Finding Research Questions: Look at Both the New and the Old

September 23, 2016

Josie Briggs MD

NIA – Aging Research for the Specialties

Quirky Ideas From Outside the Mainstream

Physical resistance training is good for people recovering from major physical trauma:
Joseph Pilates, 1915

Relaxation and breathing techniques help with pain of childbirth:
Ferand Lamaze 1940

Breast feeding is good for babies:
Edwina Froelich, La Leche League founder 1950's

Extensive palliative support, and reduced medical interventions should be provided to dying patients:
Saunders, Wald, Kubler-Ross 1960's

Quirky Ideas From Outside the Mainstream
2016

Yoga may help with pain management

Tai-chi may help prevent falls

Yoghurt may reduce antibiotic induced diarrhea

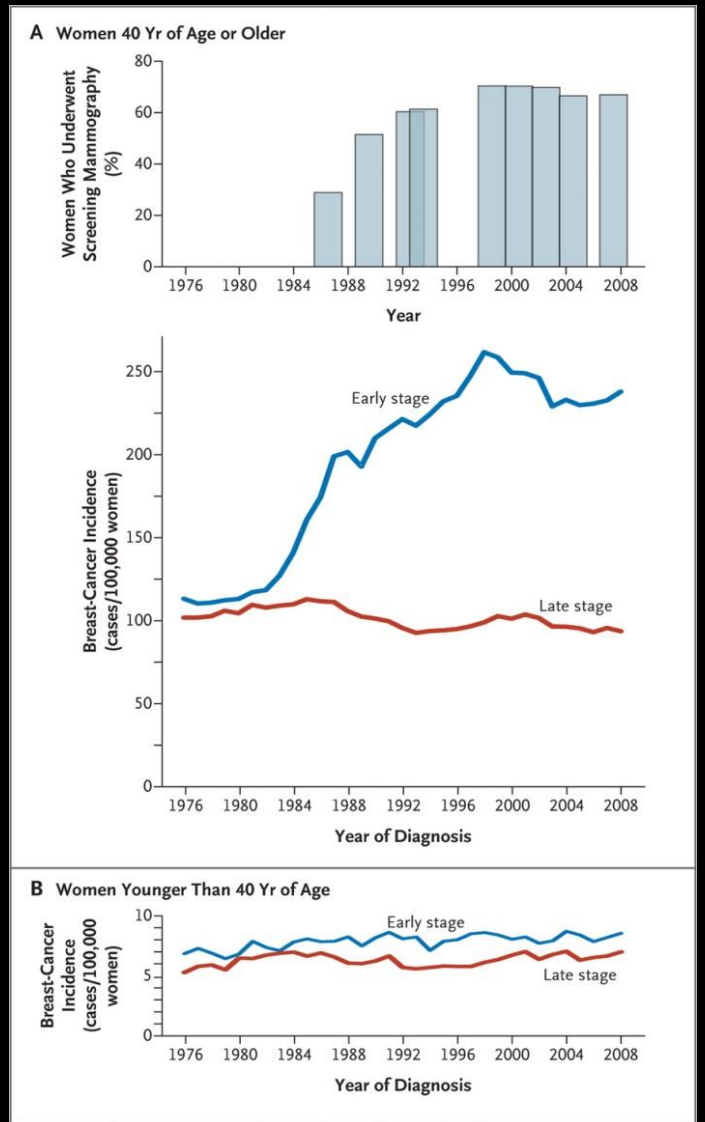
Meditation may help treat PTSD

Ask questions

Of conventional wisdom

Of the evidence

Use of Screening Mammography and Incidence of Stage-specific Breast Cancer in the United States, 1976-2008



The NEW ENGLAND JOURNAL of MEDICINE

Bleyer A and Welch HG. Effect of Three Decades of Screening Mammography on Breast-Cancer Incidence. N Engl J Med 2012; 367:1998-2005.

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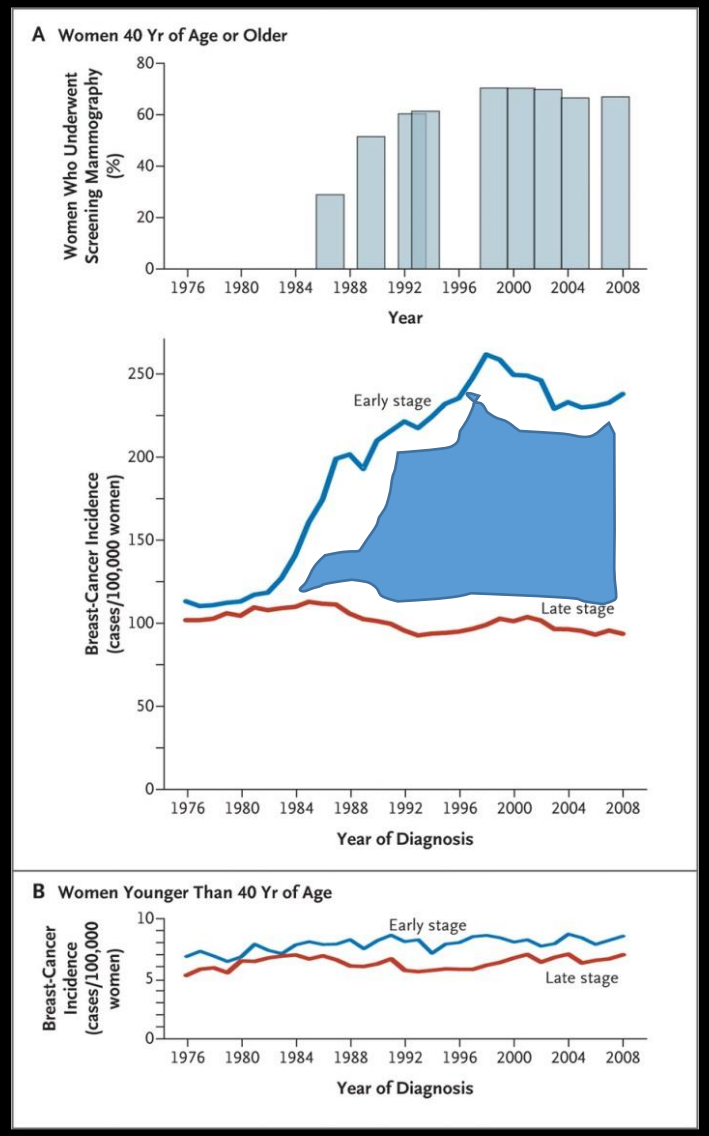

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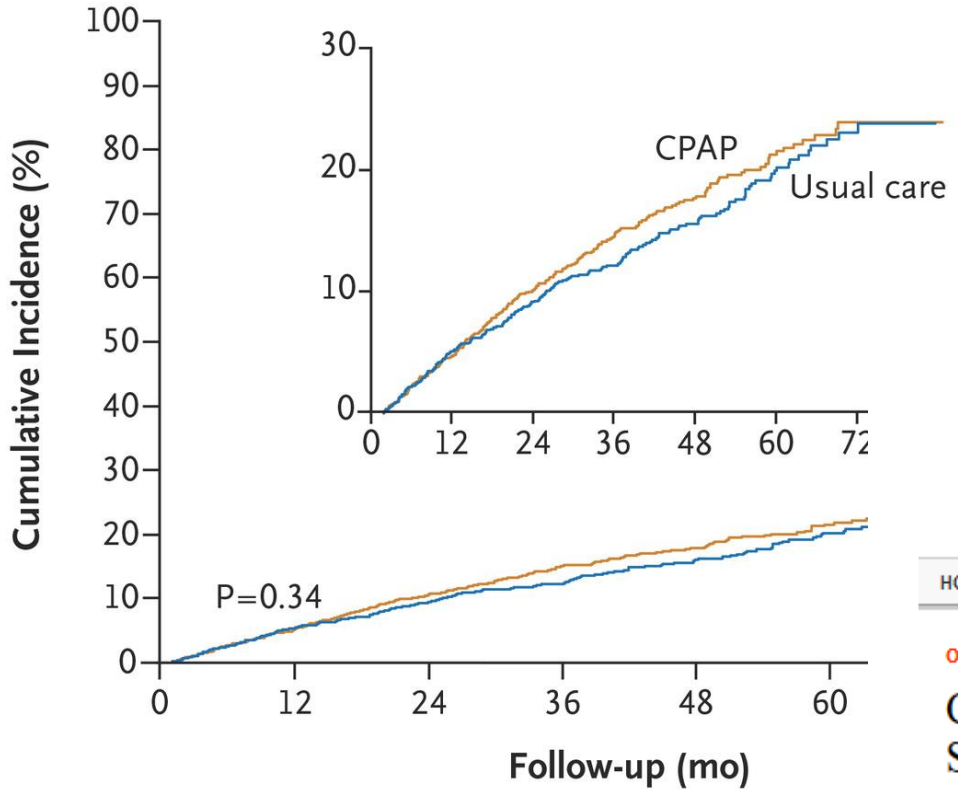
Use of Screening Mammography and Incidence of Stage-specific Breast Cancer in the United States, 1976-2008

"Unfortunately, the number of women in the United States who present with distant disease, only 25% of whom survive for 5 years, appears not to have been affected by screening."

