Biologics Effectiveness and Safety (BEST) Initiative

Azadeh Shoaibi, PhD, MHS

CBER Sentinel Lead

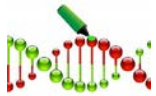
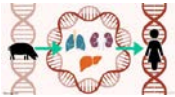
FDA Center for Biologics Evaluation and Research (CBER)

On behalf of CBER Sentinel Central Team

CBER-Regulated Products: Biologics

- Vaccines (preventative and therapeutic)
- Blood (components and derived)
- Human Tissues and Cellular Products
- Gene Therapies
- Xenotransplantation Products



CBER Surveillance Priorities

- Evaluating safety of vaccination during pregnancy
- Signal detection – use of natural language processing and artificial intelligence
- Pandemic preparedness – near real-time surveillance
- Emerging infectious disease surveillance & monitoring

Biologics Effectiveness and Safety (BEST) Initiative

- CBER Active Post-market Surveillance Program
- A component of Sentinel Initiative
- Commenced in October 2017

Why the BEST Initiative?

- Biologic products' special characteristics
  - Require special components in an active surveillance system
- Upgrading infrastructure
  - Access to EHR data sources
  - Reduce data lag
  - Easier, faster, affordable access to medical charts
  - On-demand analytic capabilities (no tools)
  - Large-scale capacity

BEST Initiative Objectives

Aim 1: Build data, analytics, infrastructure for an active, large-scale, efficient surveillance system for biologic products

Aim 2: Develop innovative methods to utilize electronic health records (EHR) effectively and establish automated adverse events reporting

BEST Initiative

IBM	IQVIA/OHDSI	Acumen

Collaborators
Regenstrief Institute
Columbia University
University of Colorado
Cerner
University of California, Los Angeles

Data Infrastructure

IBM

Data Sources	Patients (millions)
MarketScan (Claims)	60
CED (Linked EHR-Claims)	**4.9**

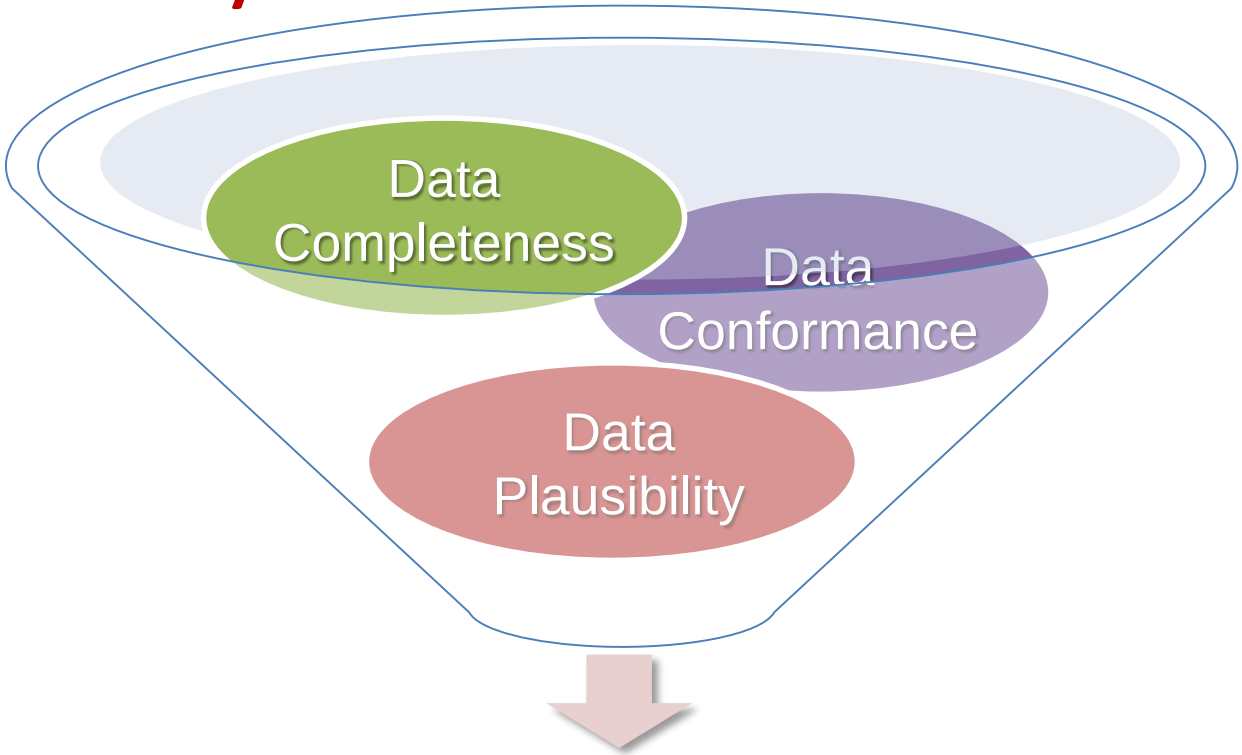
IQVIA/OHDSI

Data Sources	Patients (millions)
LRxDx (Claims)	160
Regenstrief Institute (Claims and EHR)	**19**
Columbia University (EHR)	**6.5**
University of Colorado (EHR)	**17**
Cerner (EHR)	**23**

