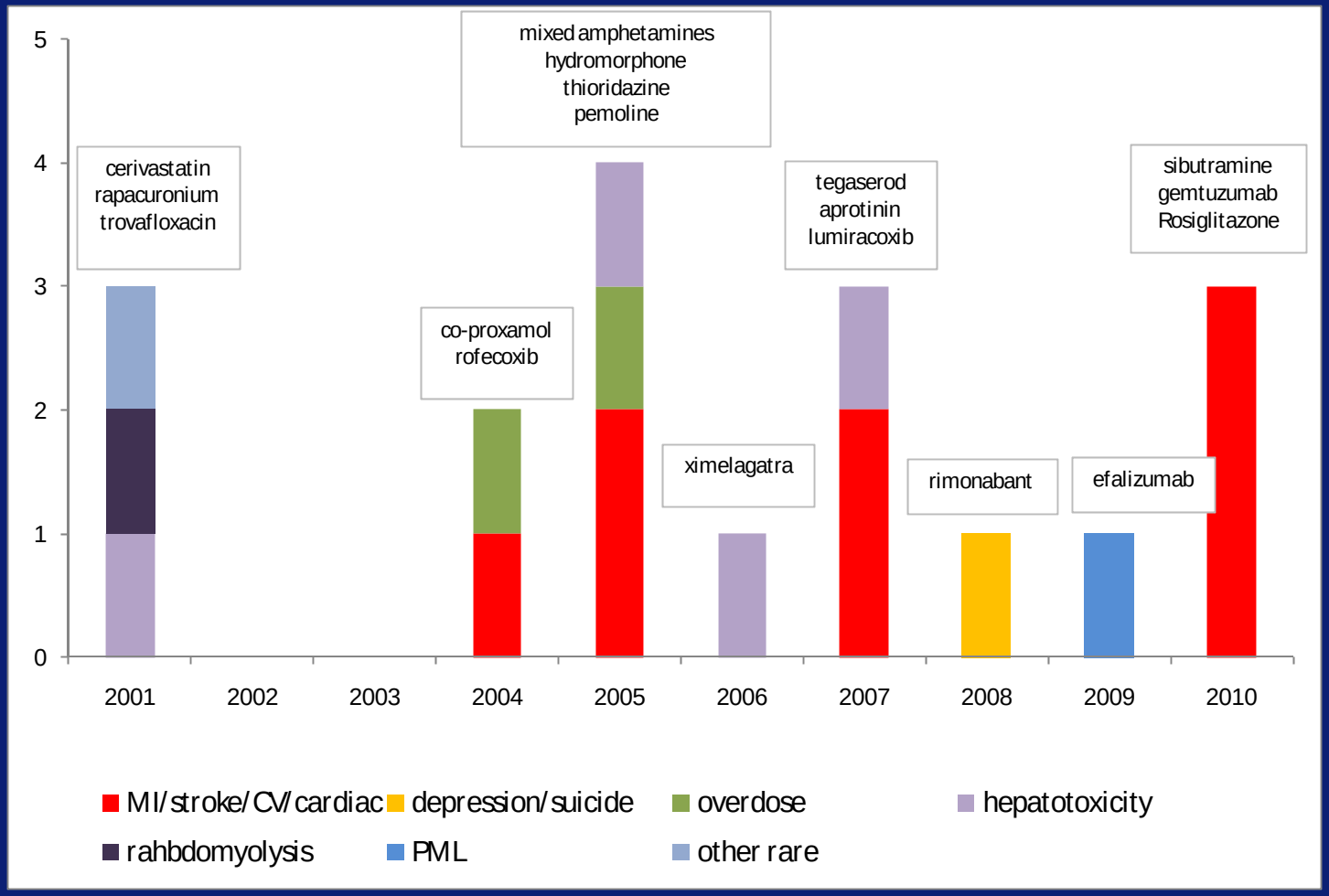


Safety signal detection

- Traditionally, regulatory agencies relied on health care professionals to send reports of suspected adverse events
  - Initially global introspection rule-based methods (qualitative) and simply reporting ratio's
  - Last ten years: quantitative datamining methods on WHO, AERS, EUDRAVIGILANCE data (disproportionality analysis, proportional reporting ratios, Bayesian confidence propagation neural network, reporting odds ratio, knowledge discovery in databases, information content, probability filtering algorithm (PROFILE), R test, Sets test, the cuscore test, and the chi square test)
  - But,

Greener, M. EMBO Rep. 2008 March; 9(3): 221–224

Drug withdrawals in last 10 years created discussion



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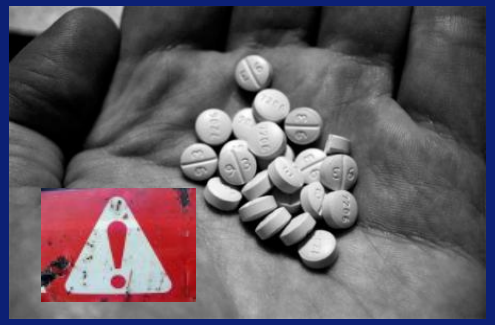
Examples and criticisms

- 2004: Vioxx withdrawn because of increased risk of MI and stroke: after 5 yrs of marketing and more than 80 million persons exposed globally

  As David Graham: "If there were an average of 150 to 200 people on an aircraft, this range of 88,000 to 138,000 (excess MI/SUD) would be the rough equivalent of 500 to 900 aircraft dropping from the sky" (testimony www.senate.gov)

- 2007: Avandia debated: risk of MI, European Medicines Agency did not withdraw but changed label, finally withdrawn in 2010
- Lumiracoxib withdrawn after 8 million exposed persons (detected with ICSR)



Difficulties in detection of signals

Timing	Acute	Delayed
Frequency		
Frequent (>1/100)	trials	?
Moderate	?	?
Rare (< 1/10,000)	ICSR	ICSR?

E.g. Myocardial infarction, stroke, arrhythmia

E.g. Hepatoxicity, rhabdomyolisis, PML

- ***"Vioxx is often quoted as an example of the failure of regulators to detect an adverse reaction once a medicine is marketed—but trying to differentiate between the effects of a medicine and the 'normal' events that occur in everyday life is not always straightforward," the EMEA commented by e-mail. Many middle-aged people suffer heart attacks and the same age group typically took Vioxx; therefore, ascribing causality is difficult (Greener, 2008).***

What changed after 2004 (Vioxx):

- Loke: “Regulators and companies wait to see what reports drop into their letter-box,”. “It is time that the regulators start adopting new, more robust methodologies. Many techniques other than spontaneous reports are required to build a complete picture of a drug's safety.” (Greener 2008)

New developments

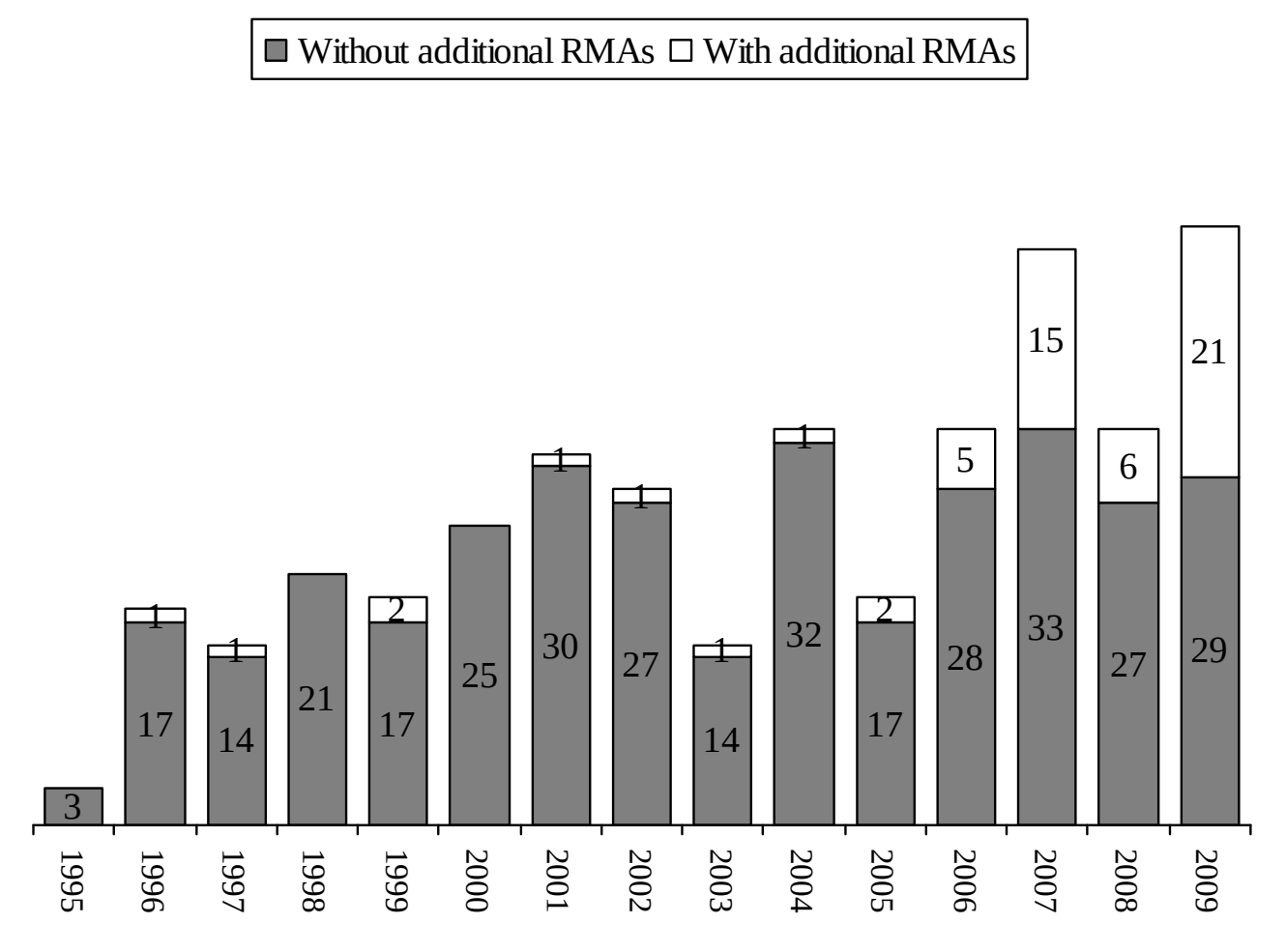
1) EU-RMP

2) More use of existing datasources and upscaling
EC: providing funding
FDA-AA : > 100,000 million subjects to be monitored
ENCePP: database resources