"We estimate that breast cancer was overdiagnosed (i.e. tumors were detected that would never have led to clinical symptoms) in 1.3 million U.S. women in the past 30 years."

Bleyer A and Welsh HG. NEJM 2012

The price of imprecision



No. at Risk

CPAP	1346	1222	1118	754	482	278
Usual care	1341	1211	1108	727	499	290

The NEW ENGLAND JOURNAL of MEDICINE

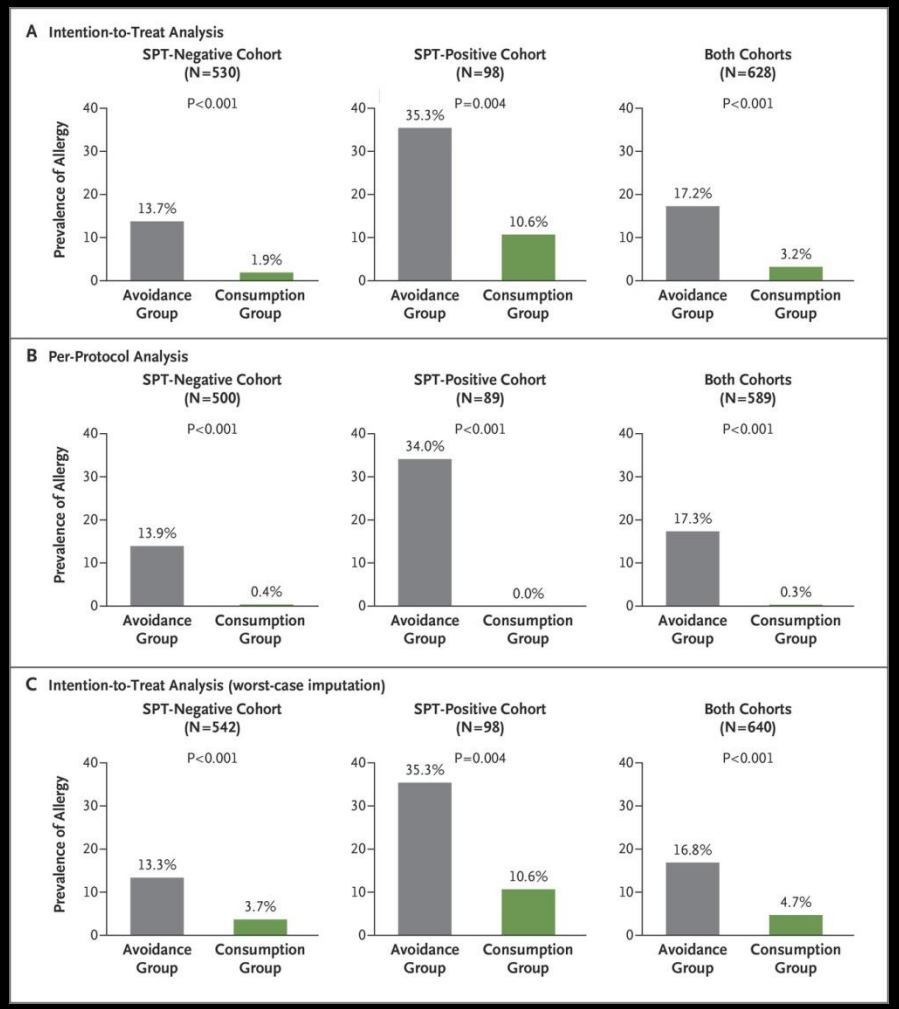
ORIGINAL ARTICLE

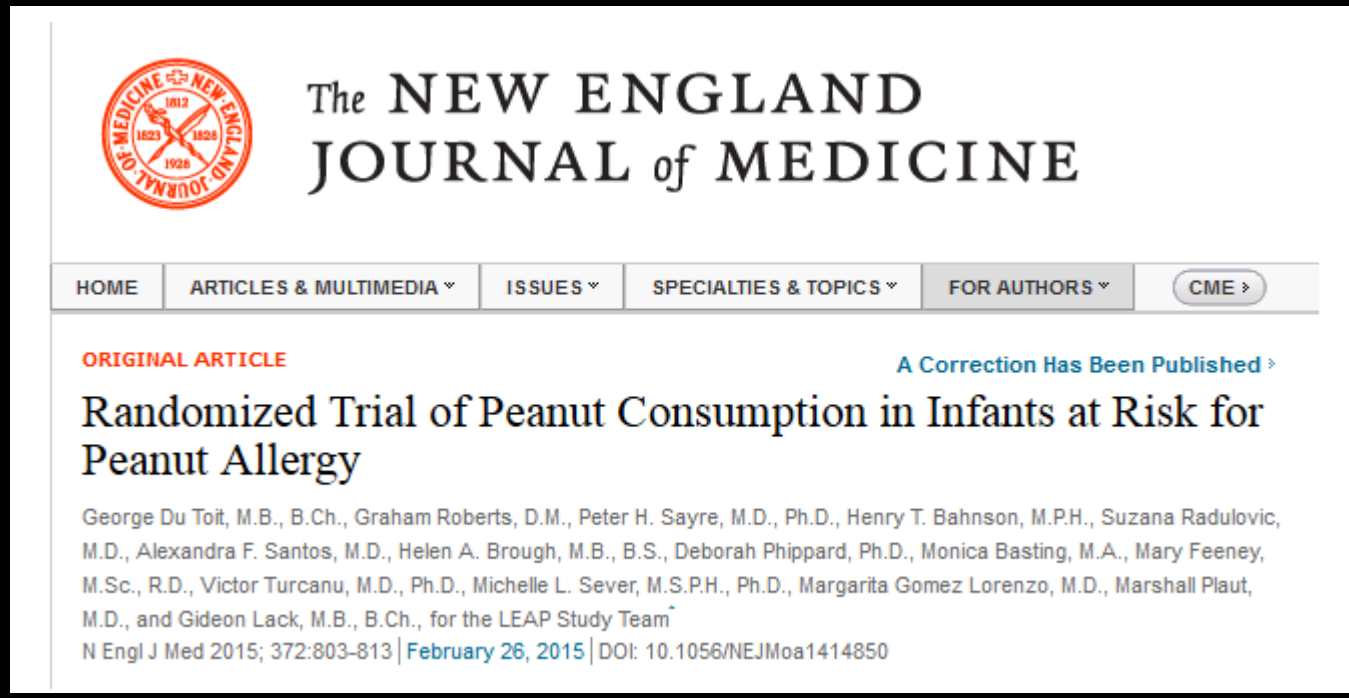
CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea

R. Doug McEvoy, M.D., Nick A. Antic, M.D., Ph.D., Emma Heeley, Ph.D., Yuanming Luo, M.D., Qiong Ou, M.D., Xilong Zhang, M.D., Olga Mediano, M.D., Rui Chen, M.D., Luciano F. Drager, M.D., Ph.D., Zhihong Liu, M.D., Ph.D., Guofang Chen, M.D., Baoliang Du, M.D., Nigel McArdle, M.D., Sutapa Mukherjee, M.D., Ph.D., Manjari Tripathi, M.D., Laurent Billot, M.Sc., Qiang Li, M.Biostat., Geraldo Lorenzi-Filho, M.D., Ferran Barbe, M.D., Susan Redline, M.D., M.P.H., Jiguang Wang, M.D., Ph.D., Hisatomi Arima, M.D., Ph.D., Bruce Neal, M.D., Ph.D., David P. White, M.D., Ron R. Grunstein, M.D., Ph.D., Nanshan Zhong, M.D., and Craig S. Anderson, M.D., Ph.D., for the SAVE Investigators and Coordinators*

N Engl J Med 2016; 375:919-931 | September 8, 2016 | DOI: 10.1056/NEJMoa1606599

McEvoy RD et al. N Engl J Med 2016;375:919-931.



