Quantifying Medication Risk As-Prescribed

Datamining to Characterize and Communicate Risk

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Outline: Focus on 2 of the 6 Issues

- Limitations of conventional risk signal detection and risk communication?
- Do these tools contain the right kind and amount of info?

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Hierarchy of Evidence to Support Risk Mgt and Comm

- Pre-market clinical trials
- Spontaneous reports (passive surveillance)
- Comparative observational studies
- Registries
- Phase IV post-market studies
- Active (virtual, datawarehouse-based) surveillance with adaptive intensification

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Spontaneous Reports

- Require significant human time and effort to initiate report (detector activation challenge)
- Involve the report submitters' subjective consideration of medicolegal and other factors that are disparate from the Agency's and the public's interests (confounding interests challenge)
- Are not directly or readily coupled to related proximate and contemporaneous clinical information, especially if care is rendered by two or more facilities or health systems (information collocation challenge)
- Are insensitive signals, given the current U.S. setting of fragmented care and the lack of a national health information network (services logistics challenge)
- Are unlikely to detect AEs whose appearance is delayed after exposure (human cognitive challenge)
- Are less likely to be submitted when patient has multiple comorbid conditions and/or when AE causation is multifactorial (combinatoric challenge)

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Right Types and Amounts of Information?

- Information is predominantly oriented to prescribers
- Consumers increasingly expect information ‘parity’ and expect to get it via the Web
- Does not permit detailed exploration of incremental risk associated with age, gender, race, comorbid diagnoses, indices of kidney and liver function, dose-range, concomitant meds, past medical or surgical history, etc.

- Solution: Increased utilization of Electronic Medical Records (EMR) HIPAA-anonymized datawarehouses of observational data – ones with sufficient detail to support analyses and communications to address issues above

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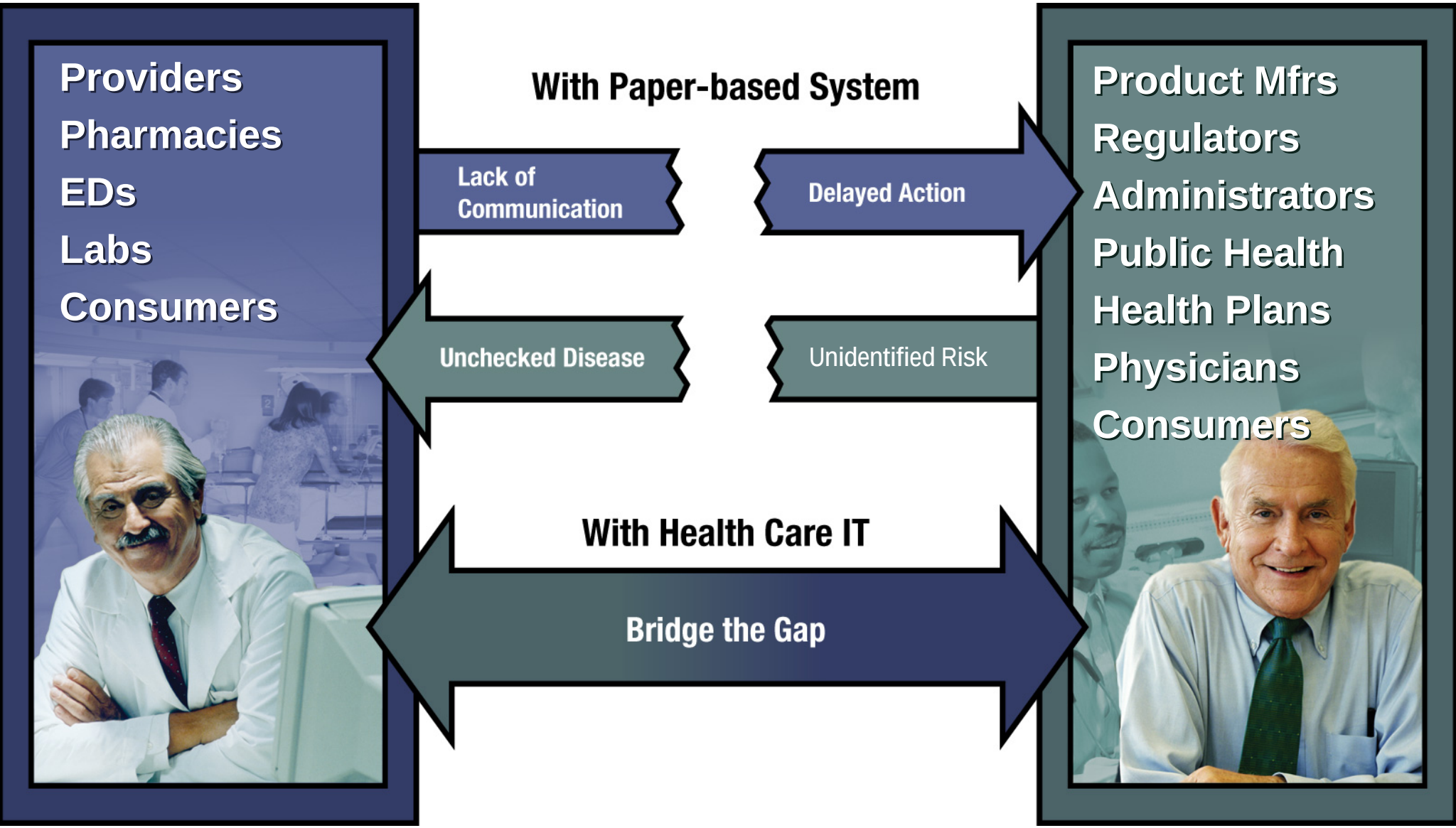
‘Risk Surveillance’ and ‘Risk Communication’ Challenges



