Enhancing the Application of Real-World Evidence in Regulatory Decision-Making

Public Conference

March 3 & 4, 2016

The Washington Plaza Hotel

PCORnet

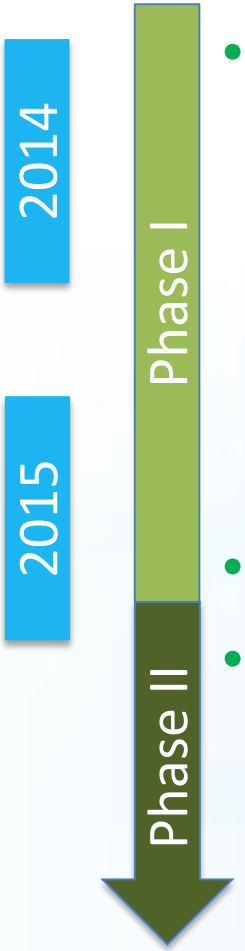
Real World Evidence in Regulatory Decision-Making: Incentives and Policy Options for Improving a Shared Infrastructure

Rachael Fleurence, PhD
Program Director PCORnet
PCORI
March 4, 2016

PCORnet's Mission

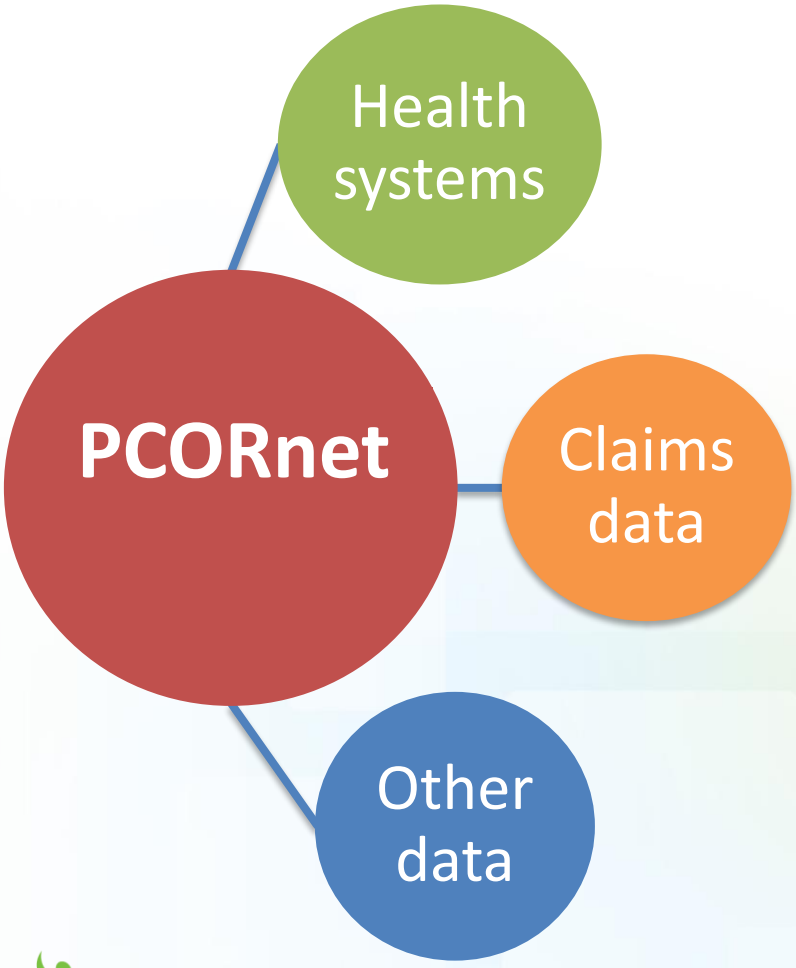
- PCORnet engages stakeholders in its community of research to enable faster, more informative clinical research that provides the evidence to transform clinical practice, improve health outcomes, and help people make better care decisions.

PCORnet Timeline



- Jan 2014 – Oct 2015: Phase I
  - 11 CDRNs
  - 18 PPRNs
  - Coordinating Center
- August 2015: Governance Structure in place
- Oct 2015 – Sept 2018: Phase II
  - 13 CDRNs
  - 20 PPRNs
  - Coordinating Center

PCORnet Clinical Data Research Networks (CDRNs) – Phase II

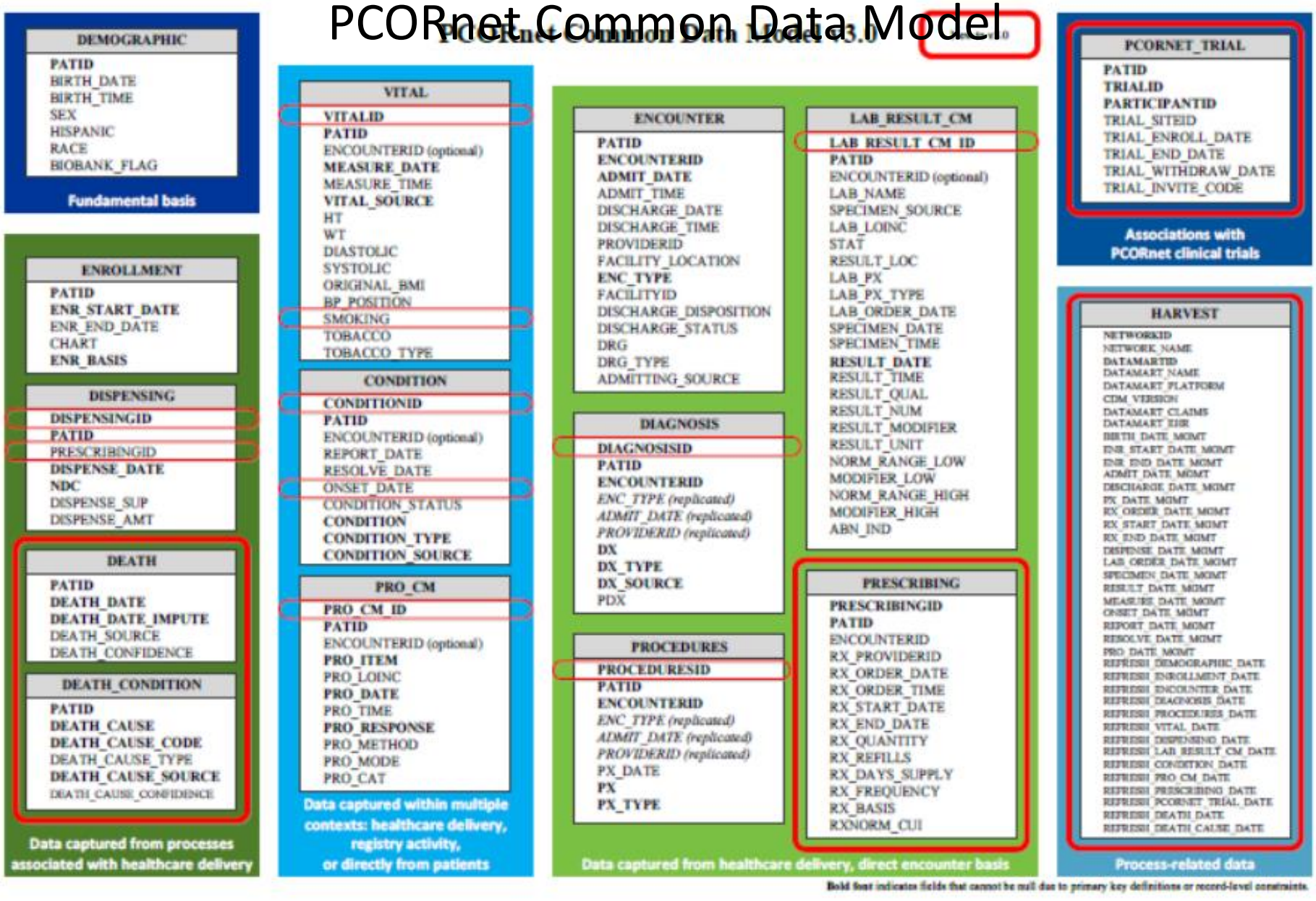


- The Chicago Community Trust (CAPriCORN)
- The Children's Hospital of Philadelphia (PEDSnet)
- Harvard University (SCILHS)
- Kaiser Foundation Research Institute (PORTAL)
- Louisiana Public Health Institute (REACHnet)
- **Mayo Clinic (LHSNet)**
- Oregon Community Health Information Network (ADVANCE)
- University of California, San Diego (pSCANNER)
- **University of Florida (OneFLorida)**
- University of Kansas Medical Center (GPC)
- University of Pittsburgh (PaTH)
- Vanderbilt University (Mid-South CDRN)
- Weill Medical College of Cornell University (NYC-CDRN)