3) Development of new methods for signal detection on longitudinal health records

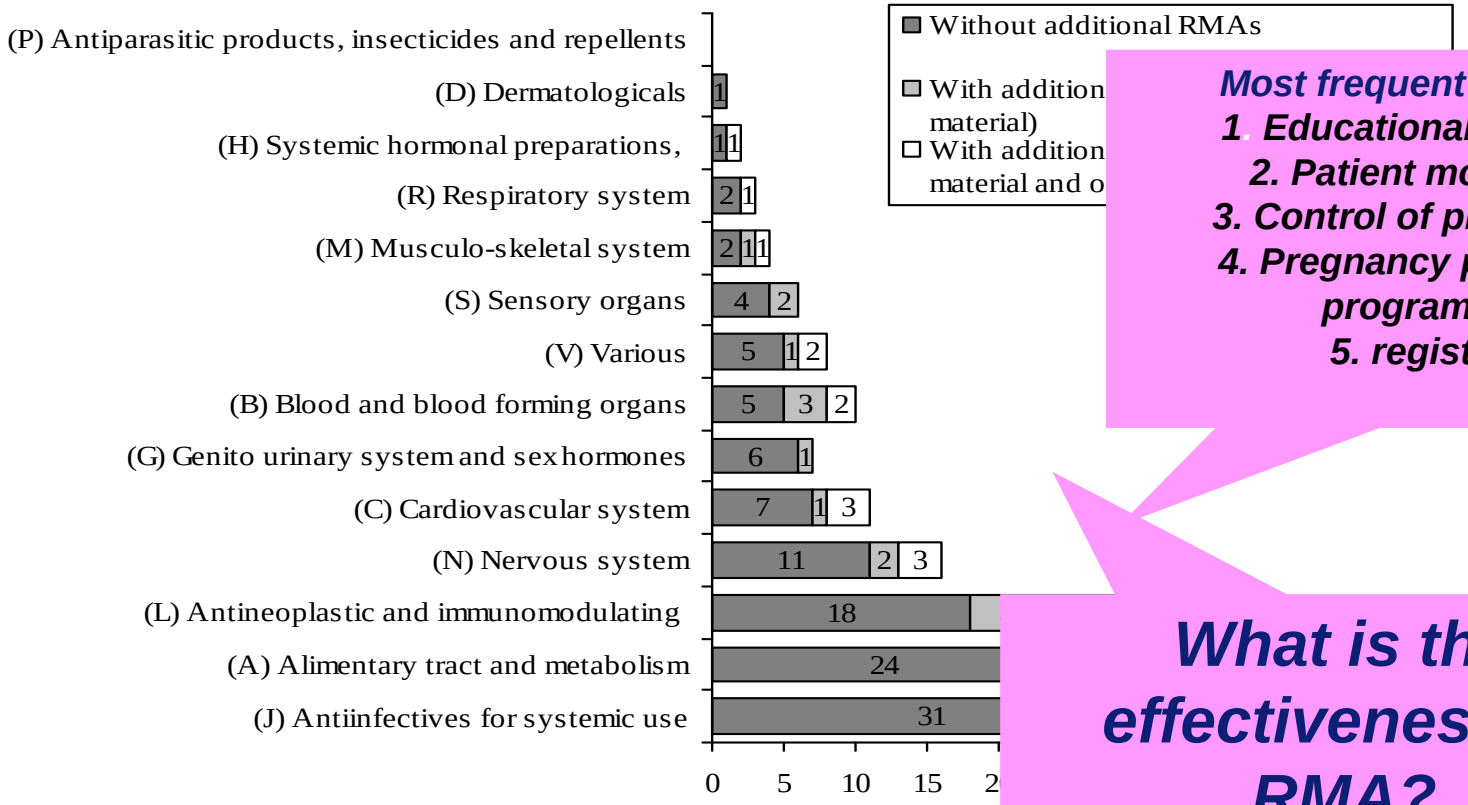
WHAT CHANGED?
1. EU-RISK MANAGEMENT PLAN

EU-RMP: Centrally authorised products (substances) with and without additional Risk minimization activities



Courtesy: Zomerdijk I, Erasmus MC

EU-RMP: Centrally authorized products



Most frequent measures

1. Educational materials

2. Patient monitoring

3. Control of prescription

4. Pregnancy prevention programmes

5. registries

What is the effectiveness of RMA?

No systematic assessment

Courtesy: Zomerdijk I, Erasmus MC

Effectiveness of RMA

Isotretinoin PPP

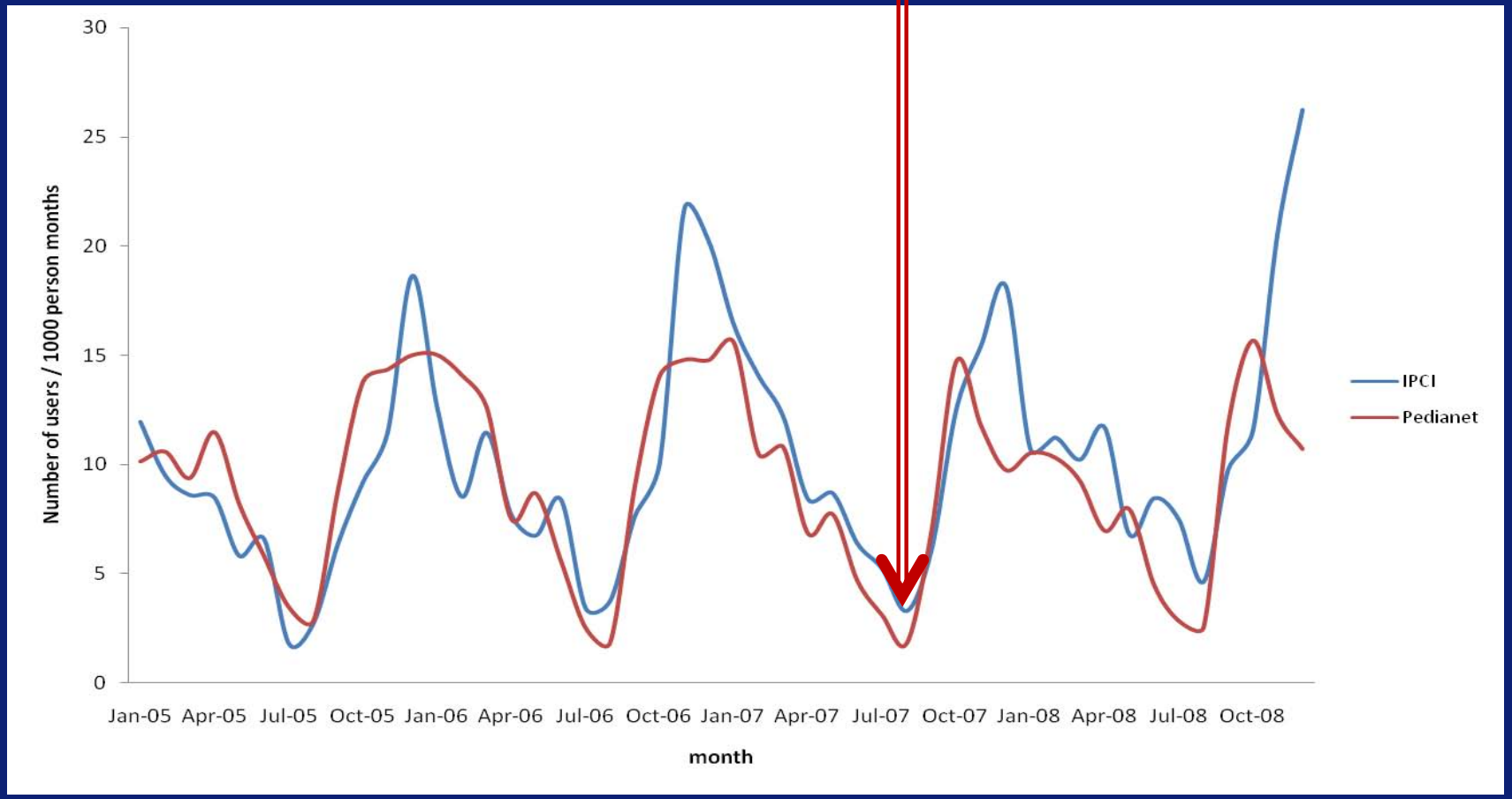
In 6-26% isotretinoin was prescribed in full accordance with the PPP.

Pregnancy incidence was seen in 0.2-1.0 per 1000 women of childbearing age using isotretinoin.

Between 65-87% of these pregnancies were terminated

Crijns HJ, Straus SM, Gispen-de Wied CH, de Jong-van den Berg LT. Compliance with Pregnancy Prevention Programs of isotretinoin in Europe: a systematic review. Br J Dermatol. 2010 Aug 12.