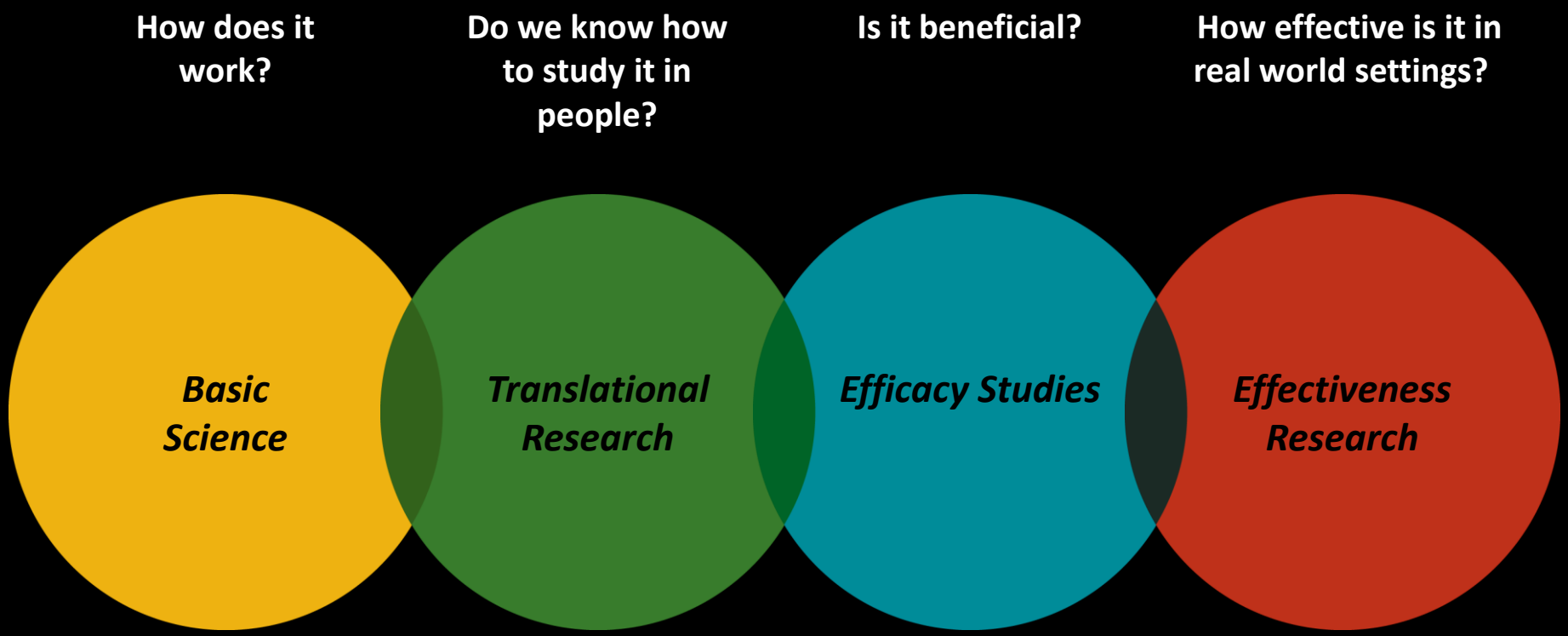


Du Toit G et al. N Engl J Med 2015;372:803-813.

(some of the) Reasons for wrong (or incomplete) answers:

- Lack of fundamental biological understanding
- Inadequate research tools – inappropriate outcome measures
- Lack of unbiased efficacy data
- Limitations of efficacy data:
  - lack of external validity,
  - heterogeneity of treatment effect

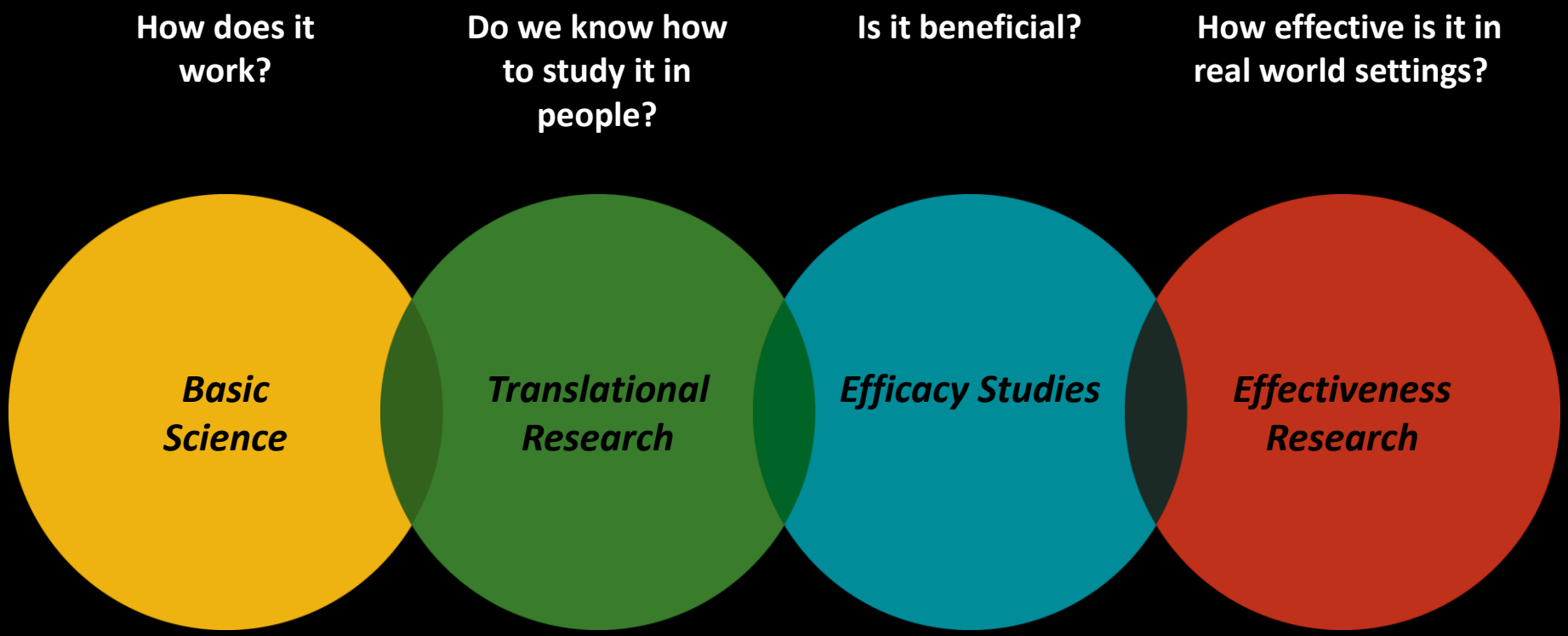
The Range of Research Questions about Interventions – (new and old)



Questioning conventional wisdom

- Understand potential intervention(s) and what doing nothing means
- Understand the measures of effectiveness
- Consider risk and benefit

The Range of Research Questions about interventions – (new and old)



What is a Practical or Pragmatic Trial?

Practical Clinical Trials

Increasing the Value of Clinical Research for Decision Making in Clinical and Health Policy

SPECIAL COMMUNICATION

JAMA®

Sean R. Tunis, MD, MSc
Daniel B. Stryer, MD
Carolyn M. Clancy, MD

Decision makers in health care are increasingly interested in using high-quality scientific evidence to support clinical and health policy choices; however, the quality of available scientific evidence is often found to be inad-

- Defined Practical (pragmatic) trials as those in which "the hypothesis and study design are developed specifically to answer the questions faced by decision makers"

