



# Post-Marketing Safety Assessments The Journey

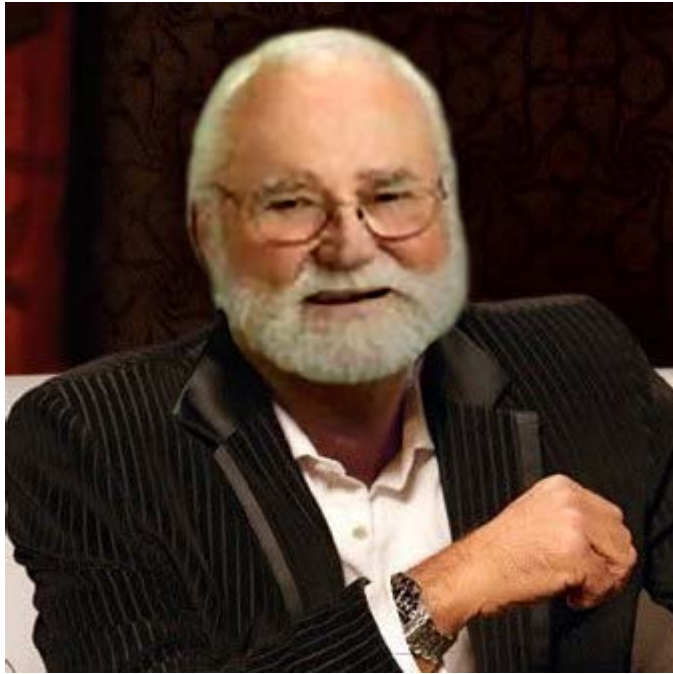
Stephen J Ruberg, PhD

Distinguished Research Fellow

Global Statistical Sciences & Advanced Analytics

Eli Lilly

Nov 2013



**BASS**

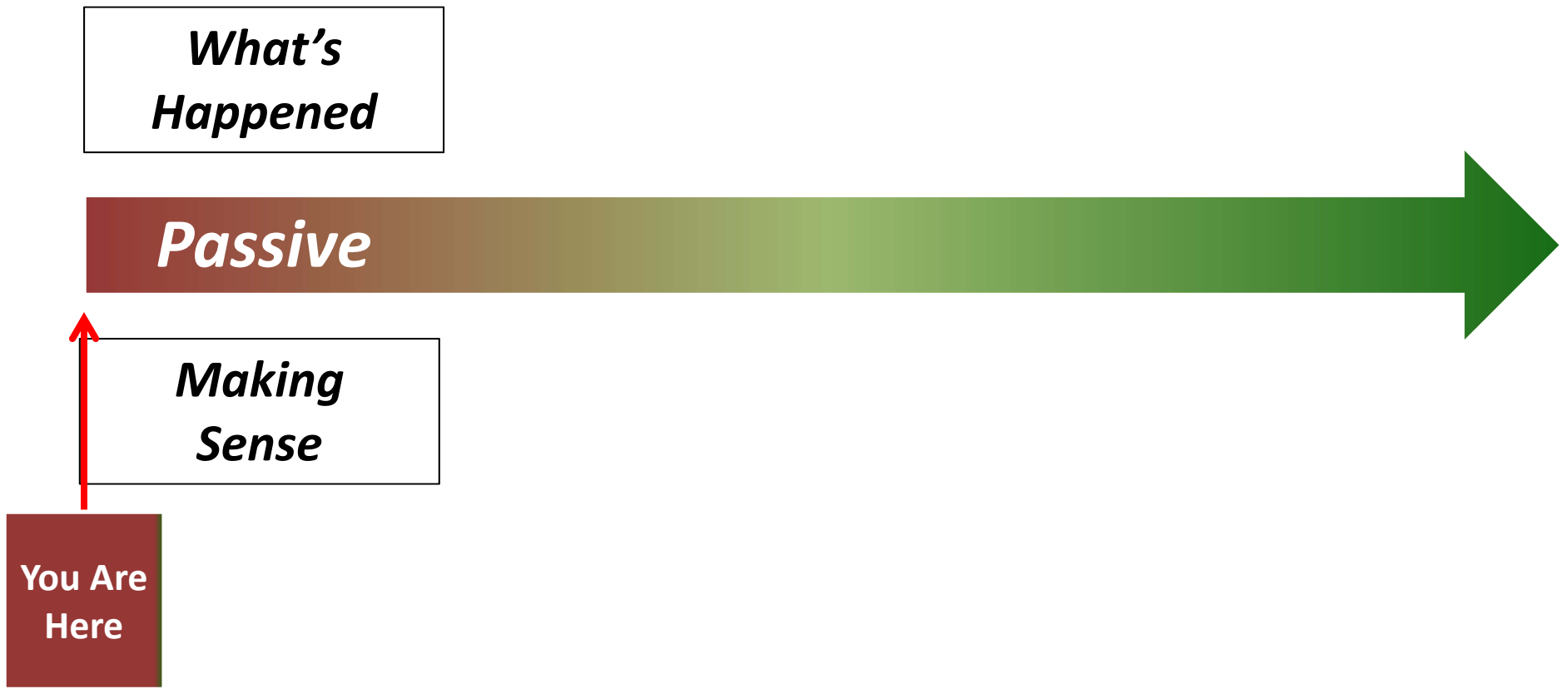


**“Stajfonikstowwędgiehd.”**

# Goal

To quantify the TRUTH about the  
benefit-risk relationship for a  
treatment as soon as possible in the  
drug development or  
commercialization process

# The Journey



# Safety Assessment

Evaluate adverse events ‘in the real world’

Events not seen in clinical trials

Unexpected frequency

Unexpected severity

# Many Issues

- Gross under-reporting (numerator)
- What's the denominator?
- Missing data in the report
  - How much drug has been taken? How long?
  - What are concomitant treatments?
- Significant lag in knowledge/understanding

# Safety Surveillance Operations

- Global PhRMA R&D spending  $\cong$  \$50B<sup>1</sup>
  - 6-8% of a company's R&D spend is on pharmacovigilance<sup>2</sup>
- ⇒ Billions spent on pharmacovigilance

<sup>1</sup> PhRMA Annual Report (2012)  
<sup>2</sup> Life Science Leader

**“Unfortunately, many health professionals do not think to report adverse events that might be associated with medications or devices to the Food and Drug Administration (FDA) or to the manufacturer. That needs to change...”**

**Introducing MEDWatch:  
A New Approach to Reporting Medication and Device  
Adverse Effects and Product Problems**

David A. Kessler, MD, for the Working Group

JAMA, June 2, 1993 Vol 269, No. 21





# MEDWATCH Form

## The FDA Safety Information and Adverse Event Reporting Program

### High-level Process

- Fill out the form
- Fax it to a Sponsor
- Sponsor does follow-up
- Reporting to FDA
- Summaries/analysis by Sponsor and FDA

U.S. Department of Health and Human Services

**MEDWATCH**

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events, product problems and product use errors

Form Approved: OMB No. 0910-0291, Expires: 10/31/08  
See OMB statement on reverse.

Page \_\_\_ of \_\_\_

**FDA USE ONLY**

Triage unit sequence # \_\_\_\_\_

| A. PATIENT INFORMATION  |  |  |                                      |
|---|--|--|--------------------------------------|
| 1. Patient Identifier   | 2. Age at Time of Event, or Date of Birth: | 3. Sex<br><input type="checkbox"/> Female<br><input type="checkbox"/> Male                         | 4. Weight<br>_____ lb<br>or _____ kg |
| In confidence   |  |  |                                      |
| B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR  |  |  |                                      |
| Check all that apply:   |  |  |                                      |
| 1. <input type="checkbox"/> Adverse Event <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)<br><input type="checkbox"/> Product Use Error <input type="checkbox"/> Problem with Different Manufacturer of Same Medicine |  |  |                                      |
| 2. Outcomes Attributed to Adverse Event (Check all that apply)  |  |  |                                      |
| <input type="checkbox"/> Death: _____ (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage  |  |  |                                      |
| <input type="checkbox"/> Life-threatening <input type="checkbox"/> Congenital Anomaly/Birth Defect  |  |  |                                      |
| <input type="checkbox"/> Hospitalization - initial or prolonged <input type="checkbox"/> Other Serious (Important Medical Events)   |  |  |                                      |
| <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)   |  |  |                                      |
| 3. Date of Event (mm/dd/yyyy)   |  | 4. Date of this Report (mm/dd/yyyy)  |                                      |
| 5. Describe Event, Problem or Product Use Error   |  |  |                                      |
|   |  |  |                                      |
| D. SUSPECT PRODUCT(S)   |  |  |                                      |
| 1. Name, Strength, Manufacturer (from product label)  |  |  |                                      |
| #1 _____  |  |  |                                      |
| #2 _____  |  |  |                                      |
| 2. Dose or Amount   |  | Frequency  | Route                                |
| #1 _____  |  | _____  | _____                                |
| #2 _____  |  | _____  | _____                                |
| 3. Dates of Use (if unknown, give duration) from to (or best estimate)  |  | 5. Event Abated After Use Stopped or Dose Reduced?   |                                      |
| #1 _____  |  | #1 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply |                                      |
| #2 _____  |  | #2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply |                                      |
| 4. Diagnosis or Reason for Use (Indication)   |  | 8. Event Reappeared After Reintroduction?  |                                      |
| #1 _____  |  | #1 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply |                                      |
| #2 _____  |  | #2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply |                                      |
| 6. Lot #  | 7. Expiration Date                         | 9. NDC # or Unique ID  |                                      |
| #1 _____  | #1 _____                                   |  |                                      |
| #2 _____  | #2 _____                                   |  |                                      |
| E. SUSPECT MEDICAL DEVICE   |  |  |                                      |
| 1. Brand Name   |  |  |                                      |
| 2. Common Device Name   |  |  |                                      |
| 3. Manufacturer Name, City and State  |  |  |                                      |
| 4. Model #  | Lot #                                      | 5. Operator of Device  |                                      |
| _____   | _____                                      | <input type="checkbox"/> Health Professional   |                                      |
| Catalog #   | Expiration Date (mm/dd/yyyy)               | <input type="checkbox"/> Lay User/Patient  |                                      |
| _____   | _____                                      | <input type="checkbox"/> Other:  |                                      |
| Serial #  | Other #                                    |  |                                      |
| _____   | _____                                      |  |                                      |
| 6. If Implanted, Give Date (mm/dd/yyyy)   |  | 7. If Explanted, Give Date (mm/dd/yyyy)  |                                      |
| _____   |  | _____  |                                      |
| 8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?<br><input type="checkbox"/> Yes <input type="checkbox"/> No  |  |  |                                      |
| 9. If Yes to Item No. 8, Enter Name and Address of Reprocessor  |  |  |                                      |
|   |  |  |                                      |
| F. OTHER (CONCOMITANT) MEDICAL PRODUCTS   |  |  |                                      |
| Product names and therapy dates (exclude treatment of event)  |  |  |                                      |
|   |  |  |                                      |
| G. REPORTER (See confidentiality section on back)   |  |  |                                      |
| 1. Name and Address   |  |  |                                      |
|   |  |  |                                      |
| Phone #   |  | E-mail   |                                      |
| _____   |  | _____  |                                      |
| 2. Health Professional?<br><input type="checkbox"/> Yes <input type="checkbox"/> No   | 3. Occupation                              | 4. Also Reported to:   |                                      |
| _____   | _____                                      | <input type="checkbox"/> Manufacturer  |                                      |
| 5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: <input type="checkbox"/>   |  | <input type="checkbox"/> User Facility   |                                      |
|   |  | <input type="checkbox"/> Distributor/Importer  |                                      |

