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Improving healthcare decisions

Real World Evidence: Promises and Limitations

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New Horizons in GIST, May 10, 2019

What is Real World Data/Evidence?

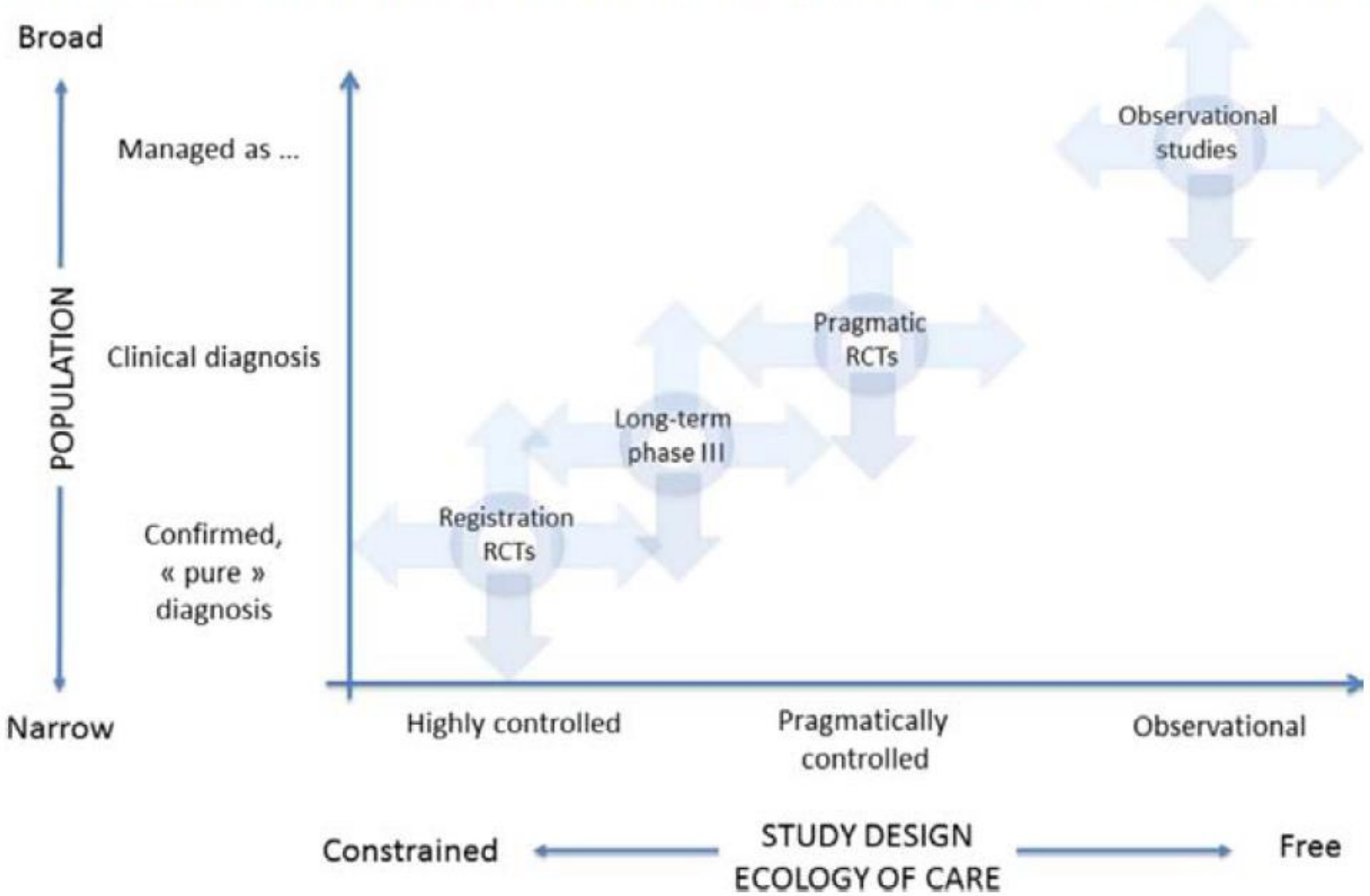
Retrospective

- Electronic health records
- Data collected from charts
- Insurance claims
- Analysis of data for purpose not originally collected
  - Prospective registries
  - RCT

Prospective

- Active prospective registries
- Observational studies
- Early Access Programs?
- Large Simple Trials?