Example: Rx for cough and cold medications in children < 2 years



Sen et al. Br J Clinical Pharmacol 2011 (in press)

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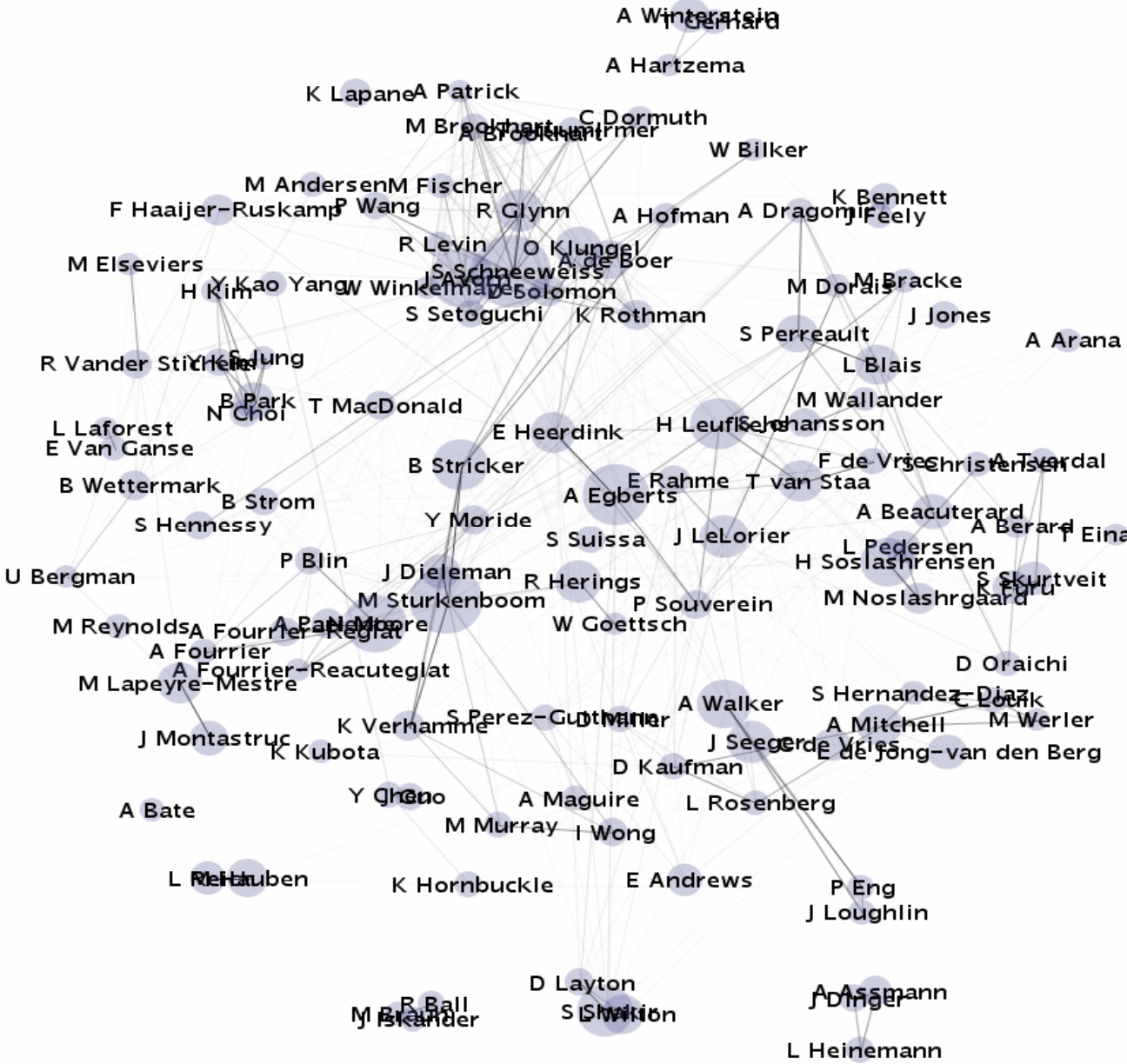
WHAT CHANGED? CONDUCT OF MULTI-DATABASE STUDIES

2. FUNDING AND COLLABORATIONS

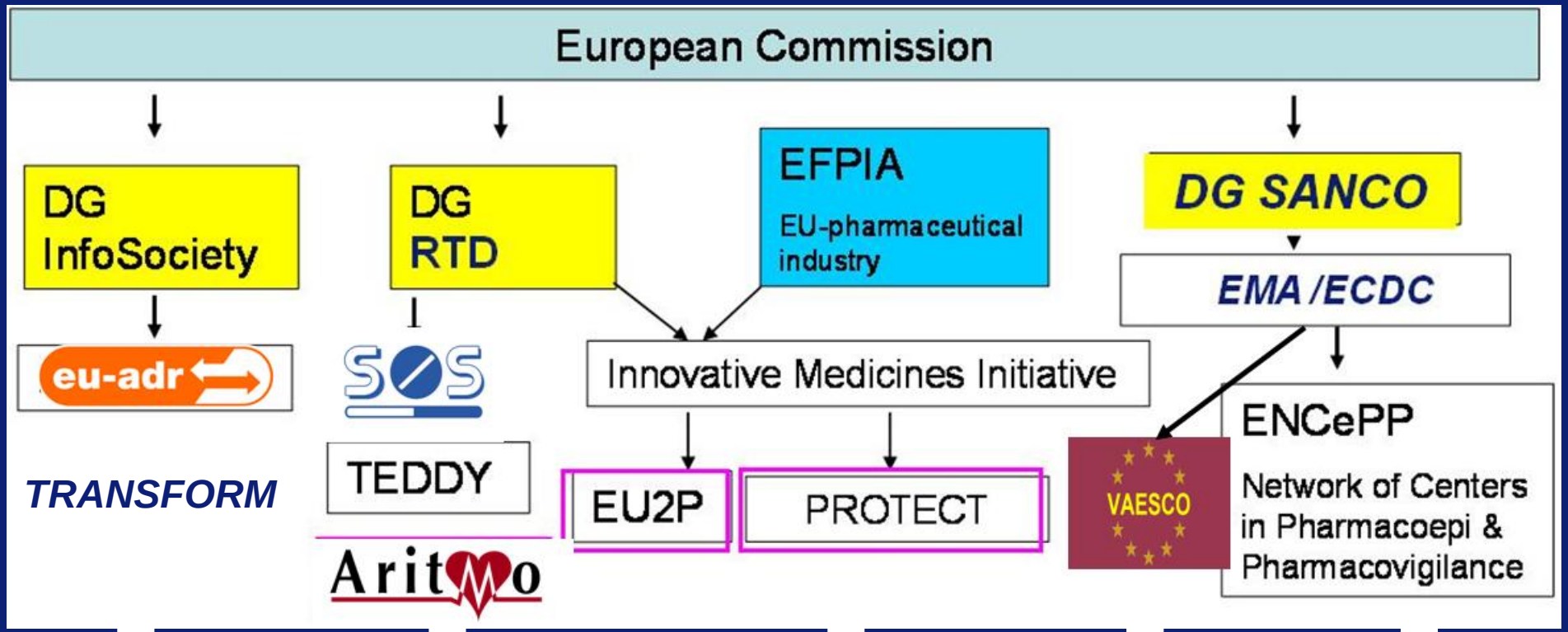
Collaborations in the area of pharmacoepidemiology
Based on abstracts to ICPE till 2009



With all collaborative projects we hope to create more interconnections in EU

Courtesy of Schuemie, M

EC Funding of drug safety projects: boosted the field



ICT in Health and patient safety

Safety topics from Pharmacovigilance Working Party

PPPS to boost EU pharmaceutical research

EU-Vaccine safety network

Capacity building

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How do we collaborate? combining data

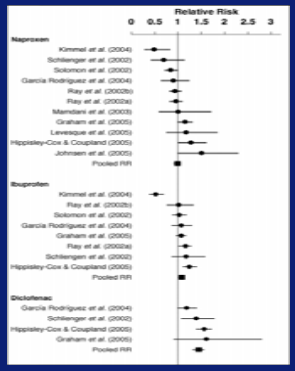
Combining of raw data in central datawarehouse

Pooling of elaborated data (individual level)

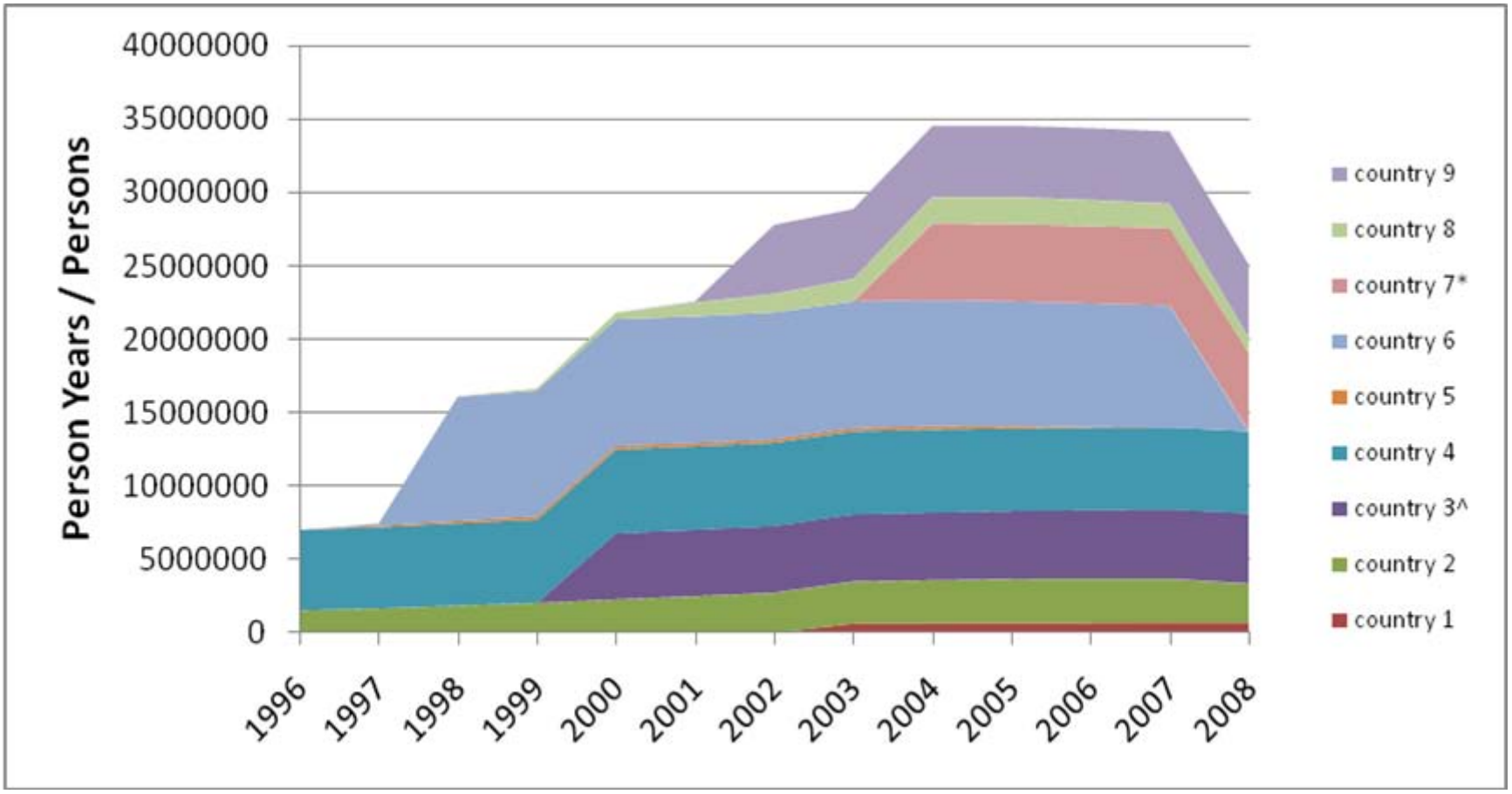
Pooling of aggregated data (not individual level)