PLEASE TYPE OR USE BLACK INK

FORM FDA 3500 (10/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

# The Journey



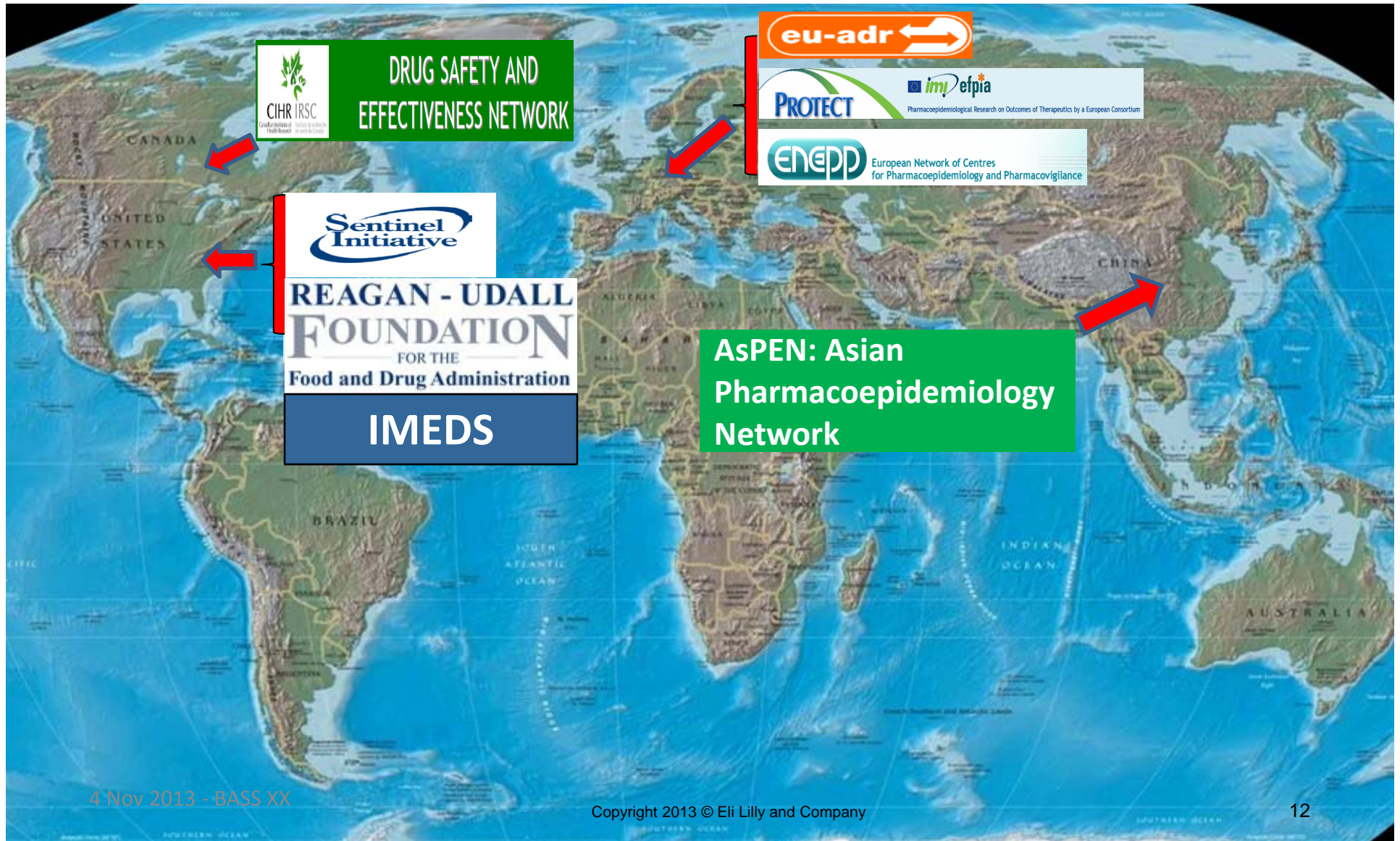
# FDA Amendments Act (2007)

## Section 905

- **Active** Postmarket Risk Identification and Analysis
- Other regulatory agencies around the world pursue similar initiatives

# Observational Study Initiatives

(Signal Detection / Evaluation)



# Active Surveillance

| Initiative                            | Sentinel/<br>OMOP | EU-ADR | PROTECT | AsPEN | DSEN   |
|---------------------------------------|-------------------|--------|---------|-------|--------|
| Geography                             | US                | EU     | EU      | Asia  | Canada |
| Signal Detection                      | ✓ (~3 years)      | ✓      | ✓       |       |        |
| Active Surveillance                   | ✓                 |        | ✓       |       | ✓      |
| Signal Clarification/<br>Evaluation   | ✓                 |        | ✓       | ✓     | ✓      |
| Comparative<br>Effectiveness          | ?                 |        |         |       | ✓      |
| Effectiveness of Risk<br>Minimization | ✓                 |        |         |       |        |
| Next Steps                            |                   |        |         |       |        |

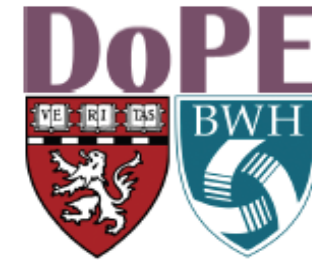
**OMOP** (Observational Medical Outcomes Partnership); **EU-ADR** (system to detect adverse drug reactions ); **PROTECT** (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium); **AsPEN** (Asian Pharmacoepidemiology Network); **DSEN** (Canada Drug Safety and Effectiveness Network)

# Real World Example

Active monitoring of the comparative effectiveness and safety of prasugrel versus clopidogrel in routine care

Joshua J Gagne,<sup>1</sup> Jeremy A Rassen,<sup>1</sup> Nitesh K Choudhry,<sup>1</sup> Rhonda Bohn,<sup>2</sup> Amanda R Patrick,<sup>1</sup> Gayathri Sridhar,<sup>3</sup> Gregory W Daniel,<sup>4</sup> Jun Liu,<sup>1</sup> Sebastian Schneeweiss<sup>1</sup>

1. Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA
2. Rhonda L Bohn, LLC, Waban, MA
3. HealthCore, Inc, Wilmington, DE
4. The Engelberg Center for Health Care Reform, Brookings Institution, Washington, DC

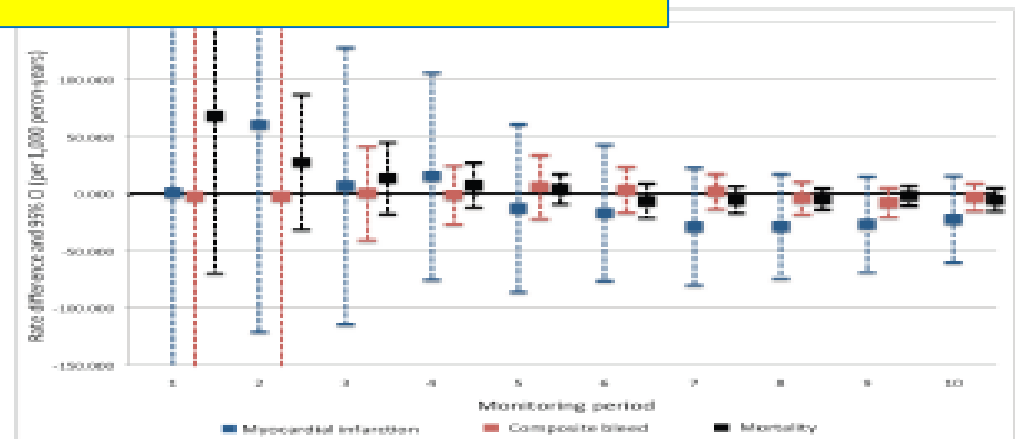


## Patient Centered Outcomes Research Institute

### Objectives

- Since its market in 2009, prasugrel has been prospectively monitored for the comparative effectiveness and safety of prasugrel, versus clopidogrel, in a large electronic data environment that reflects how these drugs are used in practice.
- We present the results of our sequential propensity score-matched incident user cohort analysis based on the first two years of prospective monitoring.

MI, bleed, and death

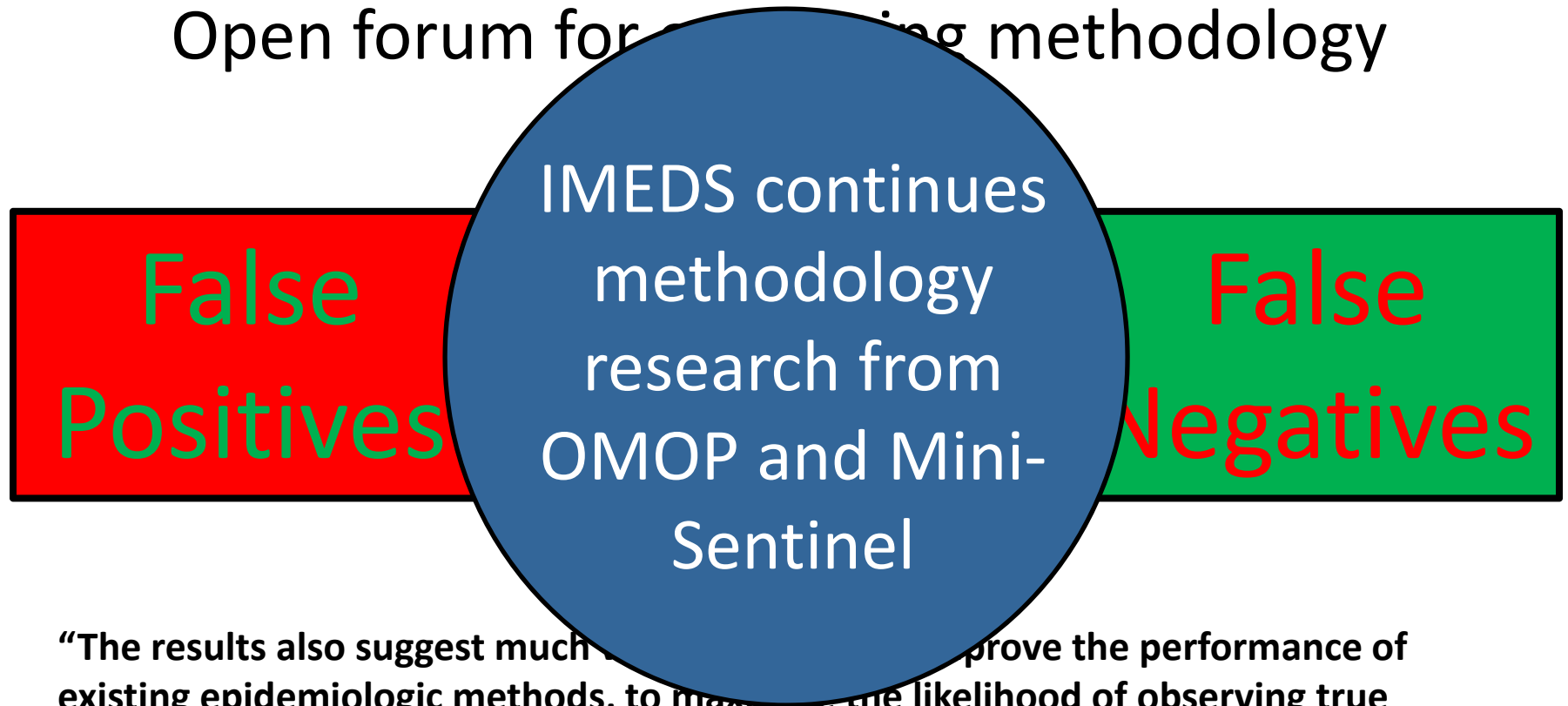


# Data Sources/Aggregators

- Data Reliability
  - How often is the data refreshed?
  - Does the data change or get updated?
  - How is it reviewed / validated?
  - Is what's reported/captured accurate?
- Integration of data/information requires meticulous standardization
- Cost of maintaining infrastructure