Acumen

Data Sources	Patients (millions)
Blue Health Intelligence (Claims)	23

Data Quality Assessment



Data Quality Assessment Checks

BEST Initiative: Data, Tools and Infrastructure for Surveillance of Biologics

ACCOMPLISHMENTS

Infrastructure

IBM	IQVIA/OHDSI	Acumen

EHR Network

Reduced data lag to 3-4 months

Analytic capabilities on demand

Access to medical charts

Portal for CBER staff to access data for feasibility analyses

Improved operational efficiency and shorter turnaround time

BEST Initiative: Data, Tools and Infrastructure for Surveillance of Biologics

DESCRIPTIVE STUDIES

Vaccines

- Seasonal Influenza
- Hepatitis B
- Herpes Zoster
- Meningococcal
- Human Papillomavirus

Blood-Derived Products

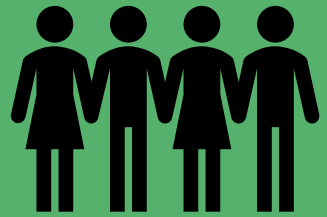
- Intravenous Immunoglobulins (IVIGs)
- Antihemophilic Factor (Factor VIII)
- Anti-inhibitor Coagulant Complex
- Fibrin Sealant
- Fibrinogen Concentrate
- Alpha-1 Proteinase Inhibitors
- C1 Esterase Inhibitors

Outcomes

- Syncope
- Thromboembolic events
- Coagulation product inhibitors (Factor VIII inhibitory antibodies)
- Hemolysis
- Anaphylaxis

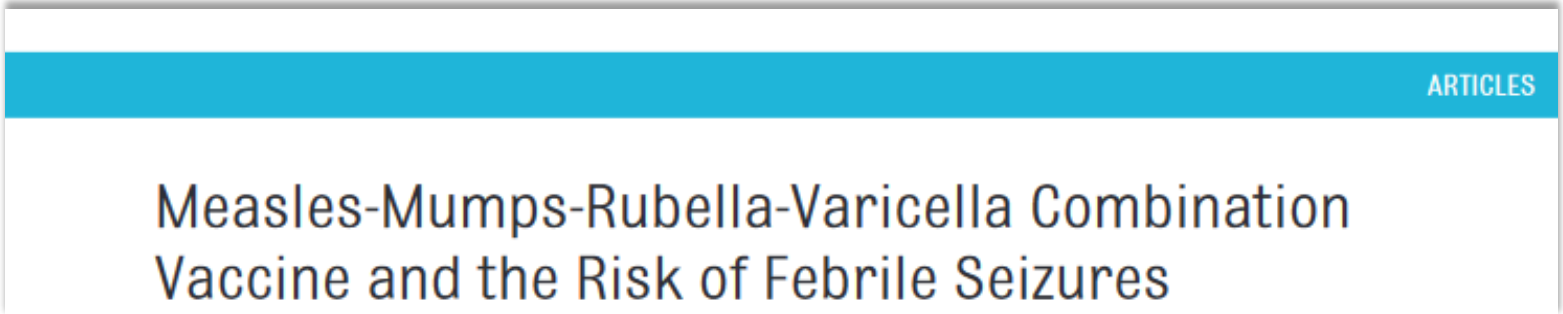
Special Populations

- Diabetics
- Hemophilia A
- Immunocompromised patients



Vaccine Study (Test Case)

- To test the new system, reproduced components of a published study



Klein NP et al. Pediatrics. 2010 Jul;126(1):e1-8.