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To Improve Risk Analytics, Invert the Pyramid

Traditional Surveillance

Manual Reporting,
Chart Review,
Case Ascertainment

Data Aggregation & Analysis

Investigate Causation

Intervene, Communicate

TIME

Virtual Surveillance

Automated AE & Risk Detection

Datamining ETL

NO DATA ENTRY

Investigate, Quantify Risk

Intervene,

Communicate

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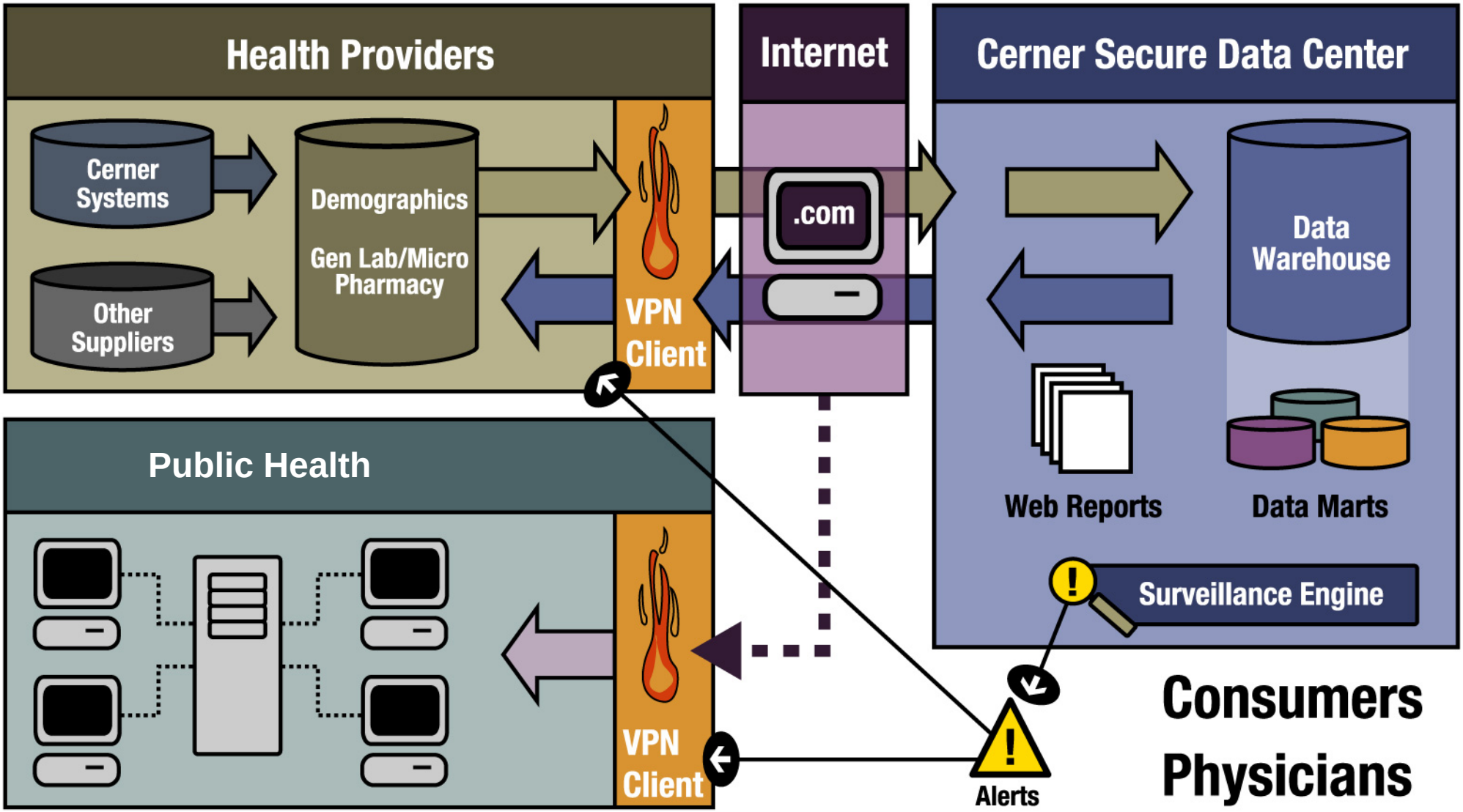
To Improve Risk Analytics, Leverage Existing IT Architecture



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Datamining for Cause-Effect Relationships

- **Observational data Cerner HealthFacts™ datawarehouse, more than 5M new encounters each year (inpatient, ED, outpatient)**
- **Individual level, longitudinal record-linkage (eMPI)**
- **Population level**
- **Ascertainment of logical "necessity" of correlations**
  - Detected adverse events may be related to concomitant medication, co-existing disease, other explanations
  - Judea Pearl. *Causality*. Cambridge Univ Press, 2000.
- **Linkage to MedDRA and NCI CTCAE terms for AEs**

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What is Safety Datamining?

- Use of computer algorithms to ***systematically and objectively*** analyze records contained in huge observational databases

- Goal: to discover hidden patterns of unexpected adverse drug occurrences and quantify, communicate and manage the associated risks

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A Drug is Less “Safe” if:

- Actual risks are greater than the predicted risk
- Actual risks are different from those disclosed on labeling
- Used in a way that increases the risk
- Used in a population that has higher risk
- Used in a way that decreases foreseeable benefit

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Challenges of Missing Data

- Missing data present more challenge in *safety* analysis than in *outcomes / effectiveness* analysis because exposure duration often has stronger impact on the occurrence of the measured events
- HealthFacts™ captures number of meds dispense events, duration of exposure, other valuable info needed for these analyses
- All events are date-time-stamped with minute-level precision, enabling eval of "Before – After" and other time relationships
- To eliminate the exposure factor, we can compare the quantitative responses of dropouts at the point of dropping out, against those of individuals who continued beyond that point (time since med order initiated, cumulative doses, etc.)