Figure 1: Conceptual framework of therapeutic research by study design



Source: Roche et al., 2013

Why do we need RWE?

Clinical Trials Answer Benefit/Risk

- Efficacy – does it work:
  - Narrowly defined population
  - Under very controlled conditions
  - Versus: placebo or one active comparator
  - For the duration of the trial
- Safety
  - Can {known} Side Effects and Adverse Events be managed under controlled conditions

Why do we need RWE?

Real-World Evidence Answers:

- Effectiveness – does it work in practice?
  - In broader populations
  - Under uncontrolled conditions
  - Over the long term
  - Versus all current standards of care
- Safety – is it safe in practice?
  - Are {known} side effects
    - reported by patients
    - Treatable in clinical practice
  - Unknown side effects
- Adherence/treatment patterns
- Cost of treatment and side effects

Where is RWE being used

1. Drug Development
2. FDA safety monitoring/safety signals and EMA post approval studies
3. HTA assessments and payer coverage determinations
    1. Initial decisions
    2. Re-assessments
4. Outcomes based contracting
5. Regulatory approval decisions

It's already happening…

Pfizer uses real-world data to score Ibrance breast cancer nod in males

NHS England Cancer Drugs Fund

FRAMEWORK FOR FDA'S REAL-WORLD EVIDENCE PROGRAM

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

Press release

CMS proposes Coverage with Evidence Development for Chimeric Antigen Receptor (CAR) T-cell Therapy

