Post-Marketing Safety Assessments The Journey

Stephen J Ruberg, PhD

Distinguished Research Fellow

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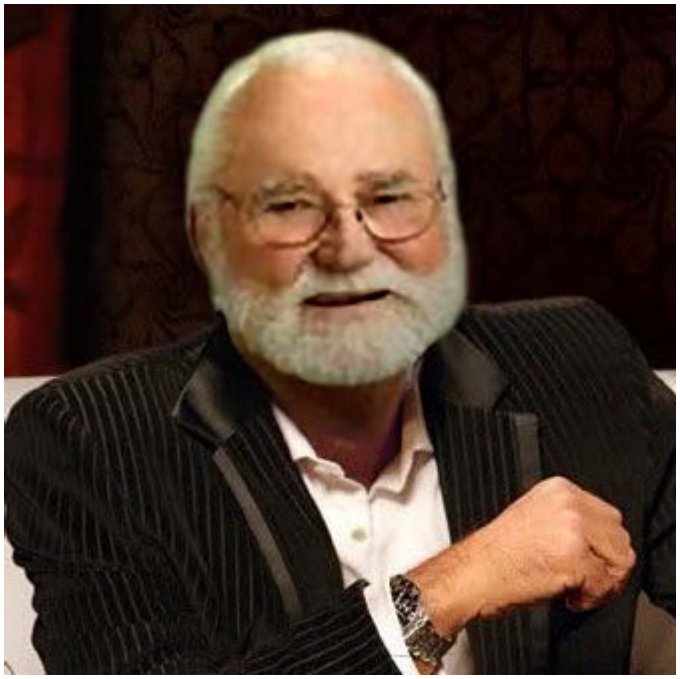
Eli Lilly

Nov 2013



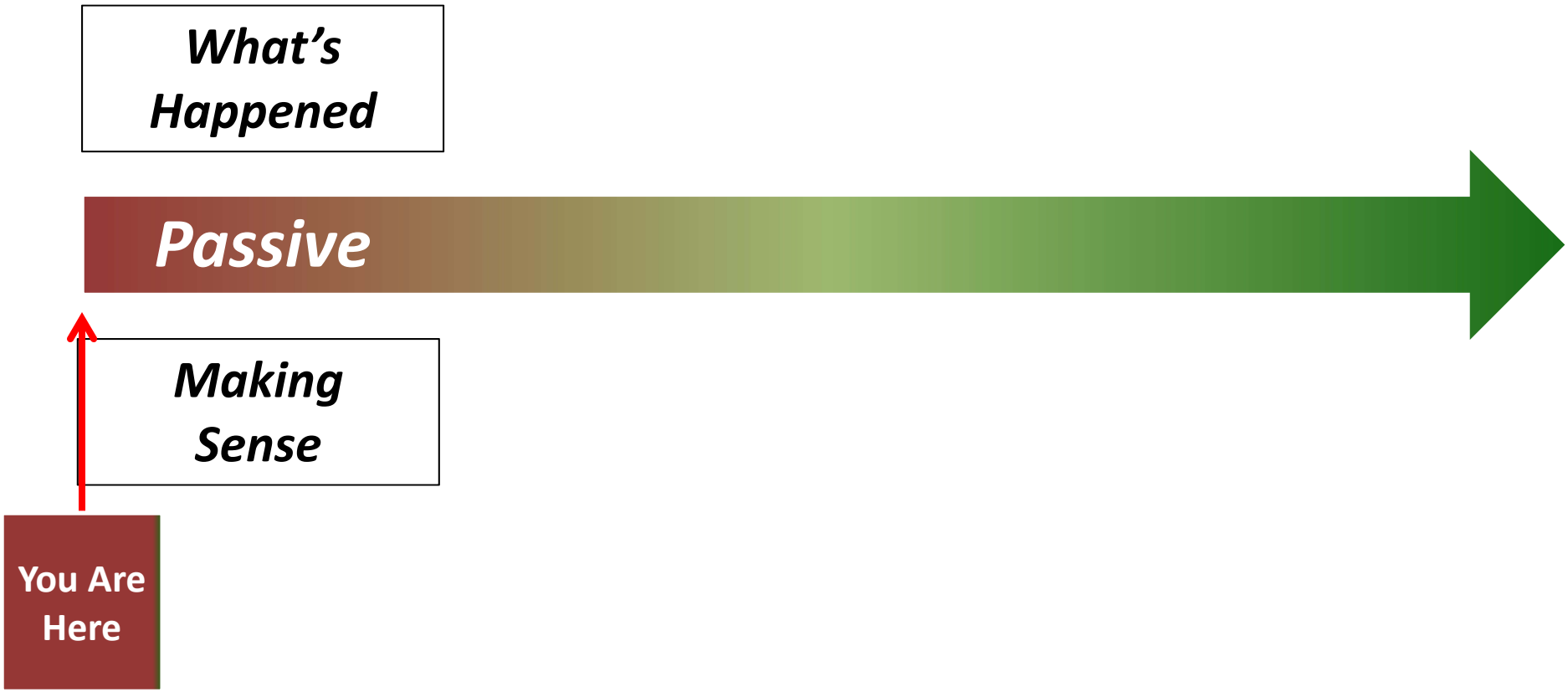
BASS XX

“Stay for the story, [illegible].”

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



Passive

Safety Assessment

Evaluate adverse events ‘in the real world’

Events not seen in clinical trials

Unexpected frequency

Unexpected severity

Passive

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

Passive

Safety Surveillance Operations

- Global PhRMA R&D spending ≅ $50B[1]
- 6-8% of a company's R&D spend is on pharmacovigilance[2]

⇒ Billions spent on pharmacovigilance

[1] **PhRMA Annual Report (2012)**
[2] **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

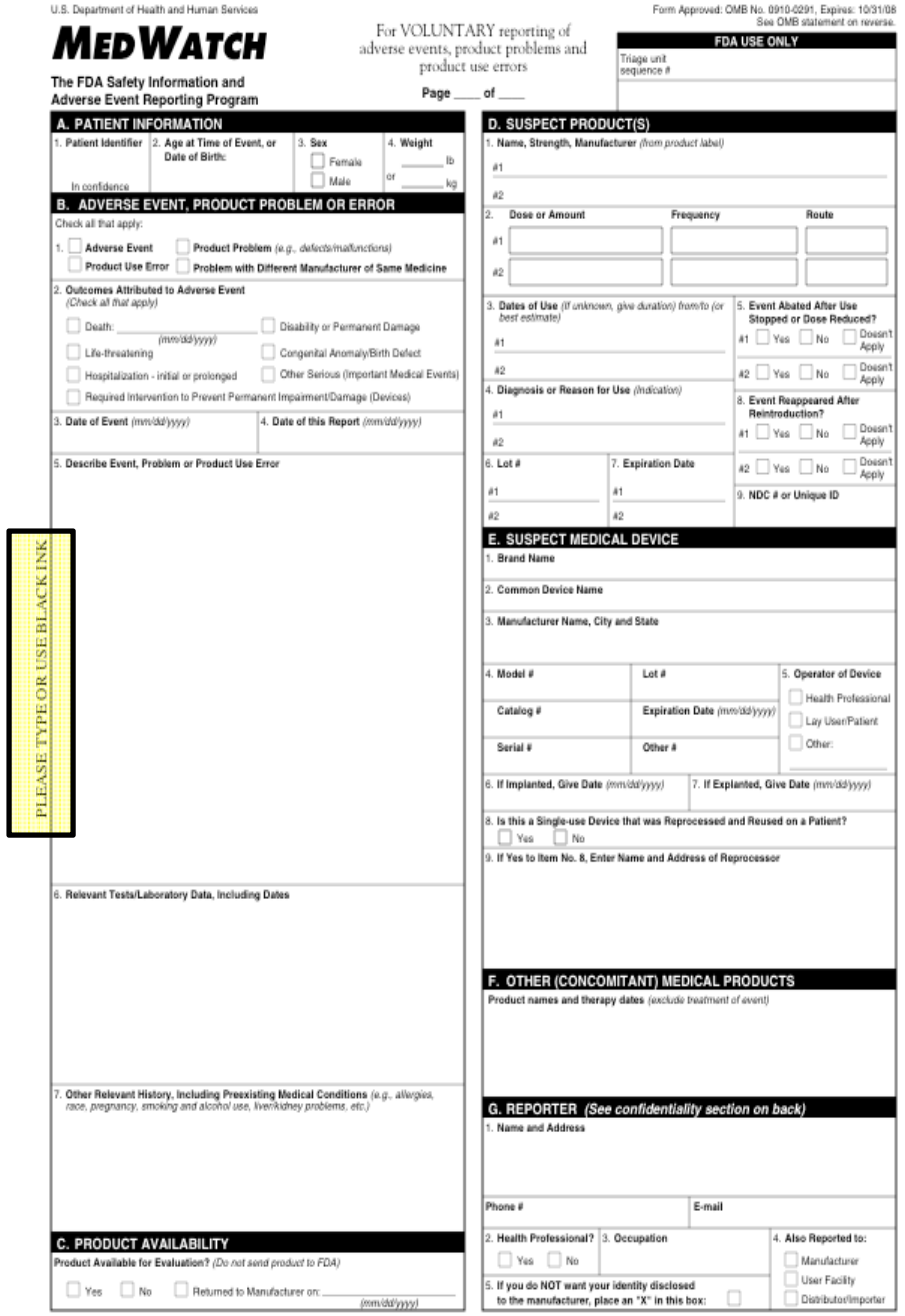
JAMA, June 2, 1993 **Vol 269, No. 21**

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

Page ____ of ____

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

FDA USE ONLY

Triage unit
sequence #

A. PATIENT INFORMATION

1. Patient Identifier — In confidence
2. Age at Time of Event, or Date of Birth:
3. Sex — Female / Male
4. Weight — ____ lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. Adverse Event / Product Problem (e.g., defects/malfunctions) / Product Use Error / Problem with Different Manufacturer of Same Medicine
2. Outcomes Attributed to Adverse Event (Check all that apply)
   - Death: ____ (mm/dd/yyyy)
   - Disability or Permanent Damage
   - Life-threatening
   - Congenital Anomaly/Birth Defect
   - Hospitalization - initial or prolonged
   - Other Serious (Important Medical Events)
   - 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

PLEASE TYPE OR USE BLACK INK

6. Relevant Tests/Laboratory Data, Including Dates
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)

Yes / No / Returned to Manufacturer on: ____ (mm/dd/yyyy)

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)
   #1
   #2
4. Diagnosis or Reason for Use (Indication)
   #1
   #2
5. Event Abated After Use Stopped or Dose Reduced?
   #1 Yes No Doesn't Apply
   #2 Yes No Doesn't Apply
6. Lot #
   #1
   #2
7. Expiration Date
   #1
   #2
8. Event Reappeared After Reintroduction?
   #1 Yes No Doesn't Apply
   #2 Yes No Doesn't Apply
9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State
4. Model # / Lot # / Catalog # / Expiration Date (mm/dd/yyyy) / Serial # / Other #
5. Operator of Device — Health Professional / Lay User/Patient / 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? Yes / 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