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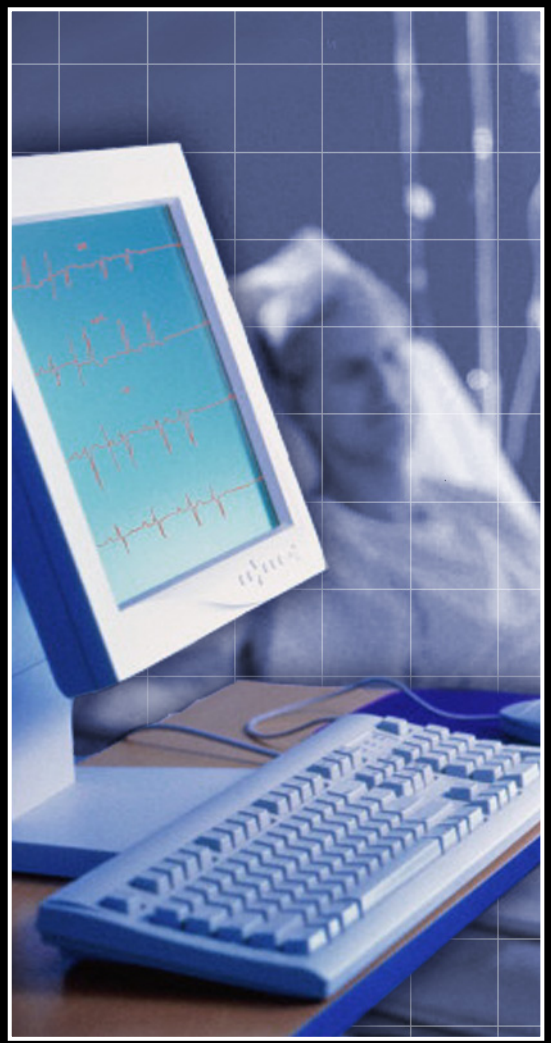
HealthFacts™ Privacy and Security



- **HealthSentry complies with HIPAA Privacy and Security policies and procedures**
  - HIPAA explicitly exempts use of identifiable information for Public Health purposes
- **Data encrypted at provider site**
- **Data securely transferred to Cerner via SHTTP**
- **Data "blinded" at point of entry, allowing view of aggregate data**
- **Data encrypted the entire time at Cerner**

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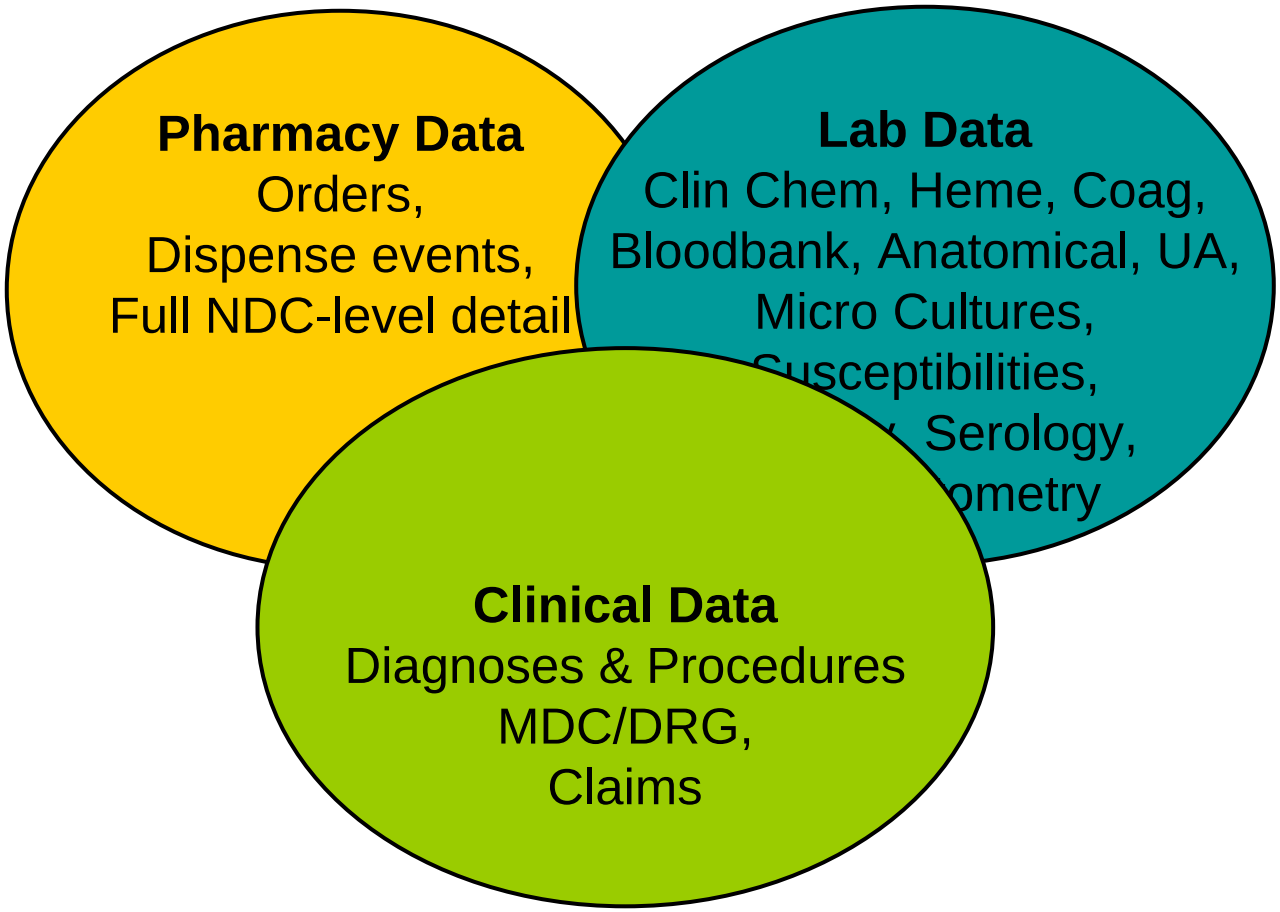
HealthFacts™ – Daily datafeeds, 3 Terabytes and Growing