# OMOP - Methodology Takeaways

Open forum for discussing methodology



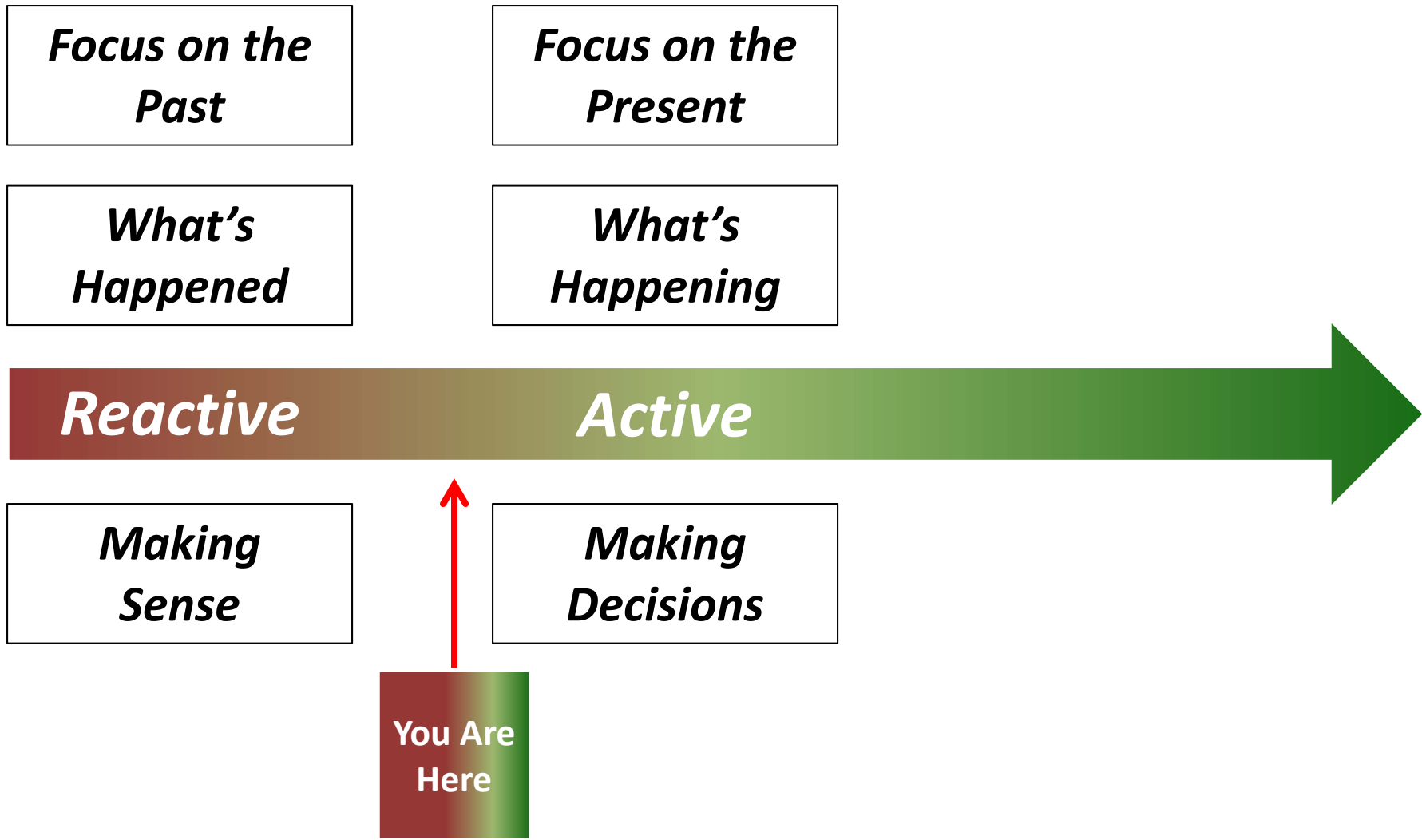
**“The results also suggest much to improve the performance of existing epidemiologic methods, to maximize the likelihood of observing true effects while reducing the risk of false positive findings.”**

**David Madigan & Patrick Ryan**

<http://www.stat.columbia.edu/~madigan/PAPERS/epi.pdf>



# The Journey



# IMAGINE...

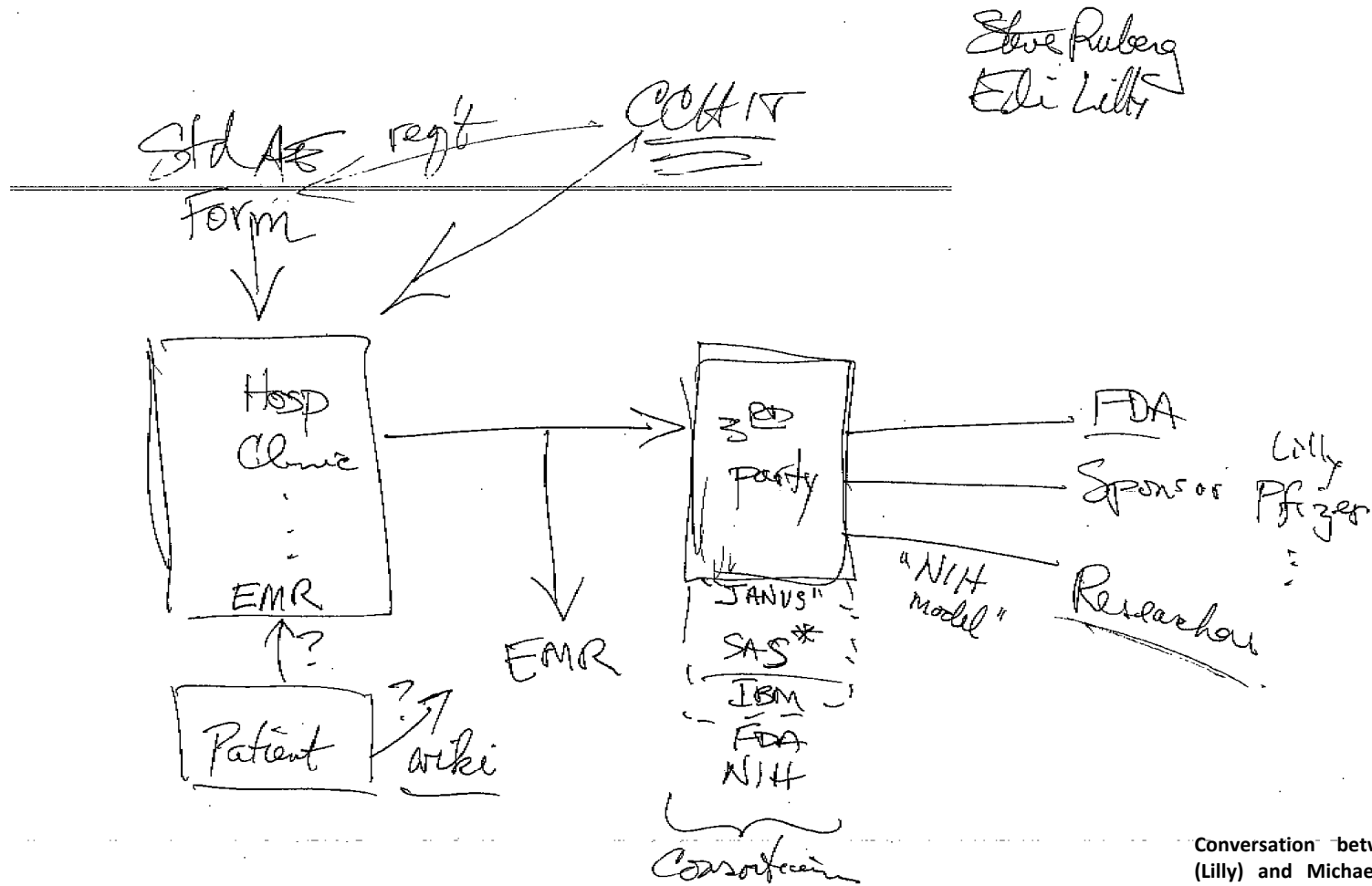
Collecting all drug discontinuations due to AEs...

Interfacing seamlessly with any clinical system using 'triggers' to recognize AEs...

Having as much safety data from source docs as we do claims data...

Having a denominator from each reporting institution...

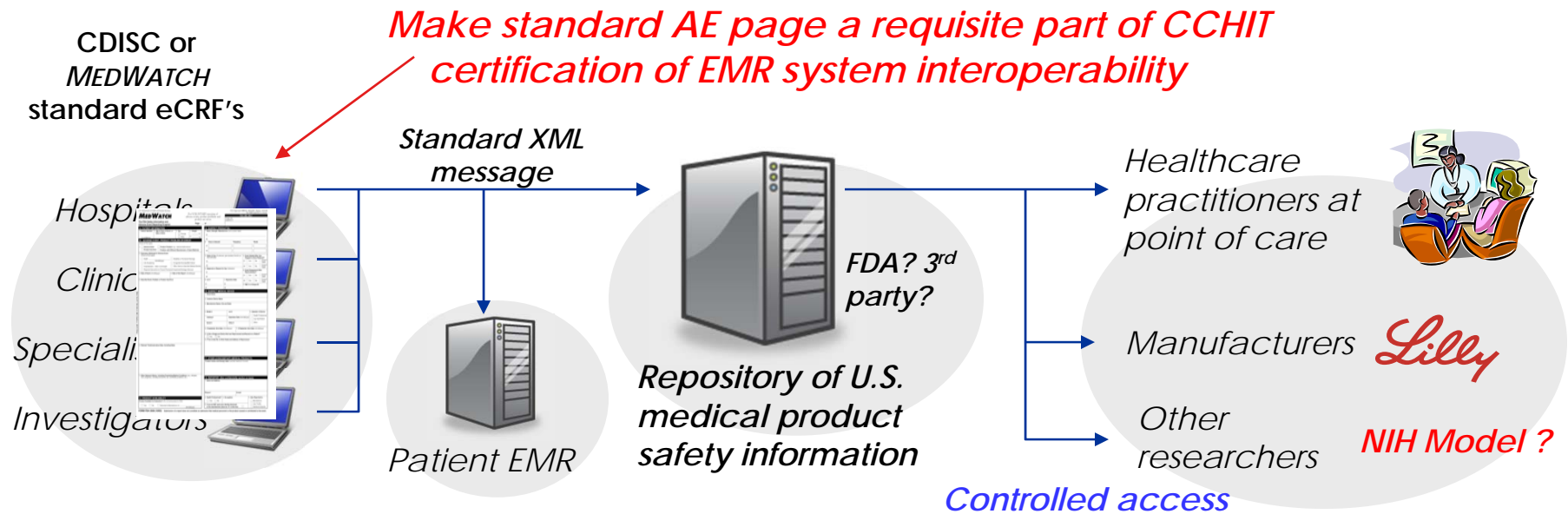
# Vision



Conversation between Steve Ruberg (Lilly) and Michael Ibara (Pfizer) over lunch at HIMSS, Feb 2007 captured on Michael's napkin.

# EMR Automated Reporting/Surveillance

Improves **patient outcomes**, **public trust** in healthcare, and **operational efficiency** for practitioners, FDA, and sponsors



## Advantages

1. CCHIT/ONC could make requirements that provides incentive for EHR companies to accelerate creation of collection and reporting functionality
2. System based on a standard for AE collection
3. Database grows as EHR use expands
4. *Market-driven approach based on private/public partnership*

# ASTER



ADE Spontaneous Triggered Event Reporting



# ASTER



1. Drug discontinued due to an adverse event (AE)
2. System triggers a prepopulated AE form (*MEDWATCH*-like) in LMR\*
3. Physician completes a small amount of additional information
4. Form released
5. Form processed by CRIX International (proper format for FDA)
  - a) ICH) E2B ICSR standard
  - b) Health Level 7 (HL7) ICSR standard
6. FDA receives a 'triggered' report
  - a) Equivalent to a care physician reported spontaneous AE

\*Partners LMR (longitudinal medical record)

# ASTER Results



...Physician interaction (n=30) – “a blink (60 secs)”

91% had never reported an AE – all reported at least 1 AE; Avg = 5 (3 month pilot)

87% said it would improve their ability “a lot”