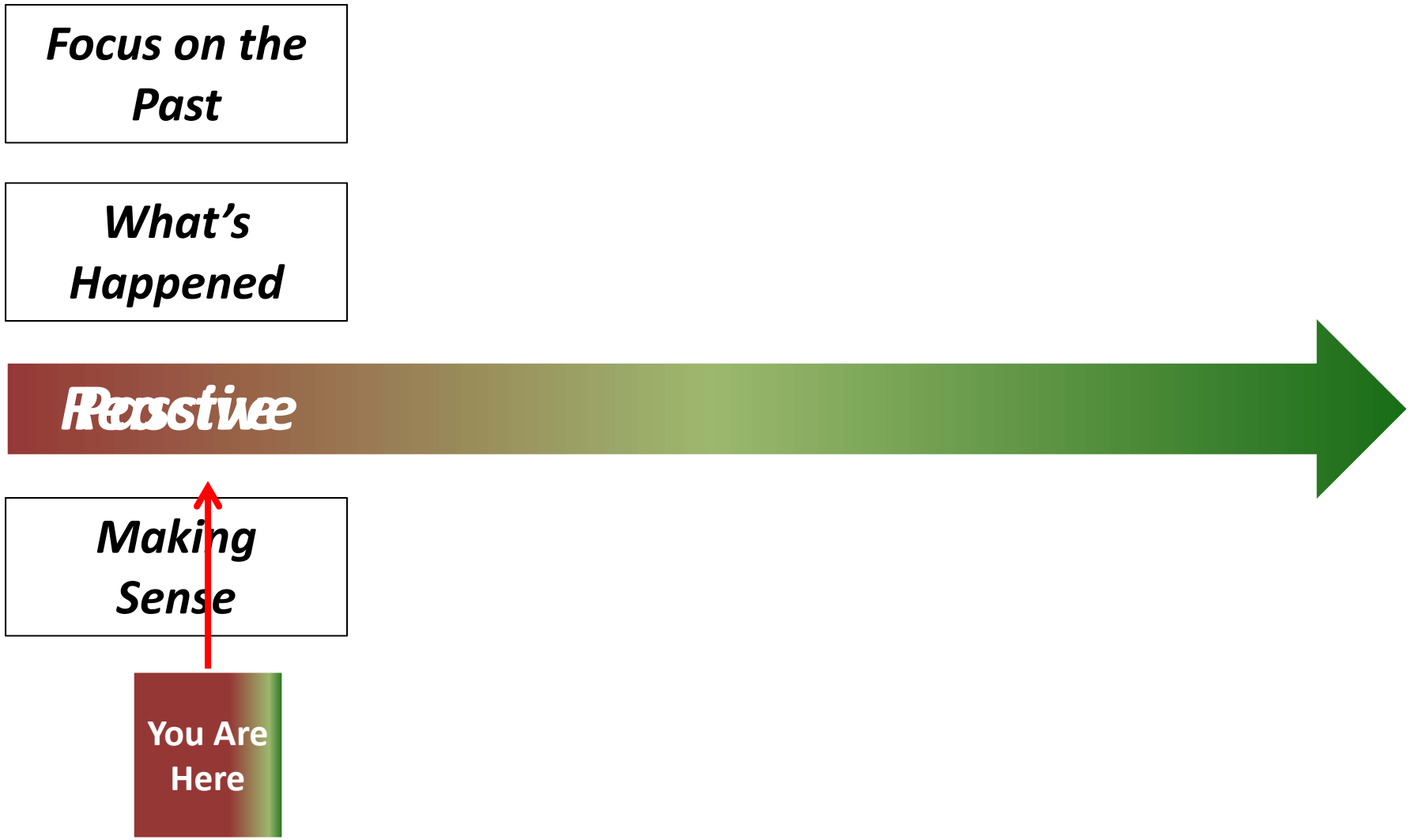
Phone # / E-mail

2. Health Professional? Yes / No
3. Occupation
4. Also Reported to: Manufacturer / User Facility / Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box:

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.

Reactive

The Journey



FDA Amendments Act (2007)

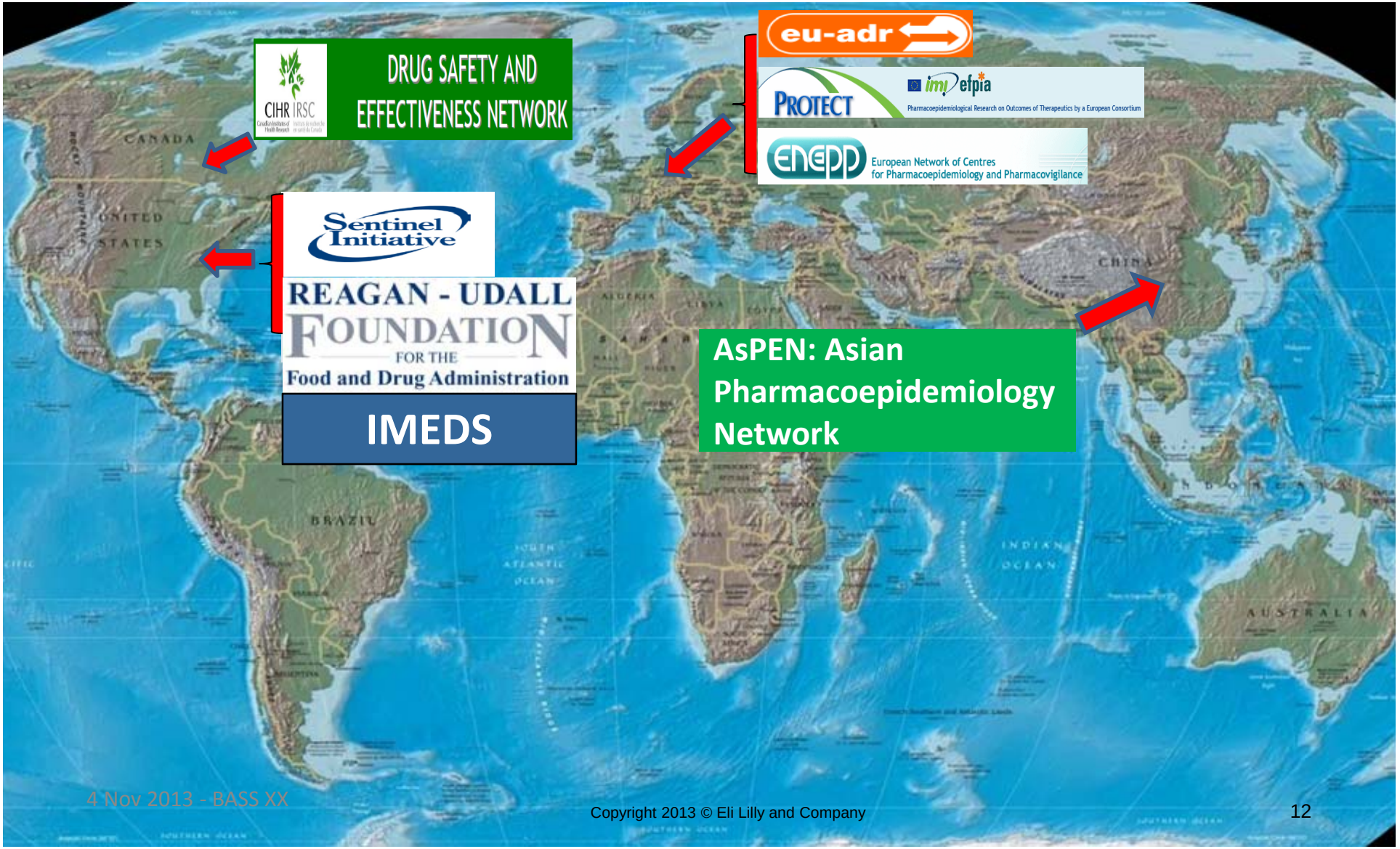
Section 905

- **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/ OMOP	EU-ADR	PROTECT	AsPEN	DSEN
Geography	**US**	**EU**	**EU**	**Asia**	**Canada**
Signal Detection	✓ (~3 years)	✓	✓		
Active Surveillance	✓		✓		✓
Signal Clarification/ Evaluation	✓		✓	✓	✓
Comparative Effectiveness	?				✓
Effectiveness of Risk 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,[1] Jeremy A Rassen,[1] Niteesh K Choudhry,[1] Rhonda Bohn,[2] Amanda R Patrick,[1] Gayathri Sridhar,[3] Gregory W Daniel,[4] Jun Liu,[1] Sebastian Schneeweiss[1]

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

DoPE

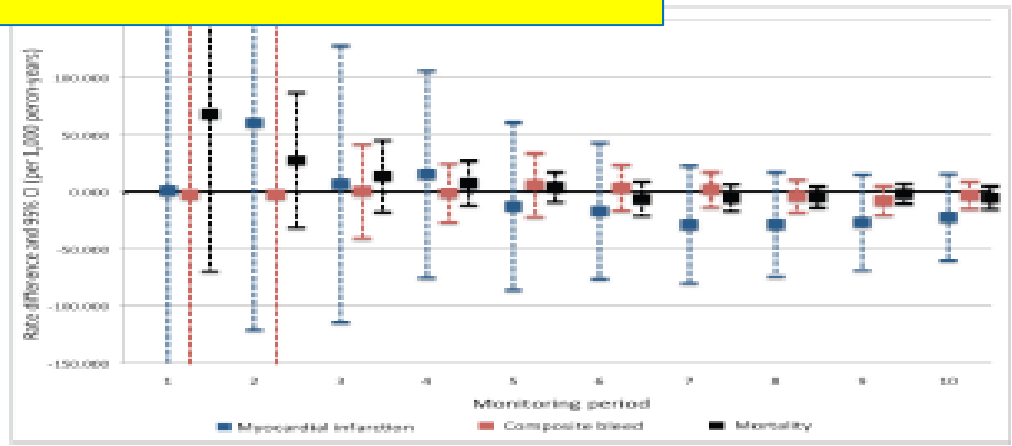
BWH

Patient Centered Outcomes Research Institute

Objectives

- Since its market in … been prospectively … and effectiveness 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.