- **EMR-level detail result info, not just orders or claims**
- **Longitudinal tracking of patients (eMPI)**
- **Date-time stamped to minute-wise resolution**
- **Time series information to help analyze sequences of events**
- **Interactions between concomitant meds**
- **Interactions between comorbid clinical conditions**

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Example: Rofecoxib, Celecoxib, Naproxen

Vioxx	AMI/CVA +	AMI/CVA -	
Rx +	2,894	35,458	38,352
Rx -	203,947	18,717,005	18,920,952
	206,841	18,752,463	18,959,304

Chi-square= 14800, $p < 0.0001$
SRR = 6.9 (6.7 - 7.2)

Celebrex	AMI/CVA +	AMI/CVA -	
Rx +	3,002	22,093	25,095
Rx -	203,839	18,730,370	18,934,209
	206,841	18,752,463	18,959,304

Chi-square= 27500, $p < 0.0001$
SRR = 11.0 (10.6 - 11.4)

naproxen	AMI/CVA +	AMI/CVA -	
Rx +	1,215	18,741	19,956
Rx -	205,626	18,733,722	18,939,348
	206,841	18,752,463	18,959,304

Chi-square= 4620, $p < 0.0001$
SRR = 5.6 (5.3 - 5.9)

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Rofecoxib, Celecoxib, Naproxen

Vioxx	Exp +	Exp -	
Rx +	11	38,341	38,352
Rx -	1,401	18,919,551	18,920,952
	1,412	18,957,892	18,959,304

Chi-square= 20.5, $p < 0.001$
SMR = 3.8 (2.1 - 6.9)

Celebrex	Exp +	Exp -	
Rx +	20	25,075	25,095
Rx -	1,392	18,932,817	18,934,209
	1,412	18,957,892	18,959,304

Chi-square= 167, $p < 0.0001$
SMR = 10.7 (6.9 - 16.5)

naproxen	Exp +	Exp -	
Rx +	3	19,953	19,956
Rx -	1,409	18,937,939	18,939,348
	1,412	18,957,892	18,959,304

Chi-square= 0.7, $p > 0.4$
SMR = 2.0 (0.4 - 6.2)

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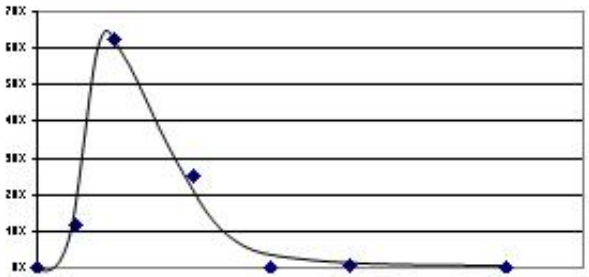
Dose-Response – 24h Exposure is Calculated in HealthFacts™

- **Exposure = Strength X Dose_Qty X Frequency**
  e.g., " Vioxx 12.5 mg ii P.O. bid " = 12.5 X 2 X 2 = 50 mg/24h

VIOXX
DOSE_QTY=1

FREQ	QD	BID	TID	QID
STRENGTH	1	2	3	4
12.5 mg	3216	407	5	2
25 mg	16677	1040	36	7
50 mg	5801	77	2	1

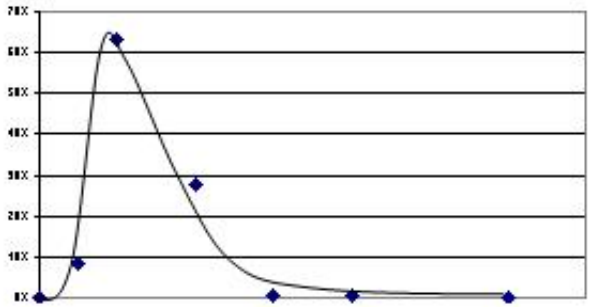
mg/24h	N	Prevalence
12.5 mg	3216	11.8%
25 mg	17084	62.7%
50 mg	6843	25.1%
75 mg	36	0.1%
100 mg	84	0.3%
150+ mg	3	0.0%



CELEBREX
DOSE_QTY=1

FREQ	QD	BID	TID	QID
STRENGTH	1	2	3	4
100 mg	1594	2960	40	4
200 mg	8944	5143	55	7
400 mg	99	59	1	0

mg/24h	N	Prevalence
100 mg	1594	8.4%
200 mg	11904	63.1%
400 mg	5246	27.8%
600 mg	55	0.3%
800 mg	66	0.3%
1200+ mg	1	0.0%