...time for reviewing instructions - no instructions needed

...searching existing data sources - no searching required

Process averaged less than 1 minute to send in a report

200 reports submitted

20% were deemed serious

...gathering and maintaining the data needed - transparent

...completing and reviewing the information - minimal interaction

100% of reports had demographics and labs

# Eli Lilly and IU Medical Group



## Project **REPORT**

**Reporting Errors and Patient Outcomes Related to Therapy**

January 2008 to September 2010

**Conclusion:** *Optional reporting of the AE* produced a markedly decreased rate of reporting compared to **ASTER**



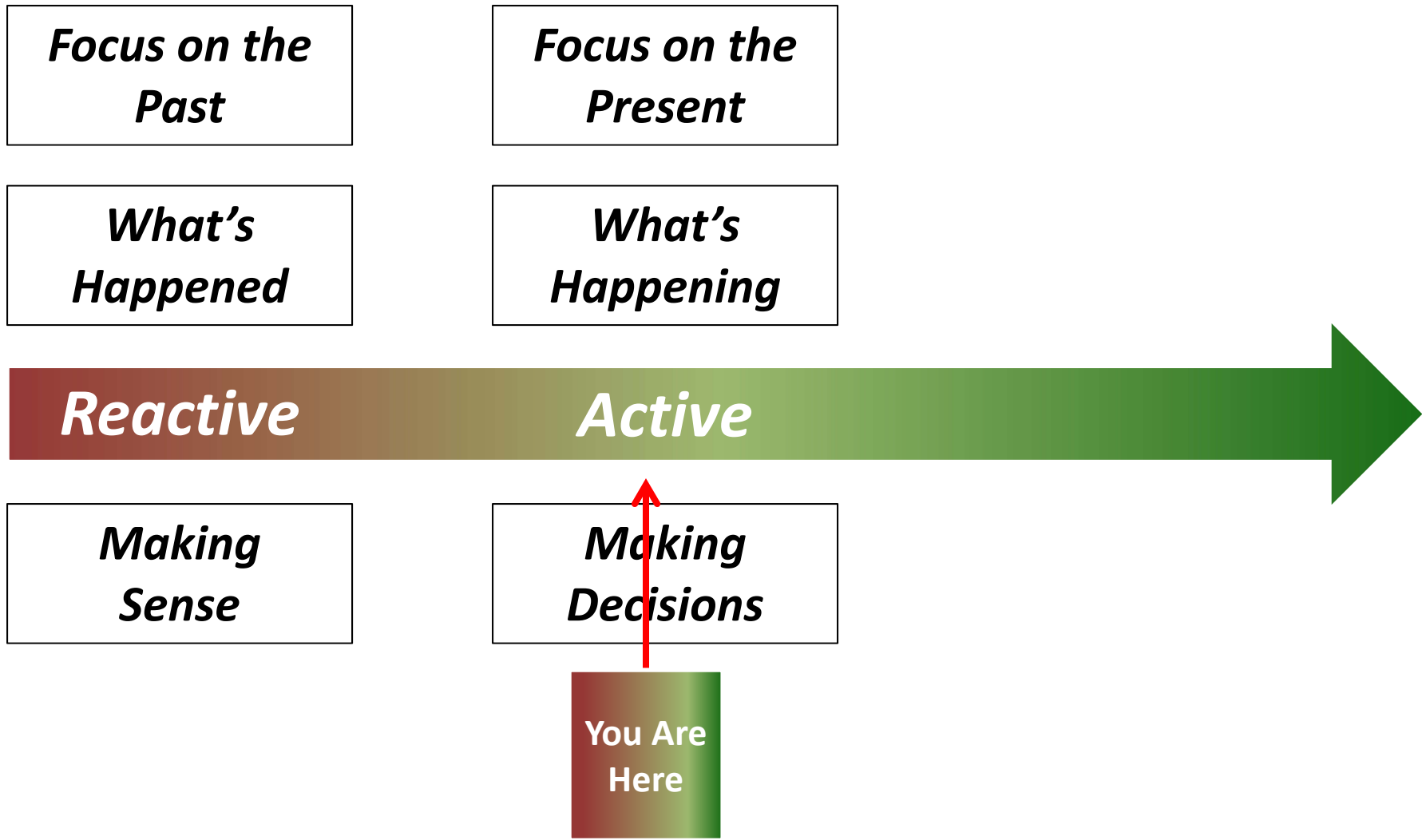
# Standard Content and Messages

“In a networked economy, ever-less energy is needed to complete a single transaction, but ever-more effort is needed to agree on what pattern the transaction should follow.”

***New Rules for the New Economy***

By Kevin Kelly

# The Journey



# July 7, 2005

- London, England
- 8:50 AM local time



# July 7, 2005

- 9:08 AM local time
- Wikipedia – the first story in “print”

“On July 7, 2005, explosions or other incidents were reported at various London Underground stations in central London, specifically Aldgate, Edgware Road, Kings Cross, St Pancras, Old Street and Russell Square. They have been attributed to power surges.”

# July 7, 2005

- 9:00 PM local time
- 2500+ Wikipedia contributors

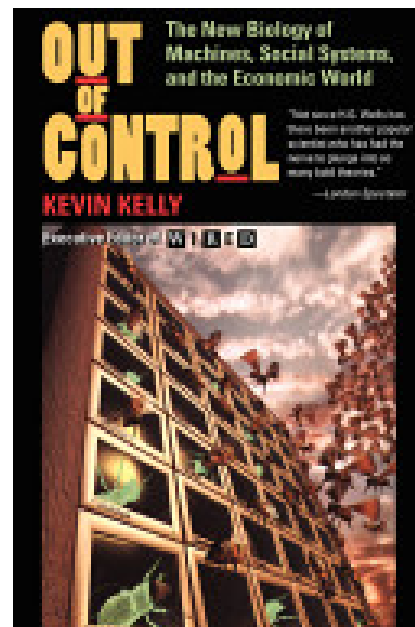
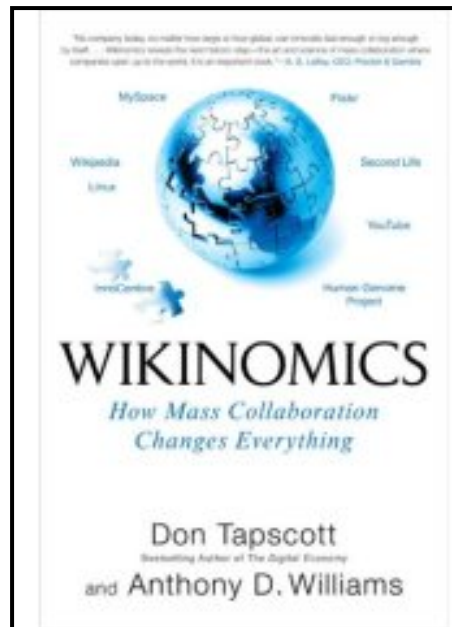
A 14 page report on the incident that was

**More comprehensive**  
**More accurate**

than any single news outlet on the planet

# Mass Collaboration

“Are we prepared to live in a world where quite possibly massive and parallel ‘dumbness’ [can] accomplish more than localized brilliance?”



Kevin Kelly  
Out of Control

# Mass Collaboration

## Principles of open systems/peer production

- ✓ Object of work is information or culture
- ✓ Tasks can be chunked into small pieces
- ✓ Cost of integrating pieces must be low

# The New York Times

November 12, 2008

## Google Uses Searches to Track Flu's Spread

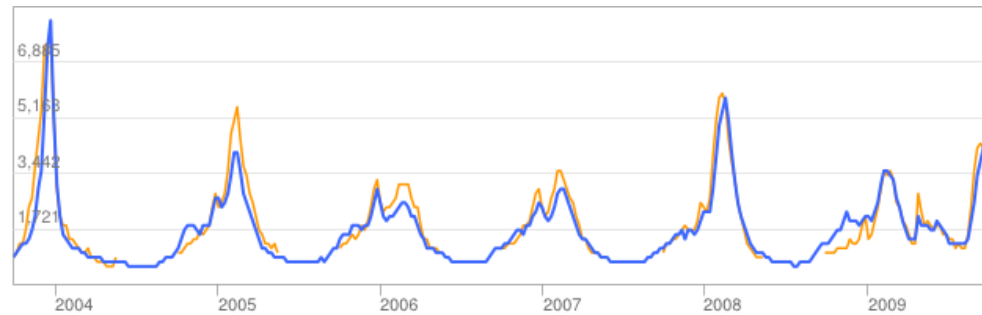
...

"Google Flu Trends appears to be the first public project that uses the powerful database of a search engine to track a disease."

### United States Flu Activity

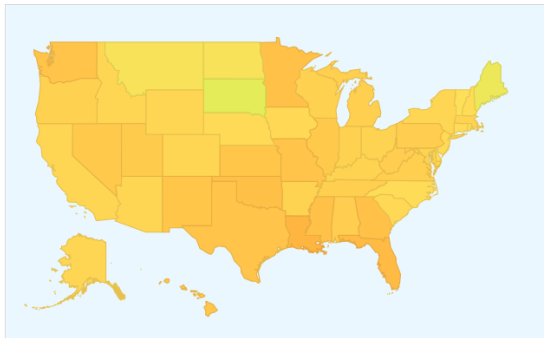
Influenza estimate

Google Flu Trends Estimate  
United States Data



### Flu Incidence - US

States | Cities (Experimental)



Estimates were made using a model that proved accurate when compared to historic official flu activity data. Data current through October 22, 2013.

4 Nov 2013 - BASS XX

### Dengue activity



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## LETTERS

## Detecting influenza epidemics using search query data

Jeremy Ginsberg<sup>1</sup>, Matthew H. Mohebbi<sup>1</sup>, Rajan S. Patil<sup>1</sup>

Seasonal influenza epidemics are a major public health concern, causing tens of millions of respiratory illnesses and 250,000 to 500,000 deaths worldwide each year<sup>1</sup>. In addition to seasonal influenza, a new strain of influenza virus against which no previous immunity exists and that demonstrates human-to-human transmission could result in a pandemic with millions of fatalities. Early detection of disease activity, when followed by a rapid response, can reduce the impact of both seasonal and pandemic influenza<sup>2,3</sup>. One way to improve early detection is to monitor health-seeking behaviour in the form of queries to online search engines, which are submitted by millions of users around the world each day. Here we present a method of analysing large numbers of Google search queries to track influenza-like illness in a population. Because the relative frequency of certain queries is highly correlated with the percentage of physician visits in which a patient presents with influenza-like symptoms, we can accurately estimate the current level of weekly influenza activity in each region of the United States, with a reporting lag of about one day. This approach may make it possible to use search queries to detect influenza epidemics in areas with a large population of web search users.

Traditional surveillance systems, including those used by the US Centers for Disease Control and Prevention (CDC) and the European Influenza Surveillance Scheme (EISS), rely on both virological and clinical data, including influenza-like illness (ILI) physician visits. The CDC publishes national and regional data from these surveillance systems on a weekly basis, typically with a 1–2-week reporting lag.

In an attempt to provide faster detection, innovative surveillance systems have been created to monitor indirect signals of influenza activity, such as call volume to telephone triage advice lines<sup>4</sup> and over-the-counter drug sales<sup>5</sup>. About 90 million American adults are believed to search online for information about specific diseases or medical problems each year<sup>6</sup>, making web search queries a unique and valuable source of information about health trends. Previous attempts at using online activity for influenza surveillance have counted search queries submitted to a Swedish medical website (*J. Hulth, G. Rydevik and A. Linde, manuscript in preparation*), visitor clicks on a US health website<sup>7</sup>, and user clicks on a search keyword advertisement in Canada<sup>8</sup>. A set of Yahoo search queries containing the words 'flu' or 'influenza' were found to correlate with virological and mortality surveillance data over multiple years<sup>9</sup>.

Our proposed system builds on this earlier work by using an automated method of discovering influenza-related search queries. By processing hundreds of billions of individual searches from 5 years of Google web search logs, our system generates more comprehensive models for use in influenza surveillance, with regional and state-level estimates of ILI activity in the United States. Widespread global usage of online search engines may eventually enable models to be developed in international settings.

<sup>1</sup>Google Inc., 1600 Amphitheatre Parkway, Mountain View, California 94043, USA. E-mail: jginsberg@google.com

# nature

## METAL IIRGY

“Because the relative frequency of certain queries is highly correlated with the percentage of physician visits in which a patient presents with influenza-like symptoms, we can accurately estimate the current level of weekly influenza activity in each region of the United States, with a reporting lag of about one day.”

## FUNTIONAL GENOMICS

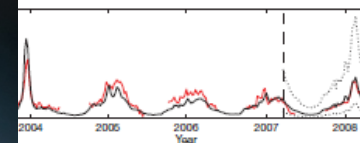
Chemists Join the Action

## POSTDOCS

A Good Career Move?

## ELECTRON DENSITY SURFACE CAPTURED

A Tunable Lightsource for Bio-friendly Nanophonics



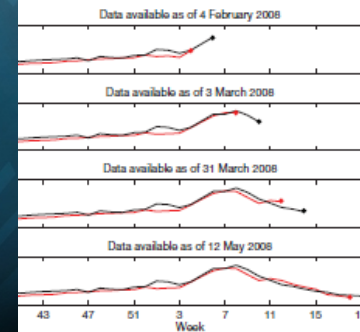
2 | A comparison of model estimates for the mid-Atlantic region against CDC-reported ILI percentages (red), including points over which the model was fit and validated. A correlation of 0.85 was obtained for 8 points from this region to which the model was fit, whereas a correlation of 0.96 was obtained over 42 validation points. Dotted lines show 95% prediction intervals. The region comprises New York, New Jersey and Pennsylvania.

weekly ILI percentages for individual states. The CDC does not make state-level data publicly available, but we validated our model against state-reported ILI percentages provided by the state health departments, and obtained a correlation of 0.90 across 42 validation points (see supplementary Fig. 3).

Single web search queries can be used to estimate ILI percentages in each of the nine public health regions of the United States. Because search queries can be processed quickly, the resulting estimates were consistently 1–2 weeks ahead of CDC ILI surveillance reports. The early detection provided by this approach may provide an important line of defence against future influenza epidemics in the United States, and perhaps eventually in international settings.