Common protocol studies and sharing of coefficients

Meta-analysis of individual studies



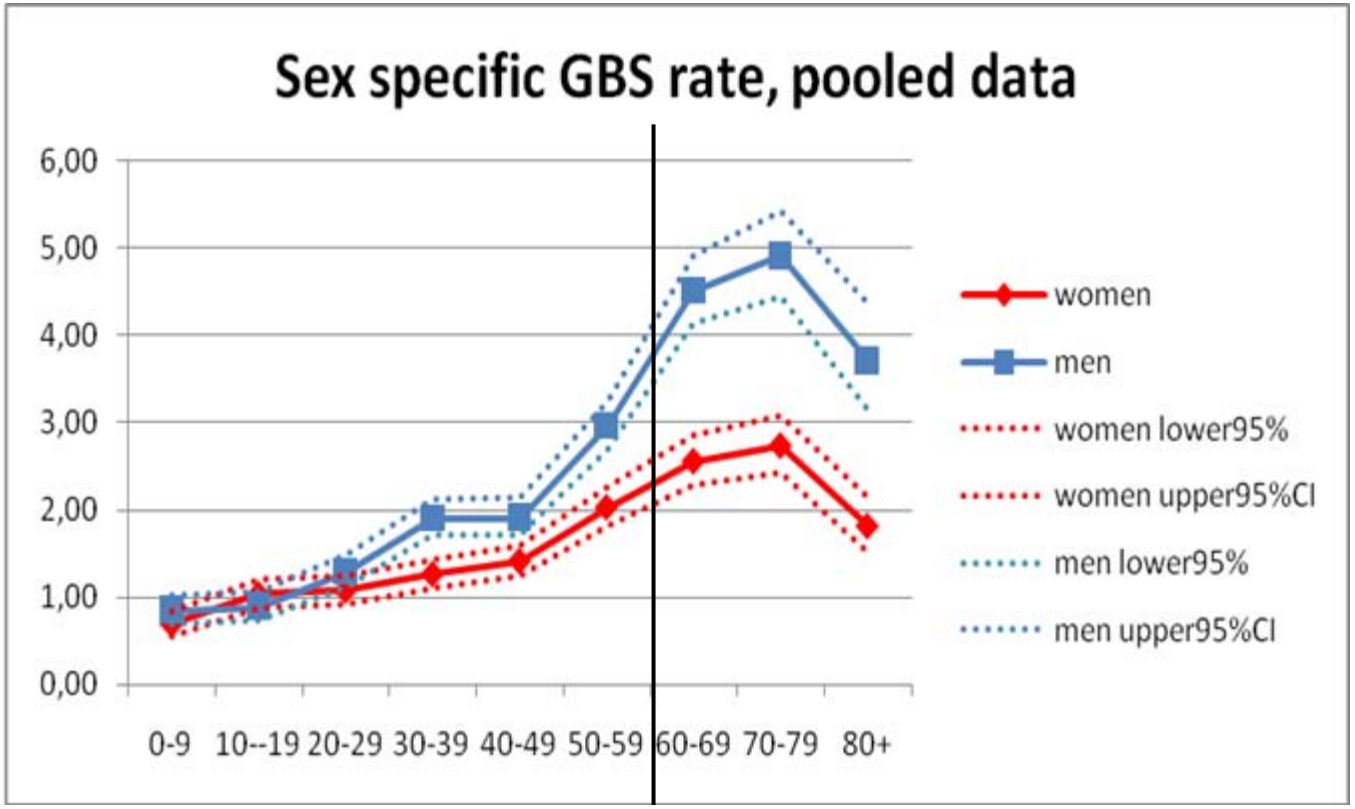
Example: Person time in source population for background rate project VAESCO (H1N1 monitoring) distributed model



Total more than 260 million PY ***50 million subjects***

Sex and age specific incidence rate of Guillain Barré for observed / expected analyses

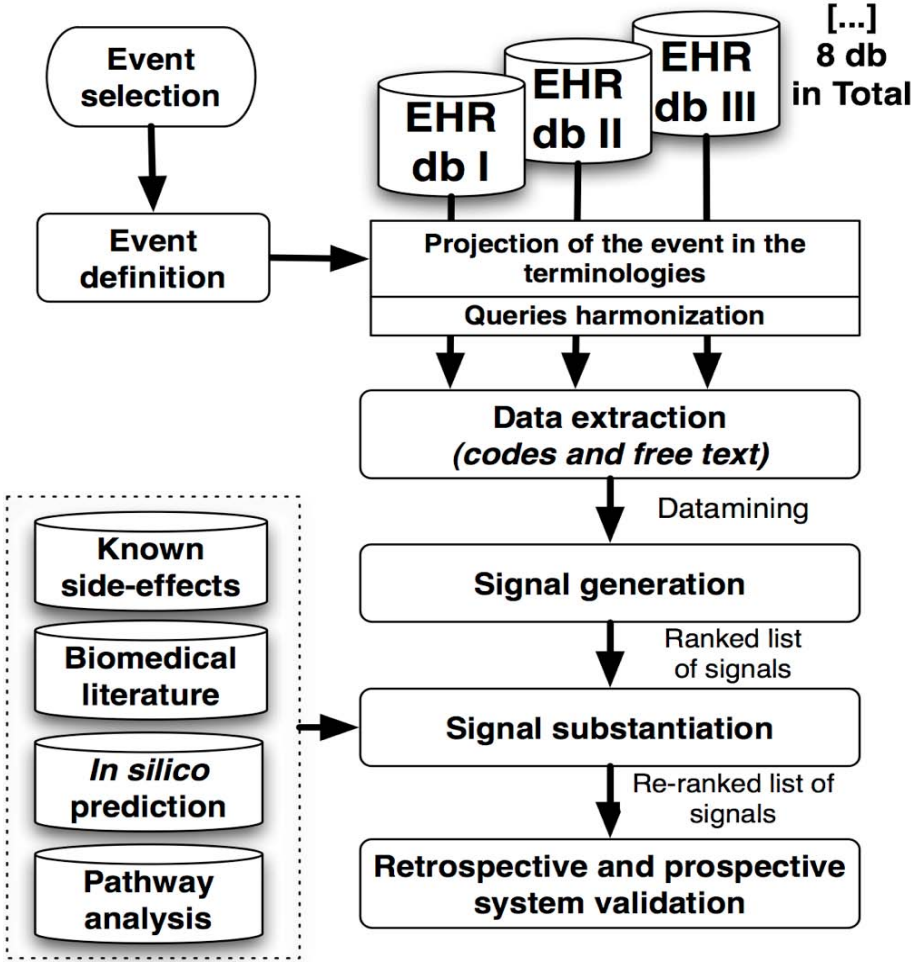
IR per 100,000 PY



WHAT CHANGED?

3. METHODS FOR SIGNAL DETECTION IN HEALTHCARE DATABASES

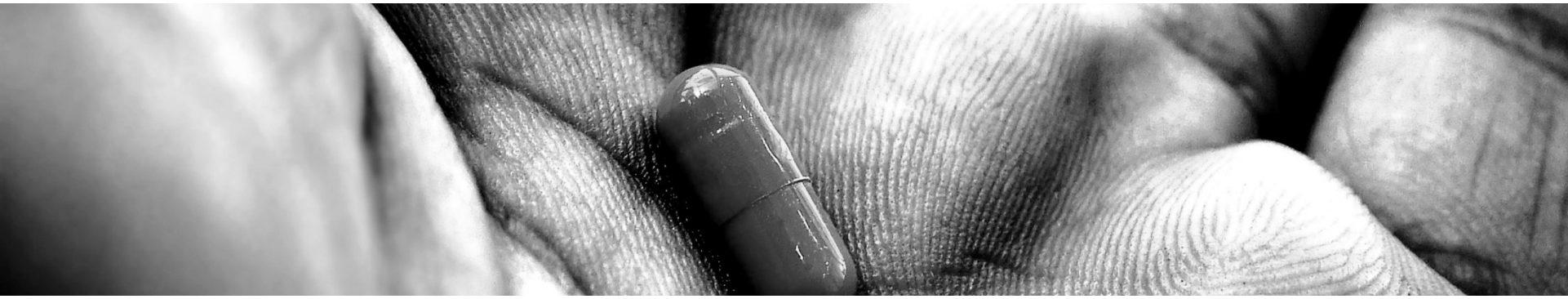
Mining of electronic records and biomedical knowledge for drug safety monitoring