- **Study Objective:** To assess the risk of febrile seizures in children receiving first dose of Measles, Mumps, Rubella, & Varicella (MMRV) compared to that of MMR and Varicella administered separately on the same day

MMRV vs. MMR+V & Febrile Seizures in Children

	Vaccine Safety Datalink (VSD) Study*	BEST: LRxDx claims database
Study Period	Jan. 2000-Oct. 2008	Jan. 2010-Oct. 2017
Age	12-23 months	1-2 years
Number of MMRV Patients (n)	83,107	920,948
Number of MMR+V Patients (n)	376,354	874,900
Risk Windows		
Week 1-2	7-10 days	7-10 days
	RR: 2.0 (95% CI=1.4-2.9)	OR: 1.86 (95% CI=1.38-2.04)
Week 1-6	0-42 days	0-28 days
	RR: 1.5 (95% CI=1.1-1.9)	OR: 1.26 (95% CI=1.22-1.42)

*Klein NP et al., Pediatrics, 2010

MMRV vs. MMR+V & Febrile Seizures in Children

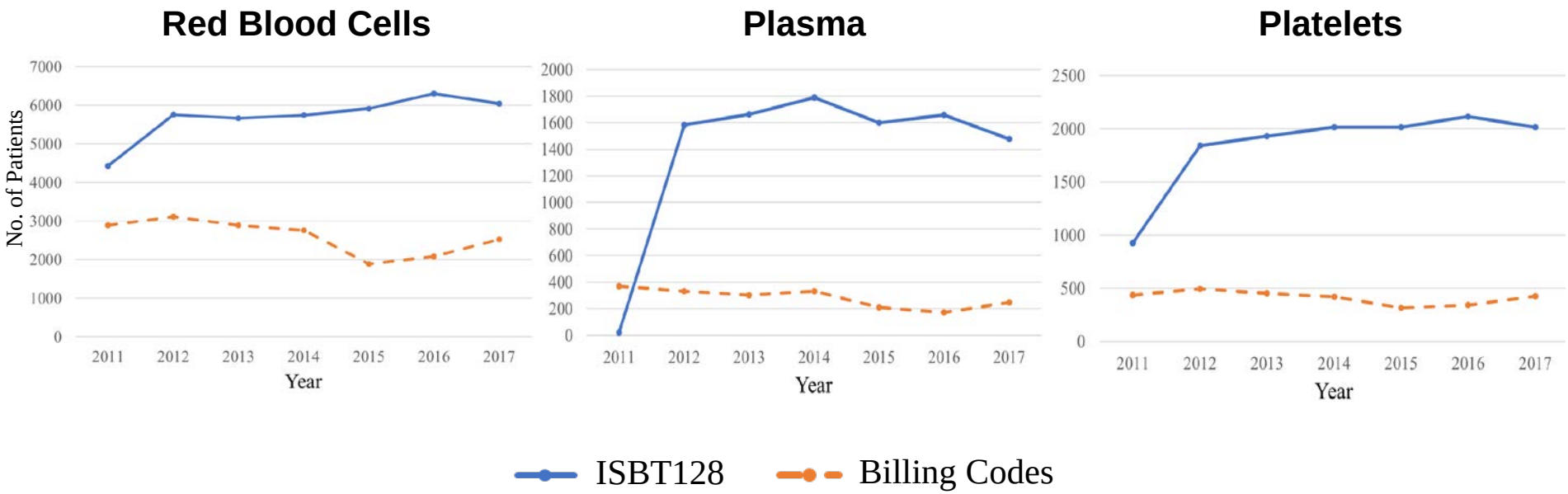
	Vaccine Safety Datalink (VSD) Study*	BEST: LRxDx claims database
Study Period	Jan. 2000-Oct. 2008	Jan. 2010-Oct. 2017
Age	12-23 months	1-2 years
Number of MMRV Patients (n)	83,107	920,948
Number of MMR+V Patients (n)	376,354	874,900
Risk Windows		
Week 1-2	7-10 days	7-10 days
	RR: 2.0 (95% CI=1.4-2.9)	OR: 1.86 (95% CI=1.38-2.04)
Week 1-6	0-42 days	0-28 days
	RR: 1.5 (95% CI=1.1-1.9)	OR: 1.26 (95% CI=1.22-1.42)

