Advancing the Development of Pediatric Therapeutics (ADEPT) Workshop Summary

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Vanderbilt University Medical Center

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Disclosures

- The speaker has no financial conflicts of interest to disclose.

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Workshop Summary

- Key Concepts
- Innovative Approaches
- Importance of Partnership
- Challenges and Caveats
- Future State and Next Steps

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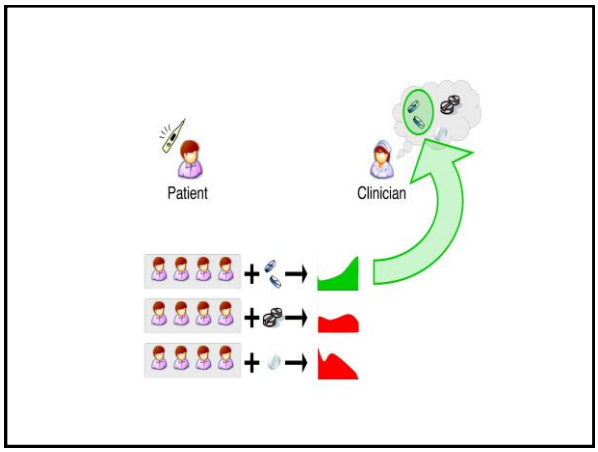

What words come to mind when you think about "Big Data" for pediatric safety?

Menti.com

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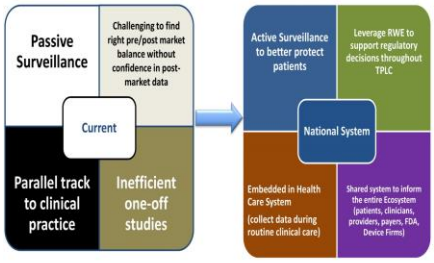
National System Paradigm Shift



www.fda.gov

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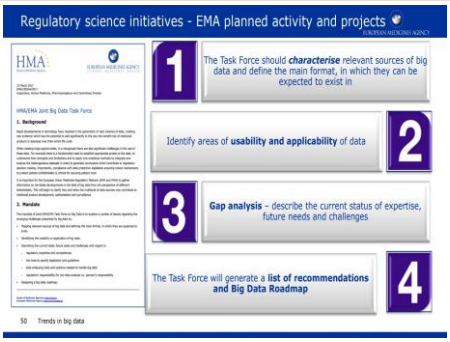
Regulatory science initiatives - EMA planned activity and projects