4 medical record DBs
4 record linkage: total 30 million persons

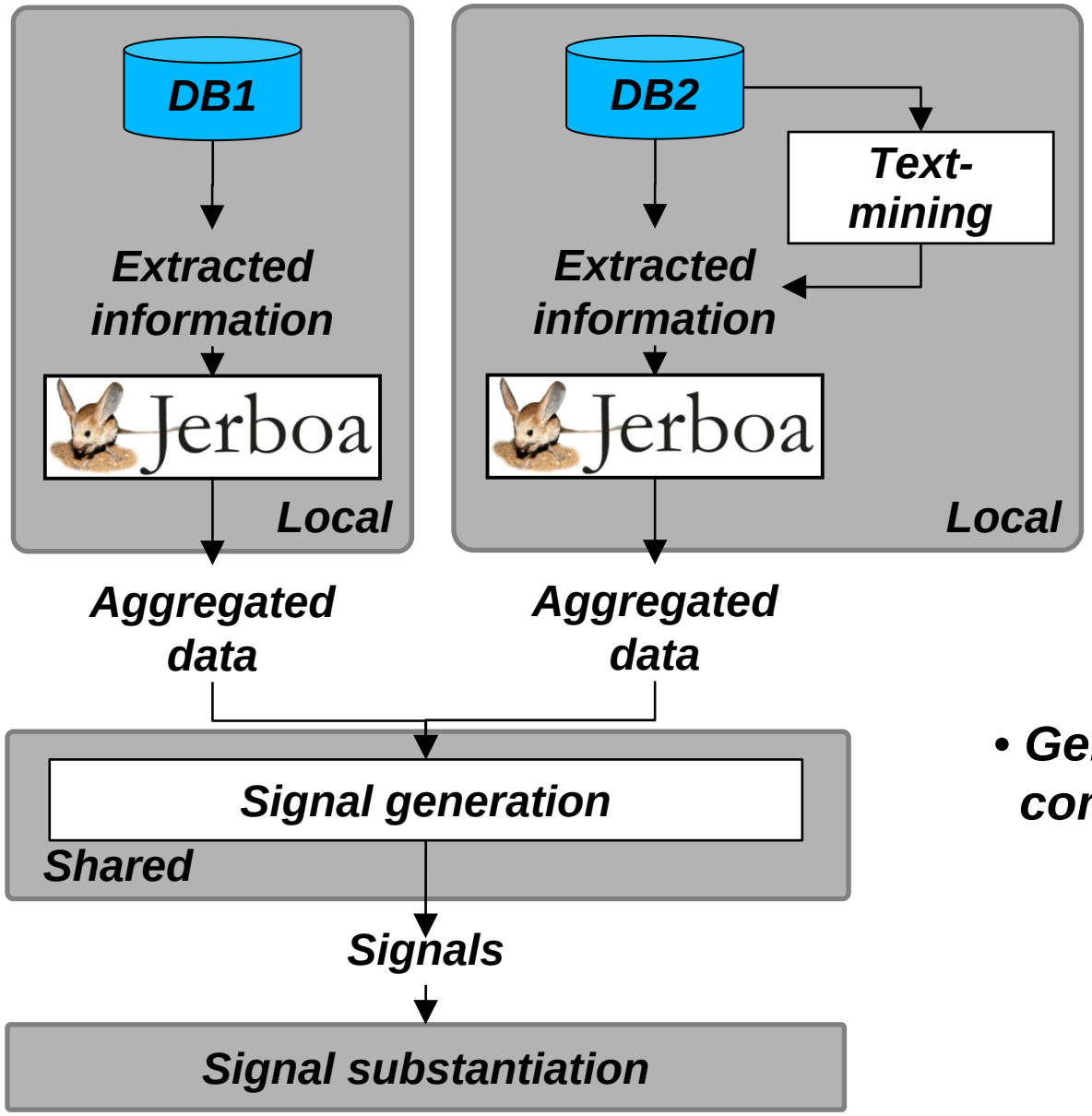
References: Coloma P et al. PDS 2010
Trifiro' G et al. PDS 2009
Avillach P, JAMIA 2009

www.euadr-project.org



Drug Safety Signal Generation

Signal generation in distributed data model



Specific events extracted: UGIB, MI, Rhabdo, Anaphylactic shock, acute renal insufficiency (being increased to 15)

- ***Generation of signals using combined aggregated data***

SEVENTH FRAMEWORK PROGRAMME

eu-adr

Methods flow for signal detection

PRIMARY SCREENING METHODS

Basic Methods for disproportionality assessment

- **GPS/ BPCNN/Fisher exact (traditional case based)**
- **Incidence rate based (Exact test)**
- **Correlation (cumulative exposure)**

Refinement

Chance?	Confounding?	Bias?
Bonferroni FDR Bayesian	*Adjustment Design (CC, SCCS/CCO)*	★ Leopard (new)

Consistency

Across databases?

LEOPARD

Longitudinal Evaluaton Of Profiles of Adverse Reactions to Drugs

Detection of **protopathic bias**

Example:

Stomach bleeding

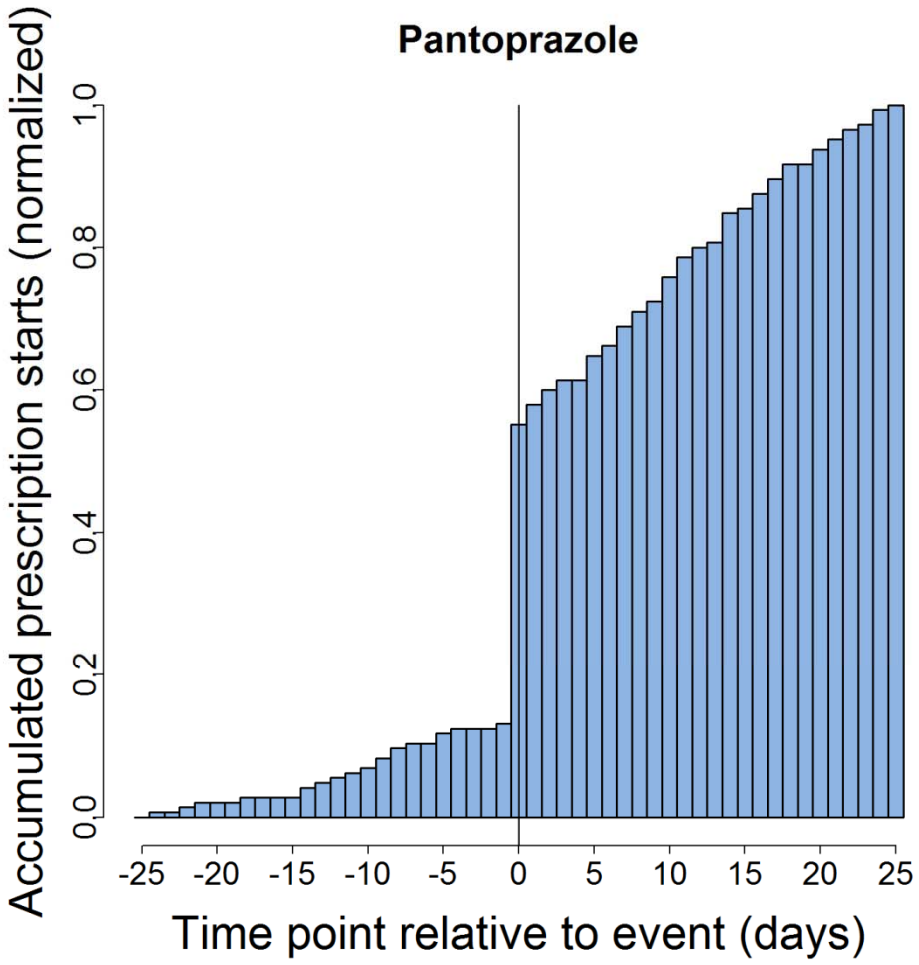
Stomach pain

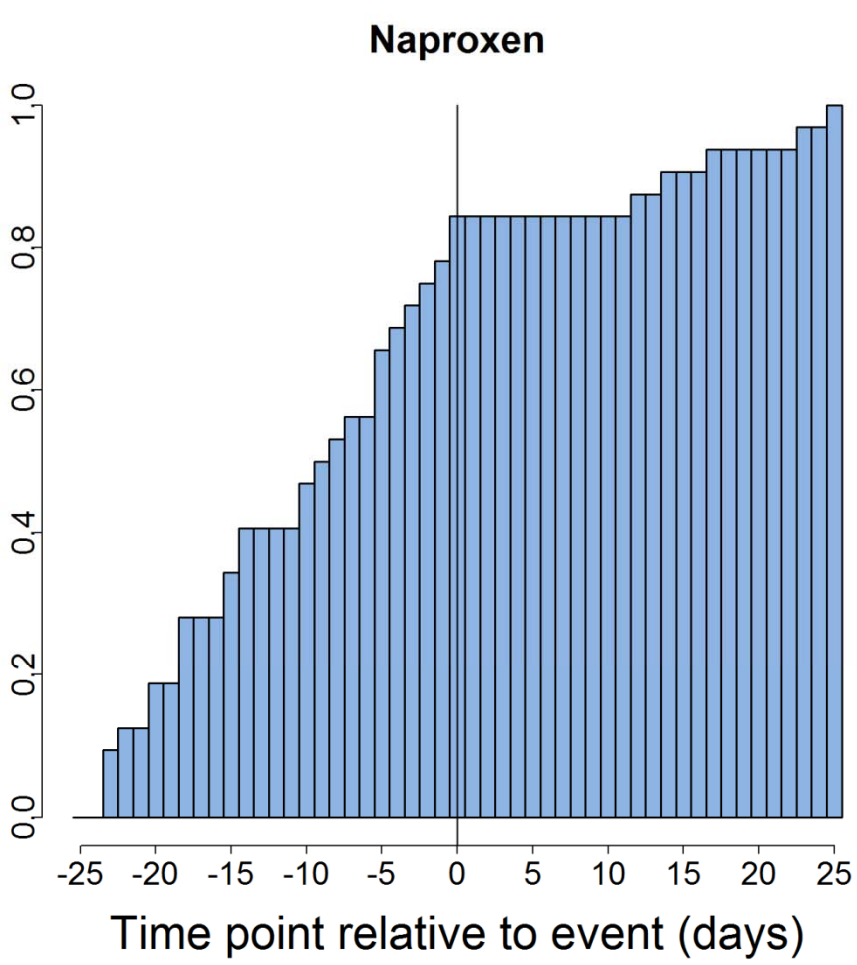
Proton pump inhibitor (PPI)

Did the PPI cause the stomach bleeding?