… ll, bleed, and death



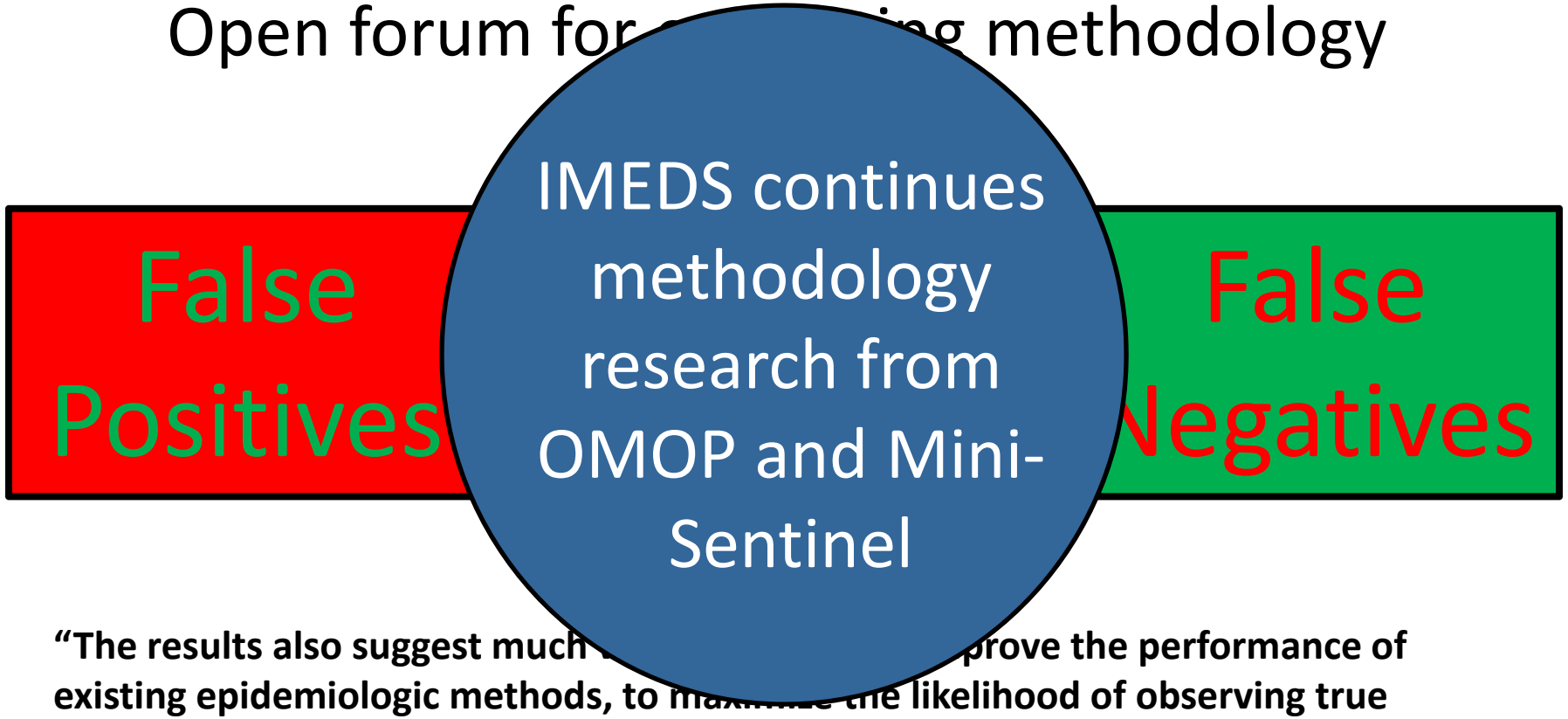
ISPE Annual Conference, Barcelona, Aug 2012.

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 [illegible]ing methodology

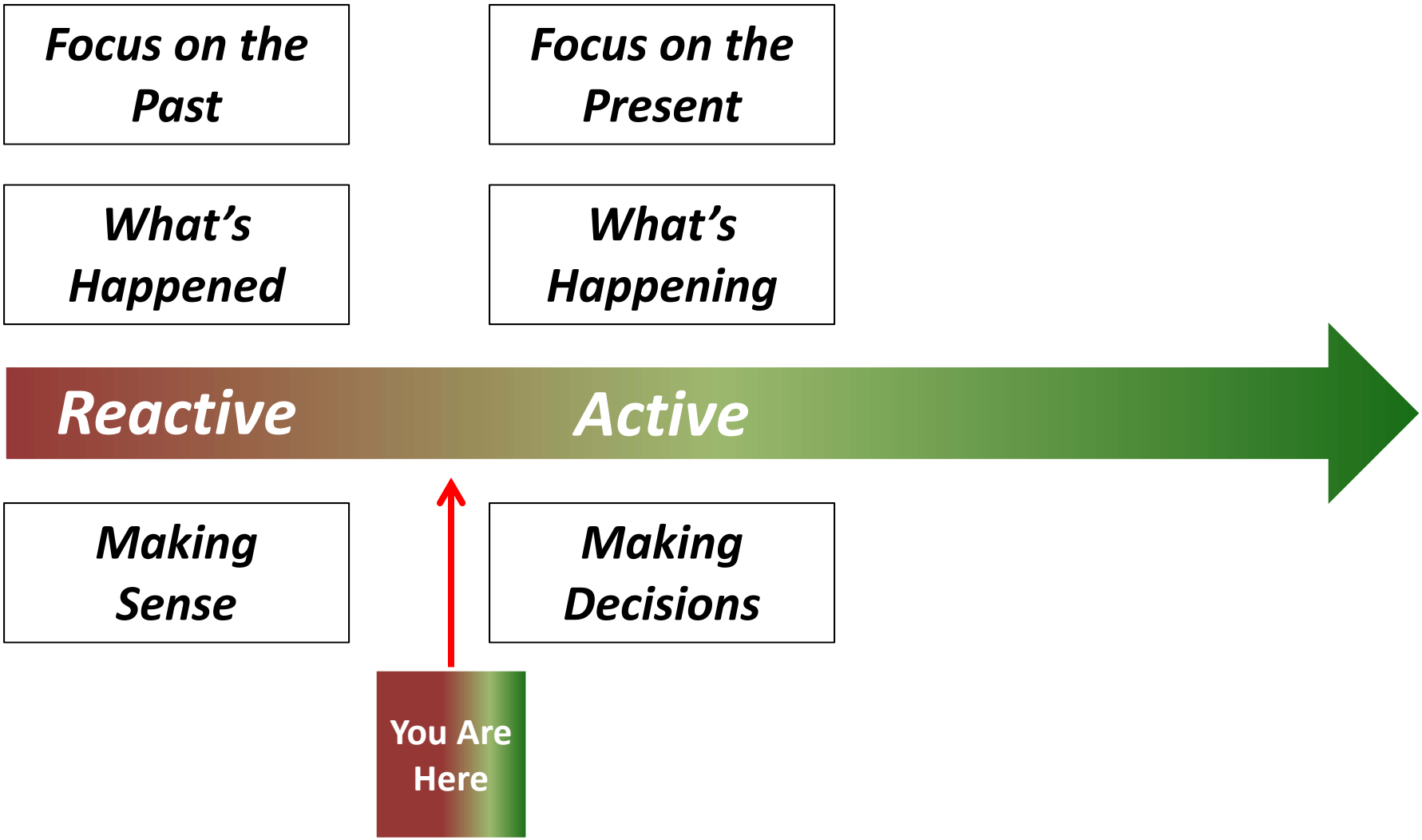


"The results also suggest much [illegible]prove the performance of existing epidemiologic methods, to [illegible] the likelihood of observing true effects while reducing the risk of false positive findings."

David Madigan & Patrick Ryan

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

The Journey



IMAGINE…

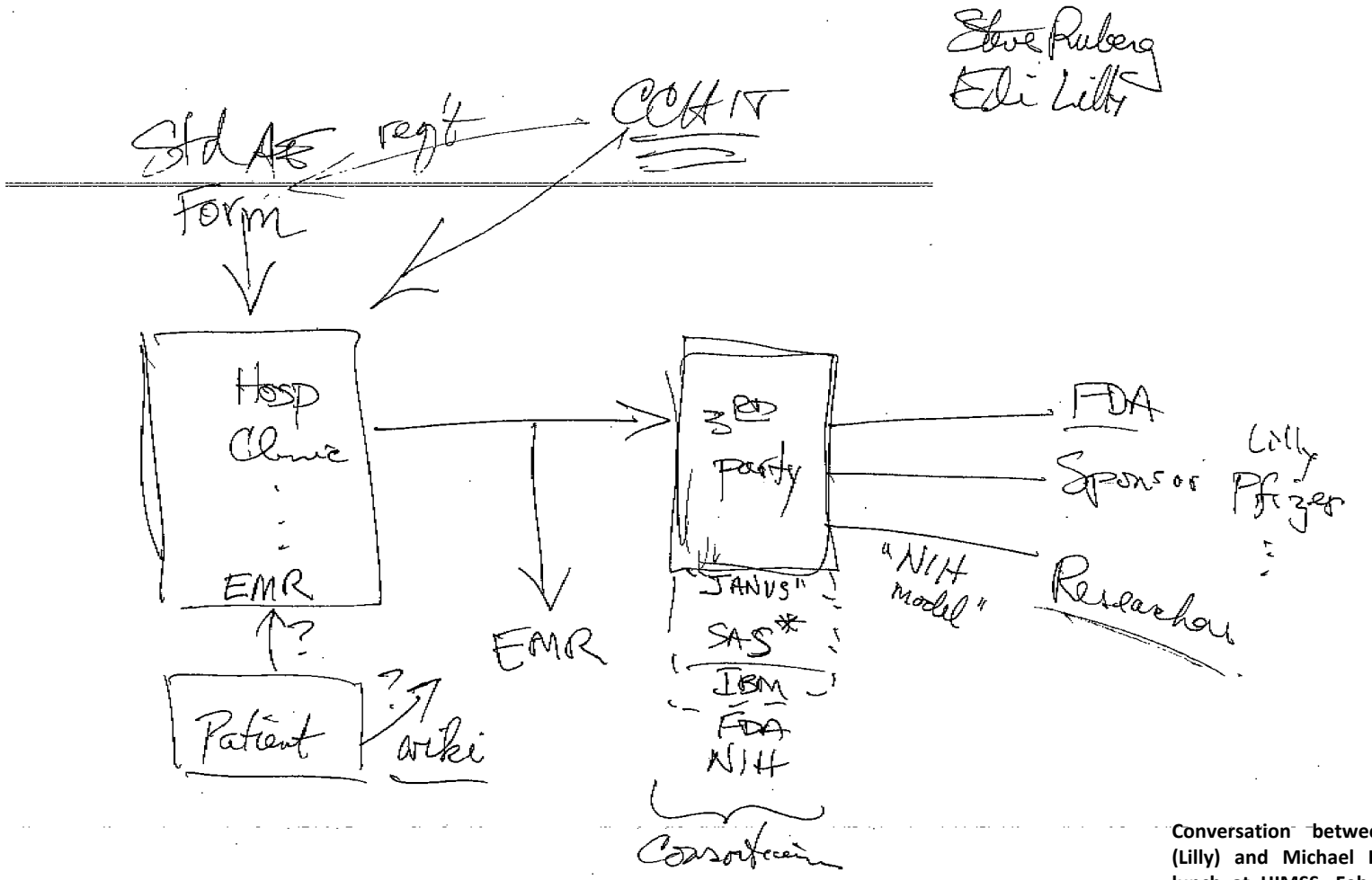
Collecting all drug discontinuations due to AEs…

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…

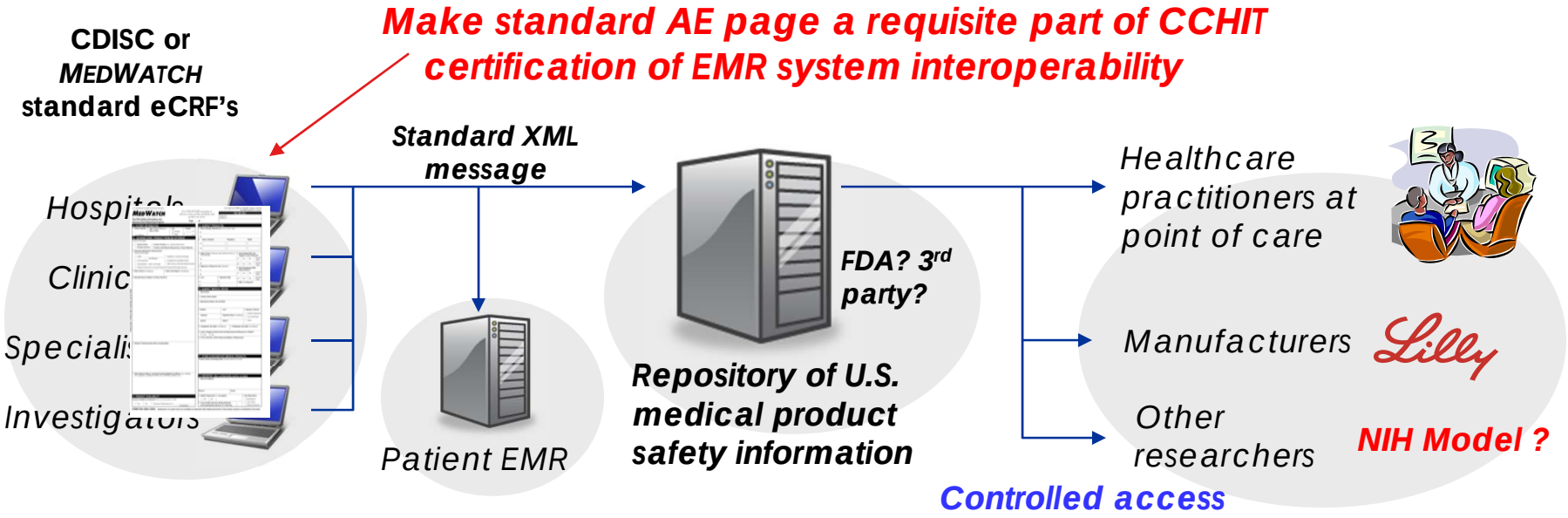
Vision



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 **E**rrors and **P**atient **O**utcomes **R**elated to **T**herapy