*Klein NP et al., Pediatrics, 2010

EHR Data Sources and ISBT128 Coding System

HEMOVIGILANCE STUDY

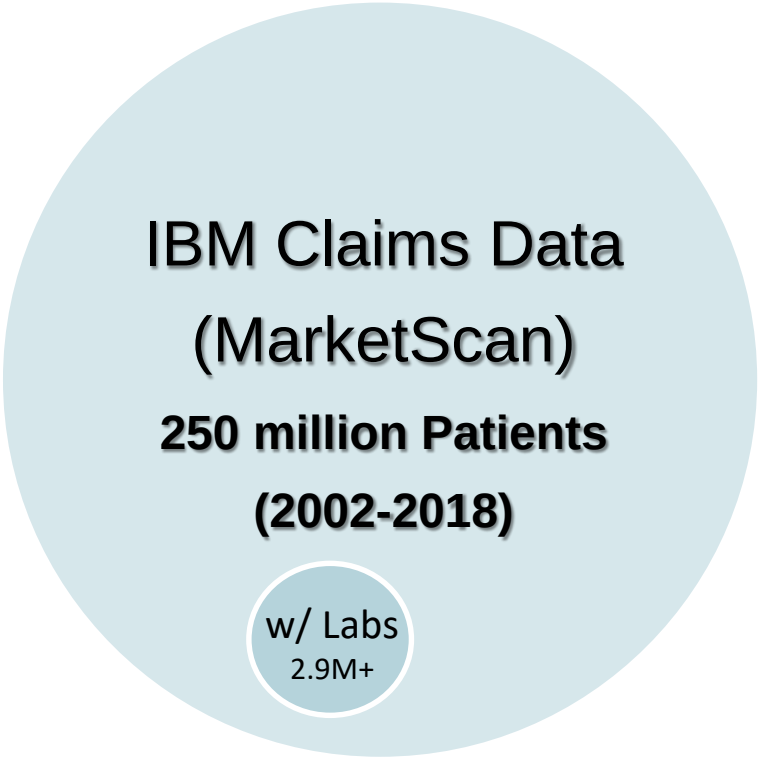
No. of Transfused Patients Identified by Billing Codes vs. ISBT128 codes



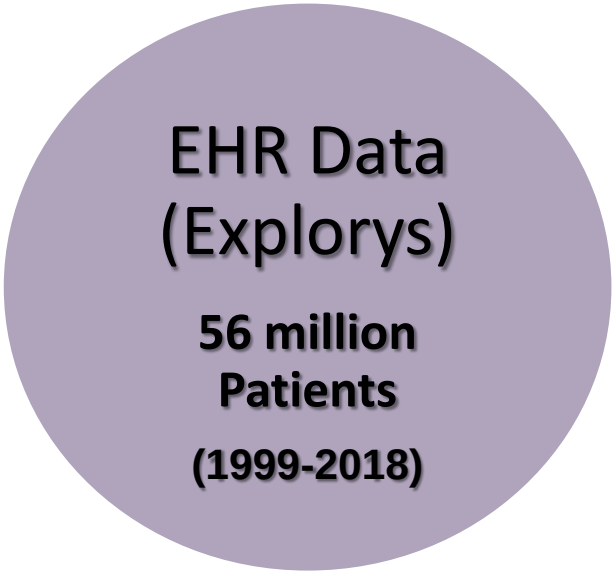
LINKED EHR-CLAIMS DATABASE

MarketScan (Claims):

- Includes more than 25% of all employer-sponsored U.S. healthcare beneficiaries
- 150 contributing employers with 200 unique carriers + 20 health plans
- Medicare supplemental plan enrollees
- Medicaid enrollees for 12 states