Schuemie M. LEOPARD. Pharmacoepidemiolgy & Drug safety 2010

Leopard: Two drugs and upper GI bleeding





P < 0.001

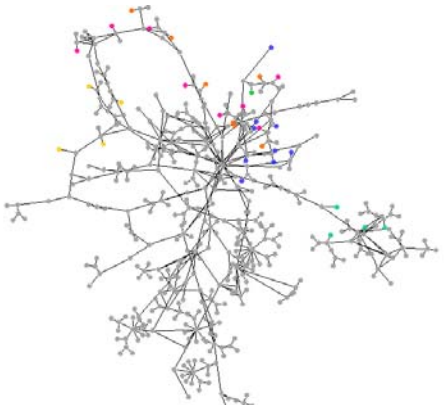
P = 1.000

Schuemie M. LEOPARD. PDS 2010

eu-adr

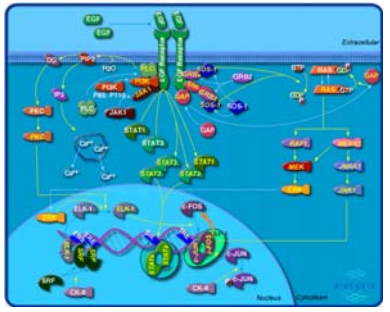
PubMed

National Library of Medicine NLM

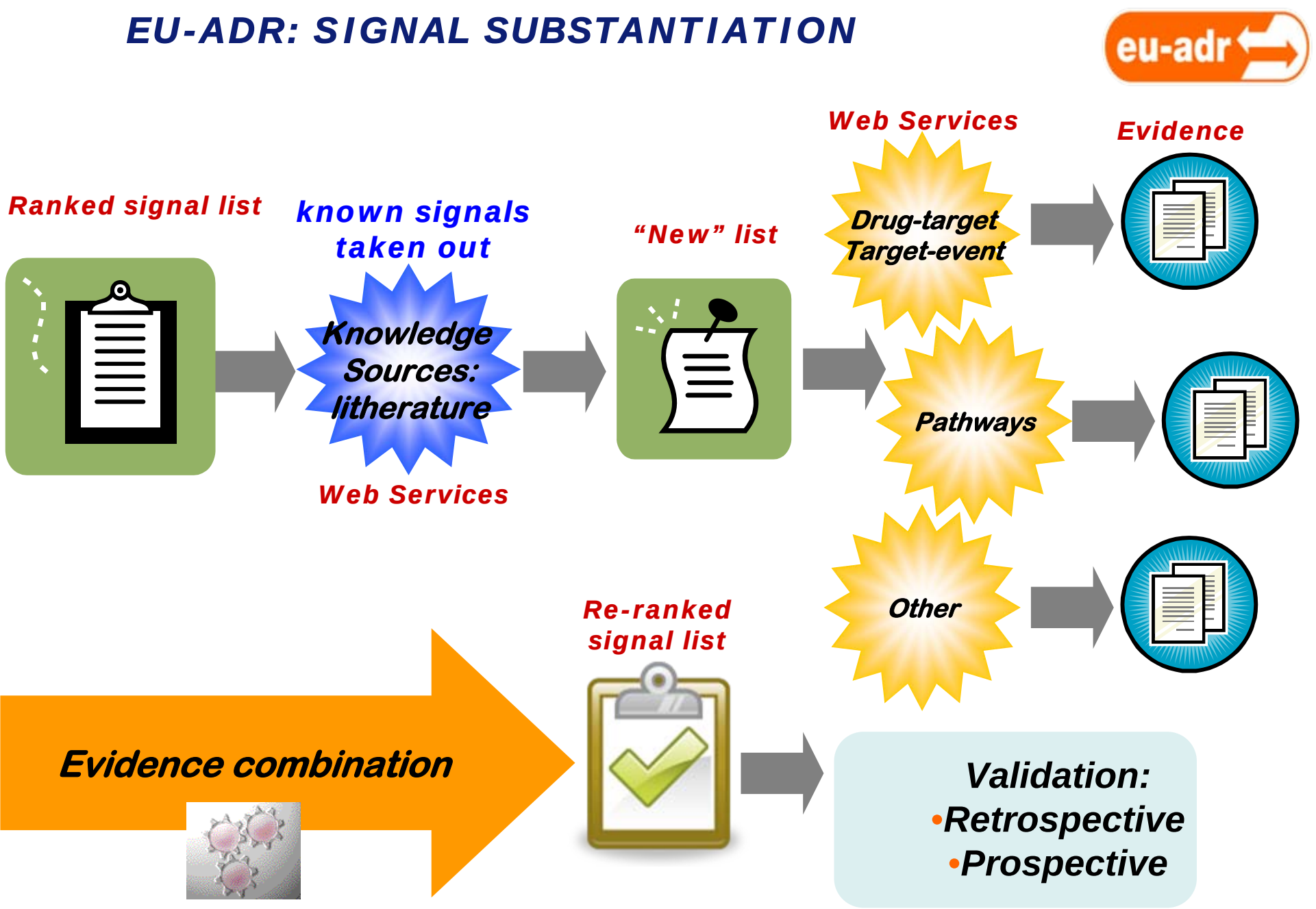


Once a signal is generated, we need to find out whether there is a possible biological explanation for the signal:

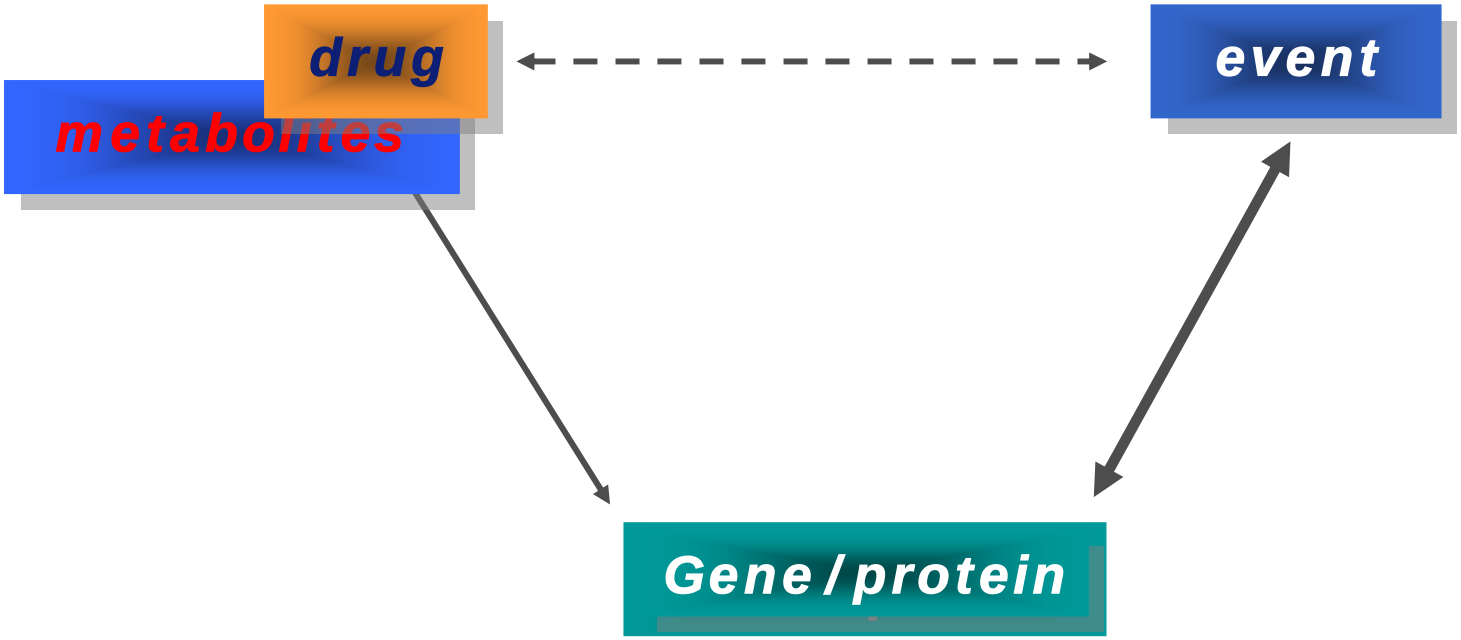
signal substantiation



EU-ADR: SIGNAL SUBSTANTIATION



Signal substantiation



Biological pathways

Courtesy of Bauer A, Furlong, L, Sanz F, Mestres J et al.