January 2008 to September 2010

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

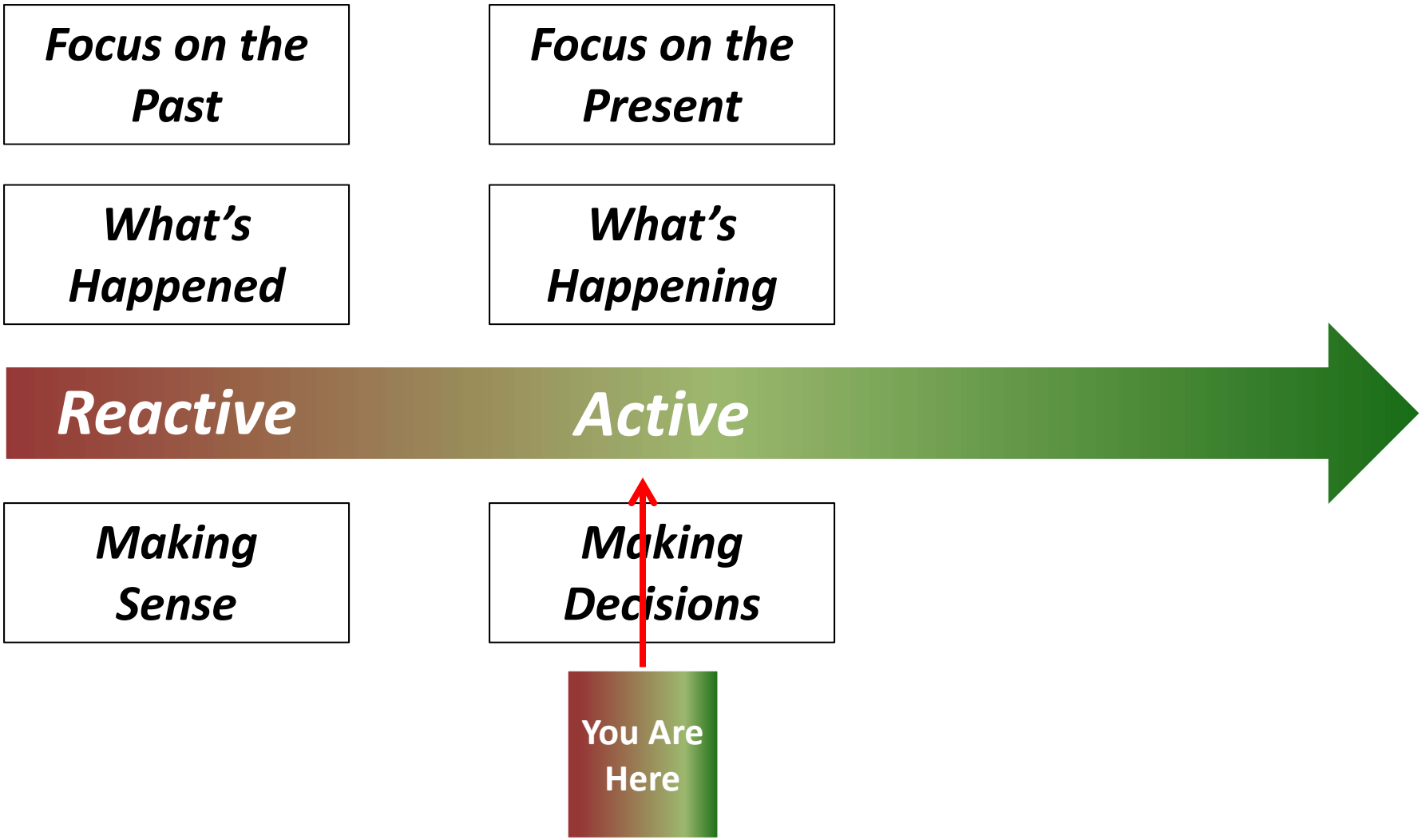
Standard Content and Messages

"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

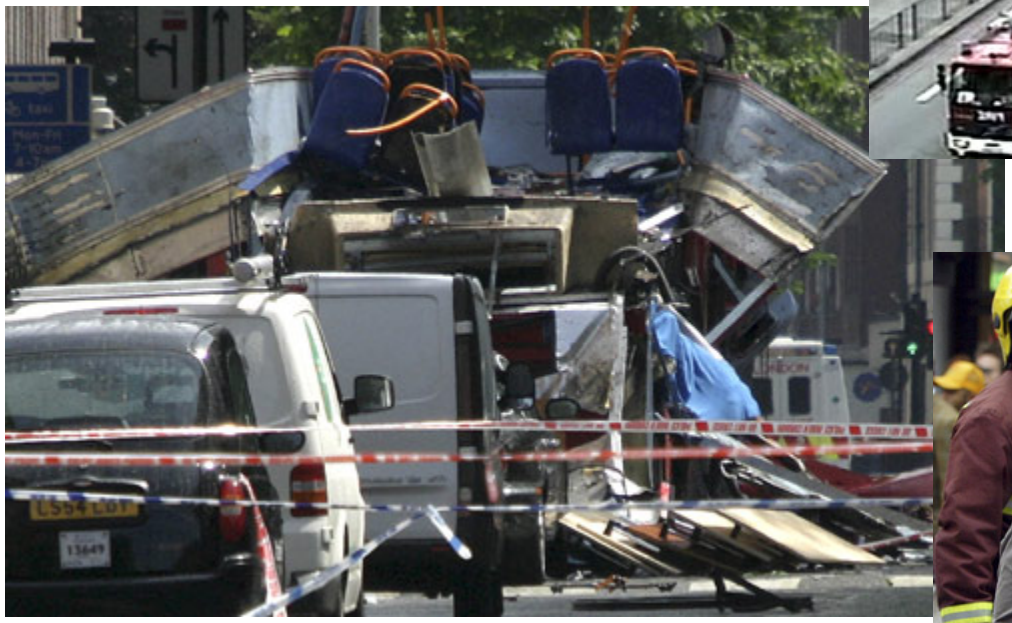
By Kevin Kelly

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, Edgeware 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

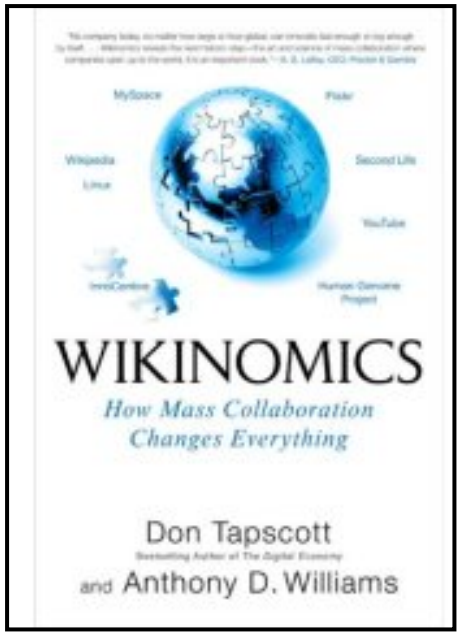
A 14 page report on the incident that was

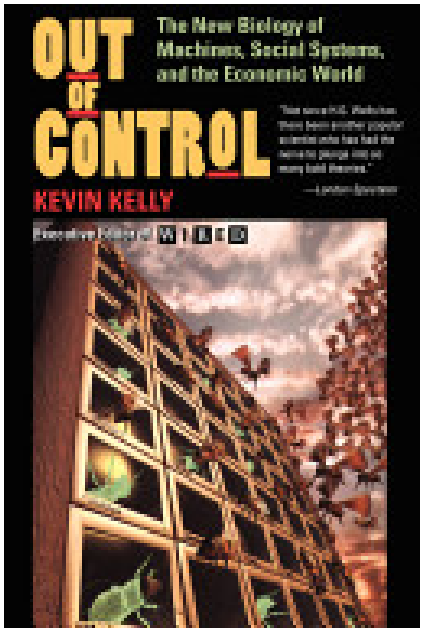
More comprehensive
More accurate

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

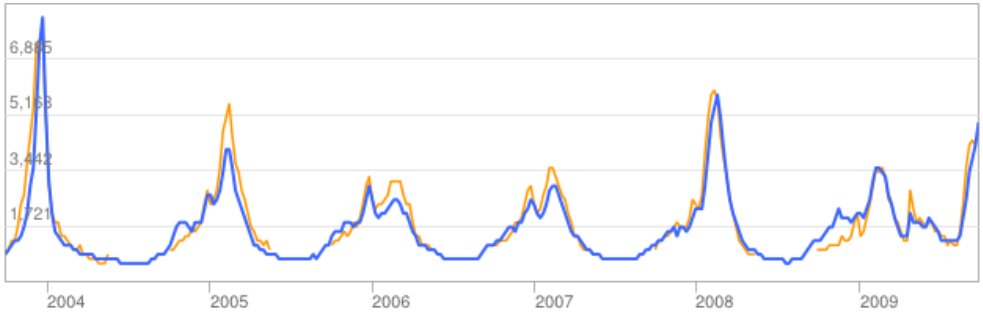
Google Uses Searches to Track Flu's Spread

...

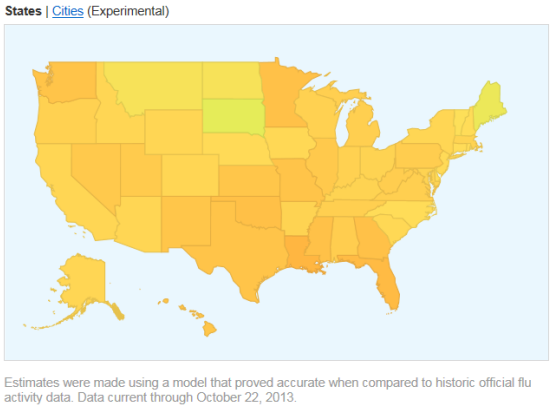
"Google Flu Trends appears to be the first public project that uses the powerful database of a search engine to track a disease."