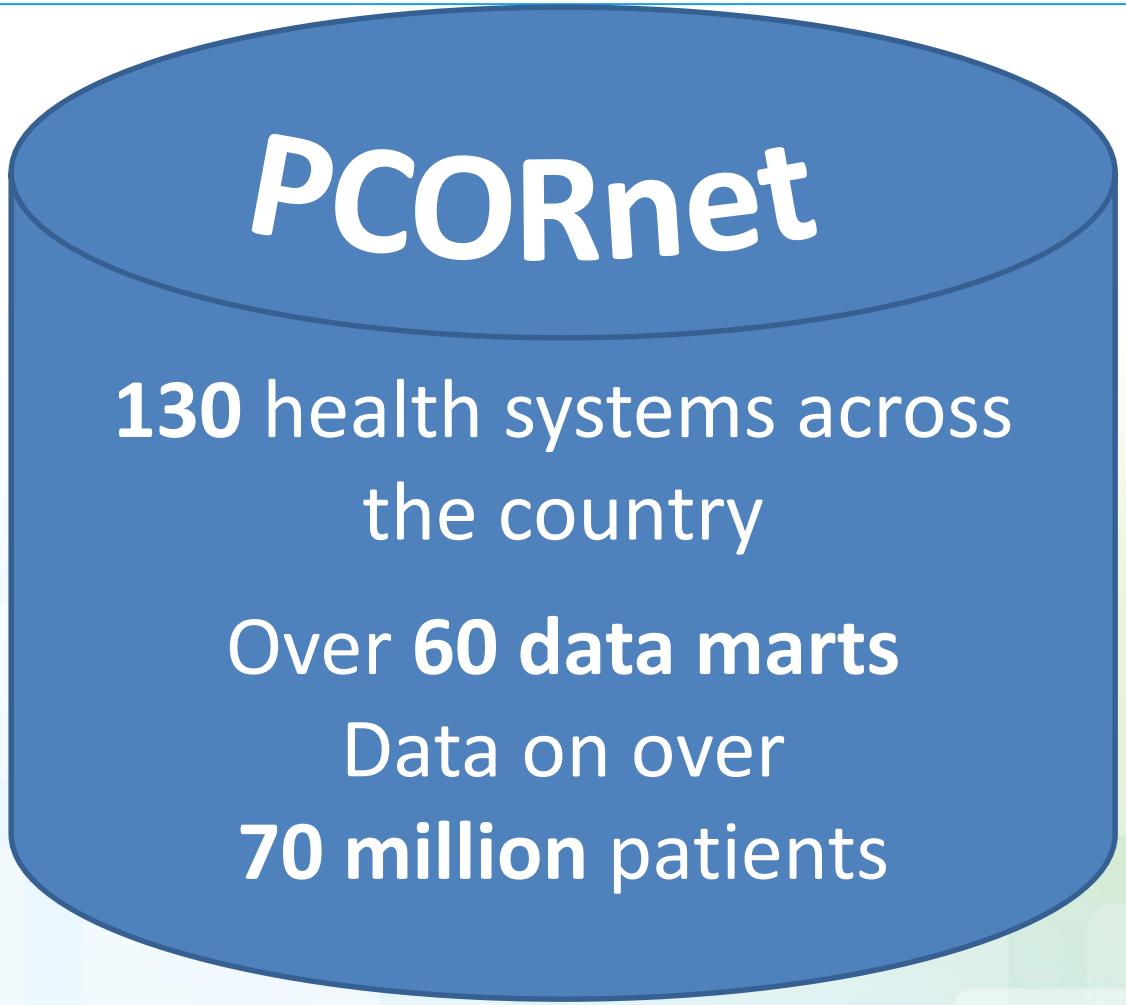
PCORnet Patient-Powered Research Networks – Phase II

- University of South Florida (ABOUT Network)
- Global Health Living Foundation (AR-PoWER)
- Mayo Clinic (AD PCPRN)
- Crohn's and Colitis Foundation of America (CCFA Partners)
- University of California Los Angeles (CPPRN)
- Genetic Alliance (CENA)
- COPD Foundation (COPD PPRN)
- Parent Project Muscular Dystrophy (DuchenneConnect)
- University of California San Francisco (Health eHeart Alliance)
- Cincinnati Children's Hospital Medical Center (ImproveCareNow)
- Kennedy Krieger Institute (IAN)
- Massachusetts General Hospital (MOOD)
- Accelerated Cure Project for Multiple Sclerosis (MS-PPRN)
- Arbor Research Collaborative for Health (NephCure)
- Duke University (PARTNERS)
- Phelan-McDermid Syndrome Foundation (PMS_DN)
- Immune Deficiency Foundation (PI-CONNECT)
- University of California San Francisco (PRIDEnet)
- Epilepsy Foundation (REN)
- University of Pennsylvania (The Vasculitis PPRN)

PCORnet Common Data Model



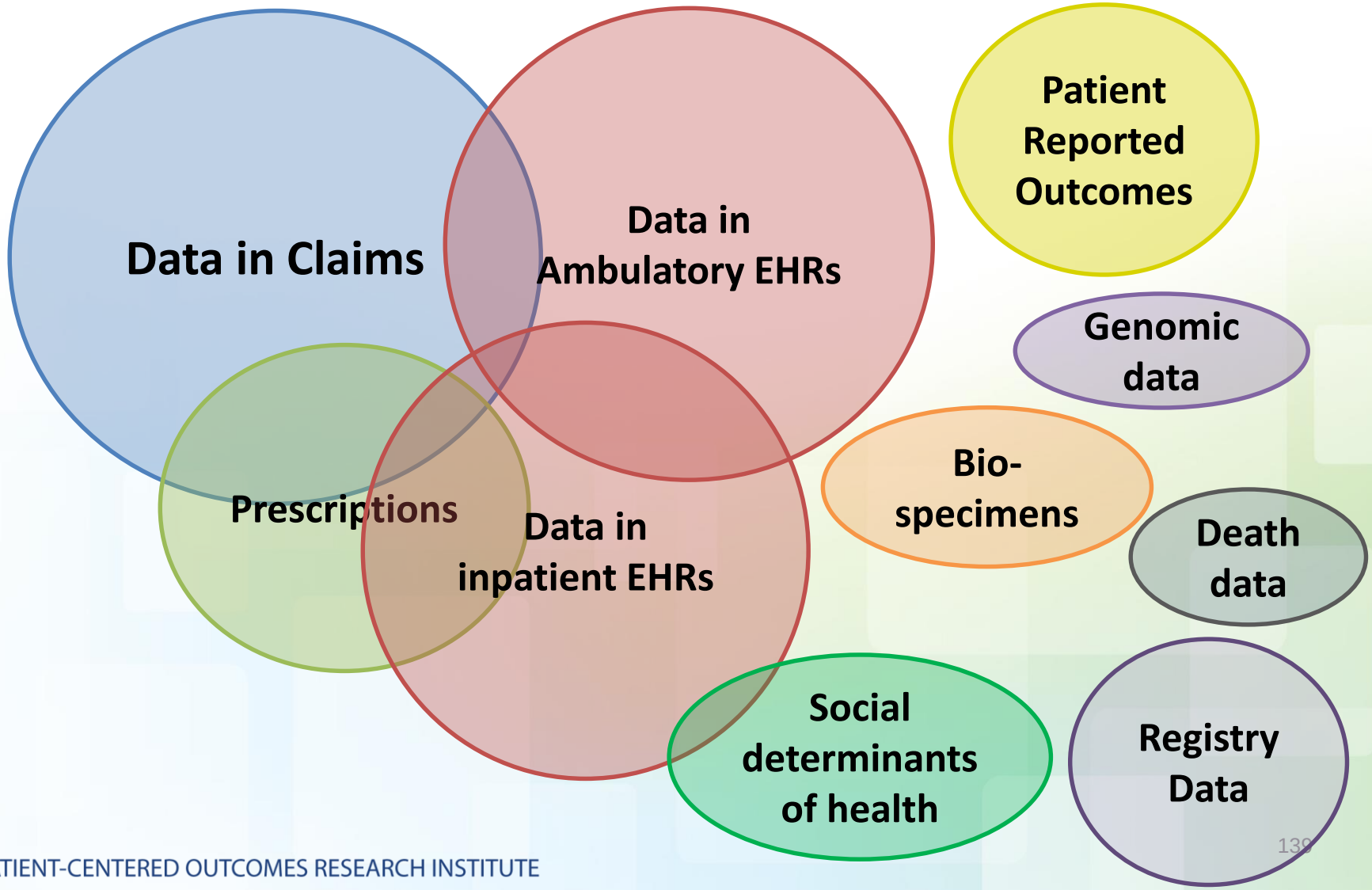
What PCORnet Offers



Patients willing to participate in research through PPRNs

March 2016 = 220,000

Challenge: getting "complete" data



PCORnet's Research

- **Pre-research**
  - Feasibility Queries
  - Engagement
  - Match-making
- **Observational studies**
  - Cross-sectional
  - Epidemiology
  - Health services
  - Comparative effectiveness or safety
- **Interventional studies**
  - Clinical trials
  - Pragmatic randomized clinical trials
    - e-Identification
    - e-Consent
    - e-Randomization
    - e-Follow-up
  - Cluster randomization