… Do the same totals for Dose_Qty = 2, 3, …

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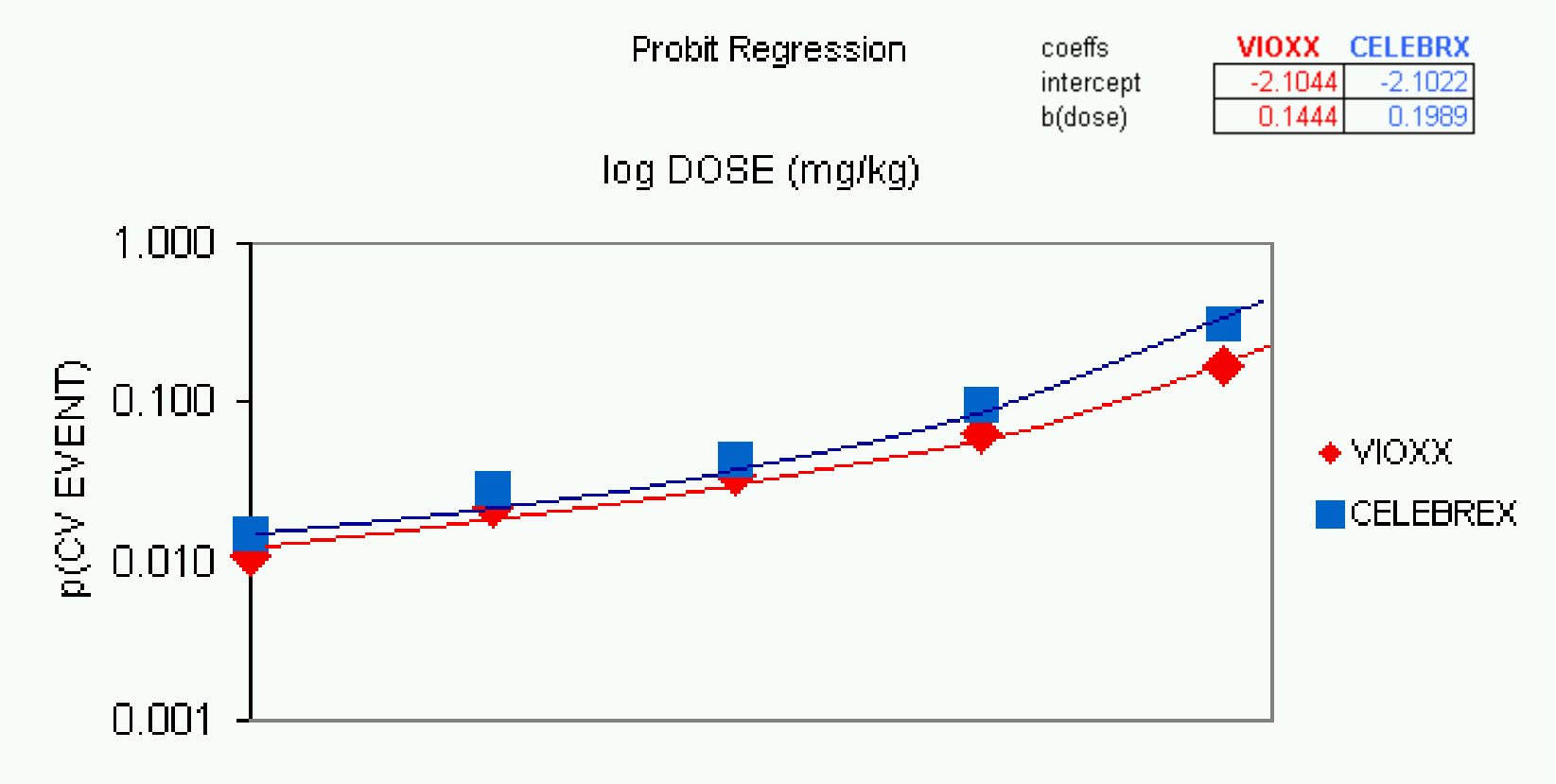
Ischemic Cardiac and CNS Events



coeffs	VIOXX	CELEBRX
intercept	-2.1044	-2.1022
b(dose)	0.1444	0.1989

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How Different are Vioxx and Celebrex AE Rates?

- **Methods for determining difference betw. "drug 1" and "drug 2"**
  - See Piegorsch & Bailer, 1997, p. 342
  - b_2 and b_3 indicate how the intercepts and slopes differ

$$\eta_{pi} = b_0 + b_1 x_{pi} + \sum b_j I_p(j) + \sum b_{k+j-1} x_{pi} I_p(j)$$

← dummy "indicator" variables:
1 if j^{th} patient and p^{th} pop match
0 otherwise

where x_{pi} is the mg/kg/24h dose for the ith dose level for the pth drug in comparison, each of k > 1 drugs compared to the k = 1 "reference" population (e.g., naproxen)

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How Different are Vioxx and Celebrex AE Rates?

```
ic = pop="C"; icdose = ic * dose24;
iv = pop="V"; ivdose = iv * dose24;
proc probit; by pop; model SAE/n=dose24 /d=logistic inversec1;
## slope difference estimate icdose 0.4773 – 0.2826 = 0.1947
--------------------------------- POP=C -------------------------------------
Variable      DF      Estimate     Std Err    ChiSquare    Pr>Chi
INTERCEPT      1       -3.1221      0.4212     102.0392    0.0001
DOSE24         1        0.4773      0.0392     114.3828    0.0001
--------------------------------- POP=V -------------------------------------
Variable      DF      Estimate     Std Err    ChiSquare    Pr>Chi
INTERCEPT      1       -2.1221      0.3384     115.2717    0.0001
DOSE24         1        0.2826      0.0392     126.1182    0.0001
```

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How Different are Vioxx and Celebrex AE Rates?

```
proc genmod; model SAE/n=dose24 ic icdose /dist=bin link=logit type1;
## slope difference estimate icdose 0.4773 – 0.2826 = 0.1947
-------------------- Analysis of Parameter Estimates ----------------------------
Variable      DF      Estimate     Std Err    ChiSquare    Pr>Chi
INTERCEPT      1       -2.1221      0.3384     115.2717    0.0001
DOSE24         1        0.2826      0.0392     126.1182    0.0001
IC             1       -1.8273      0.4191      27.1726    0.0001
ICDOSE         1        0.1947      0.5244      13.4130    0.0003
```