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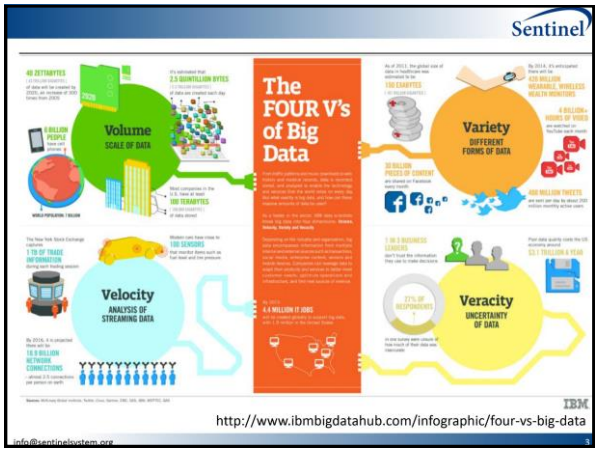
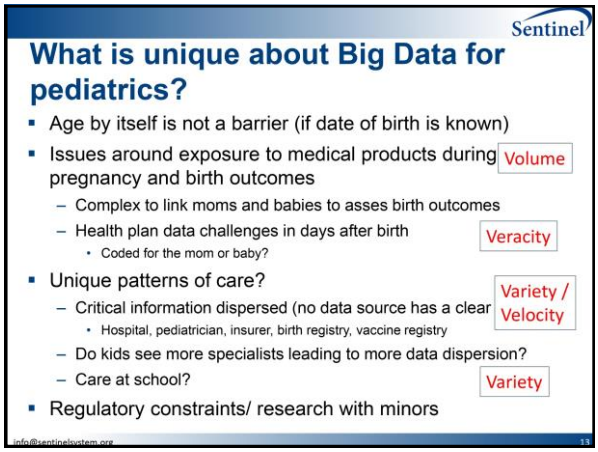
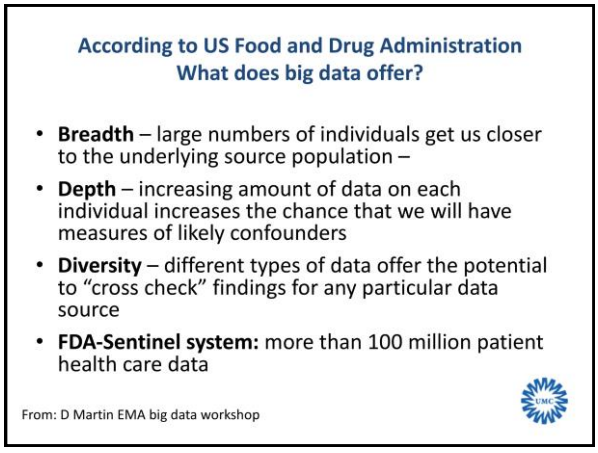
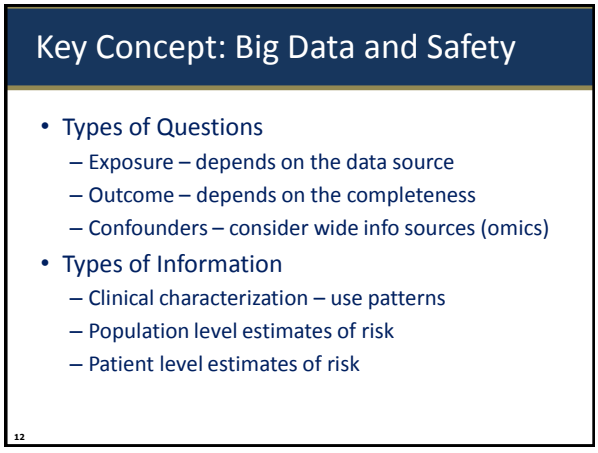

Sentinel
The FOUR V's of Big Data
Volume
SCALE OF DATA
Variety
DIFFERENT FORMS OF DATA
Velocity
ANALYSIS OF STREAMING DATA
Veracity
UNCERTAINTY OF DATA
IBM
http://www.ibmbigdatahub.com/infographic/four-vs-big-data


Sentinel
What is unique about Big Data for pediatrics?
Age by itself is not a barrier (if date of birth is known)
Issues around exposure to medical products during pregnancy and birth outcomes
Volume
Complex to link moms and babies to asses birth outcomes
Health plan data challenges in days after birth
Veracity
Coded for the mom or baby?
Unique patterns of care?
Critical information dispersed (no data source has a clear
Variety / Velocity
Hospital, pediatrician, insurer, birth registry, vaccine registry
Do kids see more specialists leading to more data dispersion?
Care at school?
Variety
Regulatory constraints/ research with minors


According to US Food and Drug Administration
What does big data offer?
Breadth – large numbers of individuals get us closer to the underlying source population –
Depth – increasing amount of data on each individual increases the chance that we will have measures of likely confounders
Diversity – different types of data offer the potential to "cross check" findings for any particular data source
FDA-Sentinel system: more than 100 million patient health care data
From: D Martin EMA big data workshop


Key Concept: Big Data and Safety
Types of Questions
Exposure – depends on the data source
Outcome – depends on the completeness
Confounders – consider wide info sources (omics)
Types of Information
Clinical characterization – use patterns
Population level estimates of risk
Patient level estimates of risk
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Key Concept: Big Data and Safety

- Driving Force
  - Need for Certainty – Fit for Purpose
    - Risk – to restrict use
    - Efficacy – to expand use
- Areas of Opportunity
  - Patient reported outcomes (surveys, apps)
  - Inference (lessons from machine learning)

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Key Concept: Validation

- Validation of Data Elements
  - Medical record review
  - Assessing temporal relationship
  - Completeness of data against expected
- Validation of Findings
  - Multiple sites
  - Multiple studies or independent sites
  - Machine Learning – Internal & External validation

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Key Concept: Big Data in Children

- Standards for age, gender, developmental
  - Note
  - Note
  - Note
- Incorporate develomental factors

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Key Concept: Big Data in Children