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PCORnet's Common Infrastructure

- Start-Up: Contracting, IRB, Data Sharing
- Standardized Data and Distributed Data Network
- Relationship Network
- Governance that supports multi-institutional collaboration
- Multi-stakeholder Engagement
- Dissemination and a Focus on Impact
- (Open-science – under discussion)

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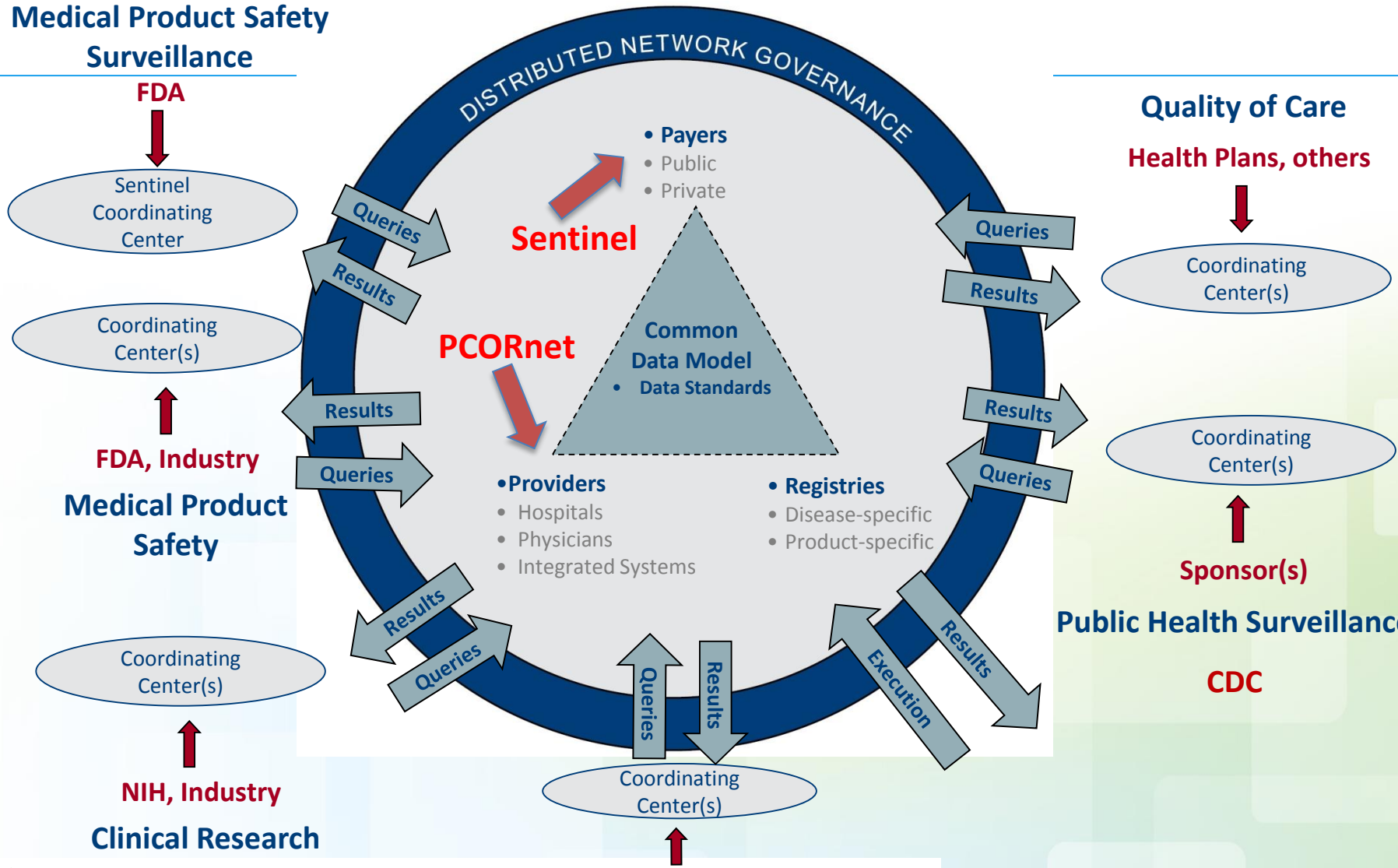
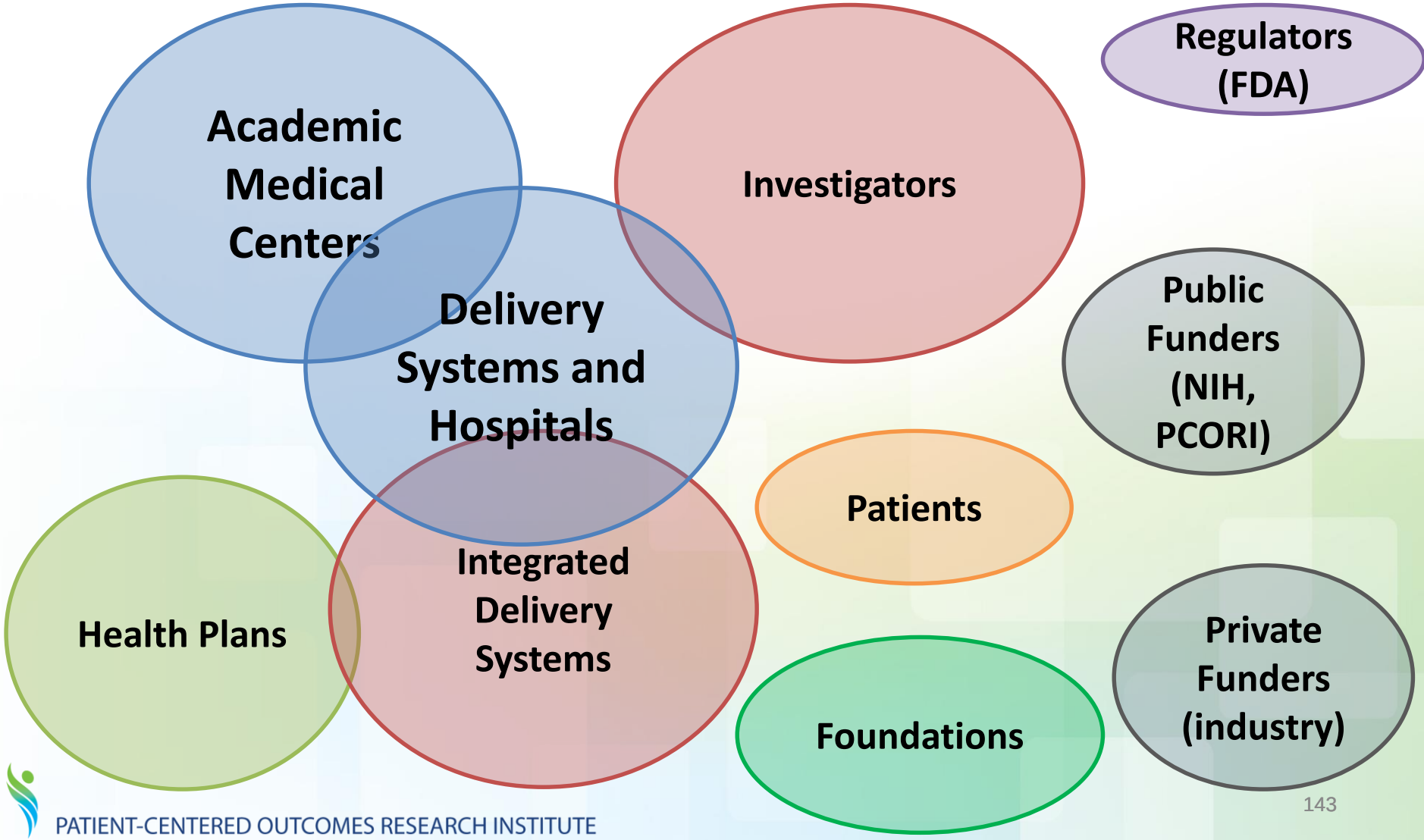
PCORnet as Part of a National Evidence Generation Infrastructure



Stakeholders in Evidence Generation



Incentives to participate in the evidence generation enterprise are fragmented and sometimes conflicted…

- Improving evidence base by funding studies
- Making regulatory decisions
- Monitoring, improving quality of care
- Increasing volume of patients or enrollees
- Securing research funding
- Pursuing a career in clinical research
- Getting answers to questions that matter
- Ensuring a disease or condition secures funding, and has portfolio of research

Etc.