United States Flu Activity

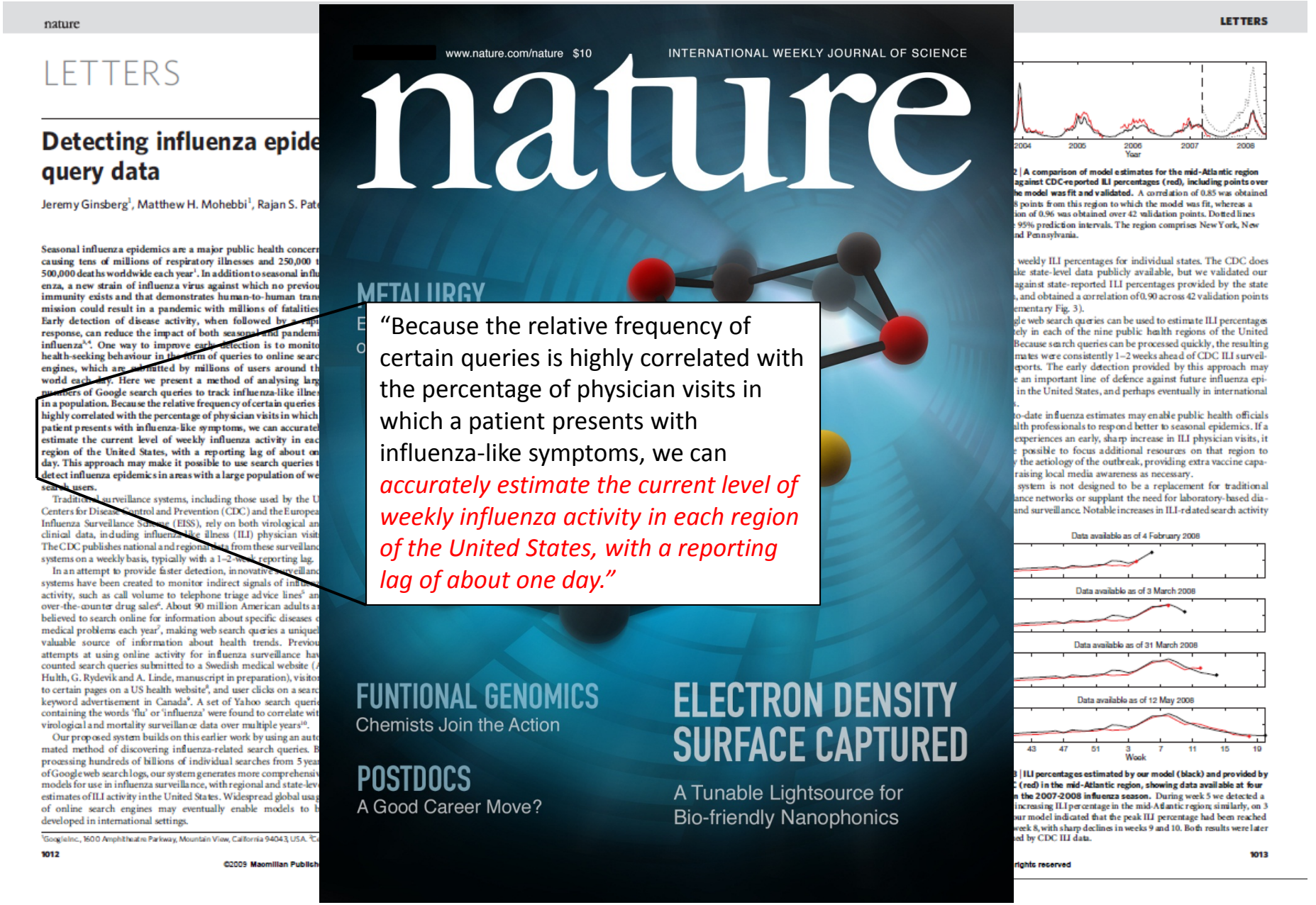
Influenza estimate	Google Flu Trends Estimate United States Data



Flu Incidence - US



Dengue activity



"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."*

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

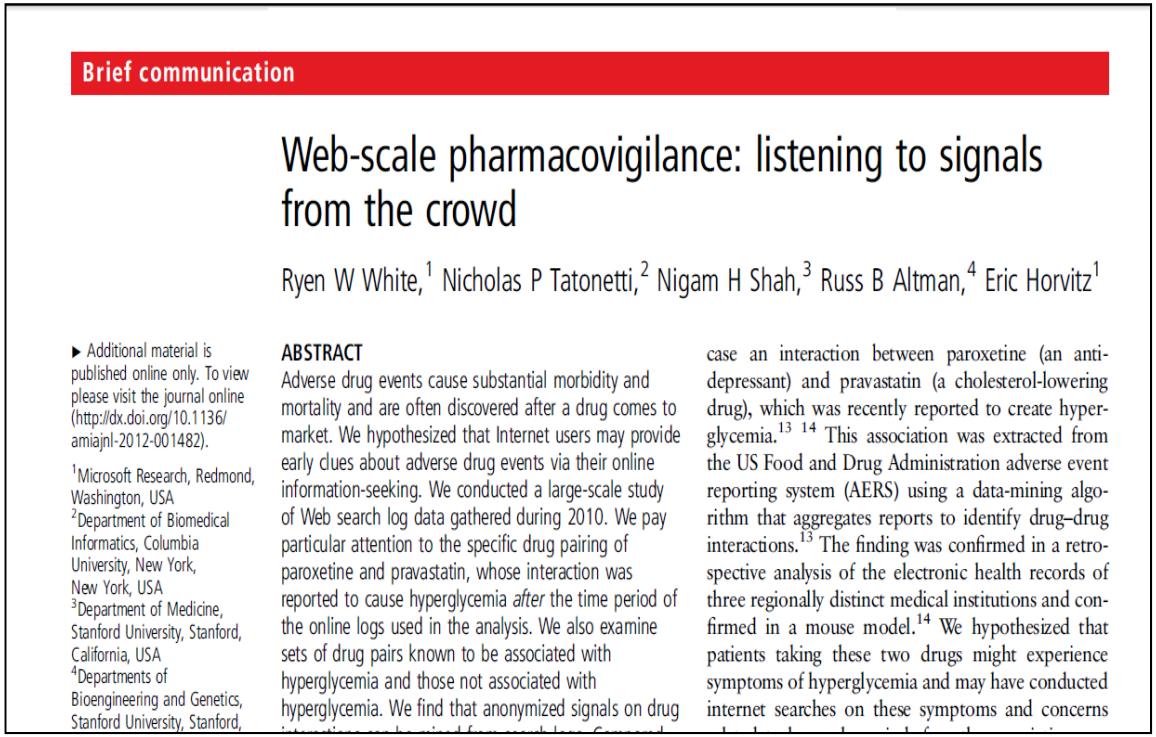
March 6, 2013

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,[1] Nicholas P Tatonetti,[2] Nigam H Shah,[3] Russ B Altman,[4] Eric Horvitz[1]

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

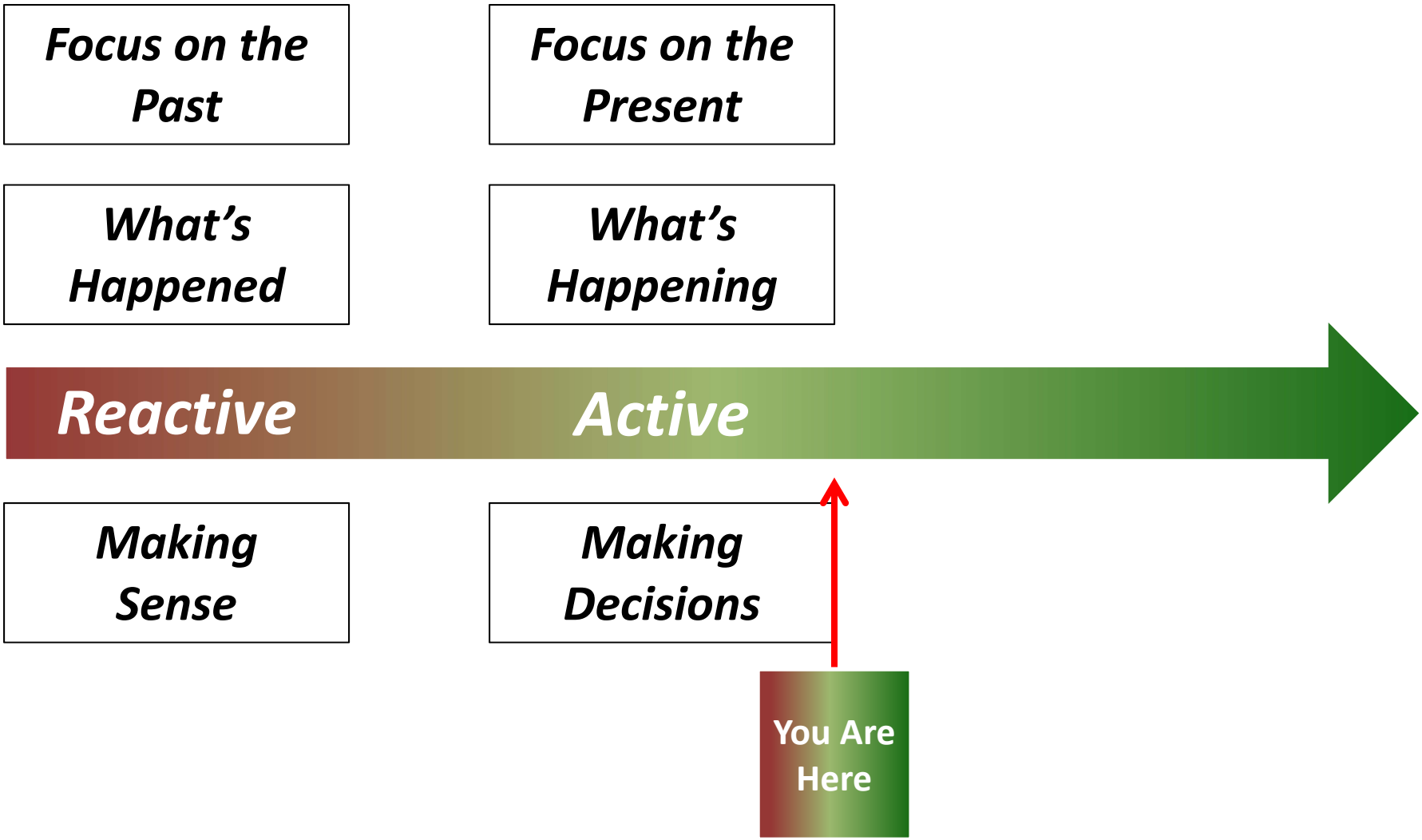
[1]Microsoft Research, Redmond, Washington, USA
[2]Department of Biomedical Informatics, Columbia University, New York, New York, USA
[3]Department of Medicine, Stanford University, Stanford, California, USA
[4]Departments of Bioengineering and Genetics, Stanford University, Stanford,

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 antidepressant) and pravastatin (a cholesterol-lowering drug), which was recently reported to create hyperglycemia.[13 14] 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.[13] 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.[14] 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 rd