Up-to-date influenza estimates may enable public health officials and health professionals to respond better to seasonal epidemics. If a region experiences an early, sharp increase in ILI physician visits, it may be possible to focus additional resources on that region to investigate the aetiology of the outbreak, providing extra vaccine capacity and raising local media awareness as necessary.

This system is not designed to be a replacement for traditional surveillance networks or to supplant the need for laboratory-based diagnosis and surveillance. Notable increases in ILI-related search activity



3 | ILI percentages estimated by our model (black) and provided by CDC (red) in the mid-Atlantic region, showing data available at four points during the 2007–2008 influenza season. During week 5 we detected an increasing ILI percentage in the mid-Atlantic region; similarly, on 3 May our model indicated that the peak ILI percentage had been reached by week 8, with sharp declines in weeks 9 and 10. Both results were later confirmed by CDC ILI data.

# The New York Times

November 12, 2008

## ***Google Uses Searches to Track Flu's Spread***

...

“Researchers have long said that the **material published on the Web amounts to a form of ‘collective intelligence’** that can be used to spot trends and make predictions.”

## ***Google Uses Searches to Track Flu's Spread***

...

“I think we are **just scratching the surface** of what's possible with **collective intelligence.**”

Professor Thomas W. Malone  
MIT Sloan School of  
Management

# The New York Times

March 6, 2013

## Unreported Side Effects of Drugs Are Found Using Internet Search Data

...

“Using data drawn from queries entered into Google, Microsoft and Yahoo search engines, scientists at Microsoft, Stanford and Columbia University have for the first time been able to detect evidence of unreported prescription drug side effects before they were found by the Food and Drug Administration’s warning system.”

## Journal of the American Medical Informatics Association

### Brief communication

## Web-scale pharmacovigilance: listening to signals from the crowd

Ryen W White,<sup>1</sup> Nicholas P Tatonetti,<sup>2</sup> Nigam H Shah,<sup>3</sup> Russ B Altman,<sup>4</sup> Eric Horvitz<sup>1</sup>

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/amiajnl-2012-001482>).

<sup>1</sup>Microsoft Research, Redmond, Washington, USA

<sup>2</sup>Department of Biomedical Informatics, Columbia University, New York, New York, USA

<sup>3</sup>Department of Medicine, Stanford University, Stanford, California, USA

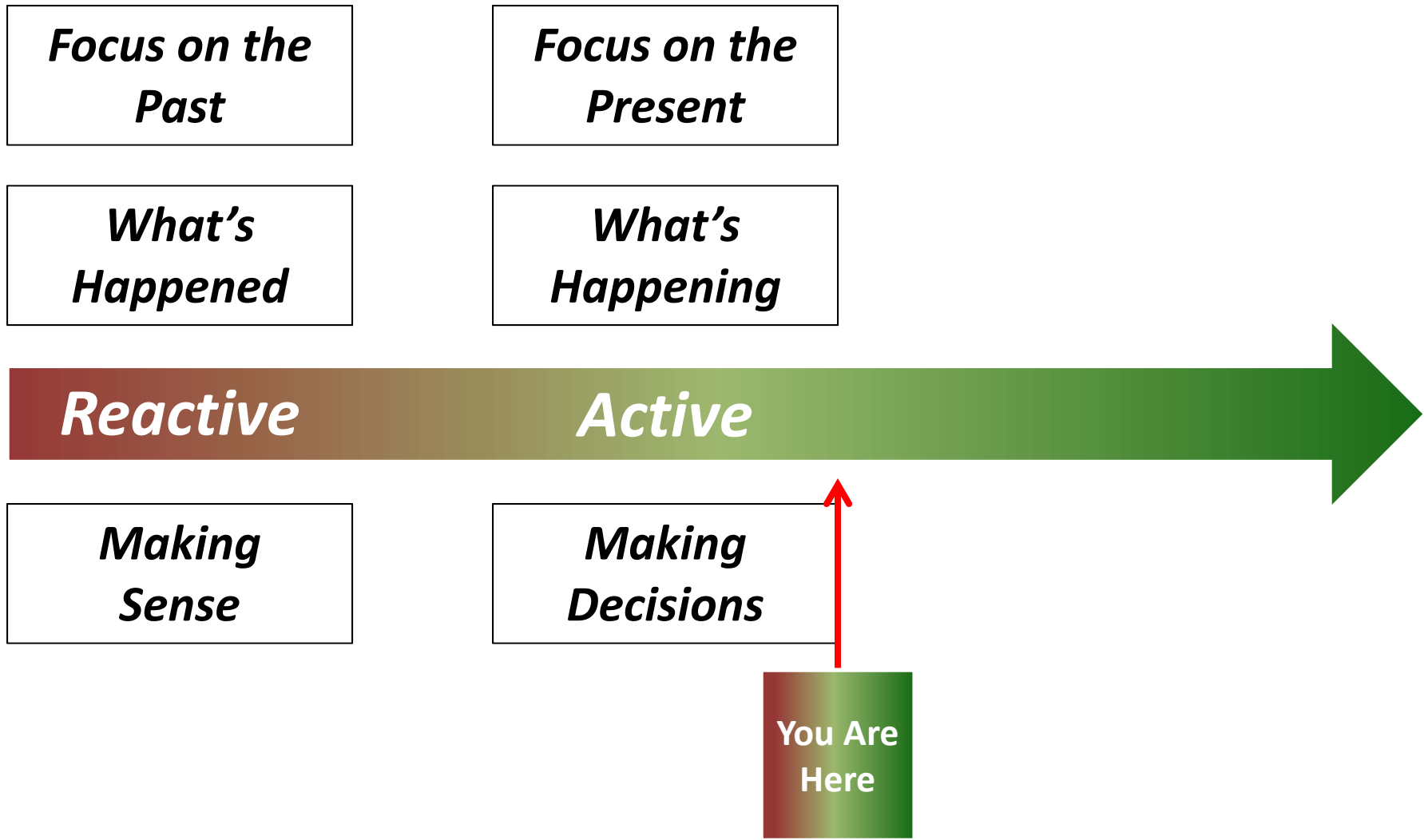
<sup>4</sup>Departments of Bioengineering and Genetics, Stanford University, Stanford,

### ABSTRACT

Adverse drug events cause substantial morbidity and mortality and are often discovered after a drug comes to market. We hypothesized that Internet users may provide early clues about adverse drug events via their online information-seeking. We conducted a large-scale study of Web search log data gathered during 2010. We pay particular attention to the specific drug pairing of paroxetine and pravastatin, whose interaction was reported to cause hyperglycemia *after* the time period of the online logs used in the analysis. We also examine sets of drug pairs known to be associated with hyperglycemia and those not associated with hyperglycemia. We find that anonymized signals on drug

case an interaction between paroxetine (an anti-depressant) and pravastatin (a cholesterol-lowering drug), which was recently reported to create hyperglycemia.<sup>13 14</sup> This association was extracted from the US Food and Drug Administration adverse event reporting system (AERS) using a data-mining algorithm that aggregates reports to identify drug–drug interactions.<sup>13</sup> The finding was confirmed in a retrospective analysis of the electronic health records of three regionally distinct medical institutions and confirmed in a mouse model.<sup>14</sup> We hypothesized that patients taking these two drugs might experience symptoms of hyperglycemia and may have conducted internet searches on these symptoms and concerns

# The Journey



# Imagine Safety

- Adverse events assessments knowing ...
  - When they started
  - How long they lasted
  - Were they intermittent
  - What other medications were being taken
  - What other morbidities were involved
  - Were any counteractive meds needed
  - Was hospitalization required
  - Was it life threatening

# Imagine Healthcare

- We know ...
  - Who took what treatment(s)
  - When they took them
  - What the outcomes were (efficacy and safety)
- The record was ...
  - Complete
  - Up-to-date in ~~near~~ real-time
  - Completely available (within a privacy construct)

# Imagine

Society taking a  
Broad **Health** Perspective

ULTIMATELY

**Optimizing Benefit-Risk**

# Imagine

What would it  
take to get there?



# Imagine

An electronic health record that ...

→ Has *all* your medical information

→ That is portable

→ Is accessible from ..

→ **anywhere, anytime, everywhere, every time.**

→ Updatable from anywhere in real-time

→ That is graphical

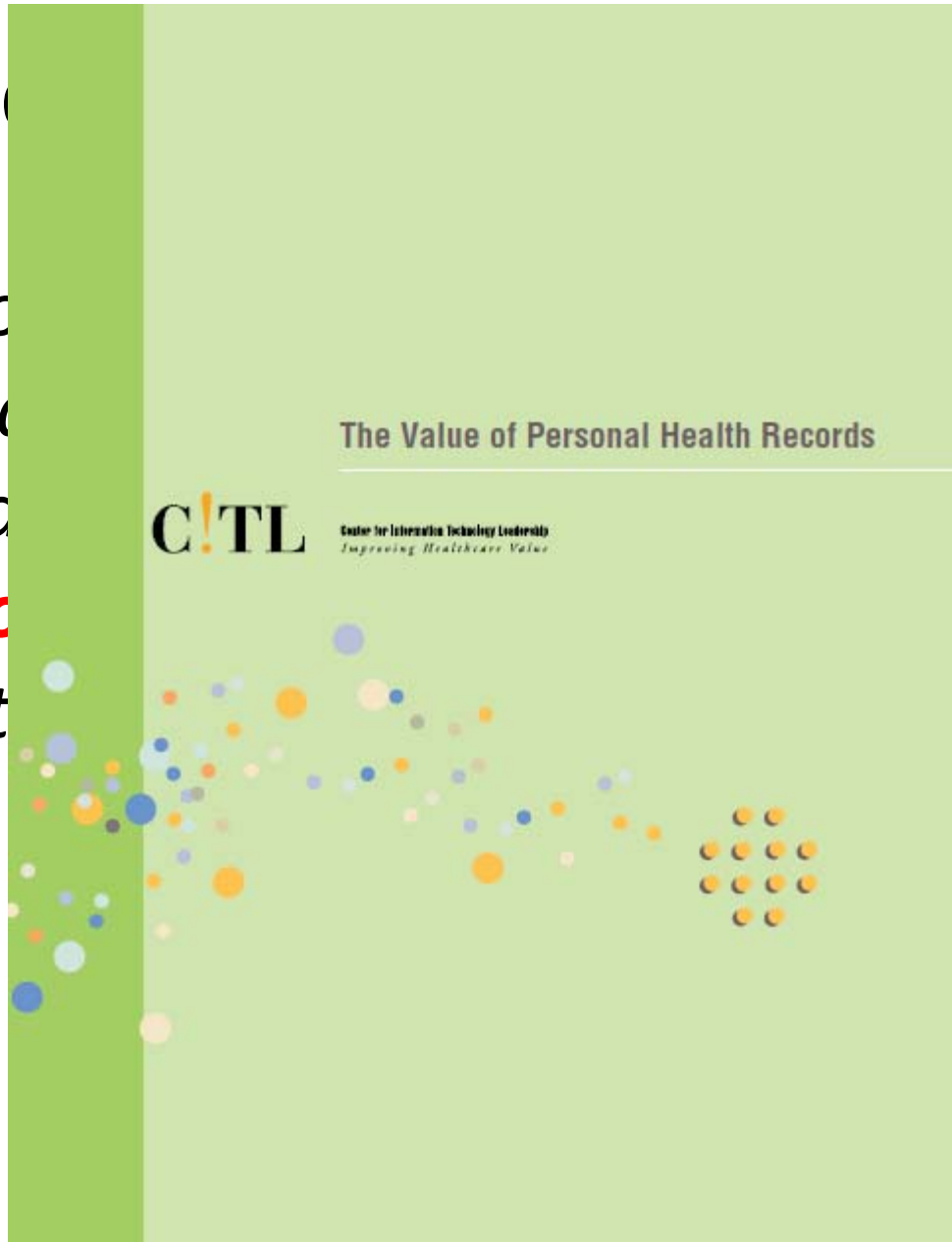
→ That is contextual

P

d

*“The Personal Health Record  
Internet-based  
access and  
**informatics**  
available to*