- **Preliminary Conclusion:** *reject* **null-hypothesis of "no difference" (C *is* worse than V)**
- **But is this difference *clinically significant* ? Is Celebrex *really* worse than Vioxx?**

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Summary: Cox-2 Inhibitor Example

- Significantly greater incidence of ischemic cc compared to controls
- Vioxx (rofecoxib, Merck) and Celebrex (celecoxib, Pfizer) SRR's are 30% to 100% higher than naproxen in terms of AMI/ACS incidence and associated risks
- Vioxx and Celebrex both show significantly (2x - 5x) greater than expected mortality, compared to naproxen-treated controls
- Vioxx, Celebrex show sigificantly different mortality rates
- Celebrex dose-tox curve is actually worse than Vioxx, although Vioxx is the drug that had received the attention in the literature, leading to withdrawal
- Currently, we are evaluating dose, concomitant meds, duration of Cox-2 therapy, age, gender and other variables

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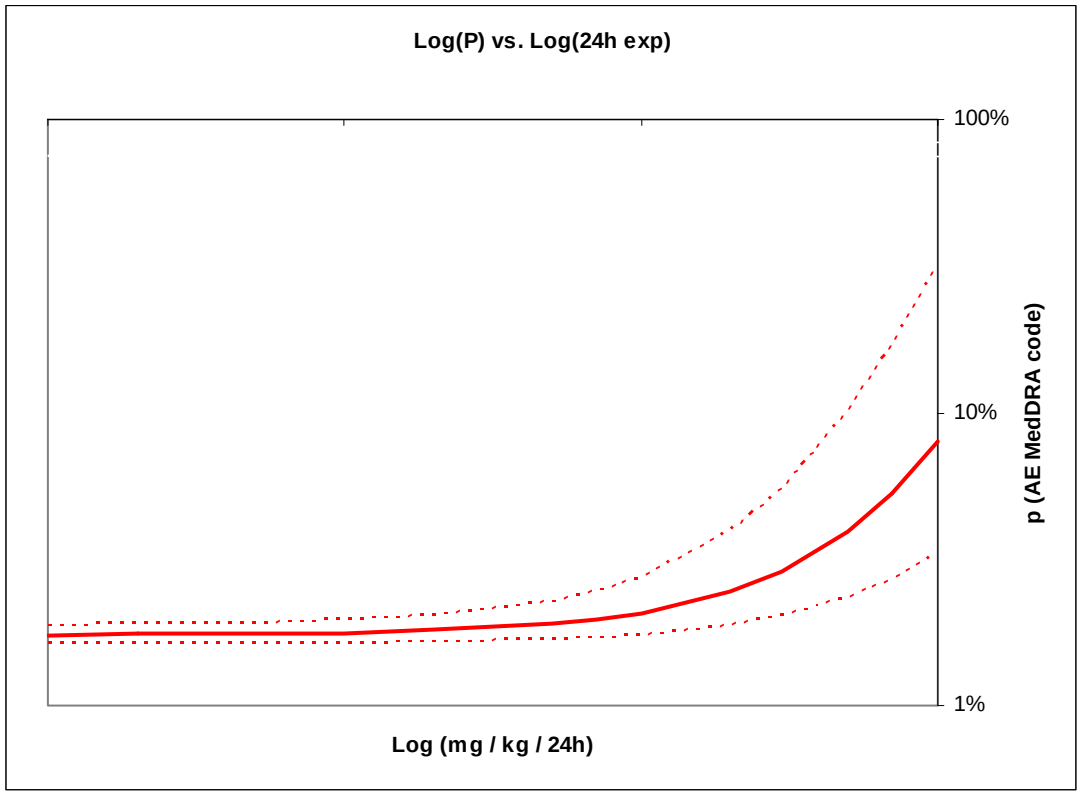
Thiazolidinediones (Actos, Avandia) and Exacerbation of CHF

General Diabetic Population, Women, Age 70 - 79



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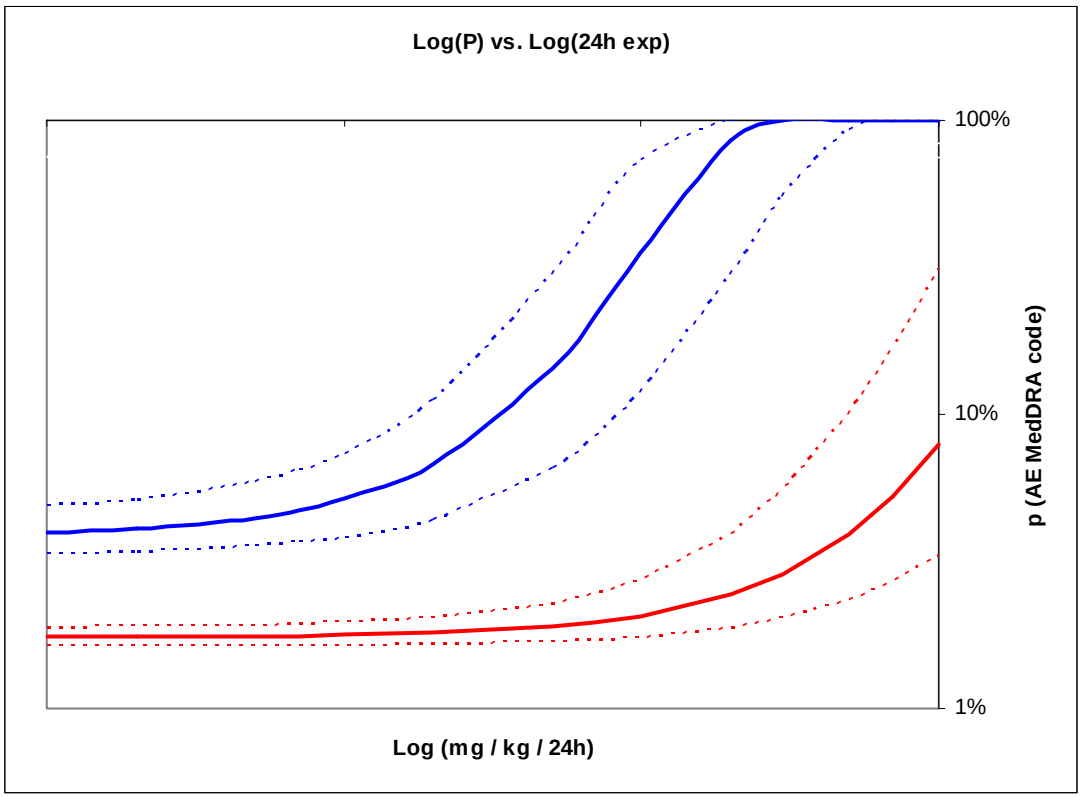
Thiazolidinediones (Actos, Avandia) and Exacerbation of CHF