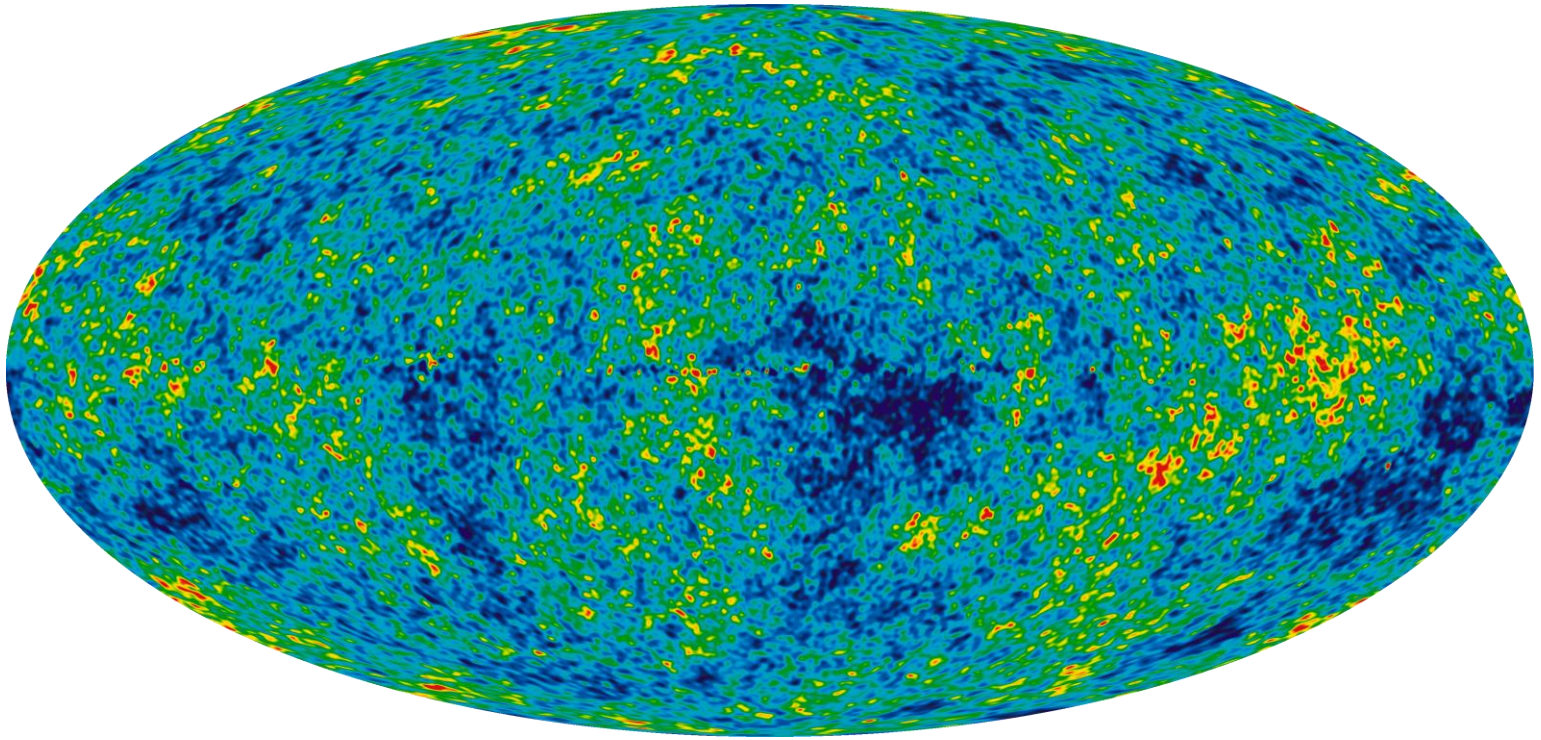
Feb 15, 2019 | Coverage, Leadership

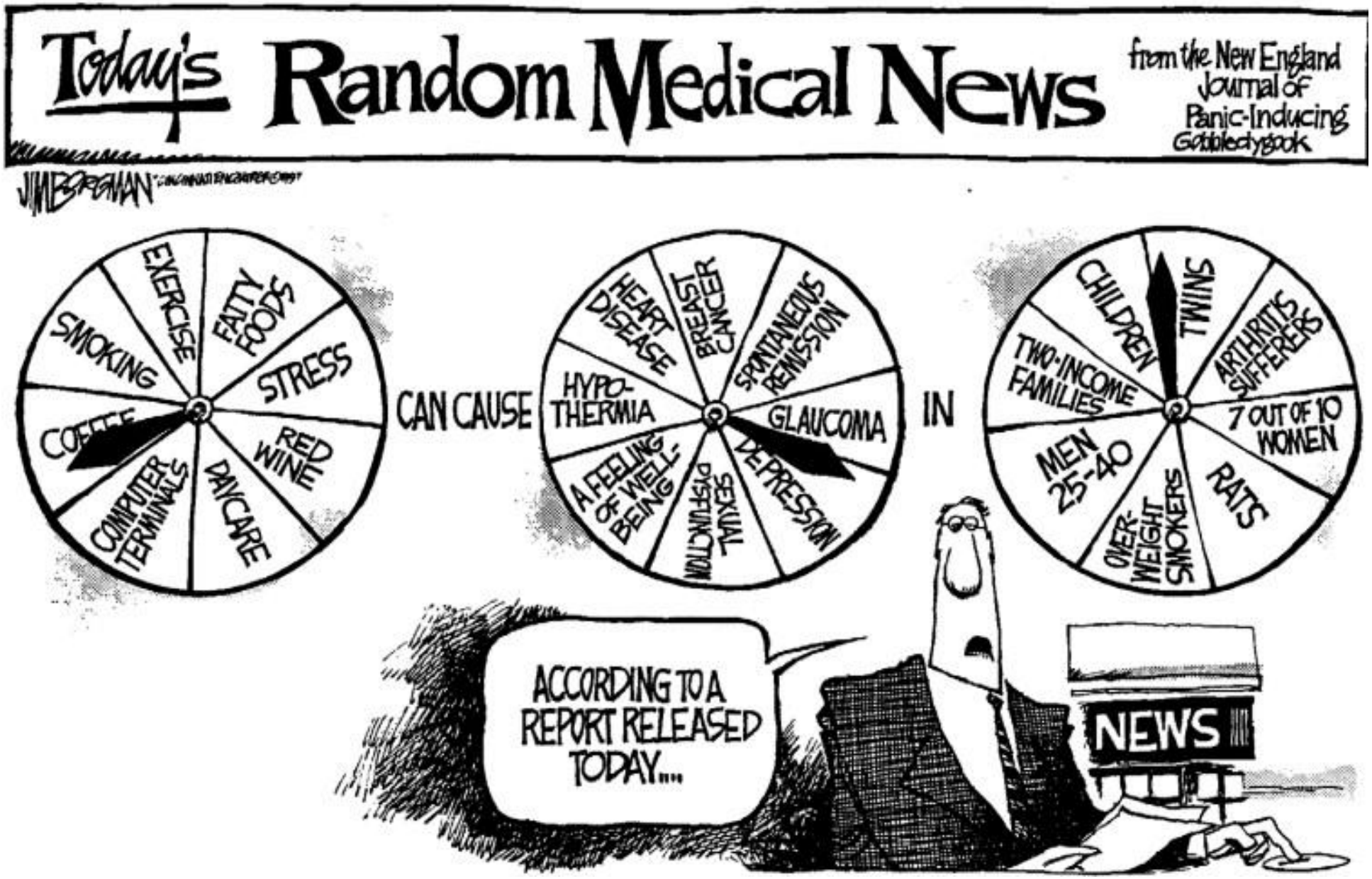
The Challenge of Real World Evidence

So much data, so much potential information

but is the evidence derived

reliable and trustworthy?