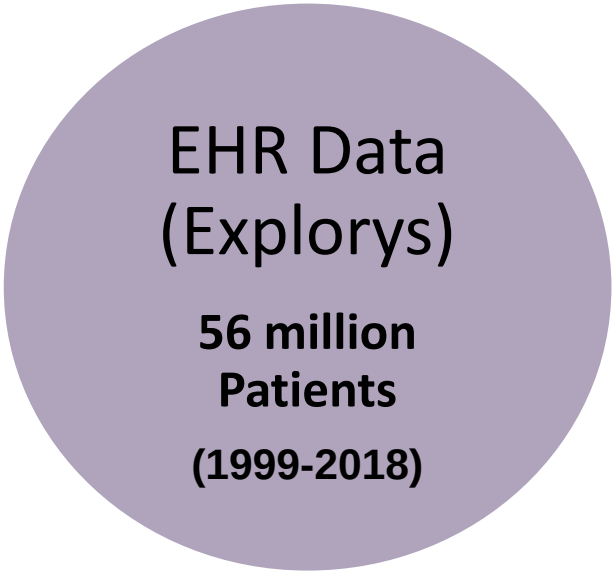
Source: IBM Watson Health, 2018

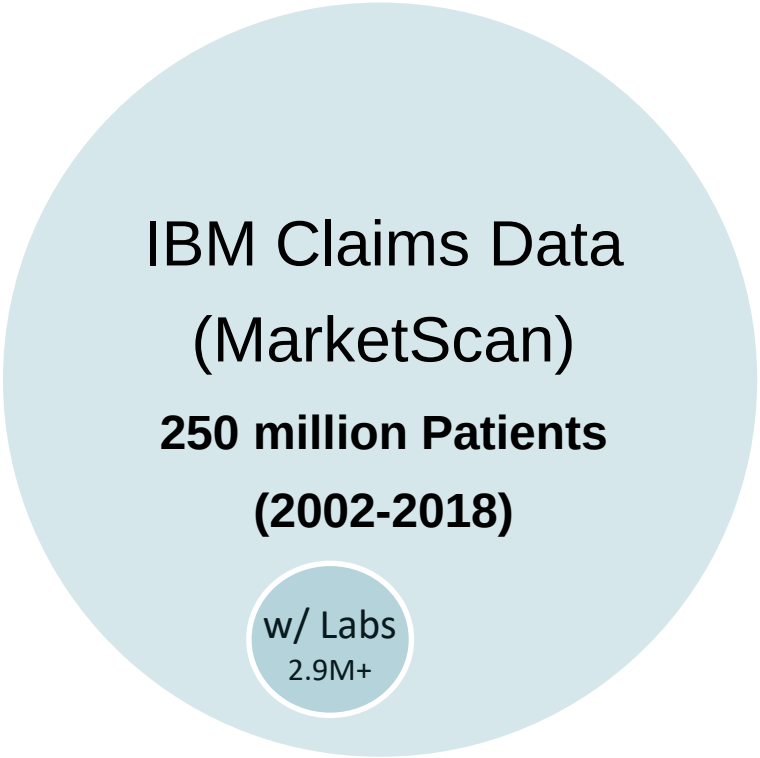


Explorys (EHR):

- 39+ Health Systems spanning academic centers and community practices
- ~344,000 Unique Providers
- Inpatient and outpatient encounters
- Clinical events and procedures
- Lab results
- Vital signs and other biometrics
- Medical and surgical history
- Patient-reported outcomes
- Inpatient drugs and ambulatory prescriptions