- Decision makers include patients, clinicians, payers, policy makers

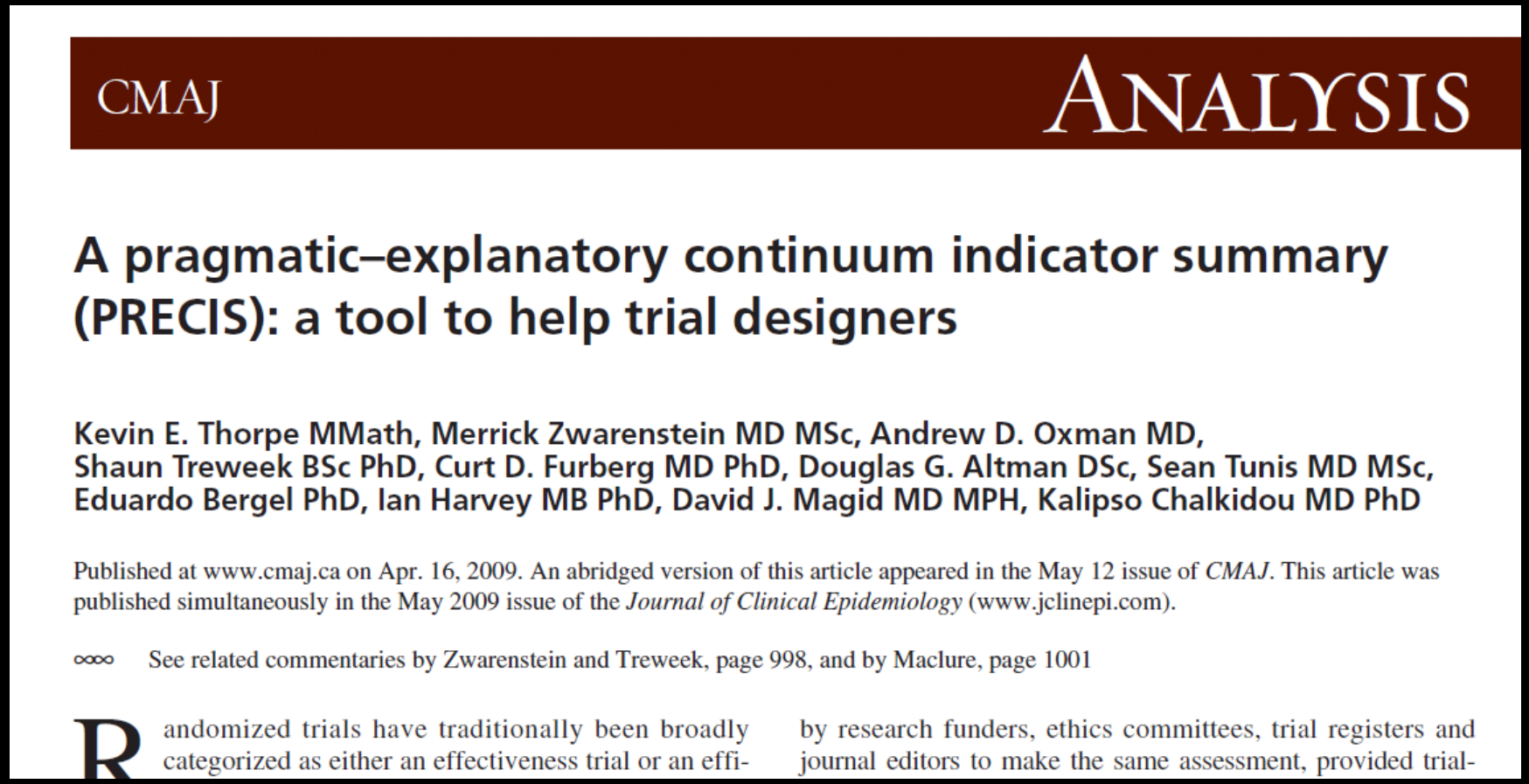
Tunis S, Stryer D, Clancy C. JAMA 2003;290:1624-32

Pragmatic vs Explanatory

Pragmatic	Explanatory
Broad eligibility	Narrow eligibility
Flexible interventions	Strict instructions
Typical practitioners	Expert practitioners
No follow-up visits	Frequent follow-up visits
Objective clinical outcome	Surrogate outcomes
Usual compliance	Close monitoring
Intent-to-treat	ITT plus per protocol

Thorpe KE et al. CMAJ 2009;180:E47

The PRECIS Tool is Developed



CMAJ ANALYSIS

A pragmatic–explanatory continuum indicator summary (PRECIS): a tool to help trial designers

Kevin E. Thorpe MMath, Merrick Zwarenstein MD MSc, Andrew D. Oxman MD, Shaun Treweek BSc PhD, Curt D. Furberg MD PhD, Douglas G. Altman DSc, Sean Tunis MD MSc, Eduardo Bergel PhD, Ian Harvey MB PhD, David J. Magid MD MPH, Kalipso Chalkidou MD PhD

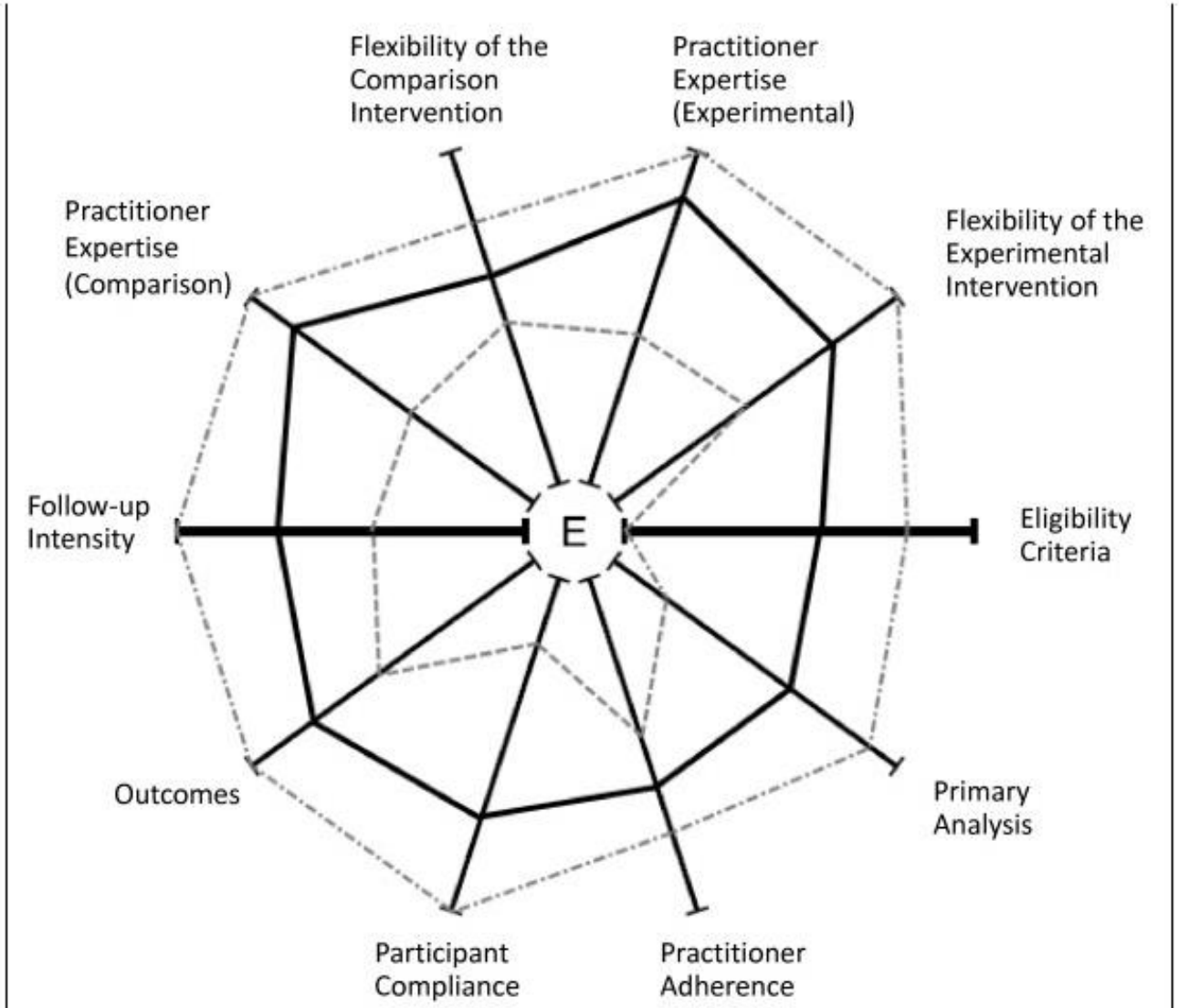
Published at www.cmaj.ca on Apr. 16, 2009. An abridged version of this article appeared in the May 12 issue of *CMAJ*. This article was published simultaneously in the May 2009 issue of the *Journal of Clinical Epidemiology* (www.jclinepi.com).