"The Perso n
Internet-ba people to
access and alth
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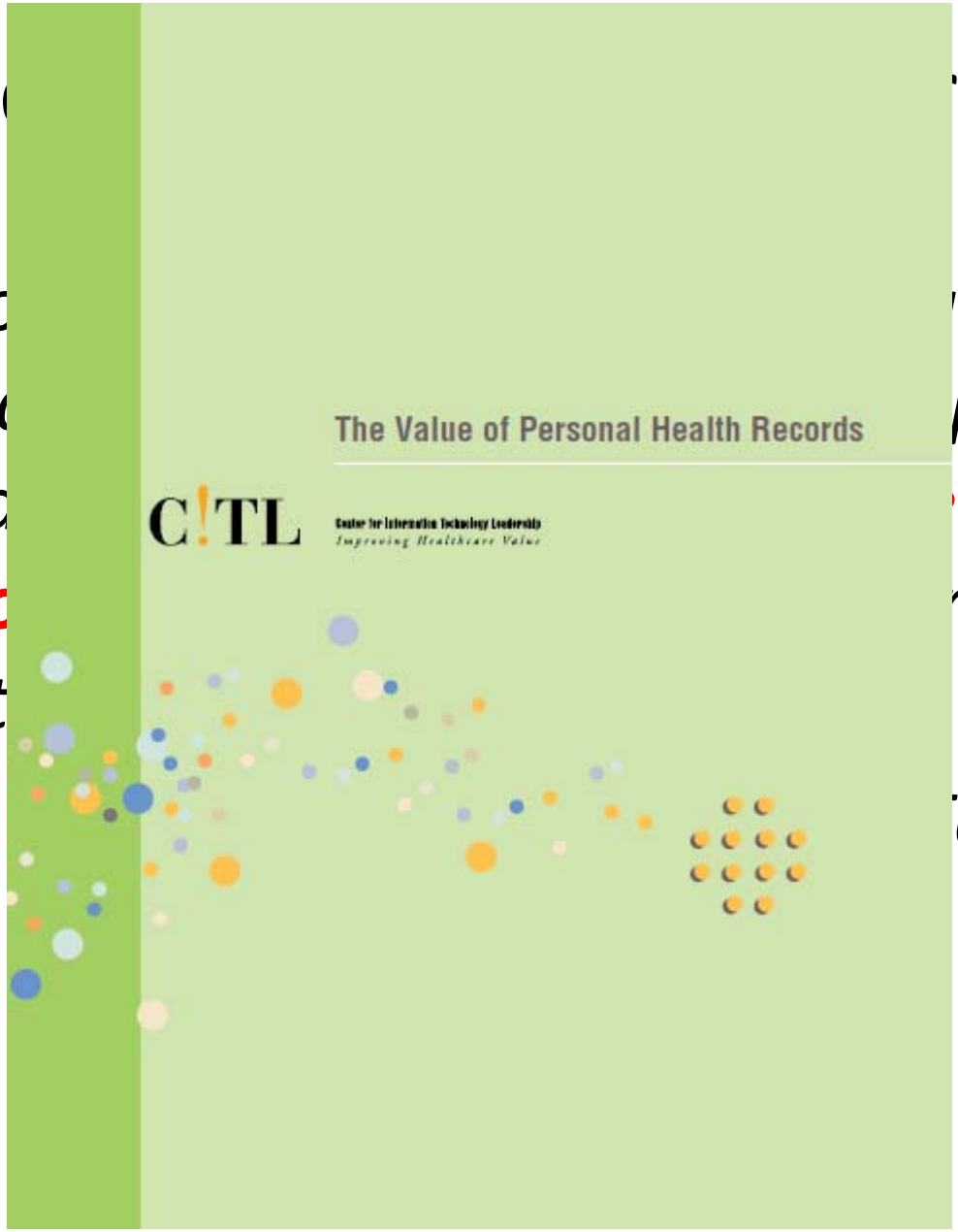
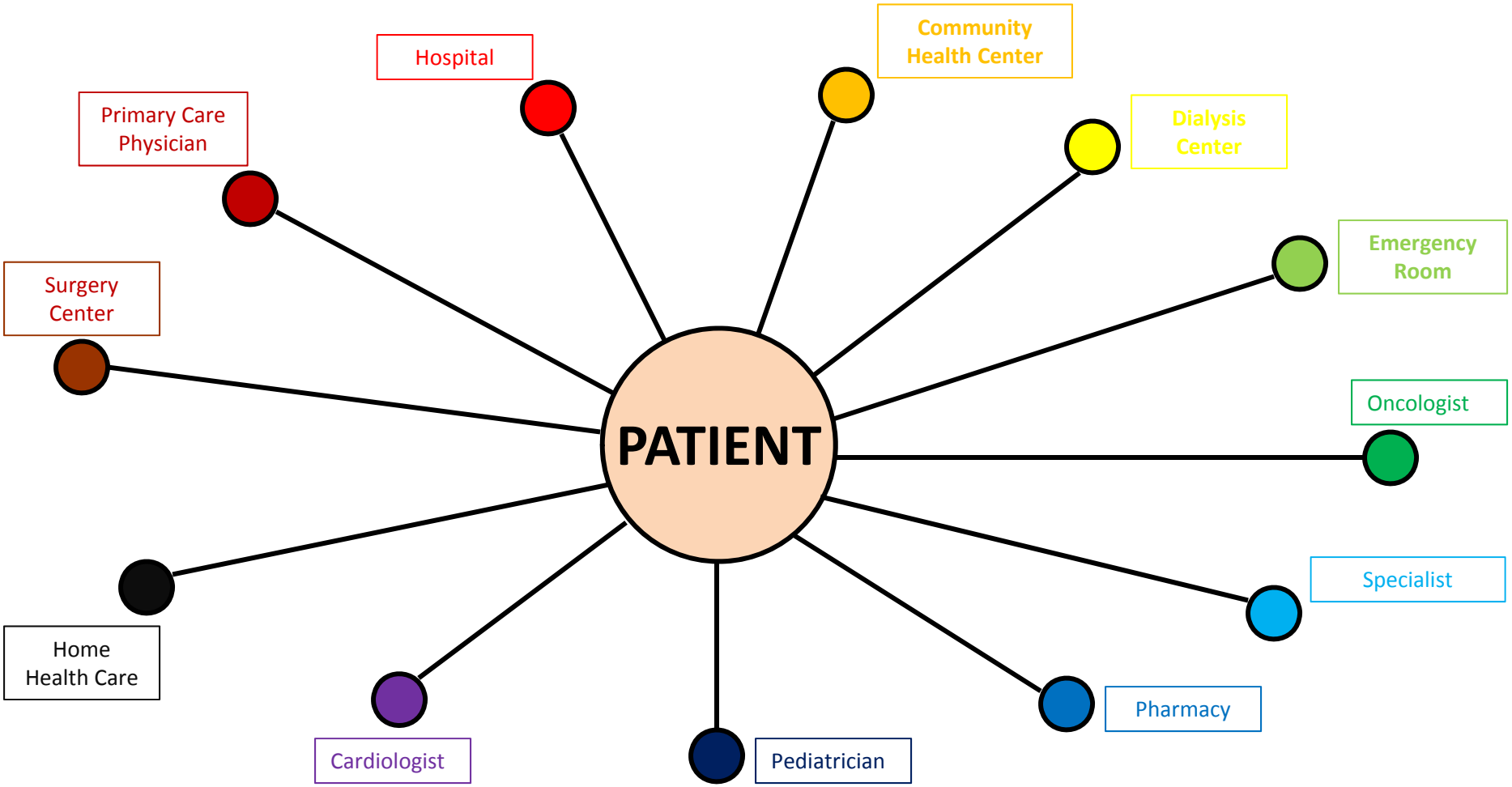
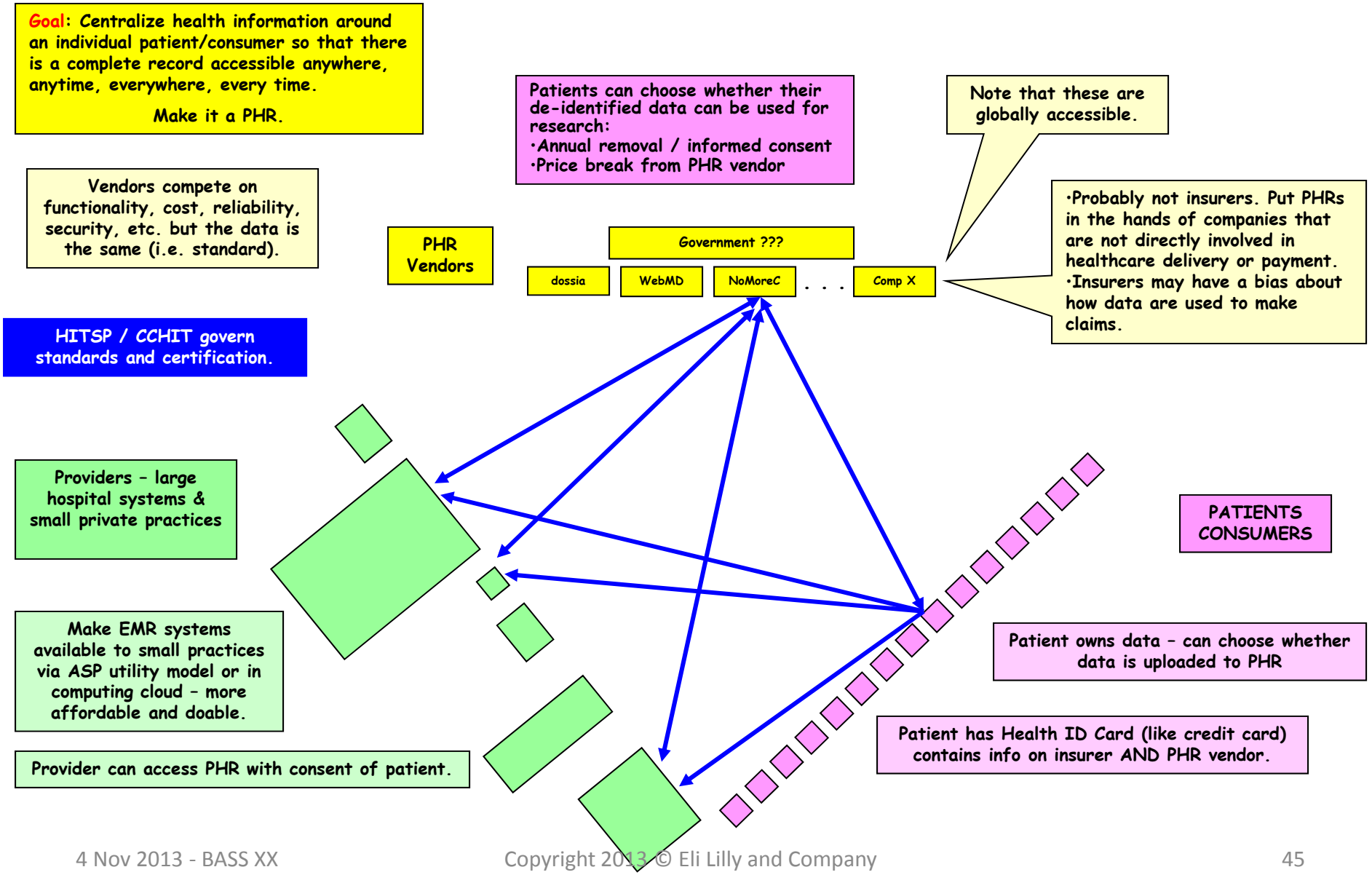