Lessons from PCORnet

- Barriers remain:
  - Technical
  - Regulatory
  - Legal
  - Commercial
  - Cultural

- But… 2016 is a window of opportunity for change

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Clinical Data Collection: “The Good, the Bad, and the Beautiful”

Michael Hogarth, M.D.
Carrie D’Andrea, BSN, RN
Washington, DC
04 March 2016

Objectives

- Discuss the importance of improving data collection so that it is accurate and useful across multiple platforms
- Address current inefficiencies in data collection by frontline providers in the clinical setting
- Discuss the needs of clinicians to collaborate using new tools to organize and synthesize clinical information to better serve patients and improve their own productivity

“The Good”: Improving Data Collection

Improving data collection in the clinical setting allows us to:

- Integrate care, research and learning
- Enable seamless movement of data across platforms
- Provide multiple stakeholders access to patient data
- Create a more personalized approach to care
- Identify the needs of patients in a streamlined way
- Empower patients to participate directly in data collection
- Promote use of accurate and high-quality data acquisition

“The Bad”: Inefficiency in Clinical Data Collection

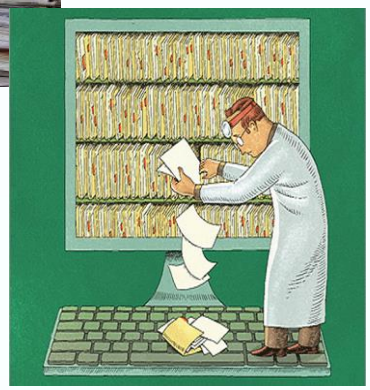
Alex

- *37 years old*
- *Works full-time*
- *Married with 2 young children*
- *Recently diagnosed with invasive breast cancer*

First point of contact- Nurse Navigator

- ❑ Details of the diagnosis
- ❑ Tests and procedures completed
- ❑ Request for outside records
- ❑ Assesses patient for additional services needed

From paper to digital – what has not improved



1907 – ~today
(pre-EHR)

"Where is that ER/PR Result?"
"Where is that outside MRI?"
"Did the path show invasion?"
"Where is that MammaPrint report?"

post-EHR

"Where is that ER/PR Result?"
"Where is that outside MRI?"
"Did the path show invasion?"
"Where is that MammaPrint report?"

Inefficiency in Clinical Data Collection

As Alex moves through the clinic…

- Initial consultation with a surgeon and an oncologist
  - Each provider reviews, synthesizes and documents Alex's information and writes **a separate clinic note**
- Deemed eligible and signs consent for the I-SPY 2 Trial
  - Research Coordinator collects and **synthesizes data from clinic notes and inputs it into a separate database**
- Ditto for 3 other clinical trials for which she is eligible (if only the surgeon had known when she saw the patient in the first visit!)

Inefficiency in Clinical Data Collection

- Cold Caps during chemotherapy
  - Research Coordinator collects study information through external surveys and inputs data into an **Excel spreadsheet**
- Pathology information
  - Clinic staff synthesizes pathology information from clinic notes and inputs data into **Microsoft Access**
  - Reports are reviewed at weekly multi-disciplinary meetings

Inefficiency in Clinical Data Collection

- Online and paper questionnaires
  - Track demographic data, family history and assist in creating appropriate referrals for additional services
  - **Scanned into the medical record**
- Survivorship
  - Survivorship nurse creates a treatment summary by synthesizing data from time of diagnosis through completion of treatment- **data input into a separate form created in the medical record**
  - Used by patient and future providers

Clear Indication Improvement is Needed

Why the current system isn't working

- Multiple systems used to collect data for the same patient (**6 different systems** for Alex within one clinic)
- Data finding is a major source of frustration and inefficiency for providers and researchers

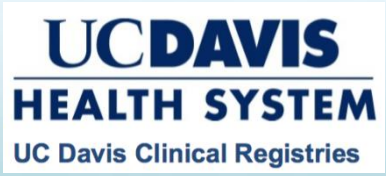
Looking ahead

- Clinicians would welcome tools to organize clinical information
  - Create a productive and efficient workflow and improve the ability to provide tailored, high-quality care
- Collaboration is key for developing systems to collect and use real-world evidence
- Build systems that allow data to be entered once (correctly!) and give multiple users access to it
  - Create opportunities for partnership, build trust and encourage shared learning
  - Platform for constant improvement

Michael Hogarth, MD, FACP, FACMI

(aka. Laura Esserman's alter ego)

Disclaimer: I'm just a "Plain Old Internist" (POI). I am not a renown scientist. I have no agenda other than improving care. I am not afraid of, nor enamored by, technology – I am a technology pragmatist!



US Health IT Today

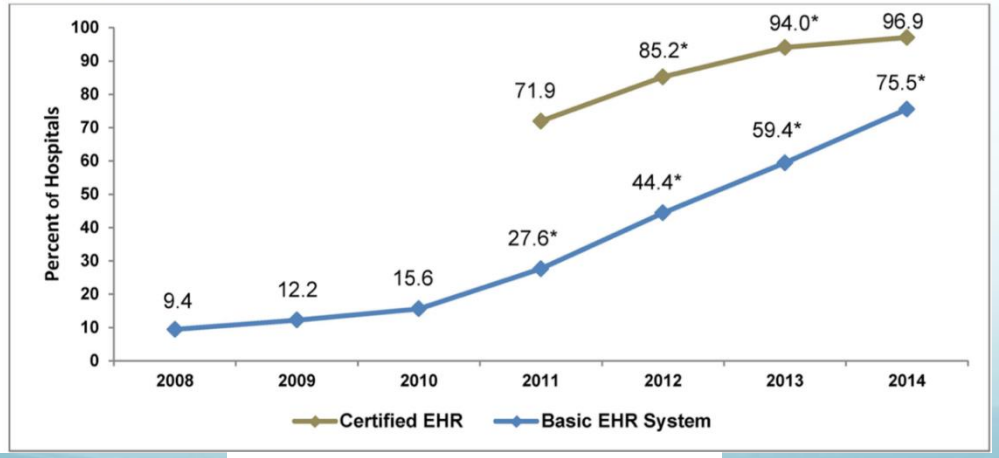
- ARRA HI-TECH has been **very successful in dramatically improving adoption of EHRs!**
- **EHRs do improve safety**!

BUT

- have NOT improved clinician usability in producing documentation - data (some data suggests it is **more** burdensome with EHRs)
- have NOT improved data quality -- “dirta” instead of “data”

Three out of Four Hospitals have a Basic EHR System.

Figure 1: Percent of non-Federal acute care hospitals with adoption of at least a Basic EHR with notes system and possession of a certified EHR: 2008-2014



ONC Data Brief ■ No. 23 ■ April 2015

The real world physician experience with EHRs

information finding takes time because notes are bloated and “new” or “key” data is hard to find...

I don’t have time, so I will cut & paste...

RESEARCH LETTER

Use of Internist's Free Time by Ambulatory Care Electronic Medical Record Systems

Physicians complain about the time costs and other effects of electronic medical records (EMRs).[1-3] In a small survey,[4] family practice physicians reported an EMR-associated loss of 48 minutes of free time per clinic day ($P < .05$). We collaborated with the American College of Physicians (ACP) to revise the instrument from this study and surveyed the ACP’s national sample of internists to determine the extent of this problem.

JAMA Internal Medicine Published online September 8, 2014

Survey of 845 primary care providers

“**48min** loss of free time per clinic day per physician”

Frustrations with EHRs rampant as development slows

From the May ACP Internist, *copyright © 2015 by the American College of Physicians*

By Elizabeth Gardner

Physicians who have mixed feelings about their electronic health record (EHR) systems are far from alone. As practices adopt EHRs in response to federal incentive payments (and impending Medicare penalties for not using EHRs), frustrations have skyrocketed, leading 2 major physician organizations to demand changes that make the systems easier to use.

Sidebar:
- Top recommendations on EHRs from ACP and the AMA

Electronic Health Records

EHR use a 'frustrating' time suck, physicians tell American Medical Association

Physicians feel investments in electronic health records failed to offer substantial returns due to impractical technology

The real world data user experience with EHR data

- **A number of 'key' data elements are not found in the record or are difficult to find** (MRI report is in scanned 'outside' documents, MRI images were never "sent"? what note has the correct clinical stage?, where is that ER/PR!!?)
- **Many key data elements are in EHR but as unstructured narrative text**
- Multiple large scale 'data networks' and value-based reimbursement projects requiring population metrics – but we have 'dirta' not data!
- "Data Stakeholders" today are focused almost exclusively on data access and data distribution
- **Limited attention is being given to data sourcing and improving data quality**

pcornet | The National Patient-Centered Clinical Research Network

CTSAcTS

CTSA Accrual to Clinical Trials (ACTs)

UC DAVIS MEDICAL CENTER
Beds: 619
Hospitals: 1
Outpatient Clinic Facilities: 16
Annual Inpatient Discharges: 32,300
Annual Outpatient Visits: 946,000
Est. DSRIP Funding Earned: $151.8M

California's DSRIP 2010-2015

Looking Ahead – 'The Beautiful'