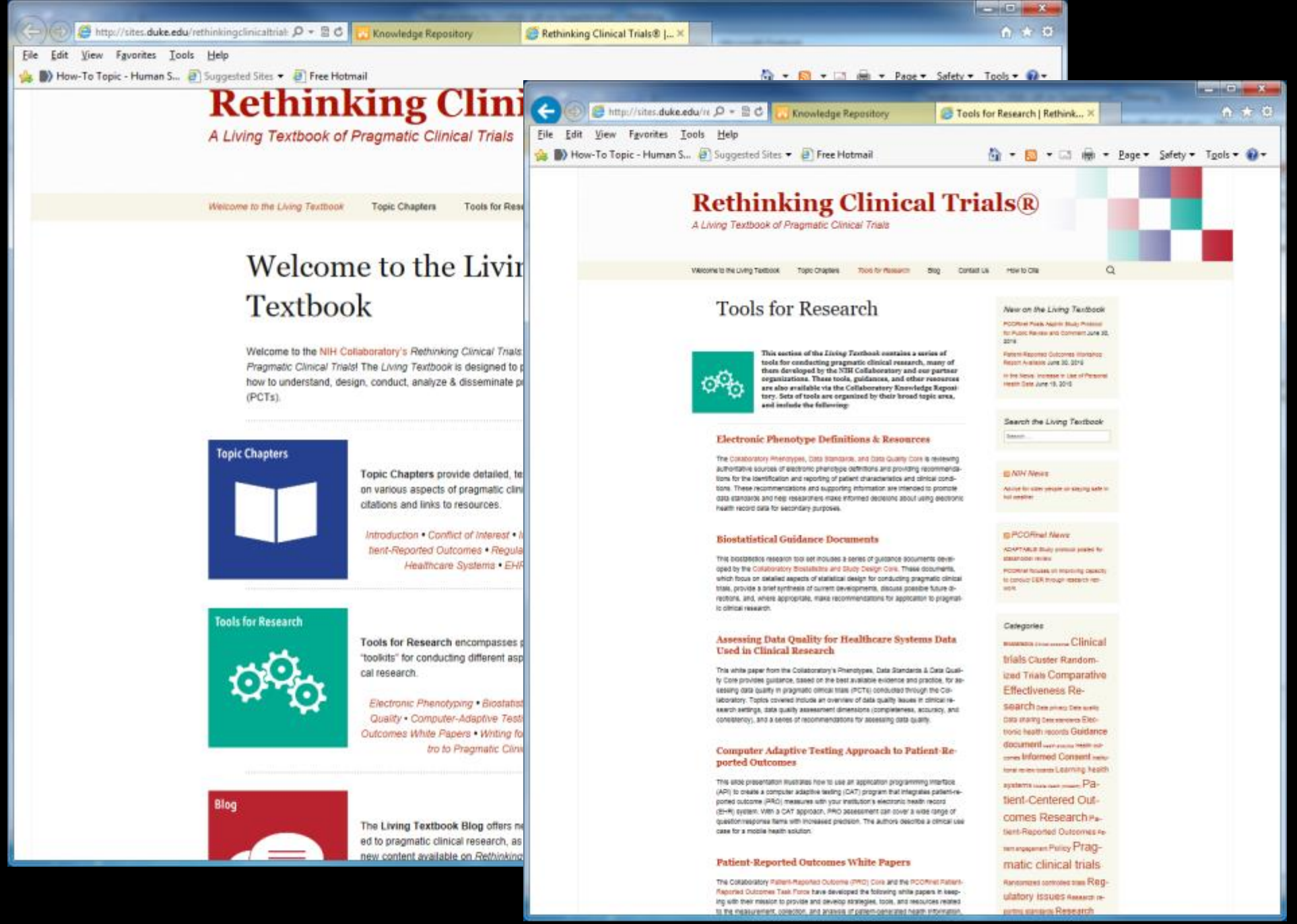
∞∞ See related commentaries by Zwarenstein and Treweek, page 998, and by Maclure, page 1001

Randomized trials have traditionally been broadly categorized as either an effectiveness trial or an effi-

by research funders, ethics committees, trial registers and journal editors to make the same assessment, provided trial-

Thorpe KE et al. CMAJ 2009;180:E47


Flexibility of the Comparison Intervention
Practitioner Expertise (Experimental)
Practitioner Expertise (Comparison)
Flexibility of the Experimental Intervention
Follow-up Intensity
E
Eligibility Criteria
Outcomes
Primary Analysis
Participant Compliance
Practitioner Adherence


Rethinking Clini
A Living Textbook of Pragmatic Clinical Trials
Welcome to the Living Textbook
Topic Chapters
Tools for Rese
Welcome to the Livin
Textbook
Welcome to the NIH Collaboratory's Rethinking Clinical Trials
Pragmatic Clinical Trials! The Living Textbook is designed to
how to understand, design, conduct, analyze & disseminate
(PCTs).
Topic Chapters
Topic Chapters provide detailed, te
on various aspects of pragmatic clin
citations and links to resources.
Introduction • Conflict of Interest •
tient-Reported Outcomes • Regula
Healthcare Systems • EHR
Tools for Research
Tools for Research encompasses
"toolkits" for conducting different asp
cal research.
Electronic Phenotyping • Biostatist
Quality • Computer-Adaptive Testi
Outcomes White Papers • Writing fo
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new content available on Rethinking
Rethinking Clinical Trials®
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How to Cite
Tools for Research
This section of the Living Textbook contains a series of tools for conducting pragmatic clinical research, many of them developed by the NIH Collaboratory and our partner organizations. These tools, guidances, and other resources are also available via the Collaboratory Knowledge Repository. Sets of tools are organized by their broad topic area, and include the following:
Electronic Phenotype Definitions & Resources
The Collaboratory Phenotypes, Data Standards, and Data Quality Core is reviewing authoritative sources of electronic phenotype definitions and providing recommendations for the identification and reporting of patient characteristics and clinical conditions. These recommendations and supporting information are intended to promote data standards and help researchers make informed decisions about using electronic health record data for secondary purposes.
Biostatistical Guidance Documents
This biostatistics research tool set includes a series of guidance documents developed by the Collaboratory Biostatistics and Study Design Core. These documents, which focus on detailed aspects of statistical design for conducting pragmatic clinical trials, provide a brief synthesis of current developments, discuss possible future directions, and, where appropriate, make recommendations for application to pragmatic clinical research.
Assessing Data Quality for Healthcare Systems Data Used in Clinical Research
This white paper from the Collaboratory's Phenotypes, Data Standards & Data Quality Core provides guidance, based on the best available evidence and practice, for assessing data quality in pragmatic clinical trials (PCTs) conducted through the Collaboratory. Topics covered include an overview of data quality issues in clinical research settings, data quality assessment dimensions (completeness, accuracy, and consistency), and a series of recommendations for assessing data quality.
Computer Adaptive Testing Approach to Patient-Reported Outcomes
This slide presentation illustrates how to use an application programming interface (API) to create a computer adaptive testing (CAT) program that integrates patient-reported outcome (PRO) measures with your institution's electronic health record (EHR) system. With a CAT approach, PRO assessment can cover a wide range of question/response items with increased precision. The authors describe a clinical use case for a mobile health solution.
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Rethinking Clinical Trials®

A Living Textbook of Pragmatic Clinical Trials

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Tools for EHR-Based Phenotyping

Created by the Collaboratory Phenotypes, Data Standards, and Data Quality Core

On this page, you will find a series of recommendations for collecting and querying data from electronic health records for patient characteristics and clinical features. These phenotype definition recommendations are intended to support the conduct of pragmatic clinical trials, as well as encourage standardized reporting of baseline characteristics of research populations in interventional and observational studies. Also included are resources for identifying additional phenotype definitions through literature search or other groups engaged in electronic phenotyping. Background information on the identification, evaluation, and implementation of phenotype definitions is available in the *Living Textbook* chapter.

Recommended Phenotype Definitions

Demographics

- Race/ethnicity
- Sex

Common Conditions

- Type 2 diabetes mellitus

Resources for Additional Phenotype Definitions

- Suggestions for Identifying Phenotype Definitions Used in Published Research
- Phenotypes Environmental Scan (survey of phenotype-related efforts)

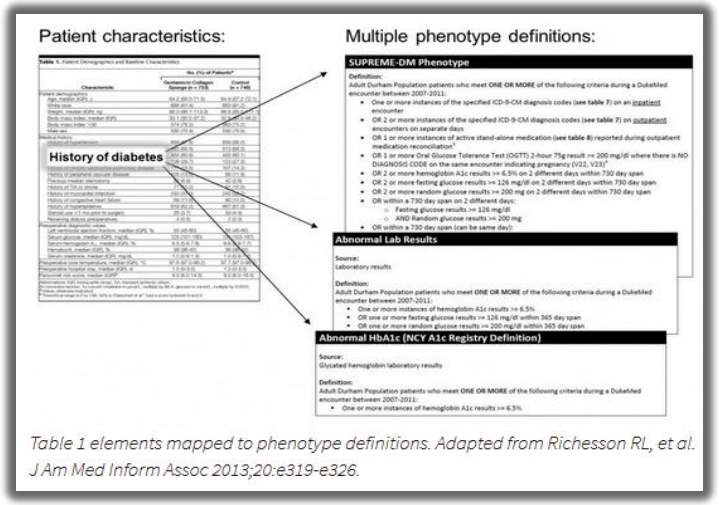


Table 1 elements mapped to phenotype definitions. Adapted from Richesson RL, et al. J Am Med Inform Assoc 2013;20:e319-e326.