Source: IBM Watson Health, 2018

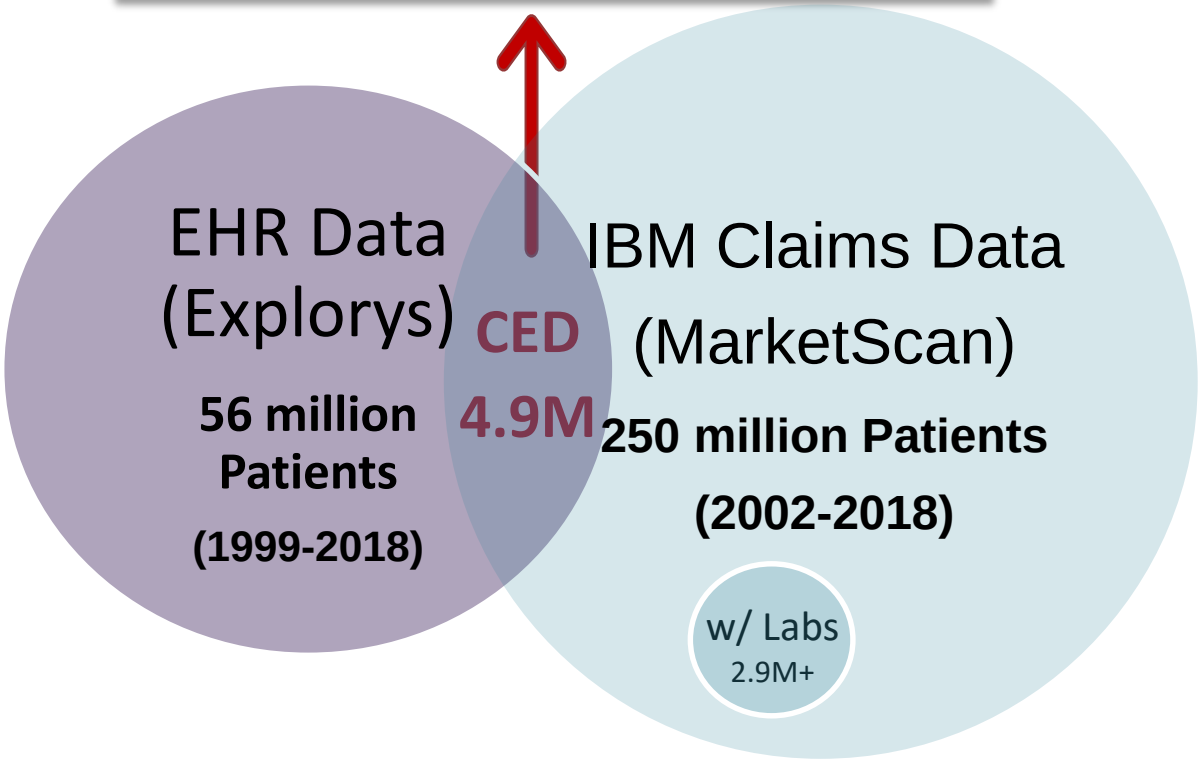




Source: IBM Watson Health, 2018

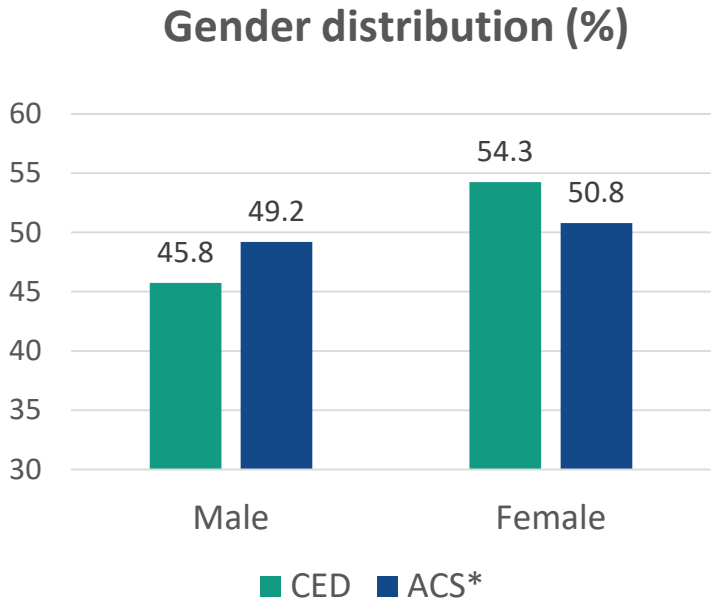
CED (Linked EHR-Claims Database)