Population with existing NYHA Class II CHF, LVEF 20% to 40%, Women, Age 70 - 79



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Active Surveillance AE Characterization using HealthFacts™

Cardiac / Cardiovascular

- ACE inhibitors, potassium-sparing diuretics and potassium levels
- Antiadrenergic agents, peripherally- acting with dose and timing
- Beta-adrenergic agents with renal dysfunction and/or bradycardia
- Calcium Channel Blockers elevated LFT's or decrease renal function
- Thiazolidinediones associated with worsening CHF
- ACS – AMI – TIA – CVA in Cox-2 inhib treated patients

Infectious Disease

- Treatment failure in MRSA, VRE, MDROs
- Empiric Antibiotic Therapy – recommendations when C & S not available, provides antibiogram data (site specific).
- Available C & S data – evaluated to provide alternative therapies when organism determined not susceptible to current therapy.
- Quinolone-induced CNS disorders in patients with increased risk of seizures – case-finding via anticonvulsants, renal studies.

Hepatotoxicity / Nephrotoxicity

- Drug-induced hepatotoxicity
- Thiazolidinediones with elevated LFT's
- Sulfonylureas with elevated LFT's or signs of lactic acidosis
- Beta-adrenergic agents with renal dysfunction and/or bradycardia
- Narcotic Analgesics – Laboratory results evaluated for any renal or hepatic dysfunction
- Calcium Channel Blockers association with elevated LFT's or decrease renal function
- Renally-excreted meds (includes applicable calcium channel blockers; beta blockers; narcotic analgesics)

Hematological

- Excessive INR during warfarin therapy
- Elevated PTT during heparin or heparinoid therapy
- Drug-induced Neutropenia
- Thienopyridines (clopidogrel, ticlopidine) associated with life-threatening hematological events

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Signal Prioritization

Major criteria

- Seriousness (WHO definition)
- Causation (definite, probable, possible, unlikely, unassessible)
- Newness (unexpected, not yet reported)
- Recency (time period since launch < 24 months)
- Public health impact (wide usage, number of cases, rapid increase in use)
- Vulnerable populations (pediatric, pregnant women, geriatric, psychiatric)
- Risk perception by general population (media)

Minor criteria

- Potential shift in benefit-risk ratio (based on epidemiology of population exposed)
- Preventability
- Reversibility, treatability
- Expected but unlabelled AE
- Clinical characteristics of AE
- Strength of association between AE and drug exposure

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Signal Prioritization

- **Signal classified as:**
  - High priority – serious, unknown, and/or unlabelled AE
  - Medium priority – potential shift in benefit-risk ratio
  - Low priority – AE already known, characterized, partially labelled
- **Post-market observational datawarehouses allow detection, identification, causality assessment, confirmation, quantification of risks**
  - Concomitant meds (esp. PD/PK interactions)
  - Comorbid diseases and severity of disease (e.g., NYHA Class III CHF)
  - Duration of exposure
  - Dose
  - Age, gender, other features denoting vulnerable populations
- **Detail identification of risk factors makes AEs more mitigatable**

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Anticipating AEs: Limitations of Premarketing Databases

- **Too few subjects**
- **Too homogenous population**
  - Age
  - Gender
  - Comorbid diseases
  - Concomitant meds
- **Too brief duration**
- **Not how it's prescribed and used in practice, post-launch**

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New Datawarehouse-based Approach

Active surveillance with adaptive intensification

- Supplements other types of surveillance
- Huge numbers of ‘subjects’ per year (drug-exposed cases)
- Heterogeneous, real-world populations
- Wide range of doses and exposure durations
- Wide range of concomitant meds, comorbid diseases

Observational prospective studies

- Able to do d’Agostino-Rubin-type ‘propensity score’ adjustments
- Able to examine pairwise and higher-order combinations (vs. PRR and EBGM)
- vs. Phase IV prospective studies
- vs. Registries

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Ways that Datawarehouse-based Tools Contribute to RM System

- Risk Assessment - estimation & evaluation of risk
- Risk Confrontation - determination of acceptable levels of risk in societal context
- Risk Intervention - actions to control risk
- Risk Communication - interactive process of exchanging risk information
- Risk Management Evaluation - measurement of effectiveness of aforementioned activities

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Labeling Implications of New Datawarehouse-based Tools