Table 1 Project

Standardizing Phenotypes for the Table 1 Project

What is the Table 1 Project?

In a research publication, the baseline characteristics for a study population are conventionally reported in Table 1. The goal of the Table 1 Project is to identify important person characteristics and clinical features, along with explicit definitions and representations, for the reporting of baseline characteristics of research populations in interventional and observational studies. Interpreting a research result without an understanding of the population enrolled in the study is treacherous at best. Validated, reproducible, reliable, and generalizable fundamental patient characteristics could support:

- The submission of datasets from NIH-funded studies for archival and secondary use
- The submission of results from NIH-funded studies for archival, retrieval, and comparison purposes
- The standardized reporting of results from NIH-funded studies to ClinicalTrials.gov
- Better practices for describing research populations in publications submitted to medical journals
- The conduct of both multisite pragmatic clinical trials and observational studies

Risk and benefit

JAMA The Journal of the American Medical Association

September 12, 2007, Vol 298, No. 10 >

Commentary | September 12, 2007

Limitations of Applying Summary Results of Clinical Trials to Individual Patients

The Need for Risk Stratification

David M. Kent, MD, MS; Rodney A. Hayward, MD

A Population Distribution of Baseline Outcome Risk

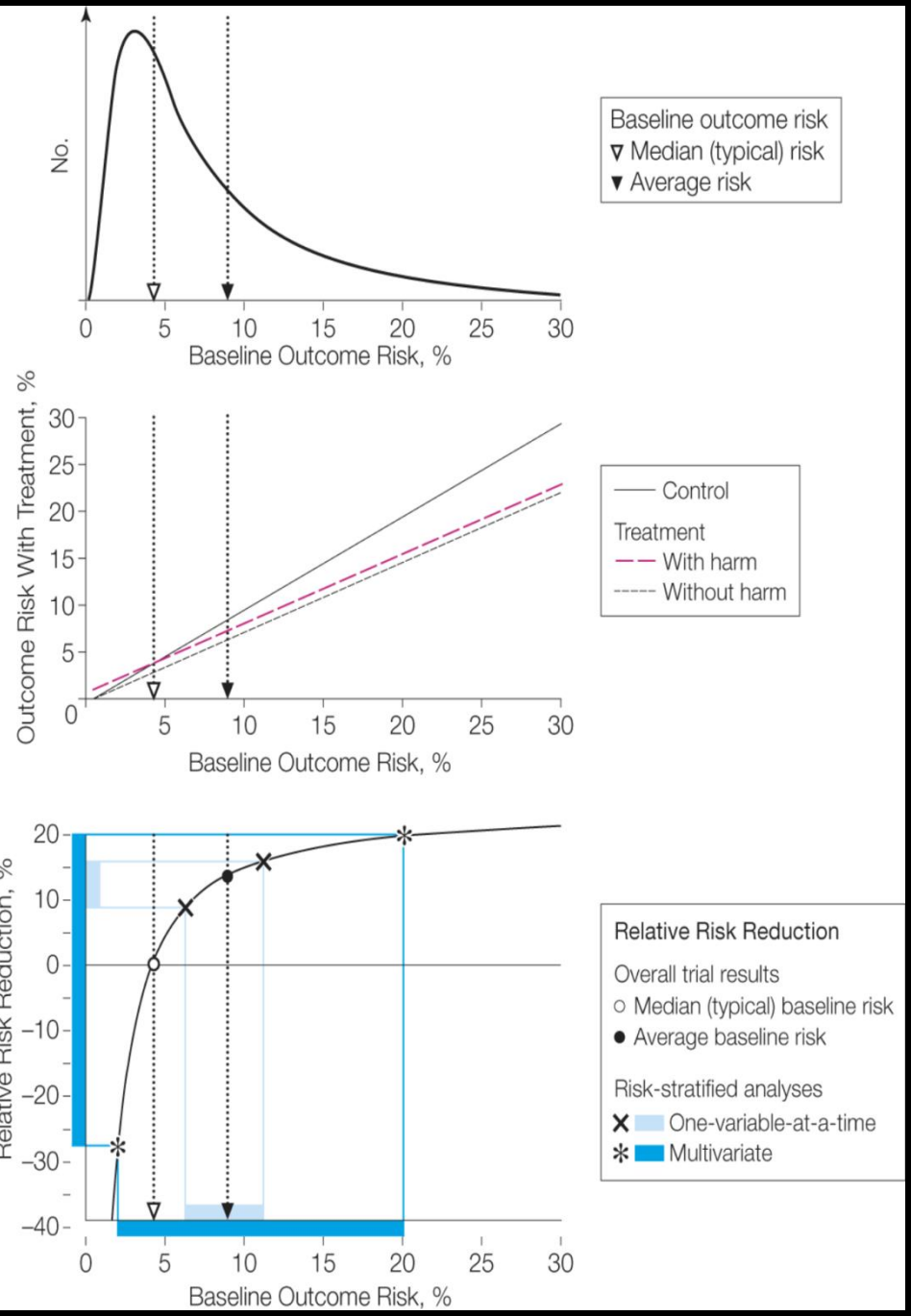
Patients enrolled in clinical trials often have greatly different baseline risks for the outcome of interest. The risk distribution is often skewed; a relatively small group of high-risk patients with multiple risk factors account for a large number of the outcomes and the mean risk might be considerably higher than the risk in the typical (median) patient.

B Outcome Risk With Treatment

A constant relative risk reduction (25% in this case) leads to increasing benefits as baseline risk increases; treatment and control outcome rates progressively diverge at higher baseline risks. When a therapy is associated with even a small amount of treatment-related harm, low-risk patients are unlikely to benefit at all. When the treatment-related risk of harm is 1%, patients with baseline risks lower than 4% have net harm from the therapy. The average baseline risk of the enrolled patients will determine whether the trial's summary results are positive overall. But the overall results may not reflect the trade-offs between the risks and benefits of many individual patients in the trial.