- Family-centric analyses
- Genomics

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Key Concept: Big Data in Children

- Long-term safety data
  - Key given long time horizon
  - Challenges
    - No unique identifiers
    - Fragmented healthcare
    - Mobility and life changes (i.e. college, military)

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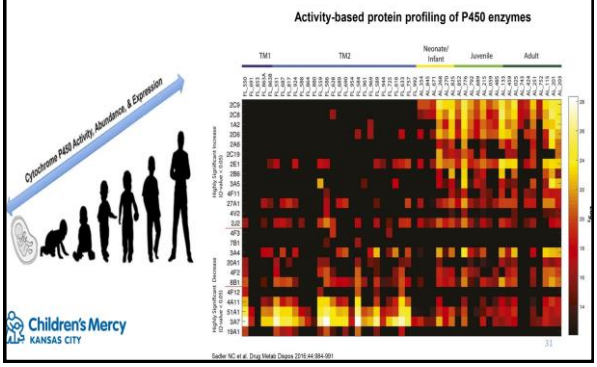
Variability



Innovative Approaches to Big Data

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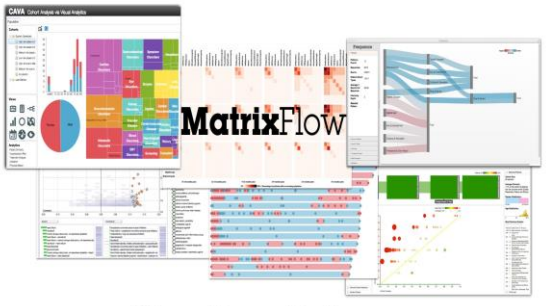
other tools for clinical exploration



Videos and Papers at **http://perer.org**

Model Interpretability

predictive model prospector

Josua Krause, Adam Perer, and Kenney Ng. Interacting with Predictions: Visual Inspection of Black-box Machine Learning Models. ACM Conference on Human Factors in Computing Systems (CHI 2016). San Jose, California. (2016).

take-aways

Clinical Data is complex and messy.

Exploratory visual analytics tools fill a much needed gap.

However, exploratory tools alone do not address their predictive desires.

There is a strong role for visualization in predictive tasks.

CareFlow (CHI 2013)

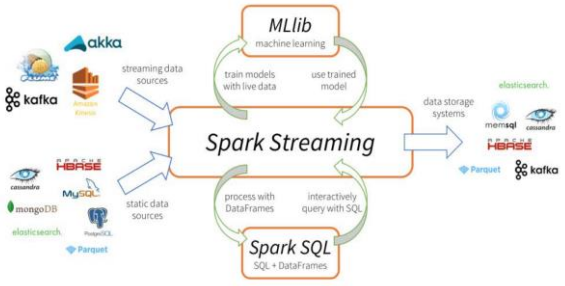
COQUITO (VAST 2015)

Prospector (CHI 2016)

Adam Perer

[papers and videos at http://perer.org]

Event Stream Processing (Spark Streaming)



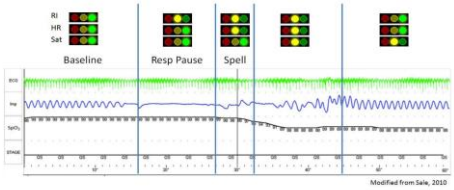
Neonatal Sepsis and Spells

Question: Can we identify neonatal spells prior to onset of nosocomial infection?

- Thommandram et al., built a neonatal ***spells algorithm*** [3] for detecting spells activity in real-time

Classifications:

- central apnoea
- vagal apnoea
- obstructive
- obstructive central
- central obstructive
- isolated blood oxygen desaturation
- isolated bradycardia.