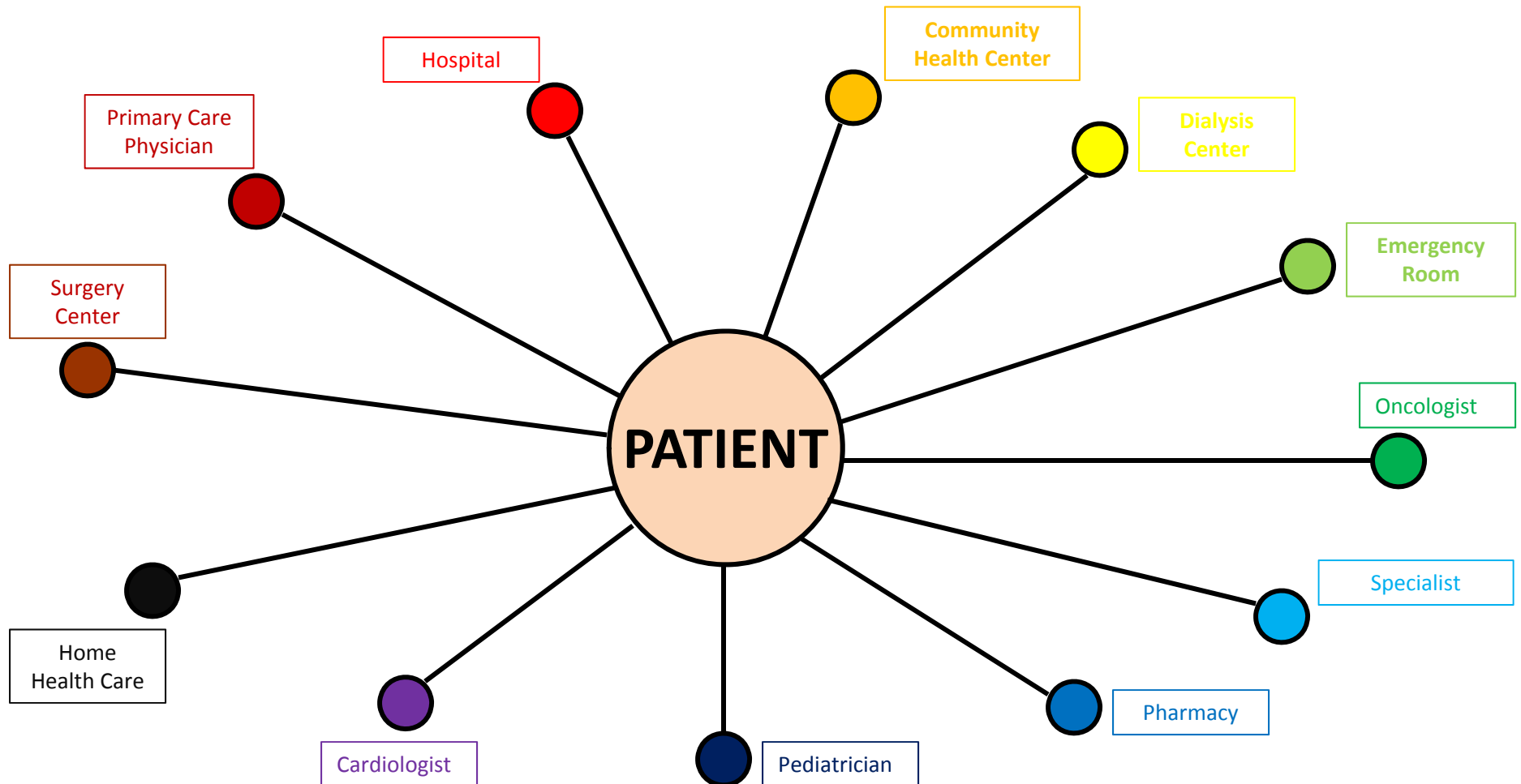
*n  
people to  
**health**  
its of it  
oundation*





# The Patient Perspective

The first sentence of the ONC Strategic Plan states, “Looking toward the future, we can envision a *health care system that is centered on each and every patient*. ... and authorized access to health *data will provide new ways that biomedical research and public health can improve individual health*, and the health of communities and the Nation.”



# The Patient Perspective

**Goal:** Centralize health information around an individual patient/consumer so that there is a complete record accessible anywhere, anytime, everywhere, every time.  
Make it a PHR.

Vendors compete on functionality, cost, reliability, security, etc. but the data is the same (i.e. standard).

HITSP / CCHIT govern standards and certification.

Providers - large hospital systems & small private practices

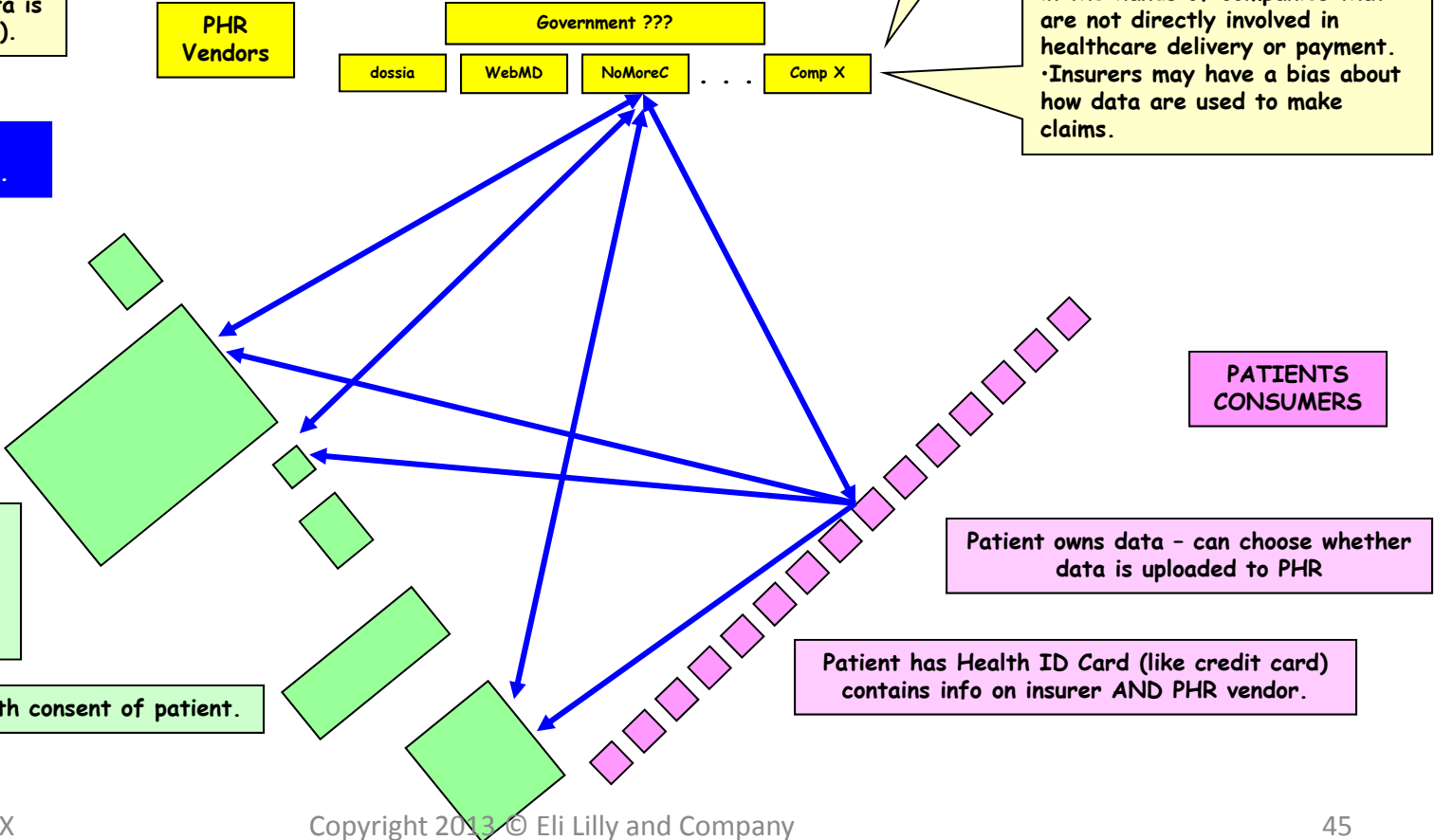
Make EMR systems available to small practices via ASP utility model or in computing cloud - more affordable and doable.

Provider can access PHR with consent of patient.

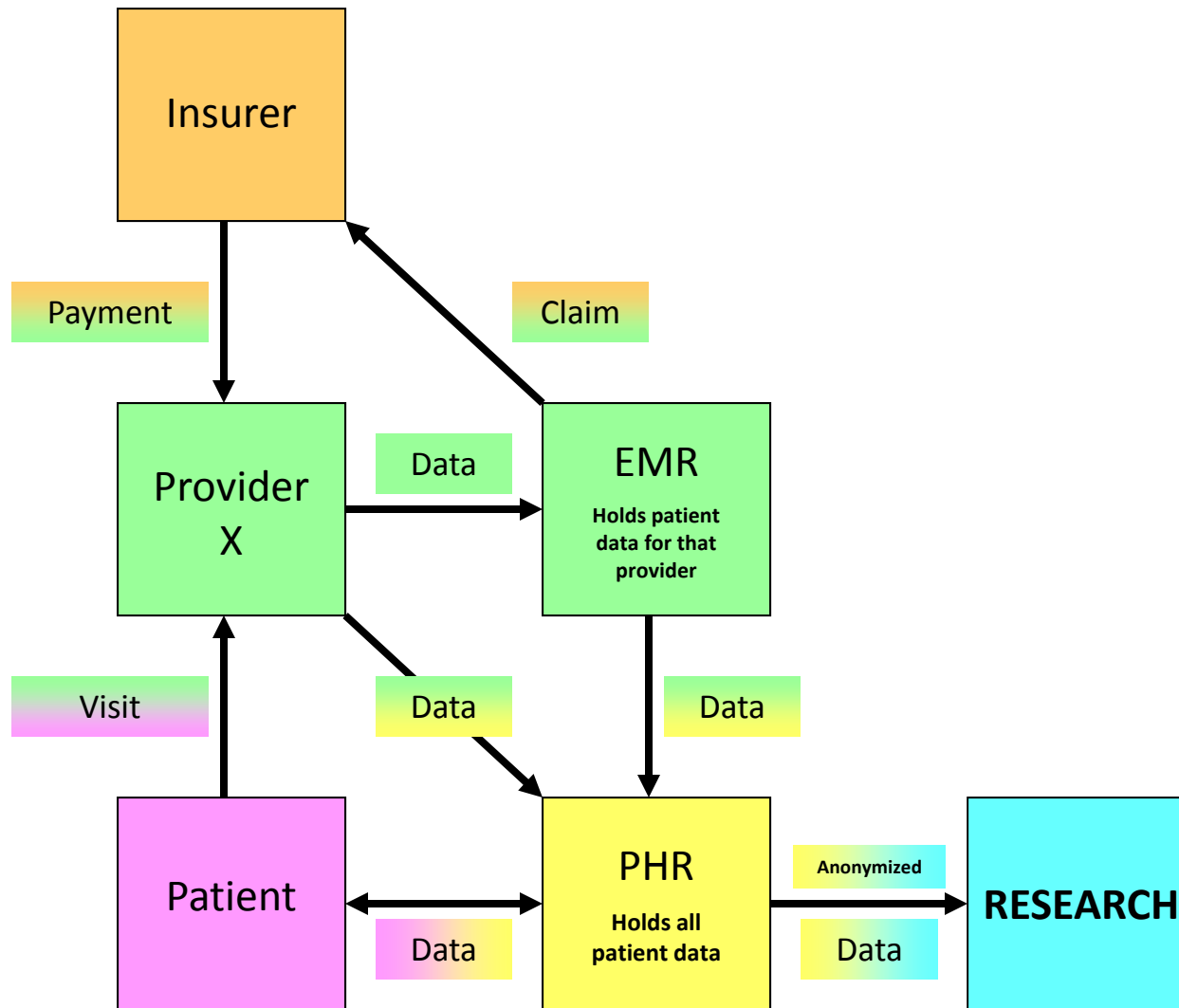
Patients can choose whether their de-identified data can be used for research:  
 • Annual removal / informed consent  
 • Price break from PHR vendor

Note that these are globally accessible.

• Probably not insurers. Put PHRs in the hands of companies that are not directly involved in healthcare delivery or payment.  
 • Insurers may have a bias about how data are used to make claims.