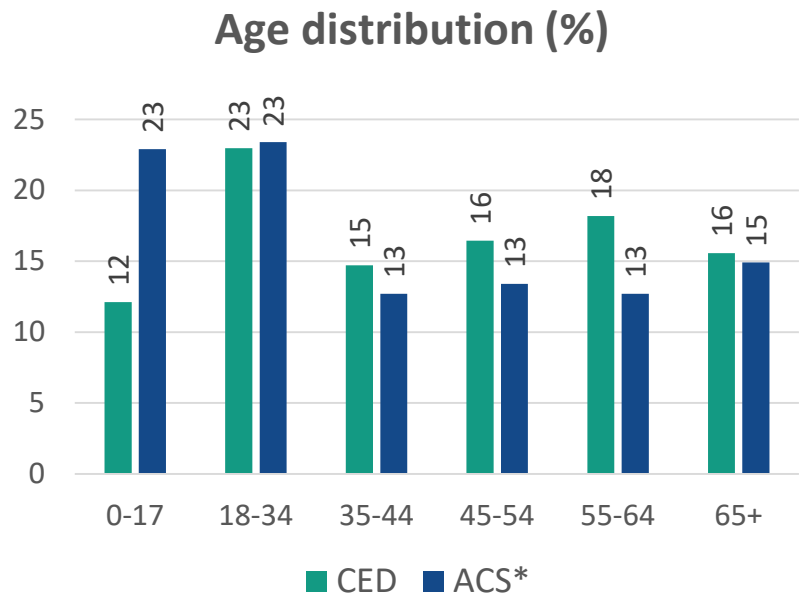
Deterministically linked patients



Source: IBM Watson Health, 2018

CED – Gender and Age Distribution

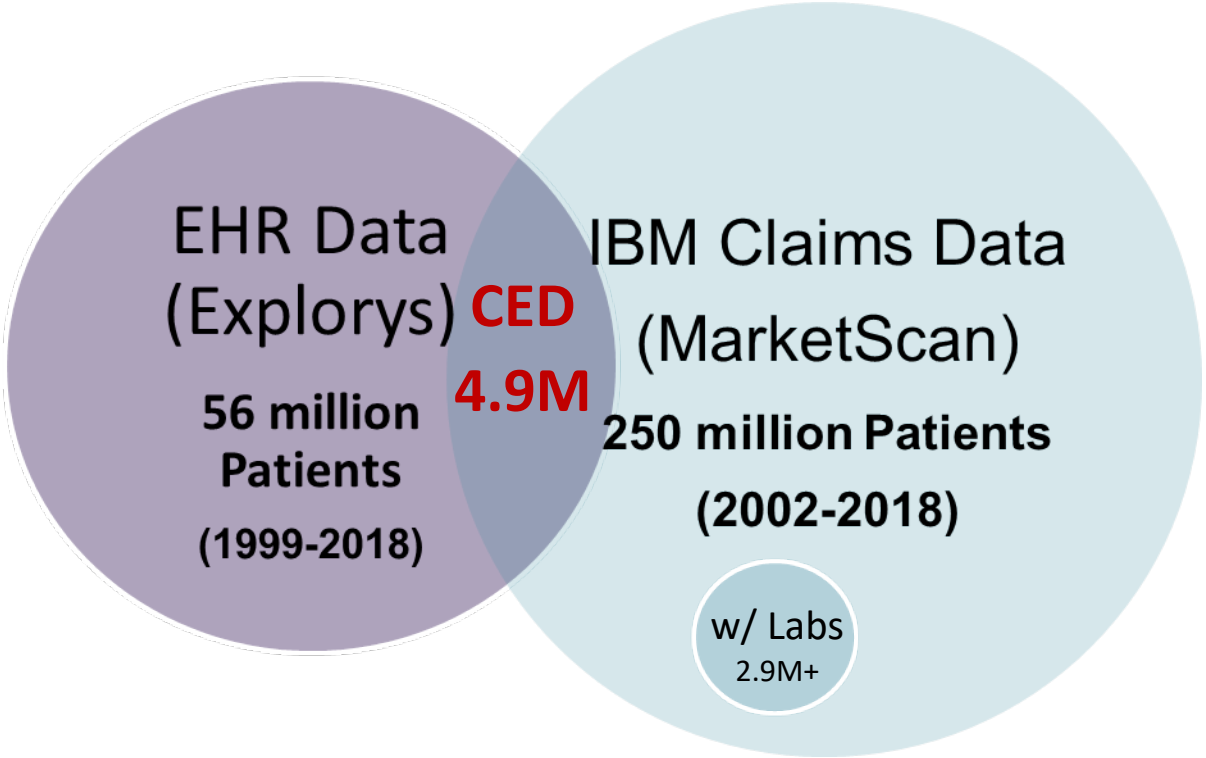




CED: CLAIMS-EHR LINKED DATABASE
ACS: AMERICAN COMMUNITY SURVEY, AN ONGOING SURVEY BY US CENSUS BUREAU

Source: IBM Watson Health, 2018 and *ACS or American Community Survey is an ongoing survey by the U.S. Census Bureau

IBM Linked Claims-EHR Database (CED)