Modified from Sala, 2010

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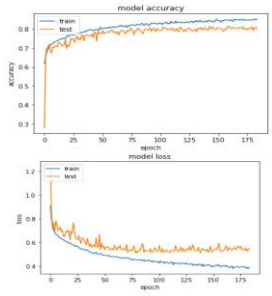
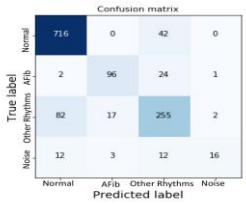
Deep Convolutional Neural Network Results





Train Score: acc: 89.14% Test Score: acc: 84.69%

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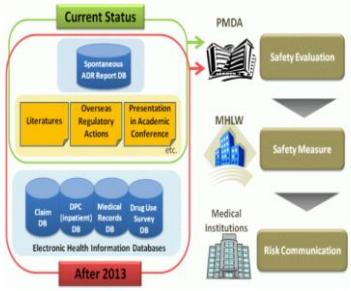
MIHARI project

Utilization of the New Data Sources in PMDA's Pharmacovigilance Practice



26 September 18-19, 2017 19 Pharmaceuticals and Medical Devices Agency (PMDA)

Clinical Innovation Network (CIN)
(Improvement of Infrastructure for Clinical Study with Disease Registry)

【Background】
·Cost of developing a new drug or other medical products is rising over the world, especially in Japan compared to other countries.
·Recently, new approaches for clinical study with disease registry has been highly interesting.

【Brief overview of CIN】
· The clinical study infrastructure in Japan is improved so that cost effective clinical studies are performed with disease registries, based on Regulatory Science. The improvement will accelerate clinical studies in Japan by entities in the world, which would results in the contribution to healthy life expectancy for people.
·CIN will also support for marketing in Asia of medial products developed in Japan.

National institute of Biomedical Innovation, Health and Nutrition
Hospitals in networks in Japan
Hospitals in Asia

·Acceleration of global clinical trials
·Asian Regulatory Training center
·Development of registries for patients with intractable diseases
·Rare diseases drug development Gateway

National Center, Clinical Research Core Hospital
·Development of disease registries
·Foundation of a clinical trial consortium, acceleration of clinical studies
·Advancement of regenerative medicine clinical studies
·Establishment of a Clinical Trial Cooperation Office

Participation in the consortium
Data provision (With consideration to personal information)
Industry
·Utilizes data in clinical studies
·Performs clinical studies quickly and cost-effectively

Activation of clinical studies in Japan by entities in the world

·Personnel exchanges
·Post marketing safety measures
·Research for method to utilize disease registry in clinical study (Regulatory Science)
·Support for R&D
·human resource cultivation in the clinical research and trial field

PMDA
Jurisdiction : MHLW
AMED
Jurisdiction : CAO, MEXT, MHLW, METI

CIN Promotion Conference
Composed of stakeholders , including National Centers, Industries and Japanese Government, and promotes the CIN project.

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http://pari.u-tokyo.ac.jp/eng/event/smp150818_mori.pdf

September 18-19, 2017 31 Pharmaceuticals and Medical Devices Agency (PMDA)

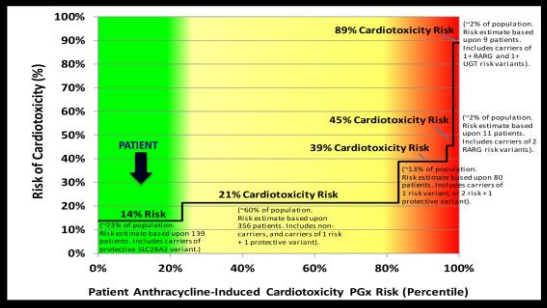
Personalized Medicine Program (PMP):
Implementation of a Pharmacogenomic ADR Prevention Program in British Columbia

Genome BritishColumbia
Provincial Health Services Authority
Province-wide solutions. Better health.
CIHR IRSC

- ADRs: Cisplatin-induced ototoxicity
  Anthracycline-induced cardiotoxicity
- Sites: BC Children's Hospital, BCCA, and VGH

CPGs Prepared	Tests Developed	Patients Tested	Results Delivered	Ongoing Follow-up
BJCP, Therapeutic Drug Monitoring	Results in 8 hrs	BCCH, VGH, BCCA		• Education • Interviews • Workshops • Focus Groups • Cost-effectiveness

Pediatric Anthracycline Cardiotoxicity Risk Prediction Tool



Potential Clinical Options for Personalized Anthracycline Therapy

Depending on risk prediction, clinician could take different actions:

Low Risk
- Echocardiogram follow-up as usual

Intermediate Risk
- Intensify echocardiogram follow-up
  e.g. patients in rural centres often miss appointments

High Risk
- Alternative medication or dose
- Add cardioprotectant (e.g. dexrazoxane)
- Start treatment with ACE-inhibitors or beta-blockers to prevent further damage