# Another Perspective – Same Model

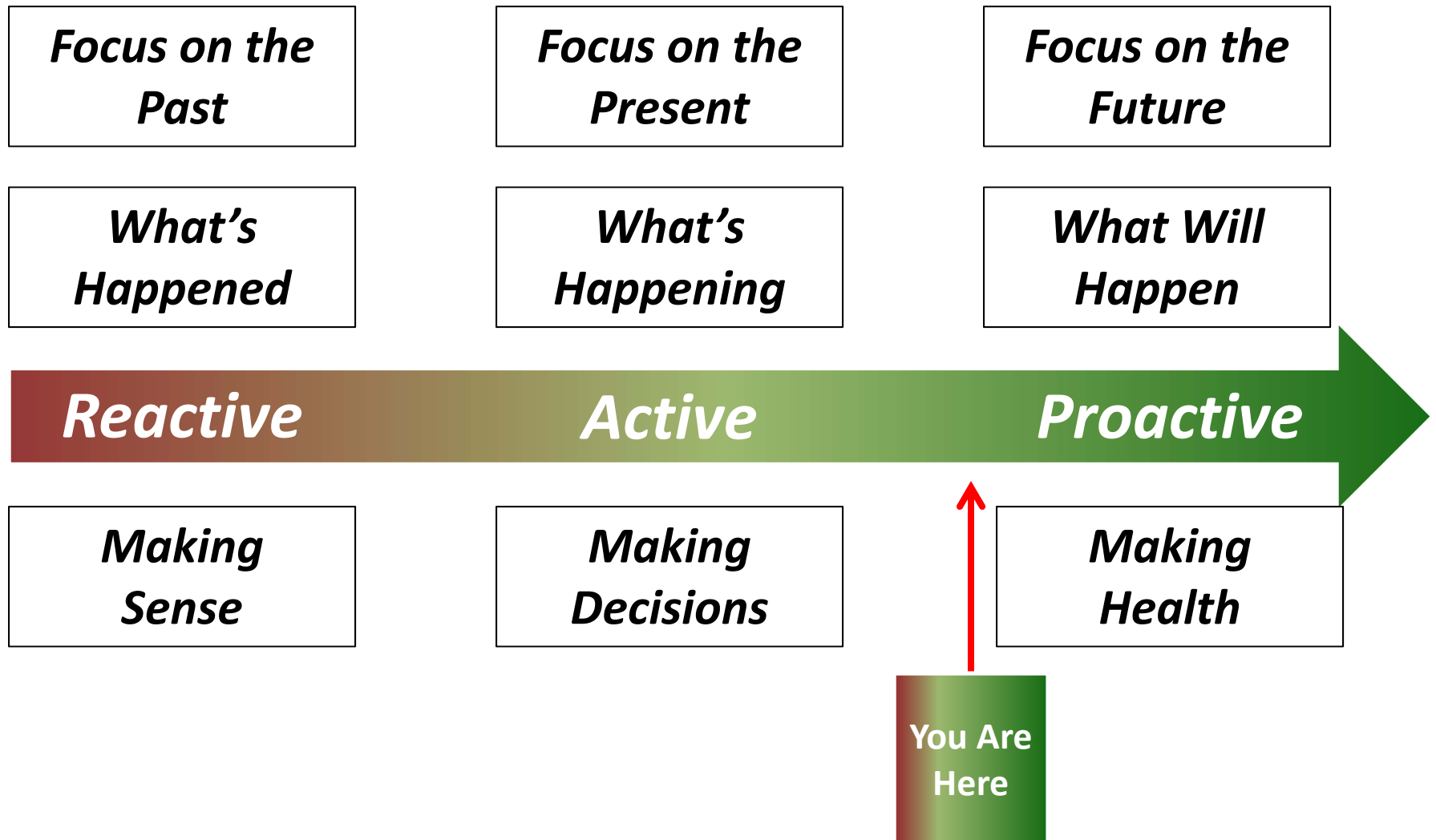


# Personal Health Records

A real chance at comprehensive **benefit-risk** !

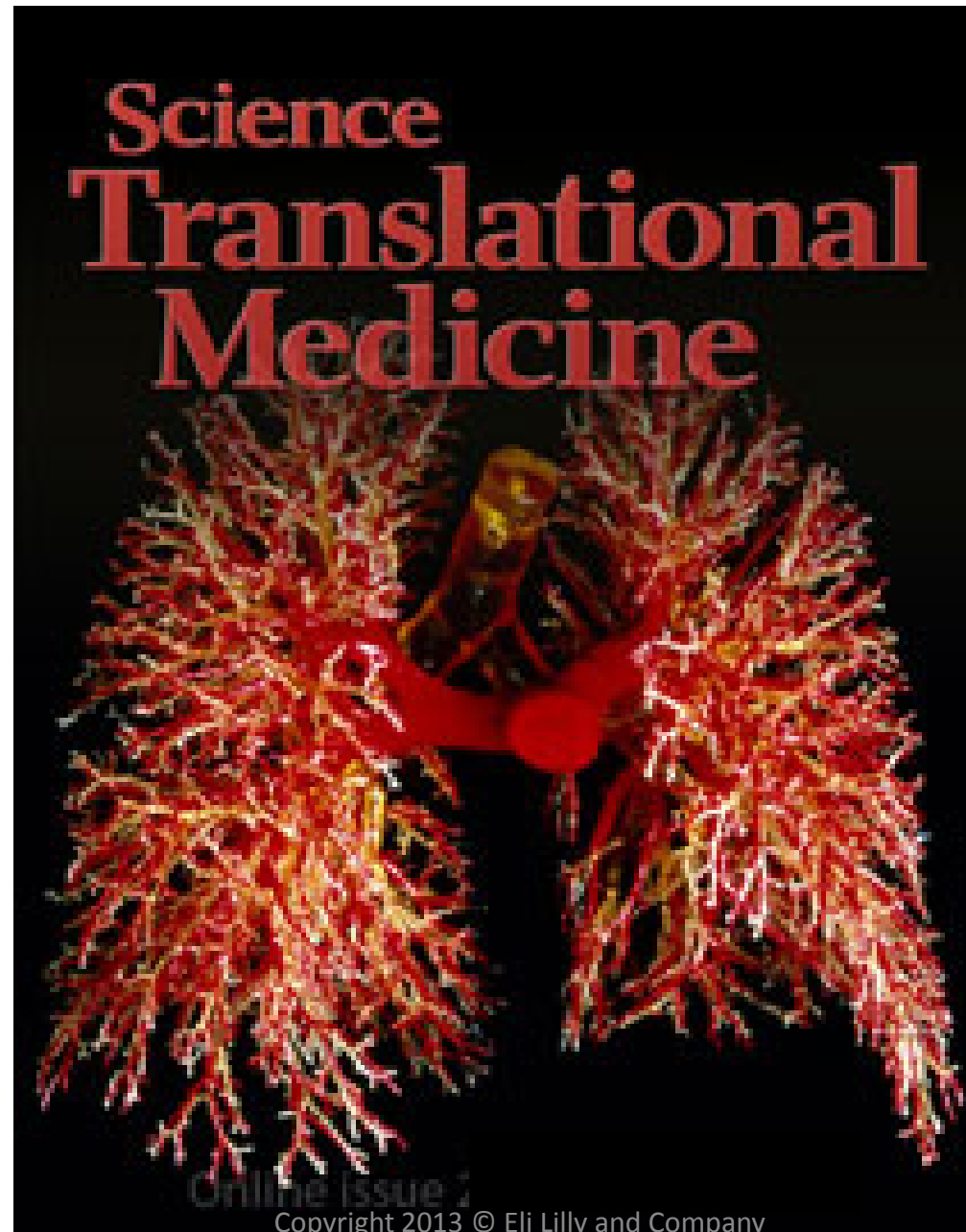
- Can patients report their own outcomes/AEs?
  - Distinguish between patient reported outcomes/AEs and HCP reported outcomes/AEs.
- Reliability of information?
  - National standards
  - Natural language processing
- *No worse than we are today ??*
- *And maybe a lot better ??*

# The Journey





October 9, 2013



4 Nov 2013 - BASS XX

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## Systems Pharmacology of Adverse Event Mitigation by Drug Combinations

Shan Zhao,<sup>1,2\*</sup> Tomohiro Nishimura,<sup>1,3\*</sup> Yibang Chen,<sup>1,2</sup> Evren U. Azeloglu,<sup>1,2</sup> Omri Gottesman,<sup>4,5</sup> Chiara Giannarelli,<sup>5,6</sup> Mohammad U. Zafar,<sup>5,6</sup> Ludovic Benard,<sup>6</sup> Juan J. Badimon,<sup>5,6</sup> Roger J. Hajjar,<sup>4,5,6</sup> Joseph Goldfarb,<sup>1</sup> Ravi Iyengar<sup>1,2†</sup>

Drugs are designed for therapy, but medication-related adverse events are common, and risk/benefit analysis is critical for determining clinical use. Rosiglitazone, an efficacious antidiabetic drug, is associated with increased myocardial infarctions (MIs), thus limiting its usage. Because diabetic patients are often prescribed multiple drugs, we searched for usage of a second drug ("drug B") in the Food and Drug Administration's Adverse Event Reporting System (FAERS) that could mitigate the risk of rosiglitazone ("drug A")-associated MI. In FAERS, rosiglitazone usage is associated with increased occurrence of MI, but its combination with exenatide significantly reduces rosiglitazone-associated MI. Clinical data from the Mount Sinai Data Warehouse support the observations from FAERS. Analysis for confounding factors using logistic regression showed that they were not responsible for the observed effect. Using cell biological networks, we predicted that the mitigating effect of exenatide on rosiglitazone-associated MI could occur through clotting regulation. Data we obtained from the *db/db* mouse model agreed with the network prediction. To determine whether polypharmacology could generally be a basis for adverse event mitigation, we analyzed the FAERS database for other drug combinations wherein drug B reduced serious adverse events reported with drug A usage such as anaphylactic shock and suicidality. This analysis revealed 19,133 combinations that could be further studied. We conclude that this type of crowdsourced approach of using databases like FAERS can help to identify drugs that could potentially be repurposed for mitigation of serious adverse events.

### INTRODUCTION

Drugs have both therapeutic and adverse effects (1). A general goal in pharmacology is to optimize the therapeutic efficacy while reducing the adverse event risks. Traditionally, this is done through medicinal chemistry by altering drug structure (2). Attempts have also been made to reduce adverse events by tailoring the choice of drug or dose to an individual patient's genomic status (3, 4). Neither approach works consistently owing to the complex physiological relationships underlying drug action. Because drug targets are nodes within cellular regulatory networks (5, 6), there may be intrinsic coupling between therapeutic and adverse effects. To separate the two effects, we need to focus on the target and its interactions within the networks underlying the physiological functions associated with the therapeutic and adverse effects. A second drug at another target may mitigate the adverse events of the first drug through network interactions.

Often drug combinations are used to minimize adverse effects—for example, the use of atropines to minimize the muscarinic adverse effects of cholinesterase inhibitors that are used for expedited recovery from nondepolarizing neuromuscular blockers (7). In a case like this, the targets for the protective drugs are predictable on the basis of the mechanisms of adverse effects of the primary agent. We hypothesize

that there may be many such drug pairs where one drug reduces the adverse effects of the other while maintaining efficacy. If we can identify such drug pairs, an analysis of the networks to which the drug targets belong may help us develop strategies to decouple therapeutic and adverse effects. To find such targets, we first identified drug combinations that result in decreased adverse event incidences. Databases such as the Food and Drug Administration's (FDA) Adverse Event Reporting System (FAERS), that link drug usage to adverse events provide a rich, albeit imperfect, and empirical source to find for such drug combinations.

The FAERS database contains millions of records of drug-induced adverse events for both single and combination therapies generated by individual reports from patients, physicians, hospitals, lawyers, and drug companies. FAERS has allowed us to identify unknown drugs and targets associated with long QT syndrome (8). Others have used this database to identify drug combinations that lead to unanticipated adverse events and developed methodologies to effectively mine this database (9). Although there are limitations of the FAERS that preclude definitive conclusions, it is a potentially useful, freely available, large data set maintained by the U.S. government. Hence, we decided to analyze FAERS, not as an end in itself, but to generate polypharmacology hypotheses that can be tested in animal models or prospective clinical trials. Theoretically, we should be able to identify not only adverse but also beneficial drug combinations from FAERS. This allows us to ask the question: Can we use FDA-approved drugs for adverse events reduction? To answer this question, we looked for combinations where "drug B," when taken with "drug A," reduces reports of serious adverse events from patients taking drug A. In short, FAERS analysis can be used as a hypothesis generator for drug combinations that could be tested in animal models or clinical trials.