- Imagine EHR/Health IT that **improves a clinician's data sourcing productivity**
  - Documenting less while creating more value!
- Imagine EHR/Health IT that **improves data quality**
- Imagine the **right data entered once by the right source** --- and made available to many data stakeholders:
  - Real world evidence (RWE) for pragmatic trials
  - Real world evidence using electronic patient reported information (ePRI)
  - Health system quality dashboards and clinical registries
  - Surveillance registries (cancer, devices, etc..)
  - Pharmaco-vigilance
  - Billers…

The OneSource Initiative

"enter the right clinical data once, use many times"

Others

eSource Widget

Enter the 'right' data once
Using dynamic XML-based checklists for data capture, rendering using the IHE SDC standard

Registries

Clinical Trials

Trial Matching

Regulators

Decision Support

Biomedical Research

Payors

Ancillary Patient Care Systems

Biopharma & Device Orgs

Home Care

Patient Engagement

Personalized Care

Clinical Efficiency

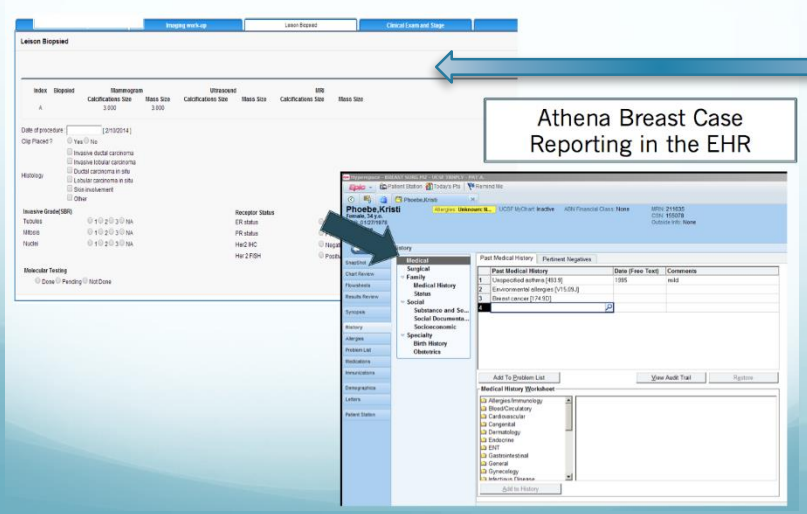
Good quality clinical care, clinical trials, registries, quality improvement, researchers, scientists, payors, regulators and others all require the same data elements…

What are we talking about?

- **Clinical Checklists → Form-based documentation of **key** data elements for high-impact diagnoses (Cancer, HIV, CHF, Alzheimer's, etc…)**
  - Each high-impact diagnosis has a set of required, structured, key data elements in a checklist "screen" in the patient's electronic health record
  - Use narrative for the 'clinical story telling' and 'rationale for decision making' – both are still absolutely essential for clinical care!

- **We need to change the documentation style in e-healthcare!!!**
  - Shift from requiring documentation "volume" and instead reward documentation "value" (key data entered into structured forms)
  - There is not much value in the EHR "complete exam", "5 component review of systems", etc... **(90% of EHR using physicians admit to cut&paste of exam, 80% say they will continue!)**

- **Documentation style is influenced heavily by reimbursement**
  - Will the evolution to value based reimbursement automatically lead to value-based documentation? (not sure – Kaiser physicians still document the traditional way…)



Family history of breast cancer	Initial Diagnosis
Referred for Genetic Counselling	Initial Diagnosis
Menopausal status	Initial Diagnosis
Interested in fertility preservation	Initial Diagnosis
Last menstrual period	Initial Diagnosis
Major comorbid conditions	Initial Diagnosis
ECOG Performance Score	Initial Diagnosis
Method of detection	Initial Diagnosis
Was cancer detected between screening intervals?	Initial Diagnosis
Multifocal disease	Initial Diagnosis
Imaging work-up	Initial Diagnosis
BIRADS Density	Initial Diagnosis
Lesion Visible, Mammogram	Initial Diagnosis
Lesion Index	Initial Diagnosis
Lesion laterality	Initial Diagnosis
Calcification Size (cm), Mammogram	Initial Diagnosis
Mass Size (cm), Mammogram	Initial Diagnosis

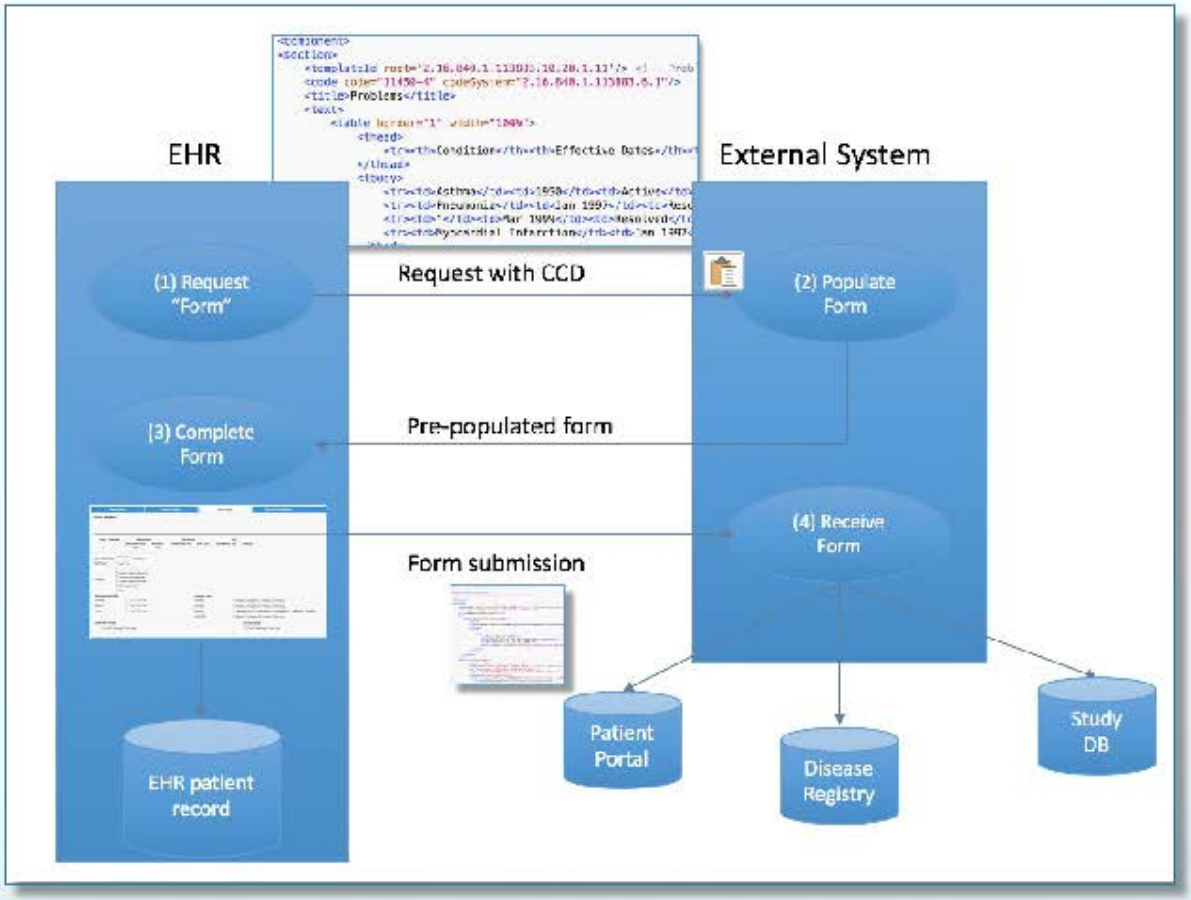
Athena core data elements

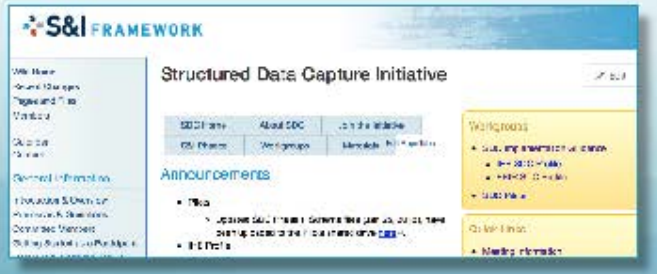
Will checklists cause further rebellion?

- **No**, because the clinical checklist has real value to the clinician!
  - The effort is rewarded if clinicians document this way for all patients with high impact conditions
  - OneSource for “key data” – makes it EASIER to provide good care!
- Clinical data checklists will NOT take “more time” – in fact, will decrease documentation time
  - Clinical checklists data elements have shared authorship with each source authoring their data (cardiologist, radiologist, pathologist, oncologist, surgeon, nurse, pcp, etc..) – much lower ‘documentation burden’ on each physician
- A clinical checklist will mean key data is in one place in the chart – makes it EASIER to find!
  - will dramatically reduce “foraging for information” by clinicians, billers, cancer registrars, quality officers, researchers, and others…
- A structured clinical checklist can be packaged and electronically shared between systems – makes it EASIER to coordinate care, EASIER to merge data for multi-institutional pragmatic trials, etc..