The Patient Perspective

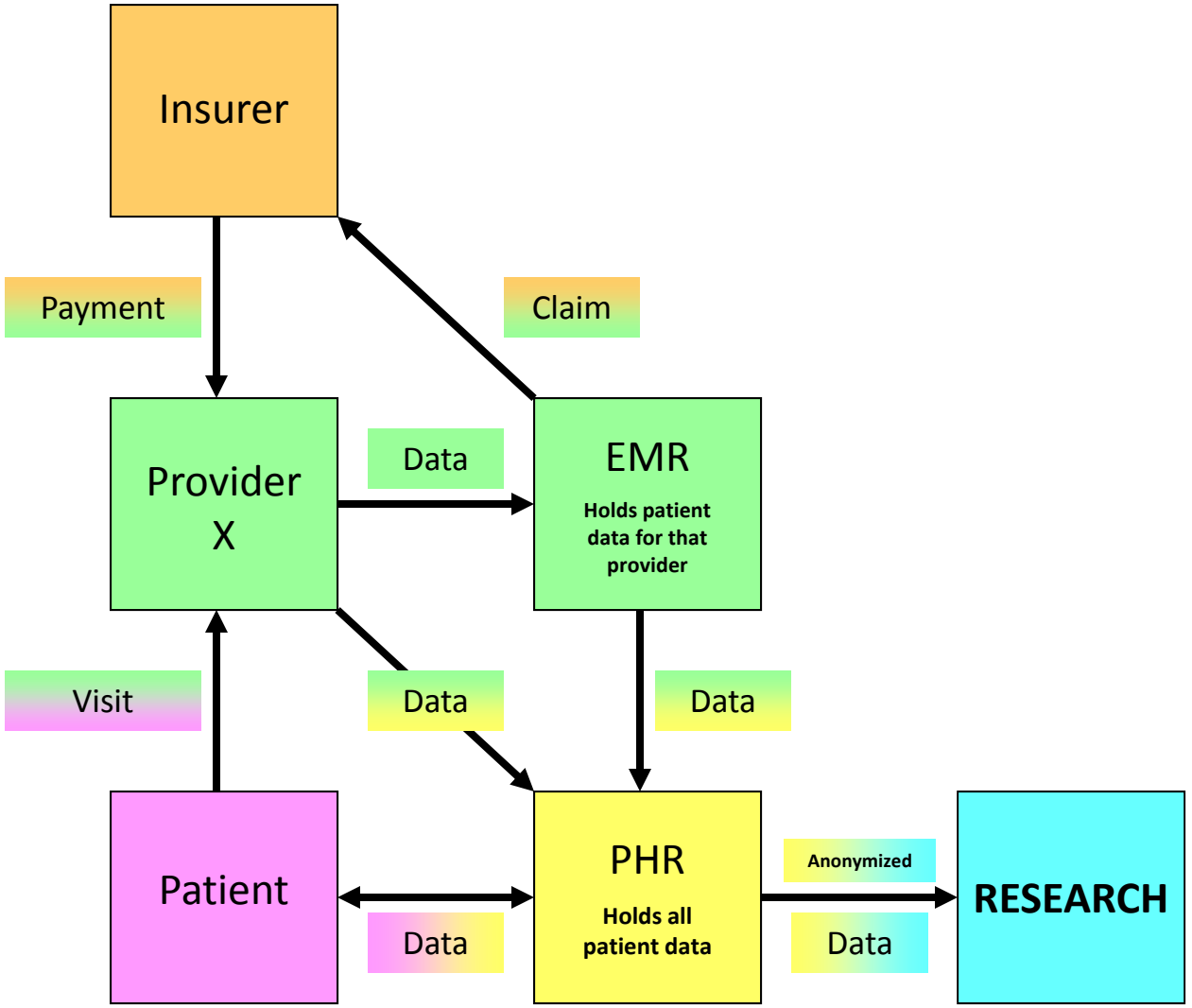
The first sentence of the ONC Strategic Plan states, “Looking toward the future, we can envision a *health care system that is centered on each and every patient*. … and authorized access to health *data will provide new ways that biomedical research and public health can improve individual health*,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



The Patient Perspective



Another Perspective – Same Model

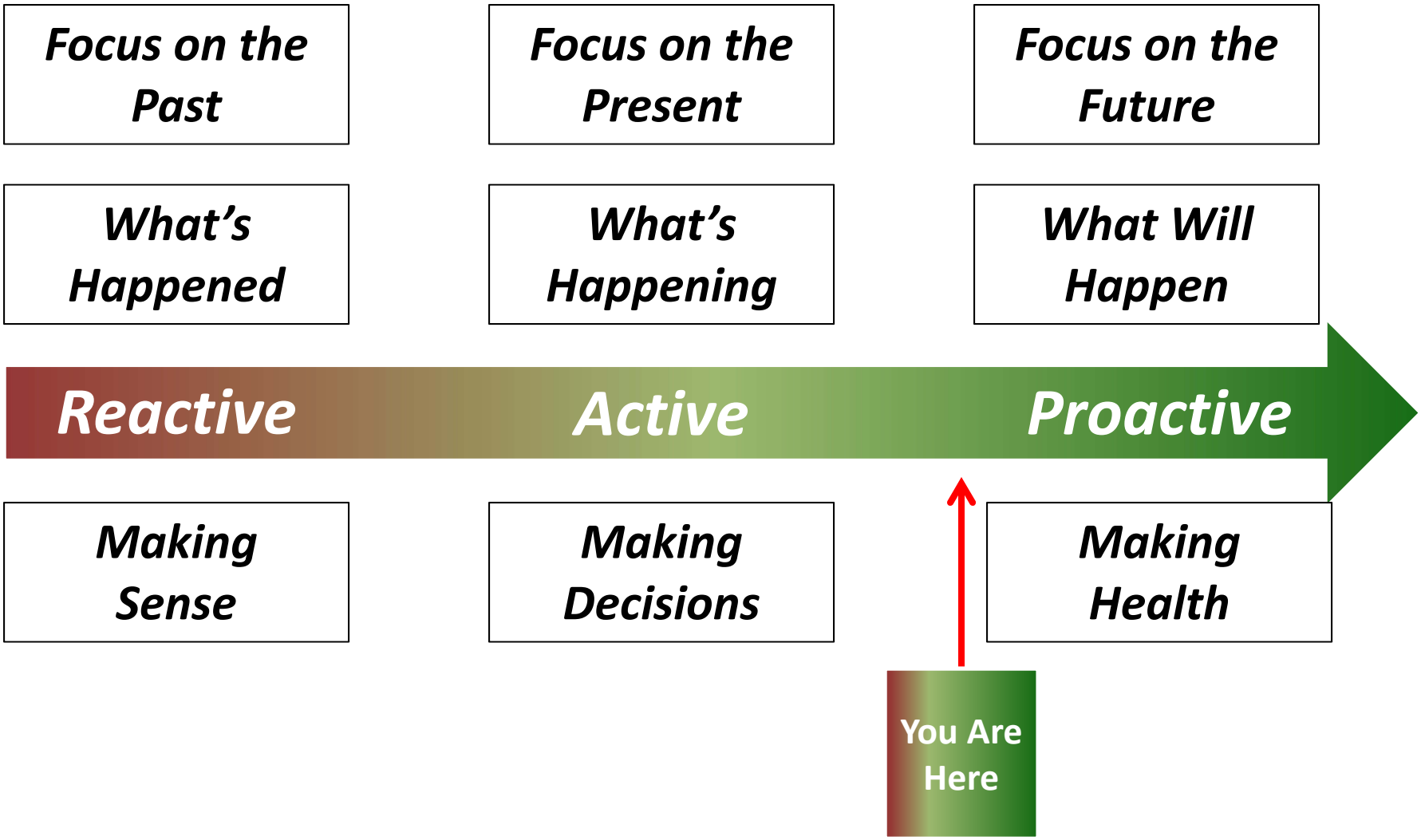


Personal Health Records

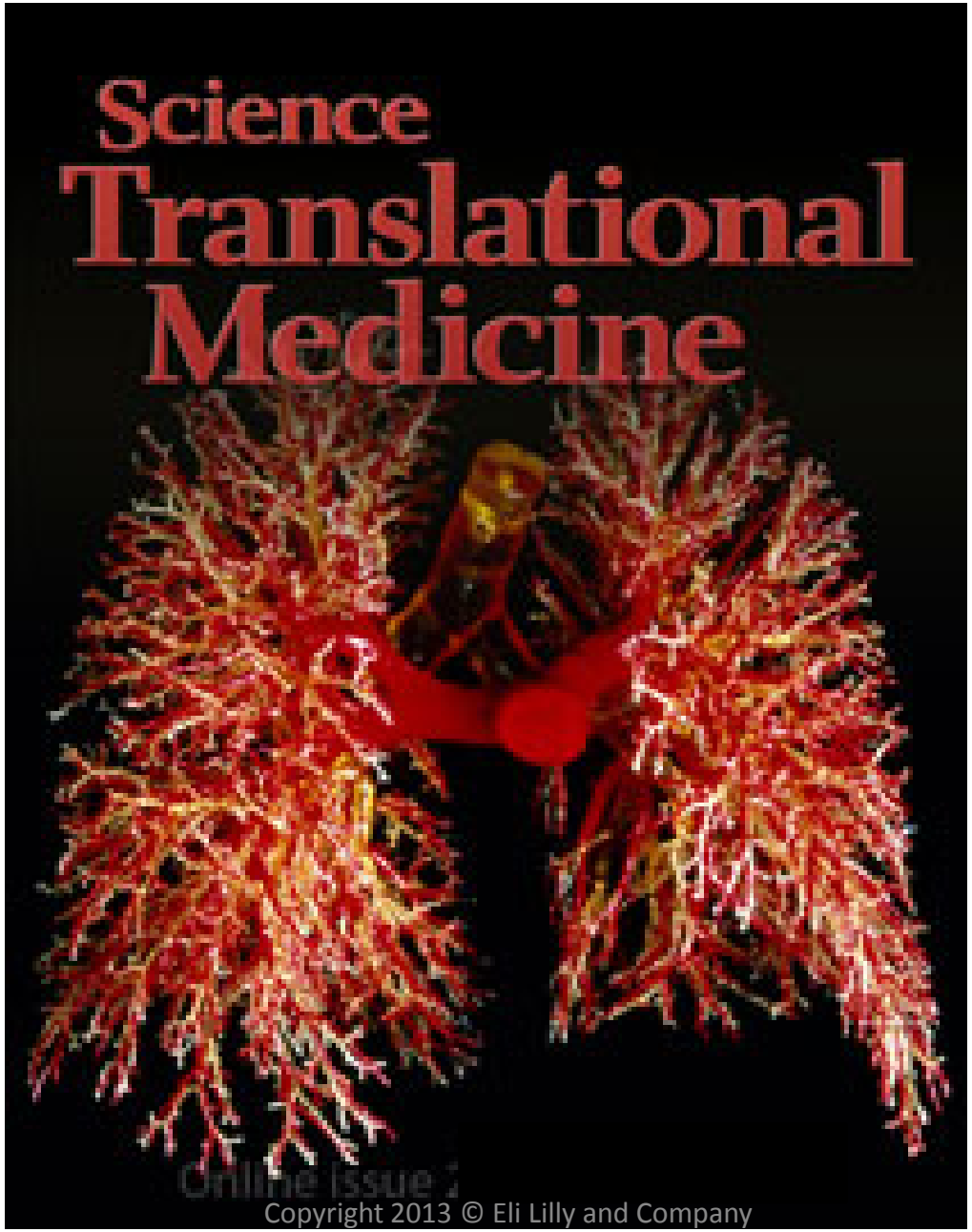
A real chance at comprehensive **benefit-risk** !

- 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



RESEARCH ARTICLE

SYSTEMS BIOLOGY

Systems Pharmacology of Adverse Event Mitigation by Drug Combinations

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

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 atropinics 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.