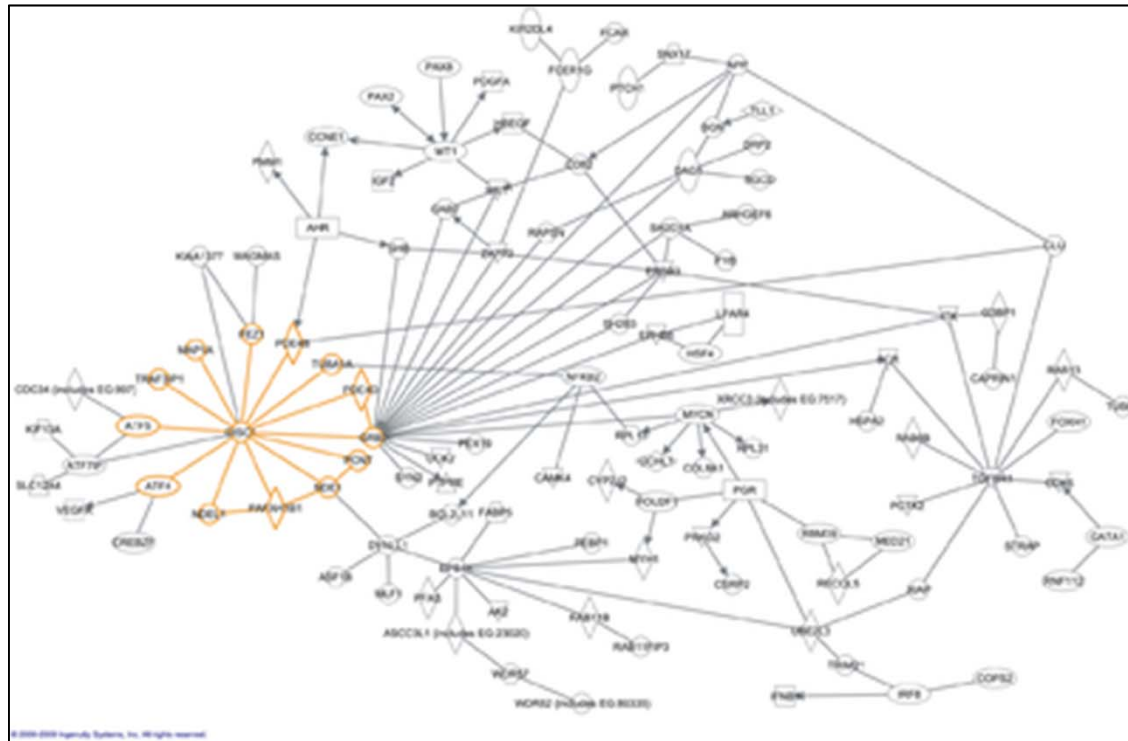
<sup>1</sup>Department of Pharmacology and Systems Therapeutics, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA. <sup>2</sup>Systems Biology Center, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA. <sup>3</sup>Division of Pharmacology, Faculty of Pharmacy, Keio University, Tokyo 105-8512, Japan. <sup>4</sup>Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA. <sup>5</sup>Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA. <sup>6</sup>Cardiovascular Research Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA.

\*These authors contributed equally to this work.  
†Corresponding author. E-mail: raviyengar@msm.edu

"In FAERS, rosiglitazone usage is associated with increased occurrence of MI, but its combination with exenatide significantly reduces rosiglitazone associated MI."

# The Interactome

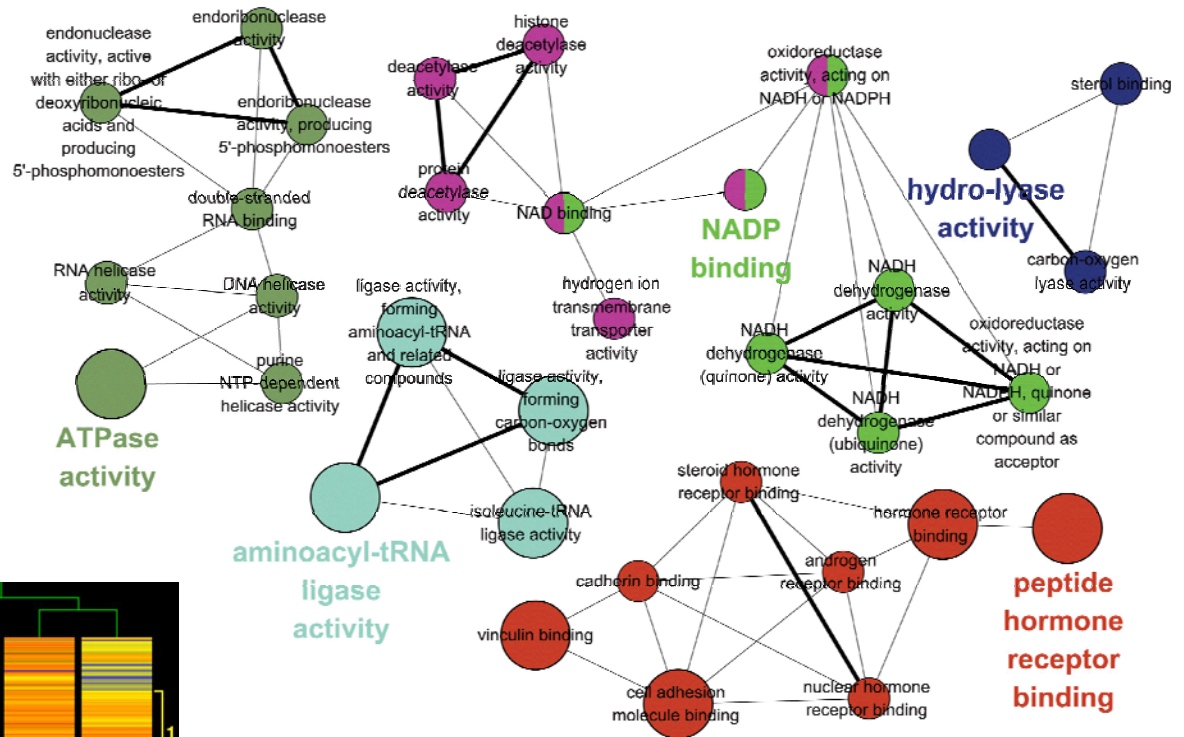
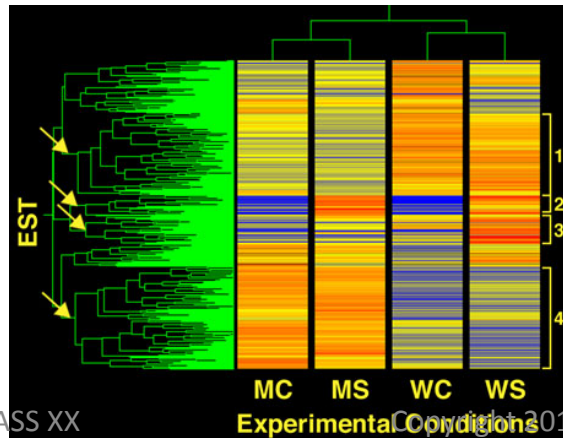
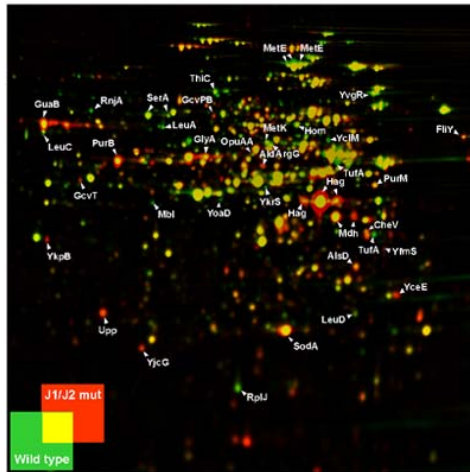
[Protein-protein interactions (PPI) or network (PIN)]



Part of the DISC interactome with genes represented by text in boxes and interactions noted by lines between the genes. From Henna and Porteous, 2009.

# The Transcriptome

The set of all RNA molecules, including mRNA, rRNA, tRNA and other non-coding RNA.



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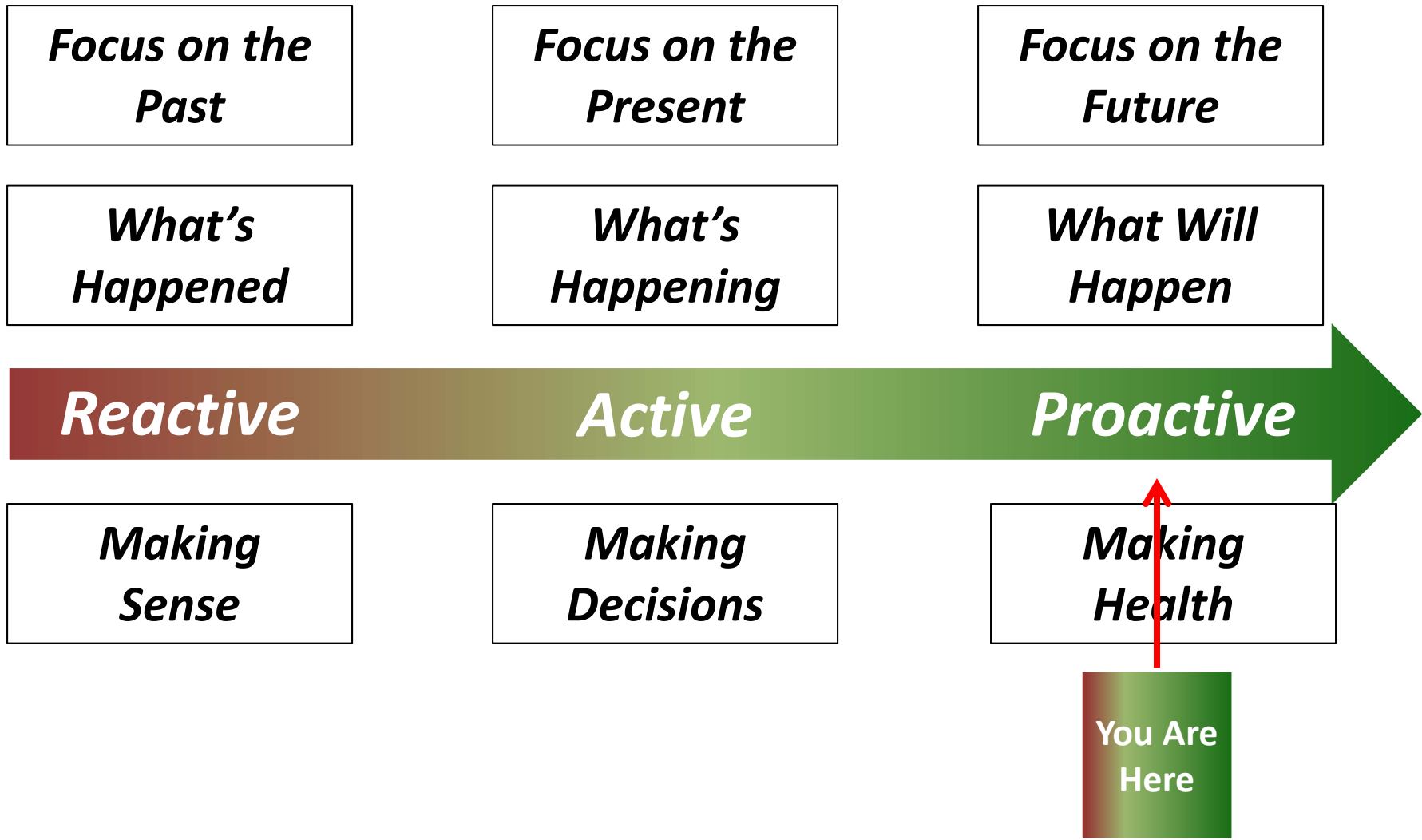
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"Just as it is possible to discover harmful side effects through retrospective examination of FAERS (9), *we show here that we can detect potential beneficial combinations* by analysis of FAERS."

"A *standardized universal electronic medical record system* that contains data from many academic medical centers with systematically recorded clinical phenotypes, *real-time updates*, and *associated molecular and genomic data* would be useful for studies such as this one."

# The Journey



# IMAGINE

**Research data at the point of clinical care.**

**Clinical care data at the point of research.**

# You May Say I'm a Dreamer ...

- I like open innovation on analytics
  - We as statisticians need to do more
- I like mass collaboration
  - “No one is as smart as everyone.”
  - The ‘wisdom of crowds.’
- I really like personal health records.
  - A real chance at real-time benefit-risk.



# The Purpose of This Presentation

“A vision is a compelling image of an achievable future.”

Laura Berman Fortgang

“The danger is not that we aim too high and miss, but that we aim too low and achieve.”

Michelangelo



# Acknowledgement

- Dr. Brenda Crowe
- Dr. Ken Hornbuckle

# THANK YOU