OneSource “Clinical Checklists” Infrastructure

Making it happen:
ONC's Structured Data Capture (SDC) Initiative





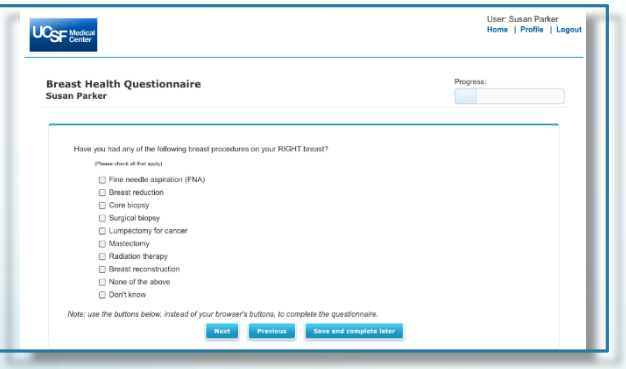
Patient as a Source of Data -- Engaging Patients

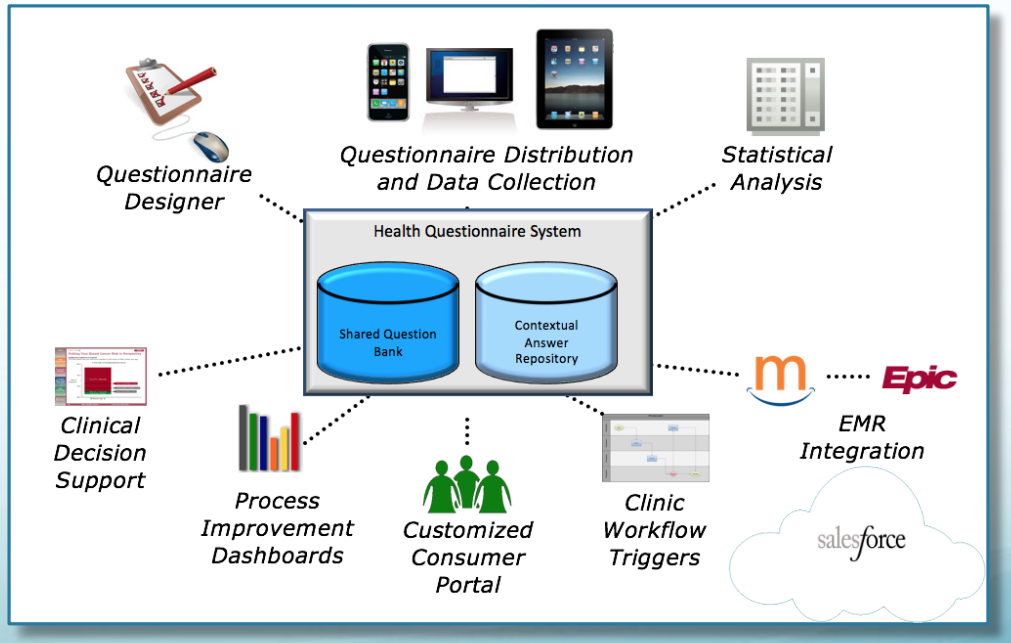
Implementing Electronic Patient Reported Data (ePRI)

athena BREAST HEALTH NETWORK

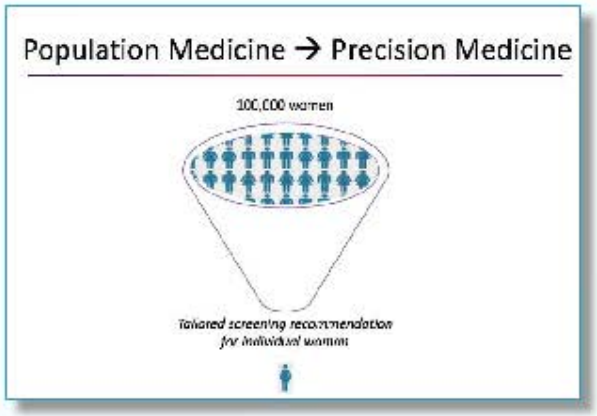
Athena Breast Health Network Screening Cohort

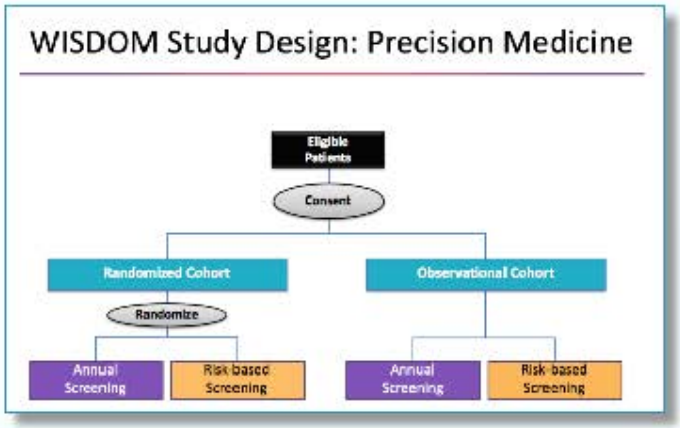
- 5 UC med centers, Sanford
- To date: 90,000+ questionnaires of women undergoing screening mammograms
  - Automated risk models as a web service
  - Composite 15yr risk of breast cancer provided to PCP
  - Risk report fully integrated with EHR record
  - High-risk referred to genetic counseling