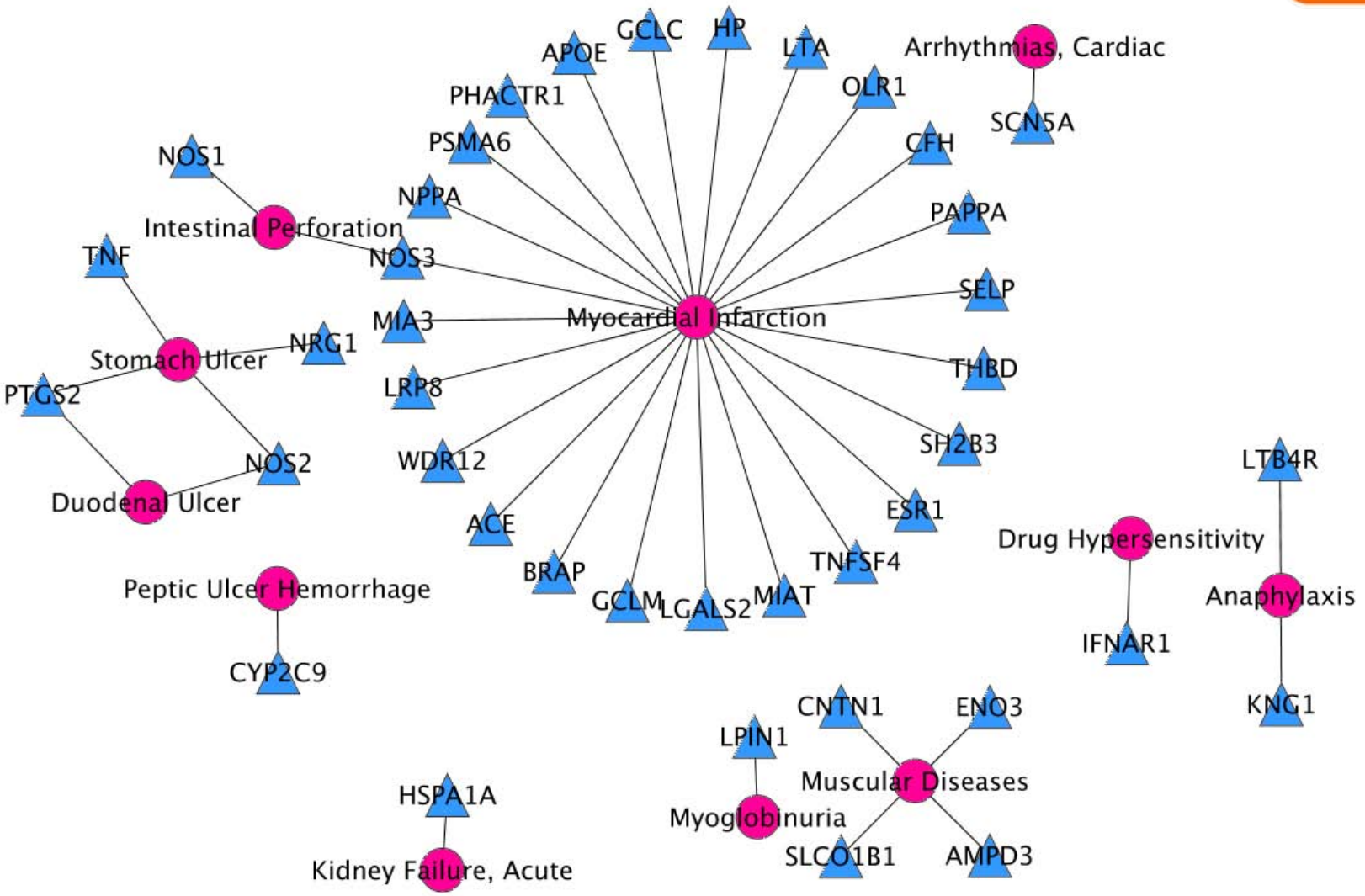
Gene/protein-event mapping

Is the event known to be associated to a gene/protein?

- **Mining of a comprehensive database on gene-disease associations**
- **Data extracted from expert curated gene-disease associations (OMIM, PharmGKB, CTD, UniProt)**
- **semantic gene-disease associations automatically extracted from biomedical literature**

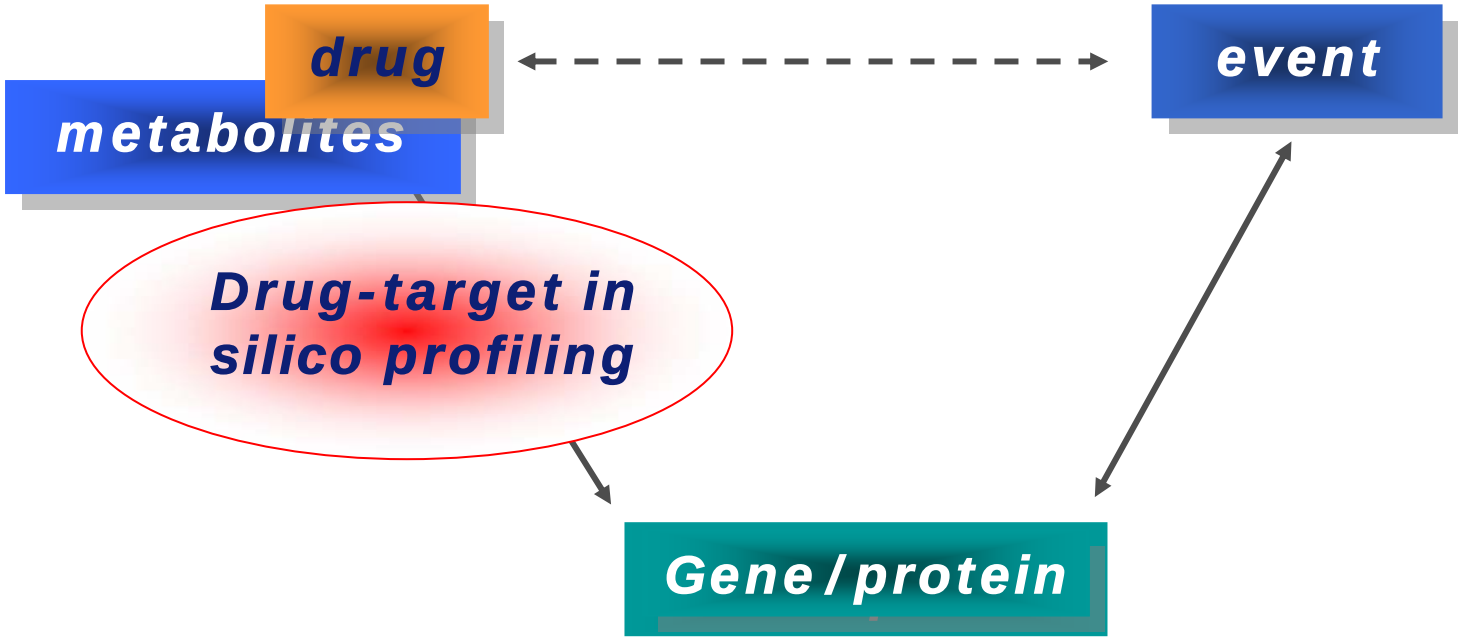
Bauer A, Furlong, L, Sanz F, Mestres J et al.

Network of genes around EU-ADR events



Courtesy of Laura Furlong

Drug-target in silico profiling



Bauer A, Furlong, L, Sanz F, Mestres J et al.

Drug-target in silico profiling

Which are the targets of drug?

- **Drug-target profiles by in silico methods, which capitalize on prior knowledge for many targets of therapeutic relevance.**
- **A compound will be active against a target if it is similar to a certain degree to a set of known ligands of this target**

Bauer A, Furlong, L, Sanz F, Mestres J et al.

Drug-target in silico profiling

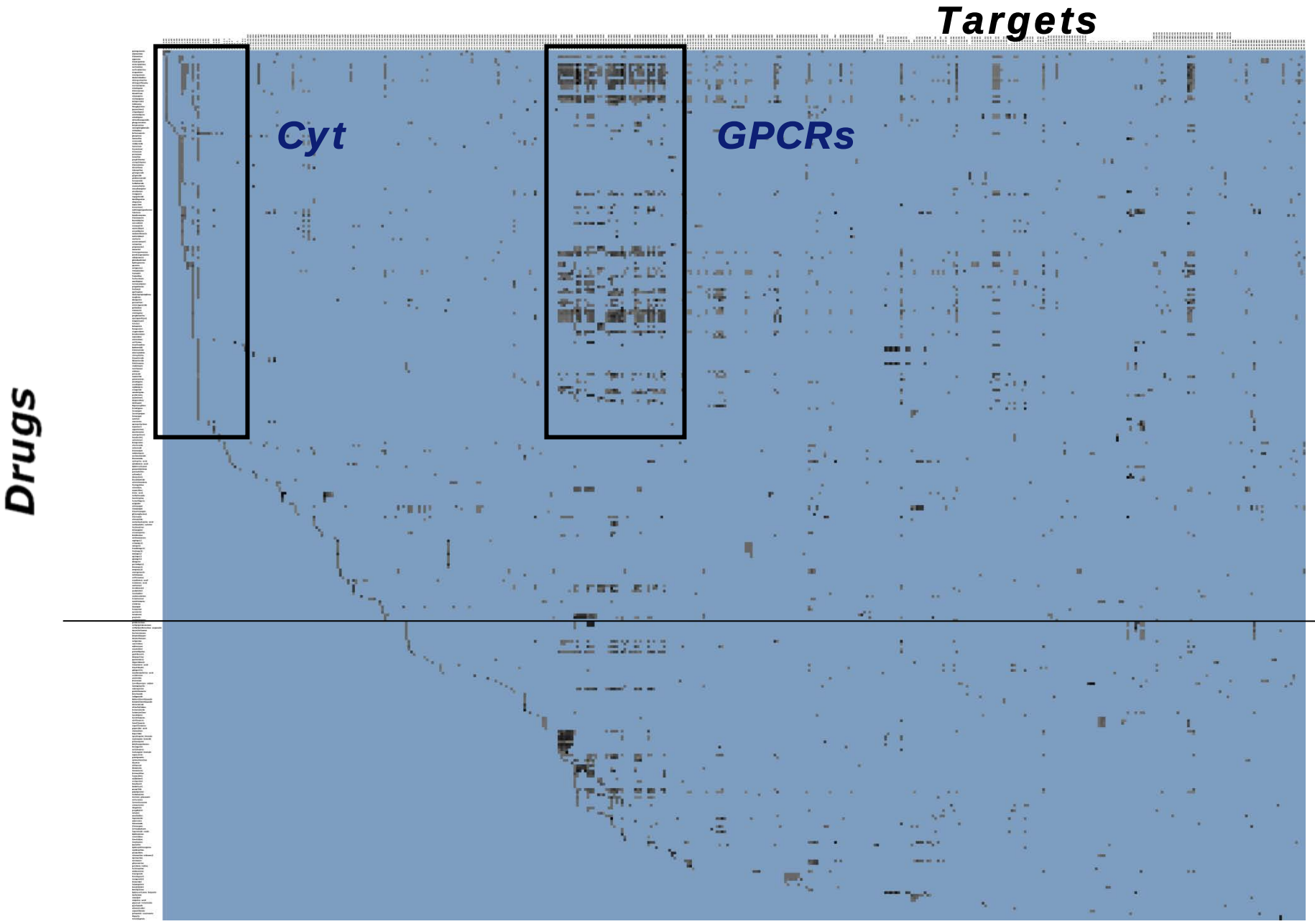
Which are the targets of drug?