Importance of Partnerships

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Key Concept: Partnerships

- Importance of Partnerships
  - Rare exposures & rare outcomes
  - Shared knowledge and experience
  - Efficient use of limited resources

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Key Concept: Partnerships

- Types of questions (hierarchy)
  - Descriptive
  - Safety
  - Effectiveness
  - More complex questions
- Caveats
  - Health care delivery and access to meds differs
  - Clinical definitions may differ (neonate, live birth)

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Key Concept: Partnerships

- Steps needed to pursue partnerships
  - Engage children, families, clinicians
  - Strategic collaborations
  - Careful design (exposure, outcomes, confounders)
  - Ethics/Data Protections
  - Sustainability

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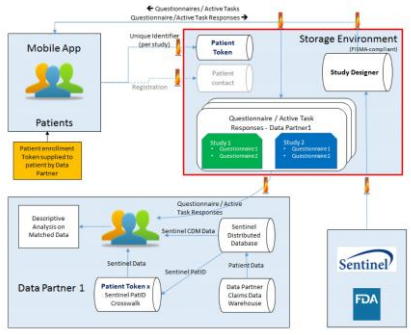
Link Primary and Secondary Data



info@sentinelsystem.org 51

OHDSI Open Source Partnerships

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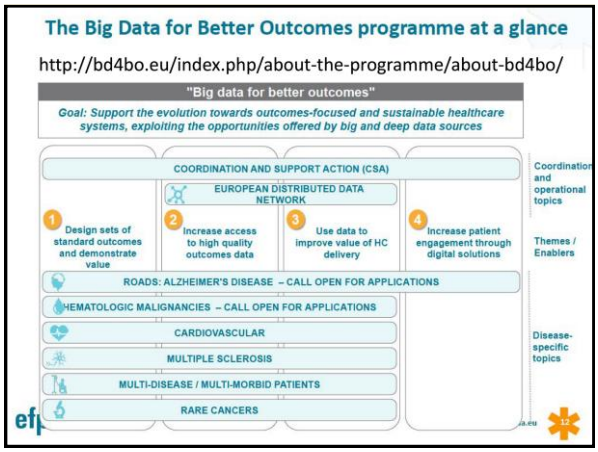
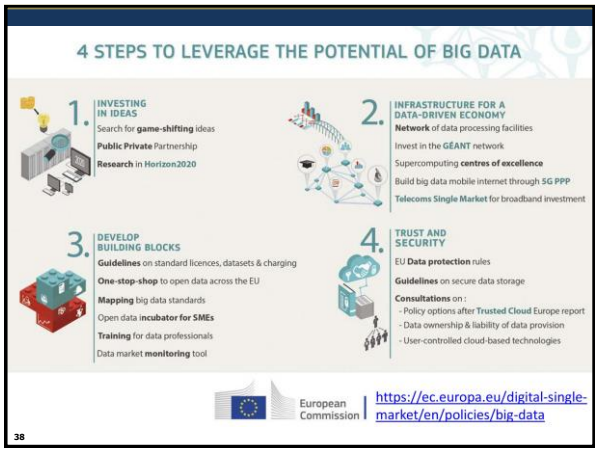

The Big Data for Better Outcomes programme at a glance
http://bd4bo.eu/index.php/about-the-programme/about-bd4bo/
"Big data for better outcomes"
Goal: Support the evolution towards outcomes-focused and sustainable healthcare systems, exploiting the opportunities offered by big and deep data sources
COORDINATION AND SUPPORT ACTION (CSA)
EUROPEAN DISTRIBUTED DATA NETWORK
1 Design sets of standard outcomes and demonstrate value
2 Increase access to high quality outcomes data
3 Use data to improve value of HC delivery
4 Increase patient engagement through digital solutions
ROADS: ALZHEIMER'S DISEASE – CALL OPEN FOR APPLICATIONS
HEMATOLOGIC MALIGNANCIES – CALL OPEN FOR APPLICATIONS
CARDIOVASCULAR
MULTIPLE SCLEROSIS
MULTI-DISEASE / MULTI-MORBID PATIENTS
RARE CANCERS
Coordination and operational topics
Themes / Enablers
Disease-specific topics