C Relative Risk Reduction

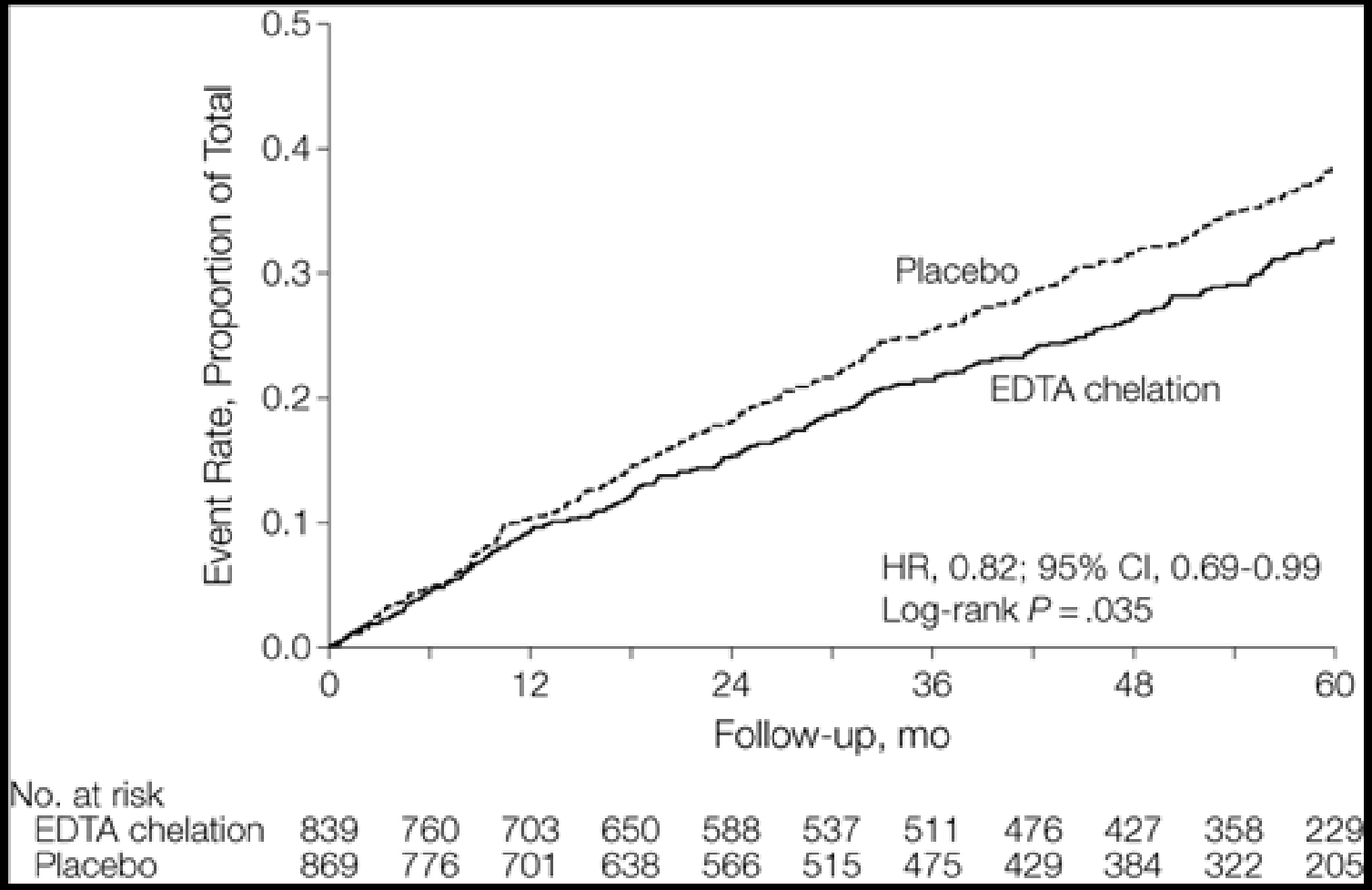
There is considerable variation in relative risk reduction given the assumptions of risks and benefits shown in B. The overall trial results (average baseline risk) indicate a 12.5% relative risk reduction but the typical patient (median baseline risk) does not benefit at all. One-variable-at-a-time subgroup analyses typically compare groups of patients that do not differ dramatically from the average risk (a 2-fold difference in risk), because the treatment effect differences may not be statistically significant, which can misleadingly imply a consistent treatment effect. Using multivariate risk indices compares patients across a broader range of baseline risks, exposing larger differences in the relative treatment effect, which are often clinically and statistically significant.



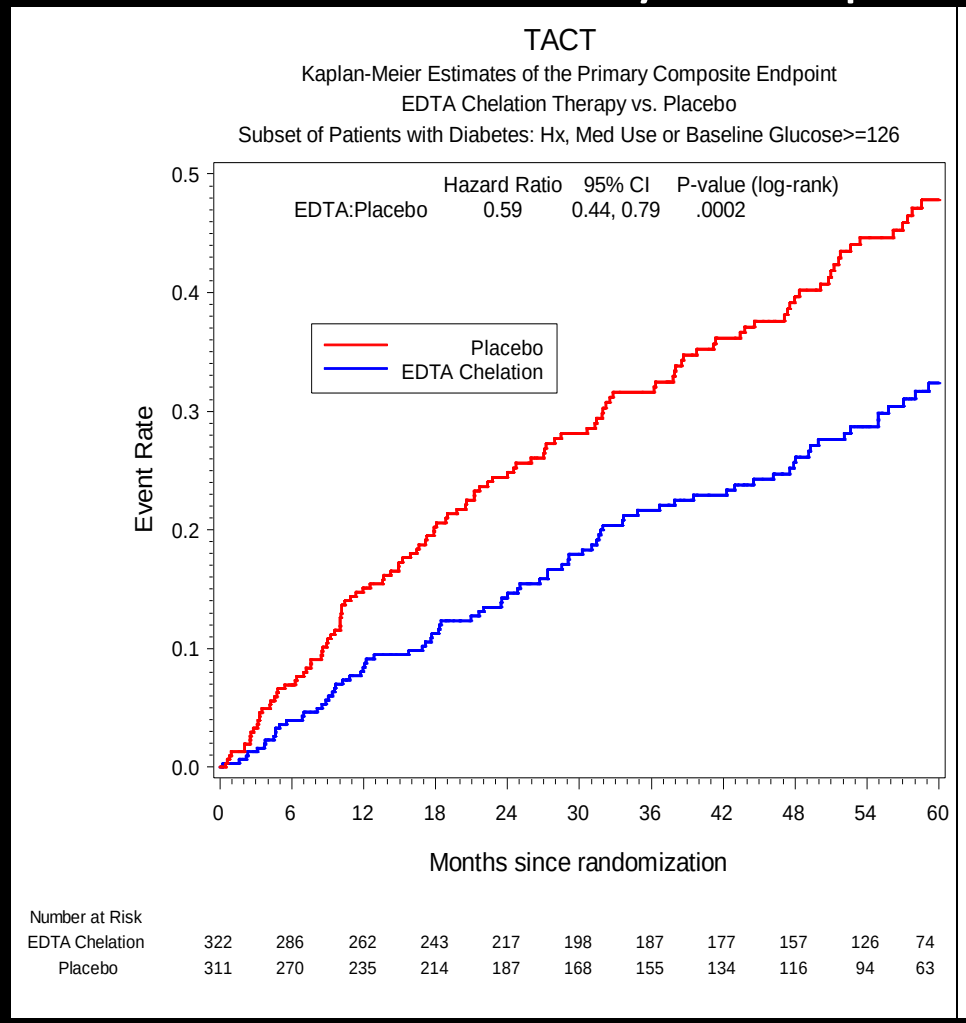
Heterogeneity of treatment effect (HTE)

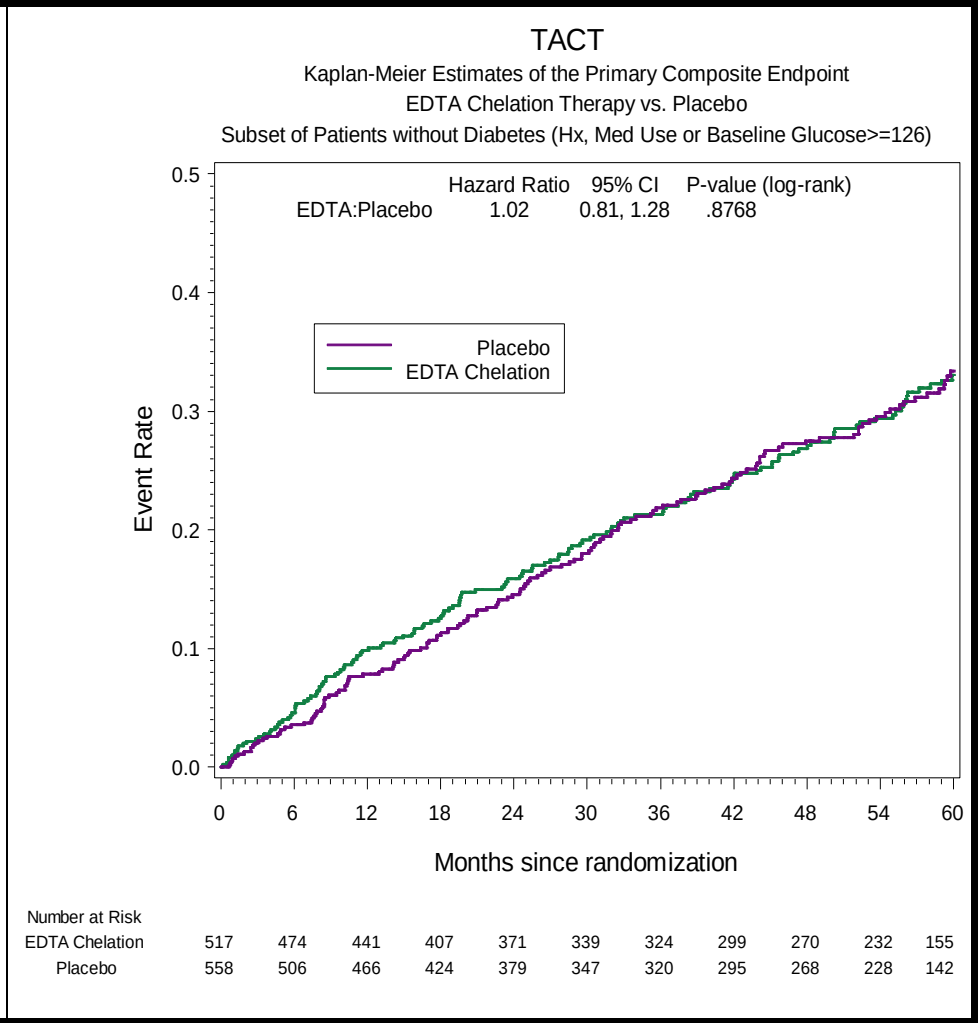
Lamas GA, Goertz, C, Boineau R, et al.
Effect of EDTA Chelation Regimen on Cardiovascular Events in Patients With Previous Myocardial Infarction.
JAMA. March 27, 2013

The TACT Trial



TACT: Primary Endpoint





Diabetes Patients (633)

No Diabetes (1075)

Escolar E, Lamas GA, Mark DB, et al. The effect of an EDTA-based chelation regimen on patients with diabetes and prior myocardial infarction in TACT. *Circulation: Cardiovascular Quality & Outcomes*. November 19, 2013.