- **Targets of the drugs are obtained by querying annotated chemical libraries (ACL)**

- **In addition, the in silico profiling methods can predict novel targets for a given drug**

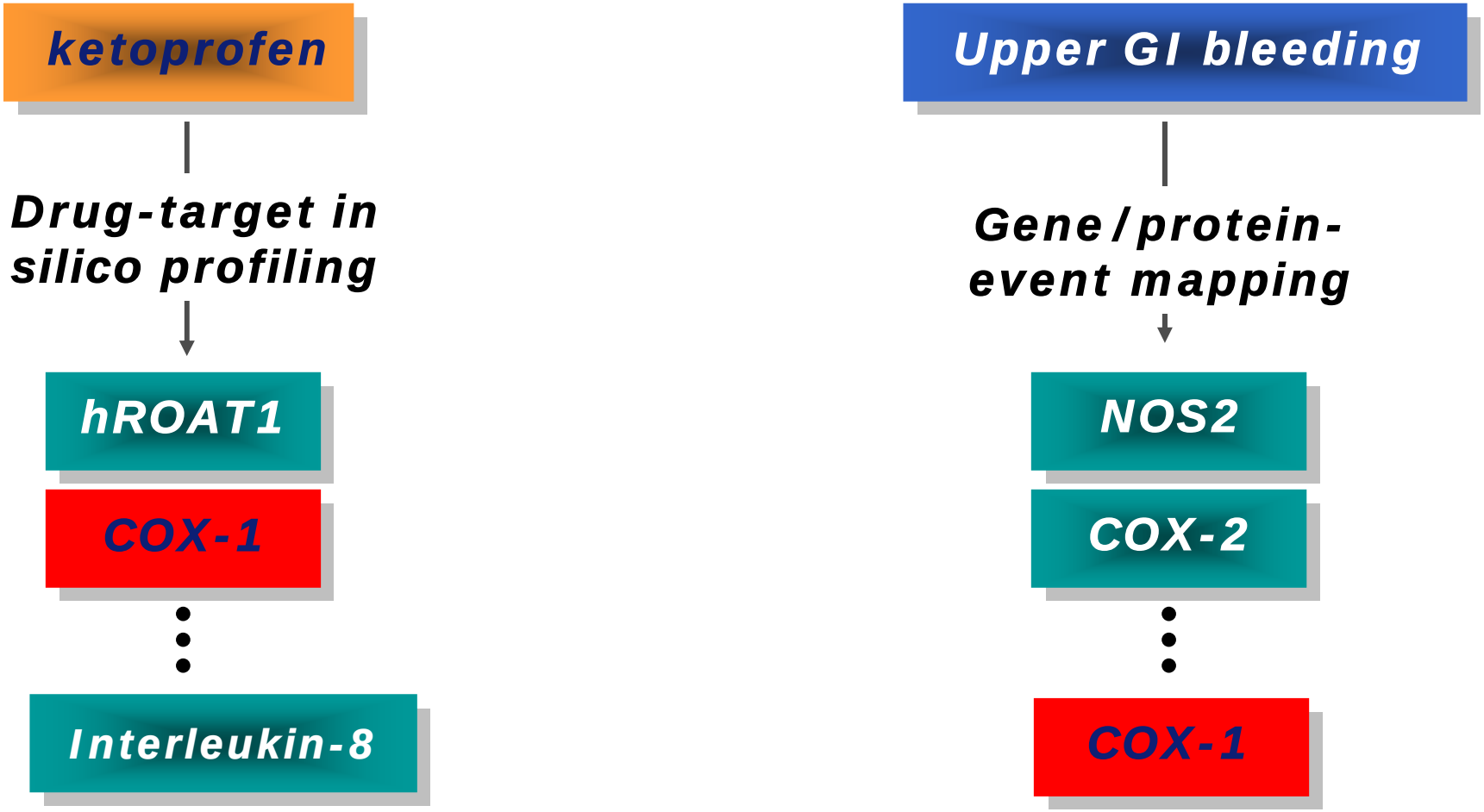
Bauer A, Furlong, L, Sanz F, Mestres J et al.

Exp+Comp predicted target profiling of UGIB drugs

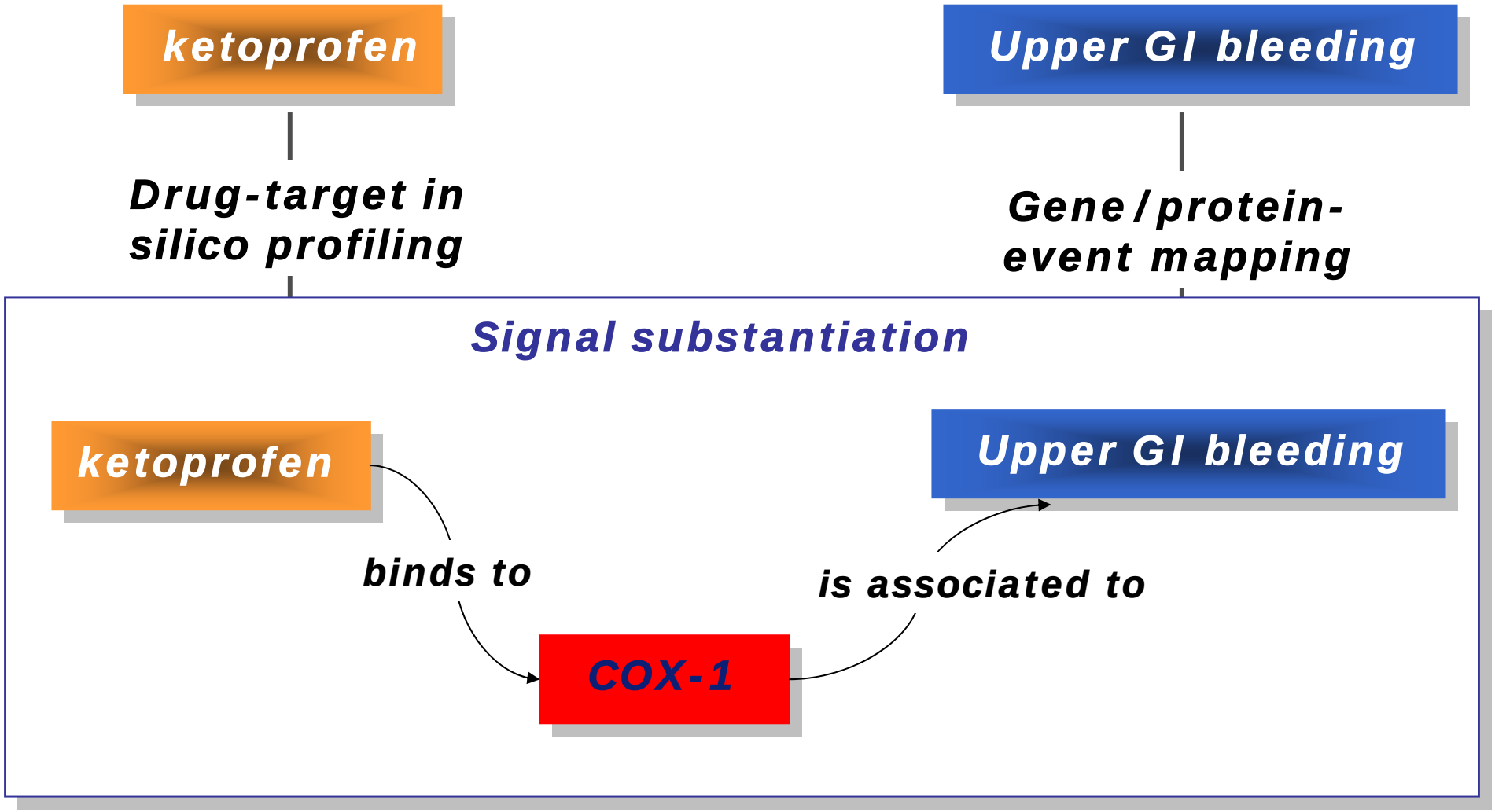


Bauer A, Furlong, L, Sanz F, Mestres J et al.

Signal substantiation: intersection of a protein



Signal substantiation: intersection of a protein



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Detecting Safety issues: will new scientific developments strengthen public health protection?

Will public health improve?

- **EU-RMP:**
  - effectiveness needs to be measured, the RMP itself is not sufficient
- **More funding -> more collaborations**
  - Better methods development
  - Better use of resources and development of tools
  - Accessibility of healthcare data improved
  - Transparency improved (mapping/benchmarking)
  - More data on background rates, actual use etc.
- **Signal detection in health care databases**
  - Both OMOP, WHO-UMC and EU-ADR do methods development
  - Methods require comparison against standard information and validation
  - Future will tell whether these methods are an addition

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Nature Biotechnology **22**, 1341 (2004)
doi:10.1038/nbt1104-1341
Profile: Thomas Lönngren
Sabine Louët[1] Dublin
Abstract
In his attempts to streamline the European Medicines Agency, Thomas Lönngren's style is one of evolution rather than revolution.

You certainly left a revolutionized field of pharmacovigilance and pharmacoepidemiology behind

Thanks on behalf of all scientists!!