4 STEPS TO LEVERAGE THE POTENTIAL OF BIG DATA
1. INVESTING IN IDEAS
Search for game-shifting ideas
Public Private Partnership
Research in Horizon2020
2. INFRASTRUCTURE FOR A DATA-DRIVEN ECONOMY
Network of data processing facilities
Invest in the GÉANT network
Supercomputing centres of excellence
Build big data mobile internet through 5G PPP
Telecoms Single Market for broadband investment
3. DEVELOP BUILDING BLOCKS
Guidelines on standard licences, datasets & charging
One-stop-shop to open data across the EU
Mapping big data standards
Open data incubator for SMEs
Training for data professionals
Data market monitoring tool
4. TRUST AND SECURITY
EU Data protection rules
Guidelines on secure data storage
Consultations on :
- Policy options after Trusted Cloud Europe report
- Data ownership & liability of data provision
- User-controlled cloud-based technologies
European Commission
https://ec.europa.eu/digital-single-market/en/policies/big-data
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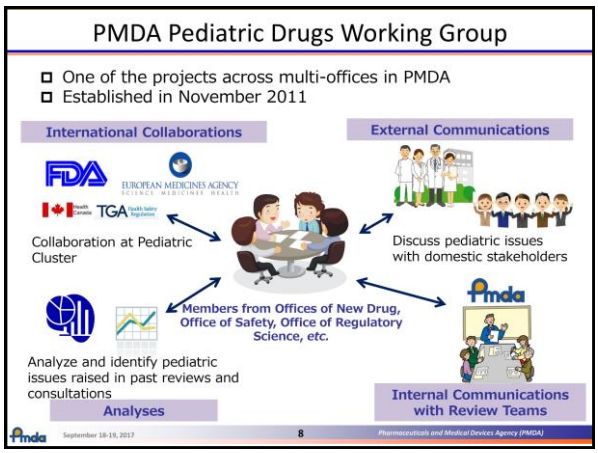
PMDA Pediatric Drugs Working Group
One of the projects across multi-offices in PMDA
Established in November 2011
International Collaborations
External Communications
FDA
EUROPEAN MEDICINES AGENCY
TGA
Collaboration at Pediatric Cluster
Discuss pediatric issues with domestic stakeholders
Members from Offices of New Drug, Office of Safety, Office of Regulatory Science, etc.
Analyze and identify pediatric issues raised in past reviews and consultations
Analyses
Internal Communications with Review Teams
September 18-19, 2017
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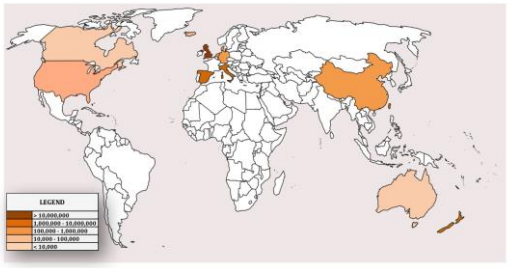
Pharmaceuticals and Medical Devices Agency (PMDA)


GRiP
Global Research in Paediatrics
Network of Excellence
OVERVIEW
OUR WORK
What is GRiP?
GRiP Virtual Learning Environment
Training and education
Epidemiological and post-marketing studies
Tools for interoperability
Paediatric clinical studies
Paediatric formulations
Drug development in neonates
GRiP was created to address the lack of appropriate testing and information on paediatric drugs. GRiP partners are working to reduce the current fragmentation of the efforts to study and develop the use of medicine in children.
NEWS AND EVENTS
NEWSLETTER
FOCUS
Meet the expert in Paediatric Formulation series

Identify healthcare databases comprising paediatric data (2012)



64 responses out of 125, 34 willing to participate in GRIP:
Health care data on more than 50 million children

Published: Ferrajolo C. https://repub.eur.nl/pub/77131/
Chapter 6

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Key Concepts: FDA/EMA Partnerships

- Pediatric Cluster
  - PMDA, HealthCanada, EMA, FDA
  - Common approaches
  - Safety signal and responses
- Monthly Pharmacovigilance Calls (EMA/FDA)