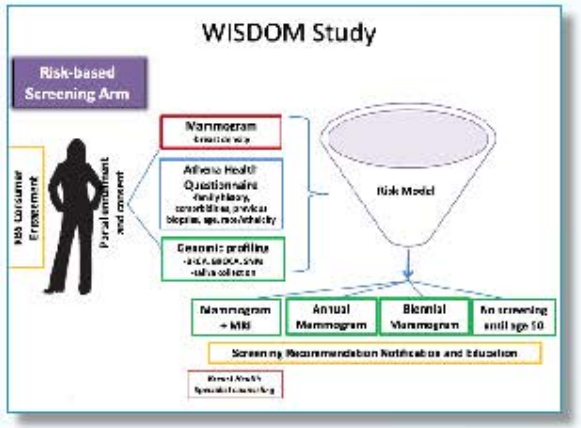




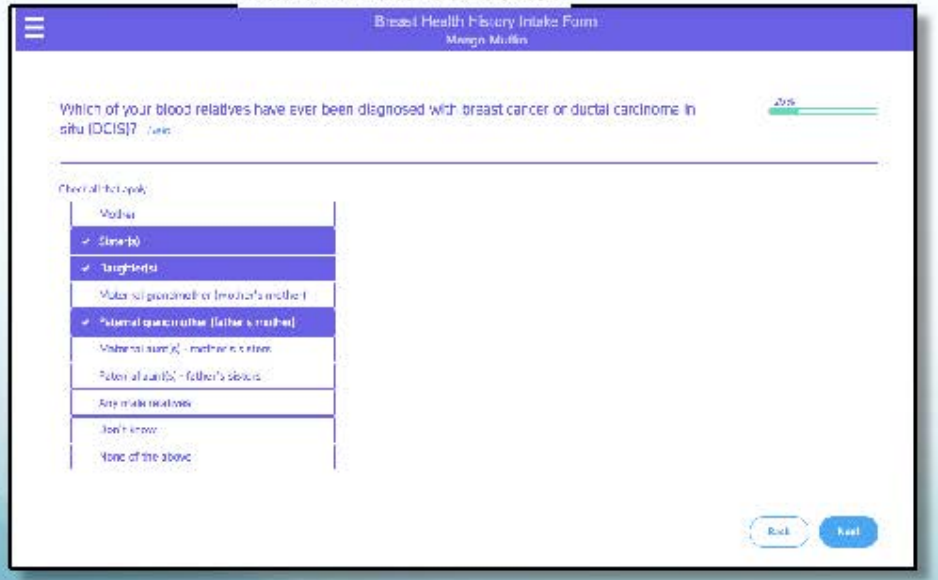
The Athena WISDOM trial



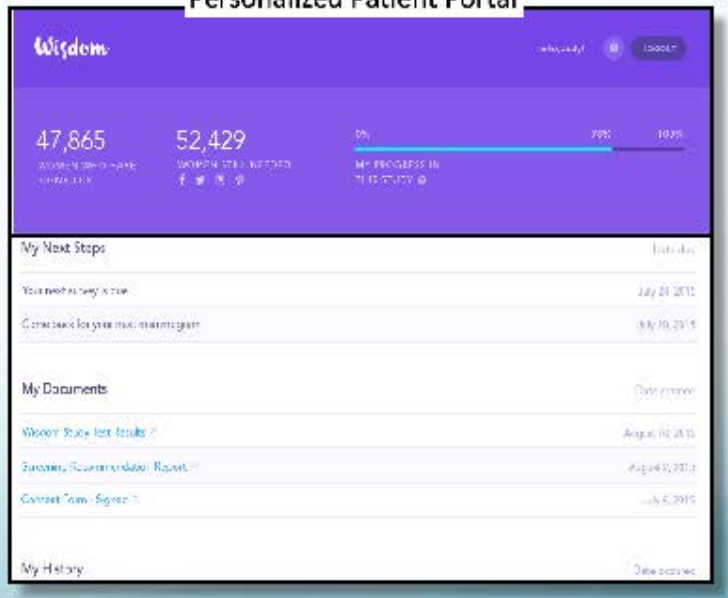




Patient Data Collection



Personalized Patient Portal



athena BREAST HEALTH NETWORK

Funded by PCORI

Share Your Wisdom

Emerging opportunities (or challenges) in real world data

END

Lake Tenaya, Yosemite National Park

https://en.wikipedia.org/wiki/Tenaya_Lake

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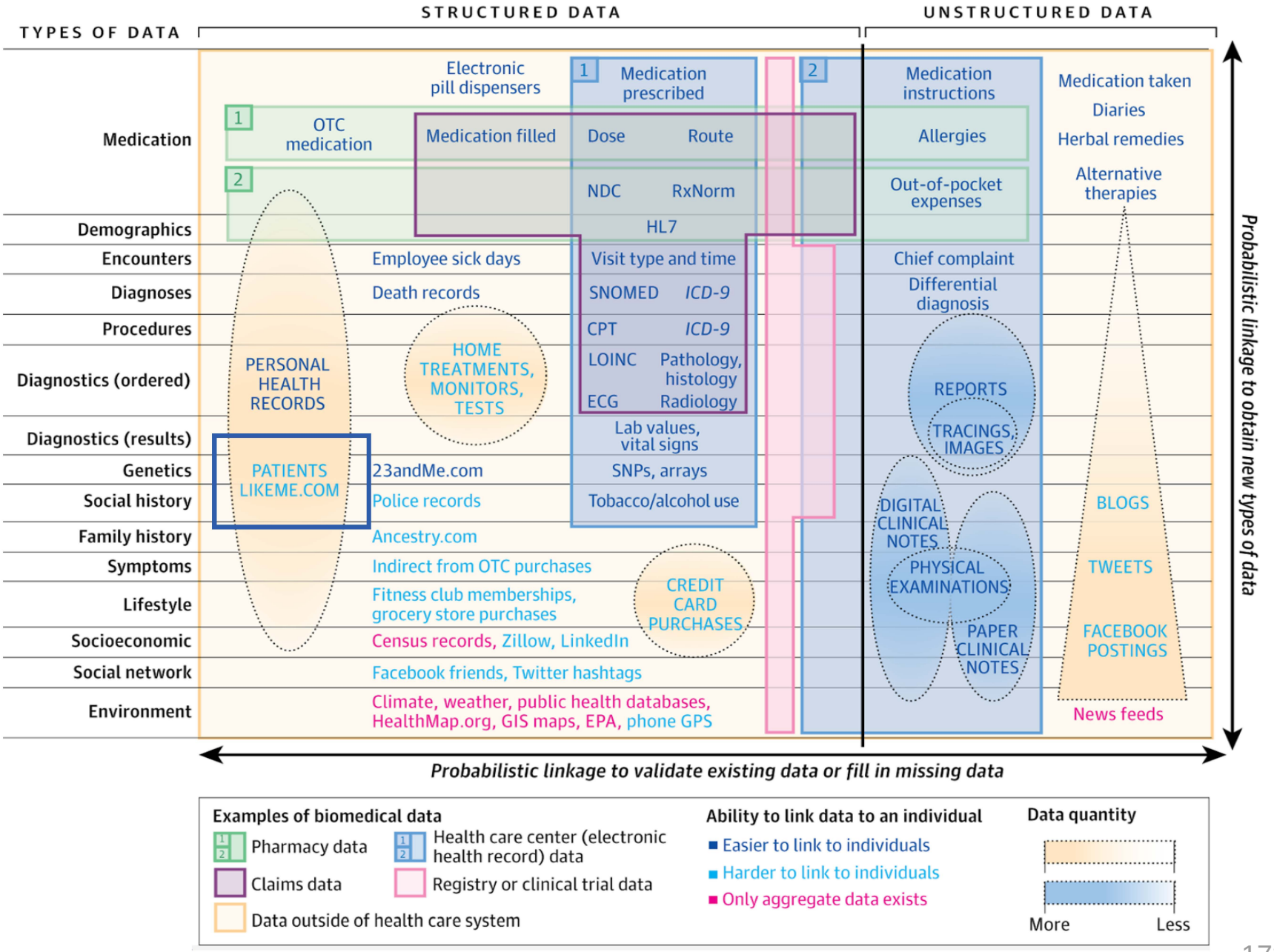
Patients as Vested Partners: The Role of Patient Generated Data

March 4, 2016

Sally Okun
VP Advocacy, Policy & Patient Safety | PatientsLikeMe

The Tapestry of Potentially High-Value Information Sources That May be Linked to an Individual for Use in Health Care

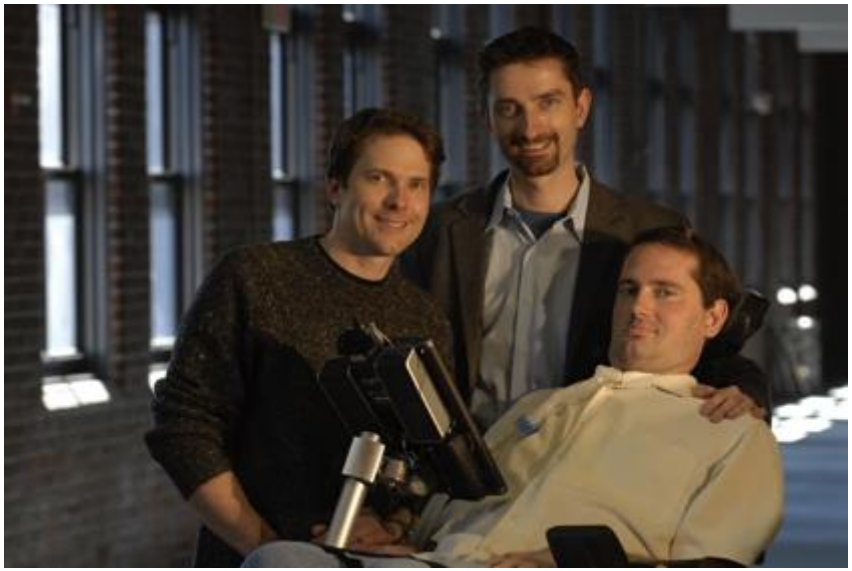


Weber GM, Mandl KD, Kohane IS. Finding the Missing Link for Big Biomedical Data. JAMA. Published online May 22, 2014. doi:10.1001/jama.2014.4228.

About PatientsLikeMe

Our mission is to improve the lives of patients through new knowledge derived from shared real-world experiences and outcomes

- Founded in 2004 as a direct response to family's experience with chronic disease
- Built as an open, patient facing research based community in a social network
- Launched as ALS community in 2005 and opened to any condition in 2011
- Deep patient data and experience in 30-40 chronic life-changing conditions
- Its global, free to join and has no adverts



Over a decade of advancing patient-generated data…

Patients	Data	Insights
• 400,000+ patients • 2,500+ conditions	• 30+ million structured data points • 3+ million free-text posts • 15+ PROMs	• 70+ publications, most peer reviewed • Patient-generated taxonomy • Safety monitoring platform • Open Research Exchange (ORE)

Members Represent Various Therapeutic Areas

Neurological and brain
- Multiple Sclerosis (48,187)
- Parkinson's Disease (11,940)
- Epilepsy (9,944)
- Migraine (8,365)
- ALS (Amyotrophic Lateral Sclerosis) (8,141)

Muscle, bone, and joint
- Fibromyalgia (62,220)
- Rheumatoid Arthritis (RA) (9,207)
- Systemic Lupus Erythematosus (18,124)
- Osteoarthritis (5,261)
- Degenerative Disc Disease (3,496)

Mental health
- Major Depressive Disorder (21,511)
- Generalized Anxiety Disorder (18,755)
- Post-traumatic stress disorder (14,735)
- Panic Disorder (10,112)
- Social Anxiety Disorder (6,022)

Metabolism and nutrition
- Diabetes Type 2 (18,156)
- Diabetes Type 1 (2,473)
- Obesity (2,099)
- High Cholesterol (Hypercholesterolemia) (1,921)
- Vitamin D Deficiency (1,681)

Gastrointestinal
- IBS (Irritable Bowel Syndrome) (4,872)
- GERD (Gastroesophageal reflux disease) (4,215)
- Crohn's Disease (4,023)
- Ulcerative colitis (1,234)
- Celiac Disease (828)