THE VISION OF PRESIDENT OBAMA

"My hope is that this becomes the foundation, the architecture, whereby in 10 years from now we can look back and say that we have revolutionized medicine."

- PRESIDENT BARACK OBAMA

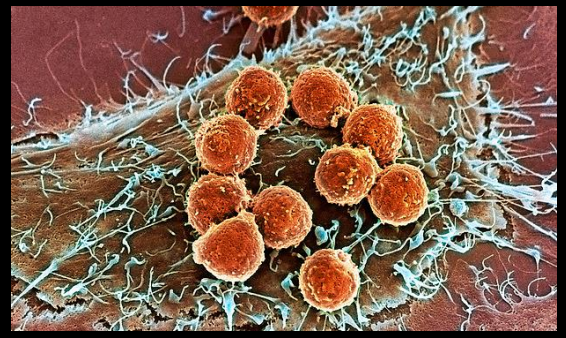
Building a Cohort of 1,000,000 Volunteers

Estimated disease incidence and prevalence in one million people

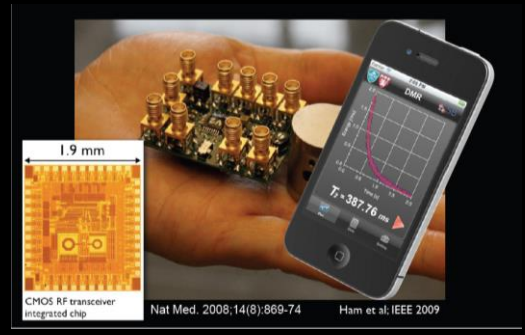
Disease	Expected prevalent cases	Incident cases	
		5 years	10 years
Type 2 Diabetes	135,658	40,411	123,196
Congestive heart failure	73,723	21,315	40,322
Asthma	62,149	17,292	44,036
COPD	48,728	15,396	33,584
Myocardial infarction	39,273	14,981	27,112
Epilepsy	33,426	4,161	11,248
Breast cancer (female)	20,470	12,068	21,382
Stroke	16,016	8,969	15,598
Lupus	14,659	3,283	6,738
Dementia	13,373	7,028	9,656
ADHD	13,039	7,213	13,582
Colorectal cancer	9,407	3,745	6,844

PMI RESEARCH PROGRAMS AT NIH

- **PMI for Oncology**: Apply precision medicine to **cancer**
  - Use NCI clinical trials as models
  - Identify new cancer subtypes, targets
  - Test precision therapies, with private sector partners



- **PMI Cohort Program**:
  - Generate knowledge base to move precision medicine into the **full range of health and disease**
  - Large longitudinal cohort donating data from self-report, physicals, biospecimens, medical records, technological and geographic sources

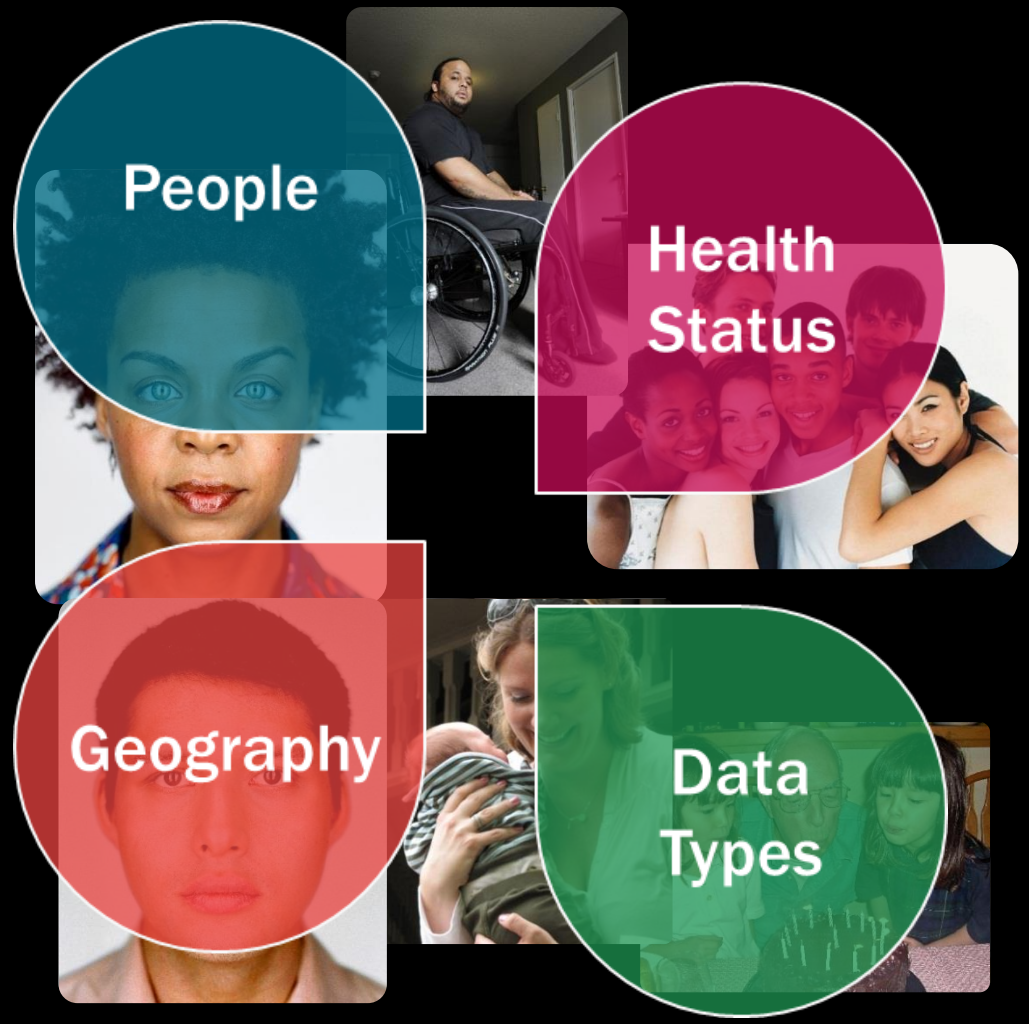


THE PRECISION MEDICINE INITIATIVE® COHORT

- One million or more volunteers, reflecting the broad diversity of the U.S.
- Opportunities for volunteers to provide data on an ongoing basis
- Data shared freely and fast to inform a broad variety of research studies

A TRANSFORMATIONAL APPROACH TO DIVERSITY

Reflecting the country's rich diversity to produce meaningful health outcomes for historically underrepresented communities



PMI Core Values

1. Participation is open to interested individuals
2. Participants are partners in all phases of the cohort program
3. Participants have access to study information and data about themselves
4. Data can be accessed broadly for research purposes
5. Adherence to the PMI privacy principles and forth-coming security framework
6. PMI is a catalyst for progressive research programs and policies

Initial Core Data Set

- Centrally collected and stored in a Coordinating Center
- Align with other data sets when possible
- Leverage existing data standards and common data models when possible

Data Source	Data Provided
Self report measures	Diet, substance use, self-report of disease and symptoms (e.g., cognitive or mood assessment)
Baseline health exam	Vitals (e.g., pulse, blood pressure, height, weight), medical history, physical exam
Structured clinical data (EHR)	ICD and CPT codes, medication history, select laboratory results, vitals, encounter records
Biospecimens	Blood sample
mHealth data	Passively-collected data (e.g., location, movement, social connections) from smartphones, wearable sensor data (activity, hours and quality of sleep, time sedentary).

Building evidence is serious business

Take on the hard questions