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Key Concepts: Partnerships

- How to bring the right people together
  - Note

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Challenges and Caveats

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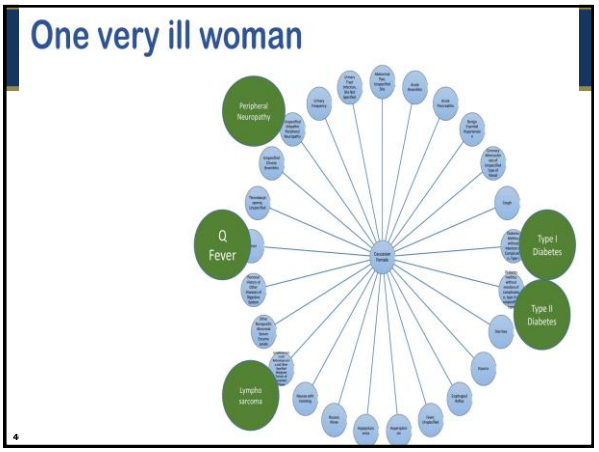
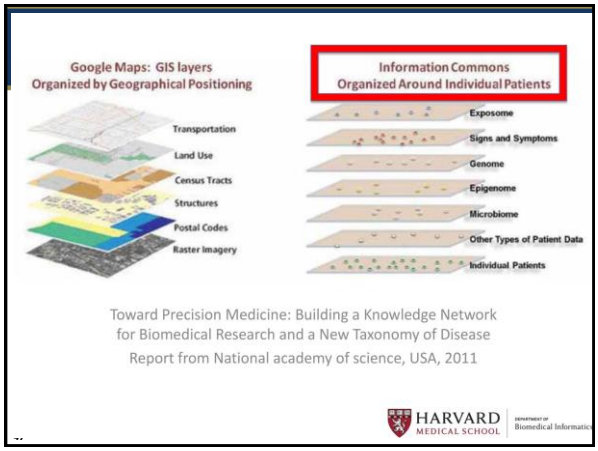
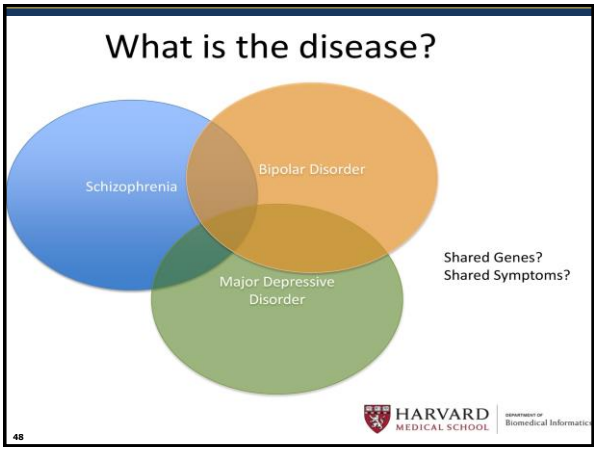
Clinical Data
EHR


One very ill woman
Peripheral Neuropathy
Q Fever
Type I Diabetes
Type II Diabetes
Lympho sarcoma
4


Google Maps: GIS layers
Organized by Geographical Positioning
Transportation
Land Use
Census Tracts
Structures
Postal Codes
Raster Imagery
Information Commons
Organized Around Individual Patients
Exposome
Signs and Symptoms
Genome
Epigenome
Microbiome
Other Types of Patient Data
Individual Patients
Toward Precision Medicine: Building a Knowledge Network
for Biomedical Research and a New Taxonomy of Disease
Report from National academy of science, USA, 2011
HARVARD MEDICAL SCHOOL
Biomedical Informatics


What is the disease?
Schizophrenia
Bipolar Disorder
Major Depressive Disorder
Shared Genes?
Shared Symptoms?
48
HARVARD MEDICAL SCHOOL
Biomedical Informatics

Exposure/stage	Outcome/stage	Interval
Penicillin/infancy	anaphylaxis/infancy	20 ***minutes***
SSRIs/pregnancy	bipolar disorder/adulthood	20 ***years***

Concerns about confounding?

Penicillin/anaphylaxis: Interval is too short to be affected by most factors other than exposure

SSRIs/bipolar disorder: Across 20 years and many stages of pediatric development, the number of potential confounders is daunting.