Source: IBM Watson Health, 2018

CED DATABASE: PREGNANCY OUTCOMES & GESTATIONAL AGE VALIDATION

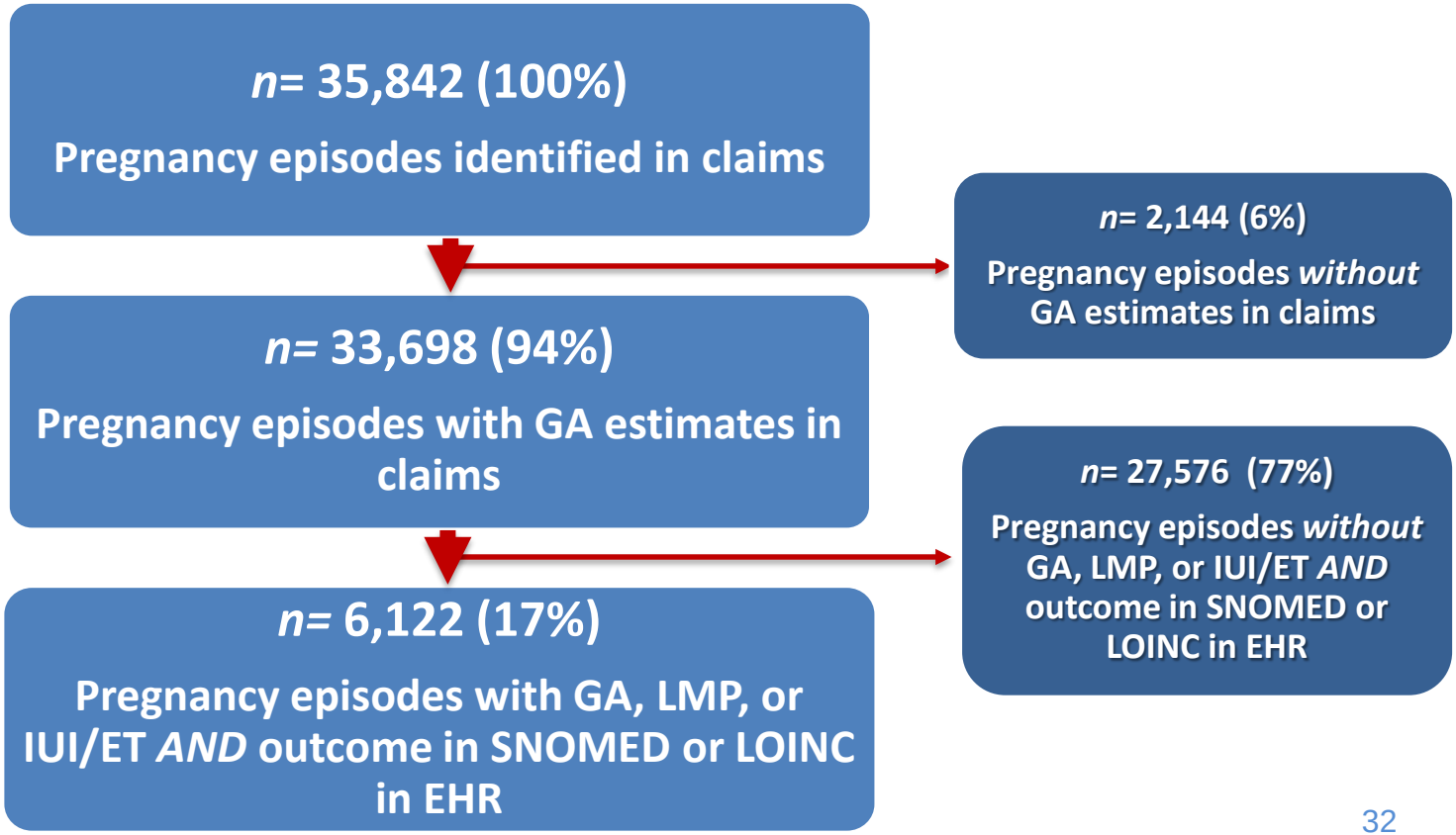
Study Objectives

1. Develop algorithms using ICD10 diagnosis codes and CPT/HCPCS procedure codes to
   a) Determine gestational age
   b) Classify pregnancy episodes as one of 4 outcomes:
      i. Full-term birth
      ii. Pre-term birth
      iii. Stillbirth
      iv. Spontaneous abortion

Study Objectives

2. Using GAIA case definitions as a reference method
   - To validate estimated gestational age and outcomes classifications
   - By comparing to clinician-adjudicated results based on review of structured CED (EHR) data elements
   - GAIA: Global Alignment of Immunization Safety Assessment in pregnancy

Study Population



Source: IBM Watson Health, 2018

Note: Preliminary results and subject to change

Clinician Adjudication Using Semi-Automated Chart Review

Data Abstraction

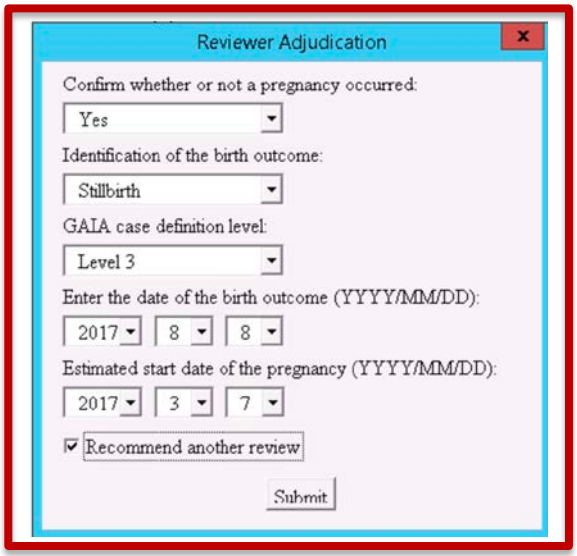
- Built-in questionnaire
- Structured components of EHR

Clinician Review

- Display GAIA-related structured EHR elements

Outcome Adjudication

- Full chart of structured EHR pregnancy episode available to clinician in detailed view



Source: IBM Watson Health, 2018

Summary

- Built a new active surveillance system for biologic products
- Incorporated multiple large sources of EHR
  - Claims & administrative databases
  - Linked EHR-claims database
- Access to EHR provides
  - Data elements for clinical data, blood coding system
  - Medical charts

Summary

- Reduced data lag to 3-4 months
- On-demand analytic capabilities
- CBER staff has access to data and tools for feasibility analyses
- Improved operational efficiency and shorter turnaround time

Acknowledgements

- CBER Sentinel Central Team
  - Kinnera Chada, PhD
  - Joyce Obidi, PhD
  - Kristin A. Sepúlveda
  - Hui-Lee Wong, PhD
  - Judith Cope, MD, MPH
- Office of Biostatistics and Epidemiology
- CBER product offices: OVRR, OBRR, OTAT
- IBM Global Business Services, IBM Watson Health Team
- Acumen Team
- IQVIA Team
- OHDSI Collaborators
  - Columbia University
  - Regenstrief Institute
  - University of Colorado
  - Cerner
  - University of California Los Angeles

Thank You