- **Patient information supplemented by web-based applets**
  - Enable patient to explore risk profile that is associated with their own medications and diagnoses
- **Provider information reveals need for increased monitoring in selected subpopulations of patients**
  - ECG for QT prolongation, LFT for hepatotoxicity, INR for bleeding risk, etc.
  - More frequent clinic visits
  - Context-dependent “flexing” of awareness of risk
  - Timely awareness of relative contraindications in subpopulations
  - Where dose-tox regressions are supported by the data, reveals opportunity to reduce risk by adjusting dose, maintaining Rx benefit
- **Agency information**
  - Pharmacovigilance planning; proactive discovery of new AE types
- **Pharma sponsor information**
  - Anticipatory surveillance, affords opportunity to undertake NDA Suppl. labeling changes in timely manner responsive to public health

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Our Perspective

- Labeling & ‘Dear Doctor’ letters relatively ineffective risk mgt tools
- Most common systems failure: getting knowledge to physicians
- Labeling and labeling changes ≠ knowledge
- Knowledge does not necessarily drive behavior
- Increasing demand for up-to-the-minute information via web portals
- Participative interaction with web portals increases likelihood of knowledge-based behavior (by prescribers, by patients)
- Web portal access tracking is powerful resource to support Risk Communication Research (CERTS, DSaRM)

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Involving the Healthcare Provider: RiskExplorer™ Portal

Programmatic support for Risk Communication Research

- Understanding how best to communicate appropriate drug usage to providers
- Understanding how to communicate to change 'risky' provider behavior once identified
- Quantifying the effects of risk management and communication efforts; how to measure message penetration, what are the outcomes of interest

Web-based risk browser

- Enter medication of interest
- Enter age, gender, diagnoses, concomitant meds, other filter criteria
- Display probit regression curves of AE probability, dose-tox relationship

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HealthFacts™ Datawarehouse

- **Comprehensive EMR detail-level data from 01-JAN-2000 to present**

- **Today's HealthFacts™ datawarehouse includes:**
  - Complete pharmacy, laboratory, billing and registration information on over 19,100,000 distinct admissions, ED, and outpatient cases
  - Currently 41 institutions providing datafeeds daily
    - *95 signed contributor institutions*
    - *Data contributor base continues to grow*
  - All regions of the U.S. represented
  - Teaching, Community/Non-teaching, Children's
  - National comparisons have shown projectability of results
  - Sample sizes large enough to power wide range of statistical analyses

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Data Quality: The Advantage of Hospital-based Data

- **ADEs occur between 1 and 30% of all inpatient admissions**

- **Incremental risk associated with concomitant meds polypharmacy, multiple comorbid conditions**
  - Strength: Opportunity for more sensitive signal detection
  - Weakness: More difficult to evaluate causality

- **Compared to ambulatory clinic datasets, hospital-based data have much lower missing-data rates for diagnoses, procedures, labs, etc.**

Source: Raschke, et al; A Computer Alert System to Prevent Injury from Adverse Drug Events; JAMA, October 21, 1998, Vol 280(15)

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Current Risk Analytics and Communication

- **Reliance on spontaneous reporting and manual data entry can take valuable resources away from other public health response or prevention activities, regulatory activities**
- **Uneven quantity and quality of reports, varying over time**
- **Less timely reports and under-reporting can lead to delayed detection and characterization of AE risks**
- **Without automated transmittals and datamining to detect patterns, reporting of AEs relies solely on manual processes**
  - Prone to logistical, sociological, medicolegal biases

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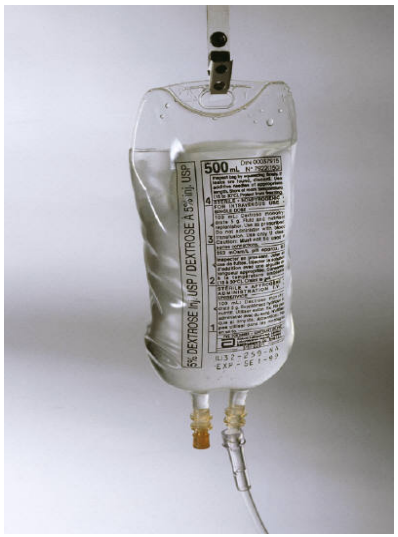
HealthFacts™ Datawarehouse

Strengths

- Inpatient and outpatient clinic Rx
  - *Datafeeds and QA process and infrastructure in place since 1996*
  - *More than 5M new cases per year*
- Clinical detail
  - *Lab results (including microbiology and anatomic path)*
  - *Full medication dispense info (including NDC detail, strength, freq, route, form)*
  - *Selected clinical procedures and outcomes can be captured*
- Longitudinal record linkage
  - *Patients currently tracked across encounters with in a health system*
  - *Automatic "eMPI" linkage logic*
- Timely recording of events
  - *< 48 hours*
- Sensitive detection of multifactorial and delayed AEs

Weaknesses

- Coverage
  - *Good coverage now but could be better*
  - *U.S. domestic now but could be extended to other countries*
- Retail and OTC meds



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Summary: Focus on 2 of the 6 Issues

- **Limitations of conventional risk signal detection and risk communication?**
  - Spontaneous reports databases are insensitive detectors of AEs, especially ones whose manifestation is ***delayed*** or whose causation is ***multifactorial***
  - Spontaneous reports databases are inherently confounded by logistical, sociological, and medicolegal biases

- **Do existing tools contain the right kind and amount of info?**
  - No, information is too "coarse" and does not reflect the particularities and clinical and physiologic context of those populations susceptible to experiencing AEs
  - No, information is too "scanty" and not "timely" enough to be responsive to emerging patterns and trends
  - No, information is primarily accessible to prescribers, and is not accessible to an increasingly interested web-capable public

- **Active surveillance via curated observational datawarehouses derived from HIPAA-anonymized coded Electronic Medical Records data and Web-based communication tools can effectively supplement existing AERS and other conventional tools**

Thank you!

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