BU Slone Epidemiology Center

Biases and Causality Leakage

- Site/specialty effects:
  - Example: obgyns prescribe prozac
- Causality leakage:

(Examples: mortality prediction from pneumonia, ICU)

Key Concepts: Challenges

- Limitations in phenotypes
  - Note
  - Note
- Heterogeneity in pediatric drug response
  - Note
  - Note

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From your perspective, what barriers do you see in using "Big Data" to support you (or your organization's) work?

Menti.com

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Ethics and Regulatory Issues

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Key Concepts: Ethics/Regulatory

- How actionable are results - regulatory
  - Depends on certainty of data
    - Future state – need standards on certainty, precision
    - Benefit:Risk Considerations
  - CURES – Real World Evidence
- How actionable are results – clinical
  - Depends on certainty of data
  - Guided by regulatory (off-label)
  - Available ≠ Accessible

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Key Concepts: Ethics/Regulatory

- Changes in clinical and regulatory processes
  - Note
  - Note
- "Big Data" serve regulatory processes
  - Note
  - Note

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Key Concepts: Ethics/Regulatory

- Adjustments that can be made
  - Recognize importance of trust
  - Where data reside is key
  - Advocate for appropriate ethics oversight

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Next Steps/Future State

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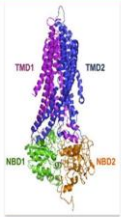
Genomic Based Mechanism of Action

- Cystic fibrosis is caused by one of nearly 2000 mutations.
- CF drug, ivacaftor which targets *G551D* mutation in the *CFTR* gene (4% of CF population).
- Delivers increases in FEV_1 ~10%.



Indication gradually expanded to covers further mutations

The future

Challenge of determining the level of evidence required to extend indications when further mutations are identified.

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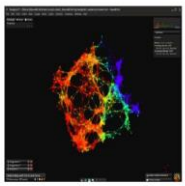
Looking to the Future

Visualization of the topology of complex data from the U-BIOPRED consortium of adult severe asthma cohorts



Cohorts are generated following the integration of multiple biomarkers

- How are the individual components validated?
- How reproducible are the cohorts?
- How is data weighted within the algorithms to define the cohorts?
- How do you identify the stability of the cohorts over time?
- Are the cohorts translatable to a defined patient population?

Aim: how do we generate certainty for regulatory decision making?

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Implications for Effective, Safe AIs

Regulation

- Identify scenarios that matter.
- Require that data relevant to those scenarios are collected.
- Seek explanation, but not transparency.

Research/Tech

- Design systems to provide explanation.
- Determine how to extract information relevant to scenarios (including proxies).

Utility: During Drug Development Life Cycle

- Provide evidence to support acceptability of efficacy extrapolation for a given indication
- Support proof of concept
- Inform need for juvenile toxicity studies
- Identify settings for opportunistic PK studies
- Identify trends in short- and long-term product safety

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Utility: Overall Product Safety

- Identify previously unrecognized, unlabeled serious ARs
- Capture product safety
  - Broader population (e.g. wider age range, more co-morbidities, variable disease severity, variety of concomitant drug use)
  - When co-prescribed with other drugs
  - With off-label use
  - With accidental exposures
  - Related to excipient content

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Utility: Capturing Long-Term Safety

- Identify trends in safety of products
  - Taken chronically during childhood or over a lifetime
  - Taken for shorter duration but during critical stages of development
- Detect ARs
  - Reversible versus permanent
  - Manifest months to years after product exposure

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What are the most important next steps?

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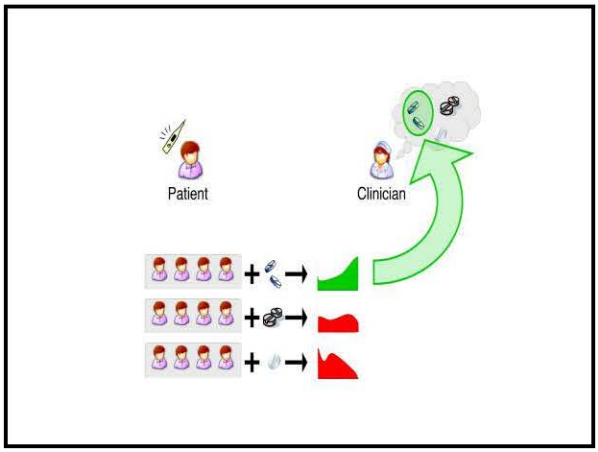
Patient
Clinician