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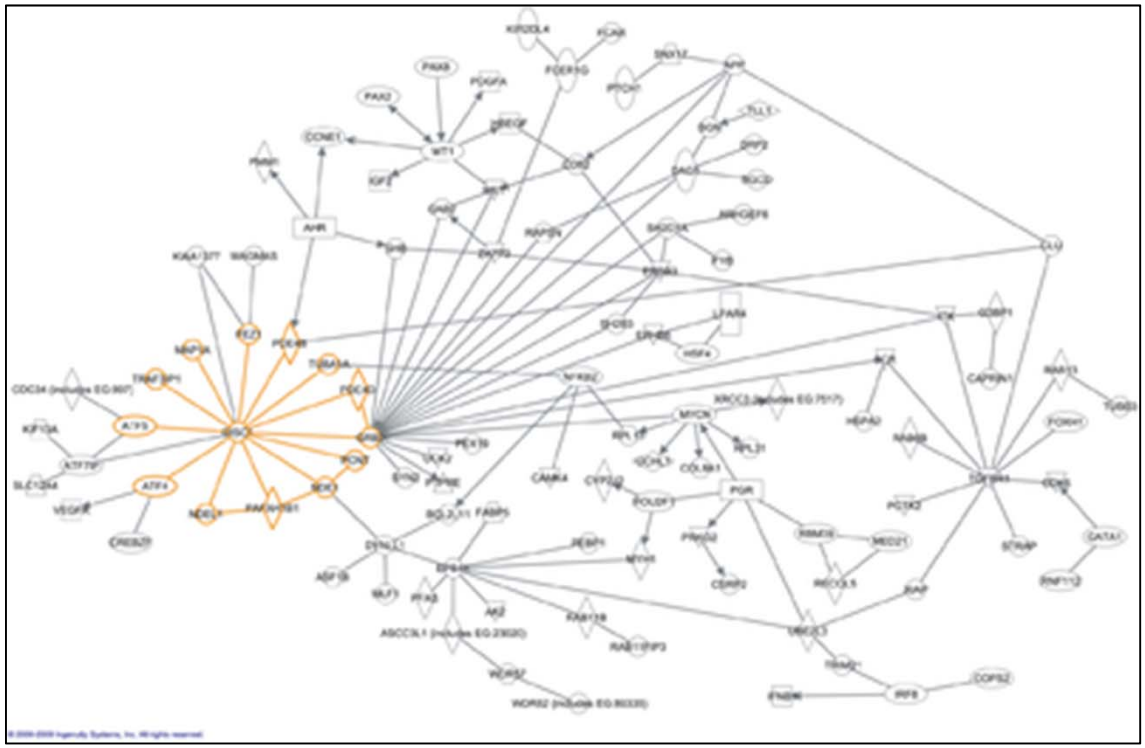
"In FAERS, rosiglitazone usage is associated with increased occurrence of MI, but its combination with exenatide significantly reduces rosiglitazone associated MI."

The Interactome

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

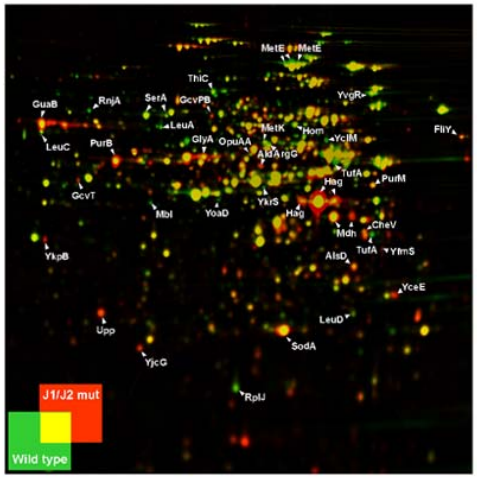


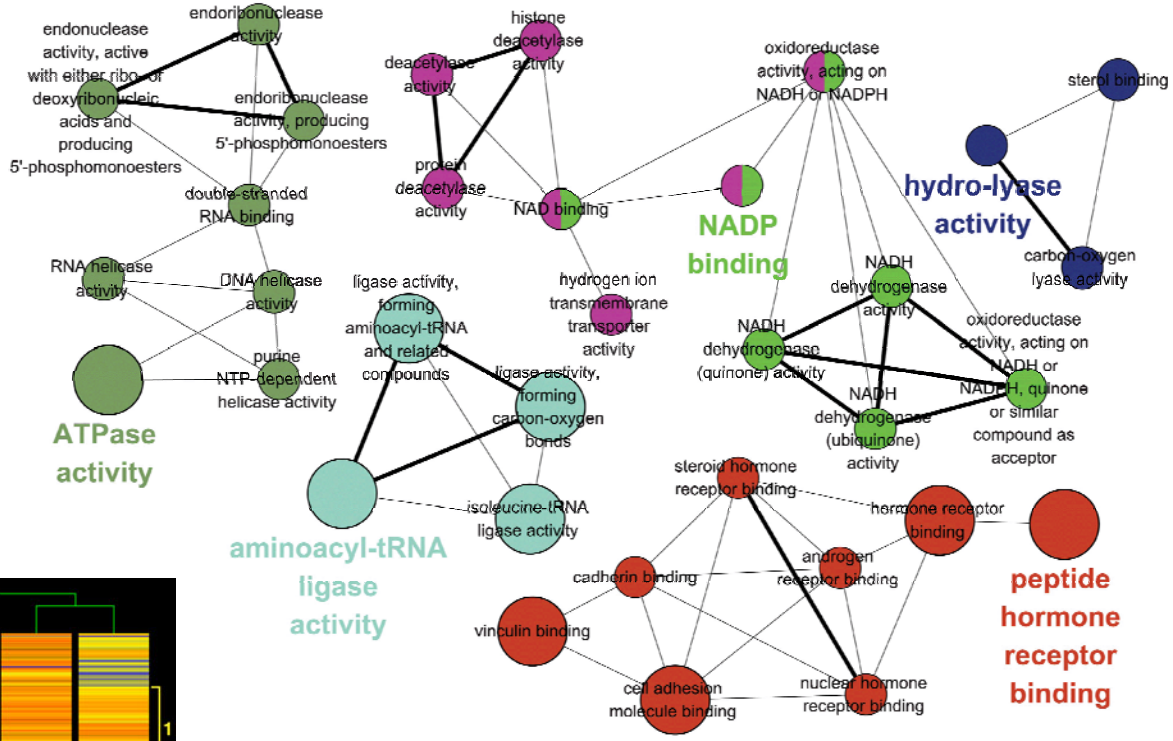
Part of the DISC interactome with genes represented by text in boxes and interactions noted by lines between the genes. From Hennah and Porteous, 2009.

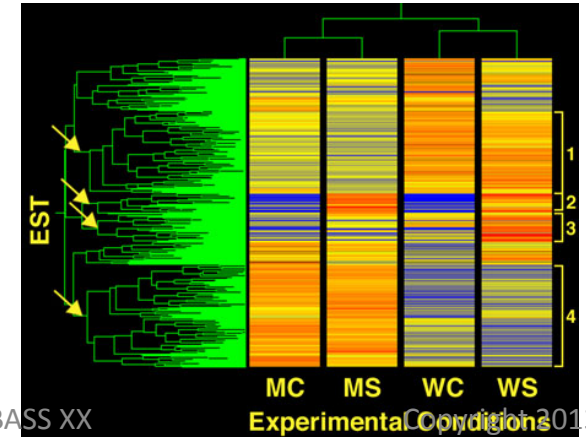
From Wikipedia

The Transcriptome

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







From Wikipedia

RESEARCH ARTICLE

SYSTEMS BIOLOGY

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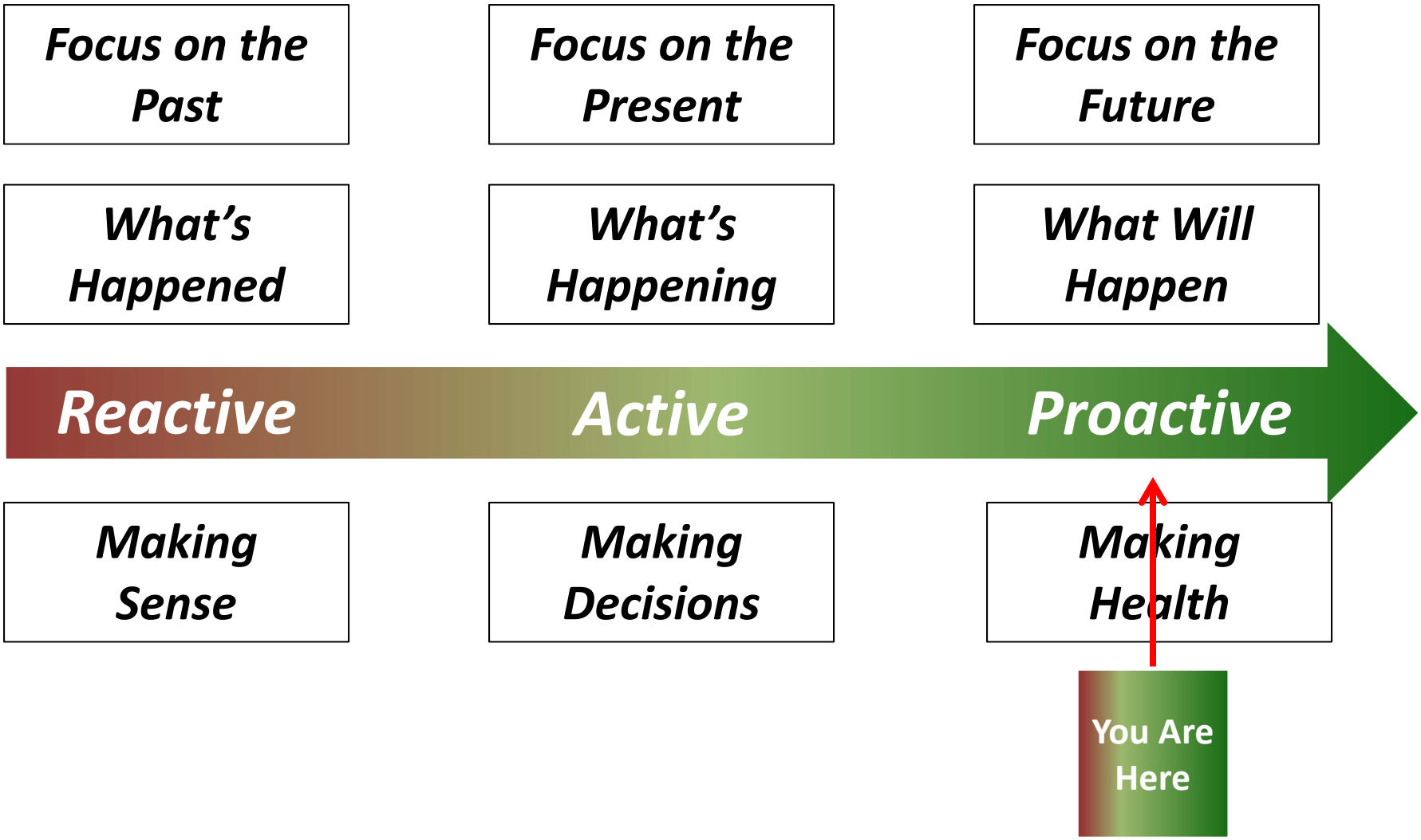
"Just as it is possible to discover harmful side effects through retrospective examination of FAERS (9), *we show here that we can detect potential beneficial combinations* by analysis of FAERS."

"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