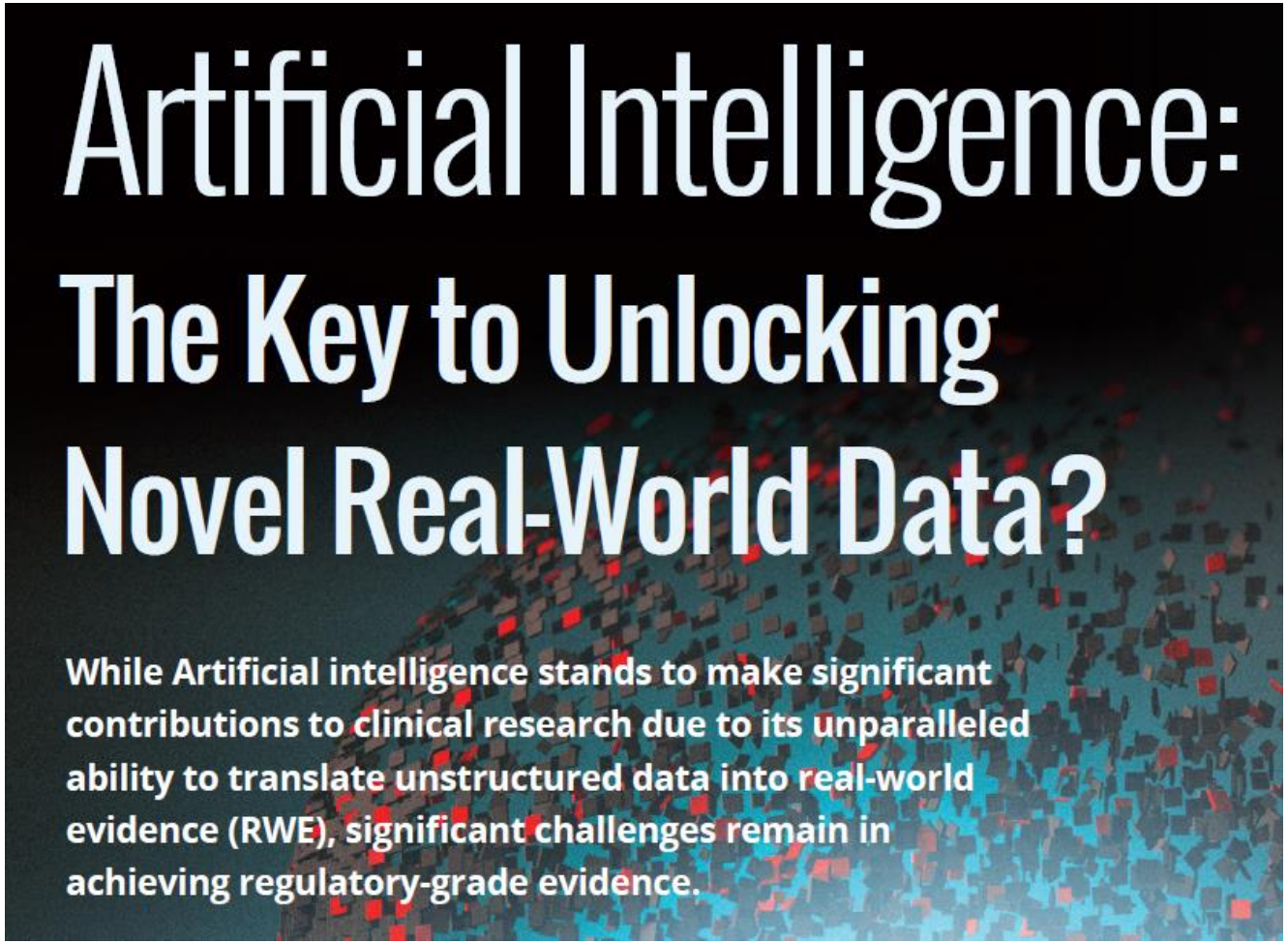



Today's Random Medical News
from the New England Journal of Panic-Inducing Gobbledygook
JIM BORGMAN
EXERCISE
FATTY FOODS
STRESS
RED WINE
DAYCARE
COMPUTER TERMINALS
COFFEE
SMOKING
CAN CAUSE
HEART DISEASE
BREAST CANCER
SPONTANEOUS REMISSION
GLAUCOMA
DEPRESSION
SEXUAL DYSFUNCTION
A FEELING OF WELL-BEING
HYPO-THERMIA
IN
CHILDREN
TWINS
ARTHRITIS SUFFERERS
7 OUT OF 10 WOMEN
RATS
OVER-WEIGHT SMOKERS
MEN 25-40
TWO-INCOME FAMILIES
ACCORDING TO A REPORT RELEASED TODAY...
NEWS

Unstructured Data and the AI 'Frontier'

- Electronic Health Records
  - Doctor's notes
  - Discharge summary
  - Lab data
  - Image reports
  - 80% unstructured data
- Social media
- Data from apps
- Wearable data
- Patient reported outcomes

Can we trust the algorithms?



RWE Challenges

- Bias and Confounding
- Incomplete Data
- Data Mining or Dredging
- Access to Data
- Universally Accepted Methods to
  - address the above
  - analysis of RWE

Bias and Confounding

- Selection Bias:
  - Selection of subjects isn't random
  - Mitigate the impact - RWE studies need to be rigorously designed and evaluated
    - describing and adjusting for covariates, matching, or using instrumental variables
- Reporting Bias
  - Some outcomes/datasets are selectively revealed of withheld
  - A mandatory national registry, such as is available for RCTs, could help mitigate this problem

Incomplete Data

- Under-reporting of diagnoses or adverse outcomes/side effects
- Missing Data or Data Gaps
  - Claims – you know what was done to the patient but not the results
  - EHR – depends on what is reported and if you can interpret it
  - Data needed for insurance payment is not what is needed for RWE (US)
  - Relying on self submitted data (patient or physician) may create gaps
- Information bias – from systematic mis-classification
- Mitigation
  - National data repositories
  - Strict reporting guidelines
  - Linking datasets

Data Mining or Data Dredging

- Re-examining datasets to generate new information
- RWE is vulnerable to manipulation via repeat analyses with
  - Continuly using different modelling approaches until one that delivers preferential outcomes is identified
  - Non-disclosure of unexpected results
- Need for *a priori* protocols, analysis plans, and well defined research questions

Access to Data

- Data sharing is not common in the US
  - Outpatient vs. inpatient
  - Specialist vs. internist
  - Labs, imaging, apps, wearables
- Privacy regulations make it difficult to link patients across data sets
  - Legal frameworks are catching up
  - Trade off between protection of private health information and informing real world research

Lack of Standards

- Universally accepted standards/principles are needed:
  - design,
  - conduct,
  - analysis
  - reporting of RWE

- There have been various best practices/standards developed but lack agreement

Conclusions

- There is a lot of promise in RWD
- The rise of Artificial Intelligence and Large Data Sets is coming – we need to be ready
- The key is -
  - Know the strengths and challenges associated with RWE
  - Design rigorous data collection and analysis plans
  - Be as transparent as possible about what was done with RWD and how it was analyzed

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