Respiratory
- Asthma (5,855)
- Idiopathic Pulmonary Fibrosis (5,457)
- COPD (Chronic Obstructive Pulmonary Disease) (2,349)
- Sleep Apnea Disorder (1,909)
- Cystic Fibrosis (1,237)

Oncology
- Lung Cancer (4,020)
- Multiple Myeloma (2,580)
- Breast Cancer (1,673)
- Prostate Cancer (827)
- Colon Cancer (428)

Cross-disease symptoms
- Anxious mood (115,512)
- Depressed Modd (116,211)
- Fatigue (117,668)
- Pain (114,463)
- Insomnia (104,507)

FDA PDUFA V Patient-focused Drug Development Activities

Conditions	PLM Members	FDA PFDD Workshop Contributions
CFS / ME	12,077	• Submitted comment to FDA public docket
Fibromyalgia	59,644	• "What's daily life like?" pre-meeting survey • In-person attendance • Provided public comment at meeting • Submitted full report to public docket
Idiopathic Pulmonary Fibrosis	4671	• "What's daily life like?" pre-meeting survey • In-person attendance • PLM member selected to present on panel • Provided public comment at meeting • Submitted full report to public docket

Parkinson's Disease	10,372	• PatientsLikeMe Parkinson's Disease Report
		  • Structured data community profile
		  • "What's daily life like?" pre-meeting survey
		  • Qualitative data analysis
		• In-person attendance
		• PLM member selected to present on panel

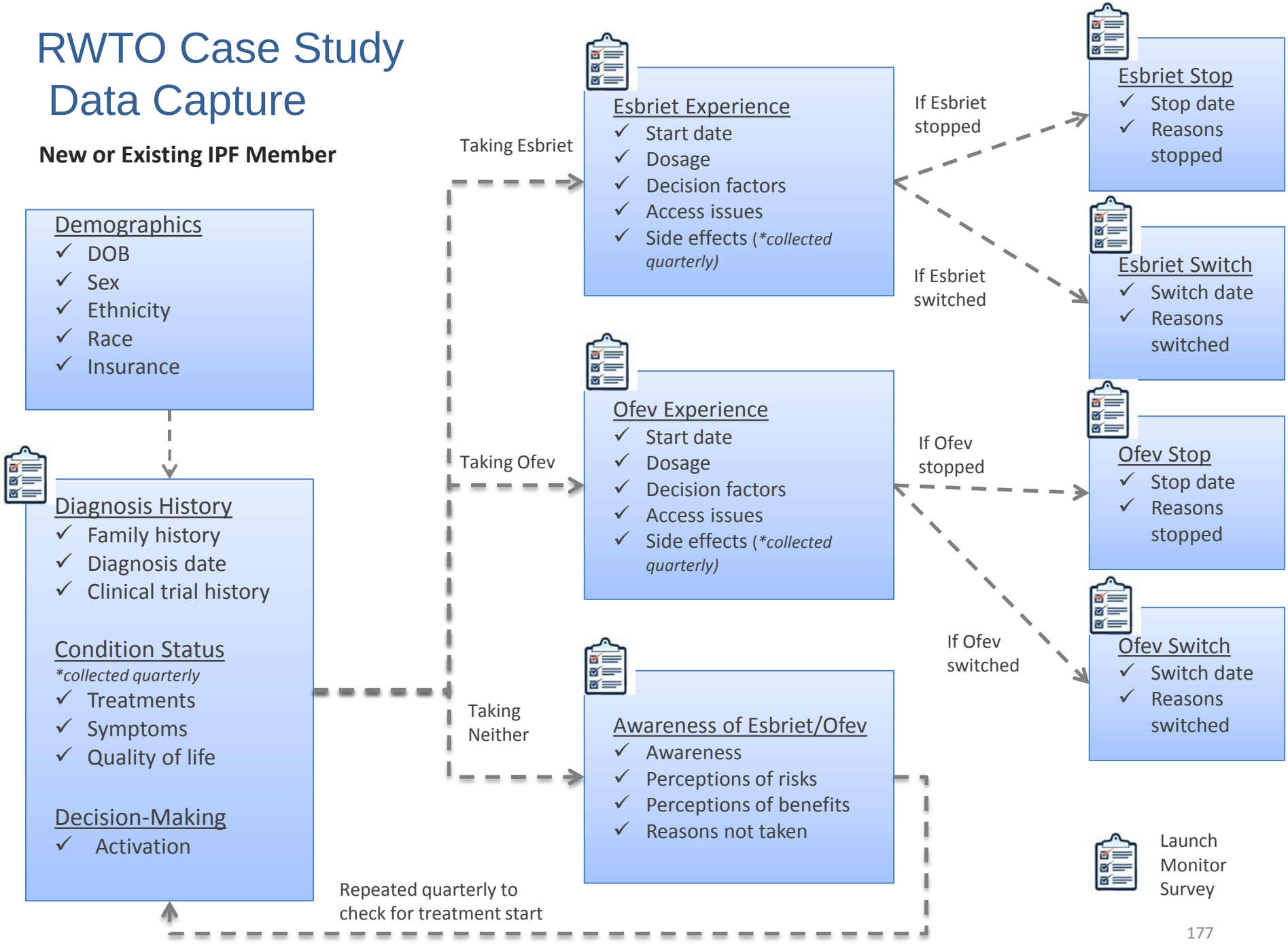
Psoriasis (3/17/16)	5,331	• Member survey & analysis plan in development • Will include PLM insights from previous projects • Planning for PLM team and members to attend

Real-world Treatment Observation in Novel Therapeutics

Study Title	Monitoring experiences of patients with nintedanib and pirfenidone, two newly approved products for idiopathic pulmonary fibrosis (IPF) in October 2014.
Study Design	Retrospective database extraction and analysis; and prospective survey data collection with analysis
Participants	757 PLM members who report the condition of IPF participated in the study
Objectives	Develop a longitudinal data entry platform to capture treatment experiences and to engage patients in real time monitoring of access, safety, tolerability and effectiveness of novel therapeutics.
Data Analysis	***On treatment arm:*** baseline survey of patients taking either product examined treatment decision making and experience with access. A reminder was sent every 90 days to complete treatment evaluation including dose, perceived effectiveness, satisfaction, likelihood of stopping treatment, side effects, disease status changes and costs. ***Off treatment arm:*** baseline survey of patient not taking either treatment to understand awareness of treatment options and reasons for not taking treatment. All IPF patients sent reminder every 90 days to update status of disease, forced vital capacity, diffusing capacity, transplant status. Descriptive statistics of survey results and member profiles were tabulated and compared.
Conclusions	• Many patients with IPF unaware of new treatment options • Similar rate of satisfaction and likely discontinuation for both treatments • Preliminary analysis found differences in side effect rates, both between medications and compared to the literature.
Overall	Too early to draw definitive conclusions. Data collection continues. Changes in disease status will be examined as well as sub-populations of interest to better inform patients and clinicians during treatment decisions.

RWTO Case Study Data Capture

New or Existing IPF Member



FDA and PatientsLikeMe Collaboration

Research Collaboration Agreement (RCA)

Goals	To analyze and evaluate ***data from a novel source*** for use by the FDA in support of its mission to protect the public health by assuring the safety, efficacy and security of medical products and devices.
Objectives	PatientsLikeMe and the FDA will systematically explore the potential of patient-generated data to inform regulatory review activities related to risk assessment and risk management.
FDA Team	Regulatory Science Staff (RSS) within the Office of Surveillance and Epidemiology (OSE) of the Center for Drug Evaluation and Research (CDER)

Progress	• Weekly Core Team teleconferences
	• PLM onsite visit to FDA in July
	• FDA onsite visit to PLM in September
	• PLM Data Science Workshop held at FDA in October
	• Data identification and transfer processes initiated
	• Research priorities identified relevant to four main program areas within OSE:
	  • Pharmacovigilance
	  • Pharmacoepidemiology
	  • Medication Error Prevention and Analysis
	  • Drug Product Risk Management

FDA and PatientsLikeMe Collaboration, cont.

Research Prioritization, Planning and Project Development	
Early Projects	**Data Characterization Projects** • MedDRA coding validation study • PLM ICSR quality study from reports submitted from MedWatch pilot • Drug treatment coding validation study • PLM patient population generalizability study • Data density and site engagement of PLM population
Emerging Project Development	• Off label use – perceived effectiveness and side effect reports • Real World Treatment Observations of novel therapeutics • Drug safety communication • Exploration of PLM side effect / tolerability information • Detection of medical errors • Exploration of signal from patient-generated data • Evaluation of REMS
Publications in development	• History of PLM's Patient-first Drug Safety Reporting System • Perspective on FDA / PLM Collaboration • History of PLM's patient-generated data

Given my status,
what is the best outcome
I can hope to achieve
and how do I get there?

Enhancing the Application of Real-World Evidence in Regulatory Decision-Making

Public Conference

March 3 & 4, 2016

The Washington Plaza Hotel