

Establishing Treatment Standards through Comparative Effectiveness Research

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Comparative Effectiveness Research Priorities

Patient-Centered Health Research is Vital to Health Reform

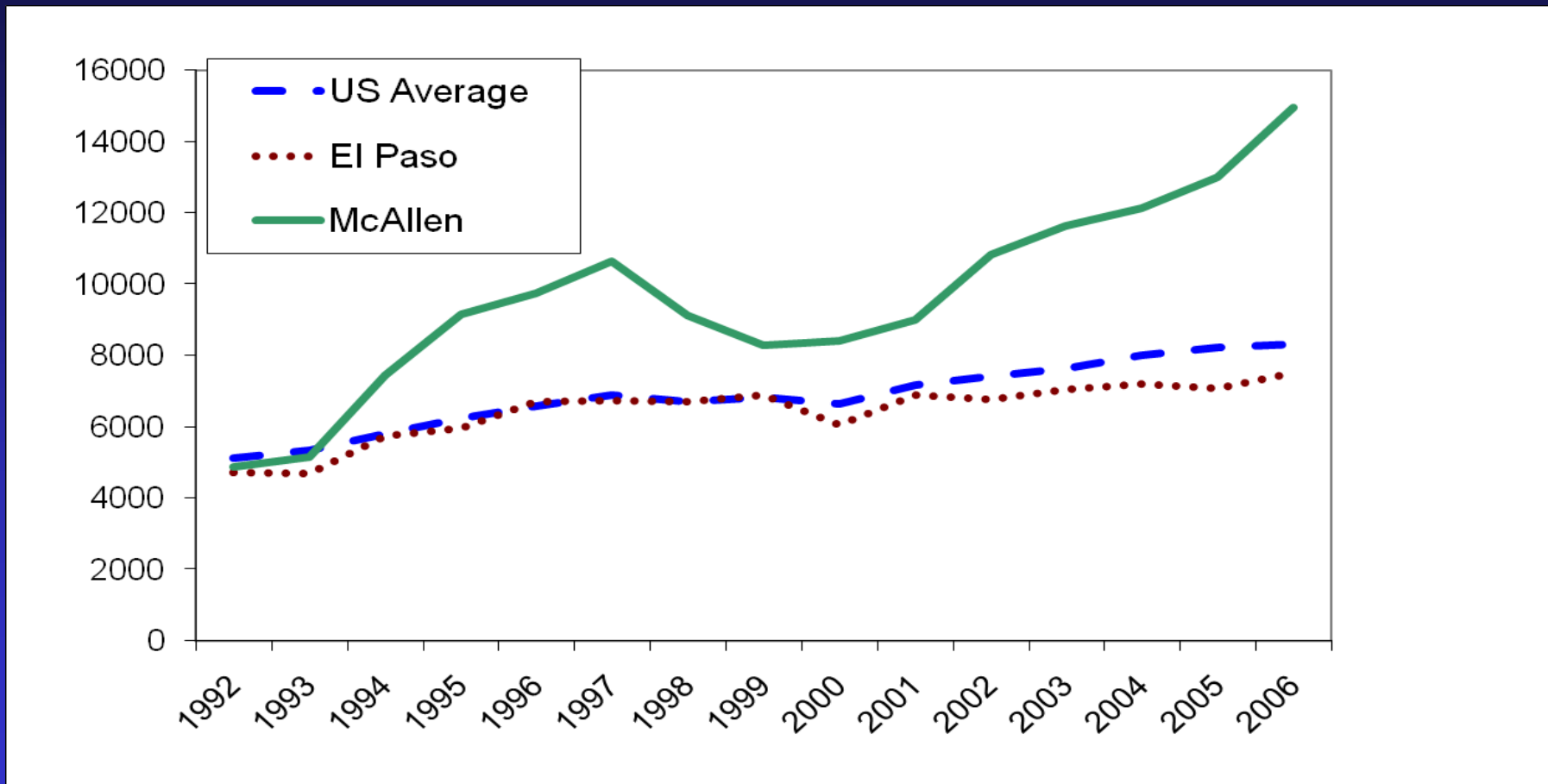
In situations where the right thing to do is well established, physicians from high- and low-cost cities make the same decisions.

But in cases where the science is more unclear, some physicians pursue the maximum possible amount of testing and procedures; some pursue the minimum.

And what kind of doctor they are depends on where they came from. In case after uncertain case, more was not necessarily better.

(Atul Gawande, New Yorker Magazine)

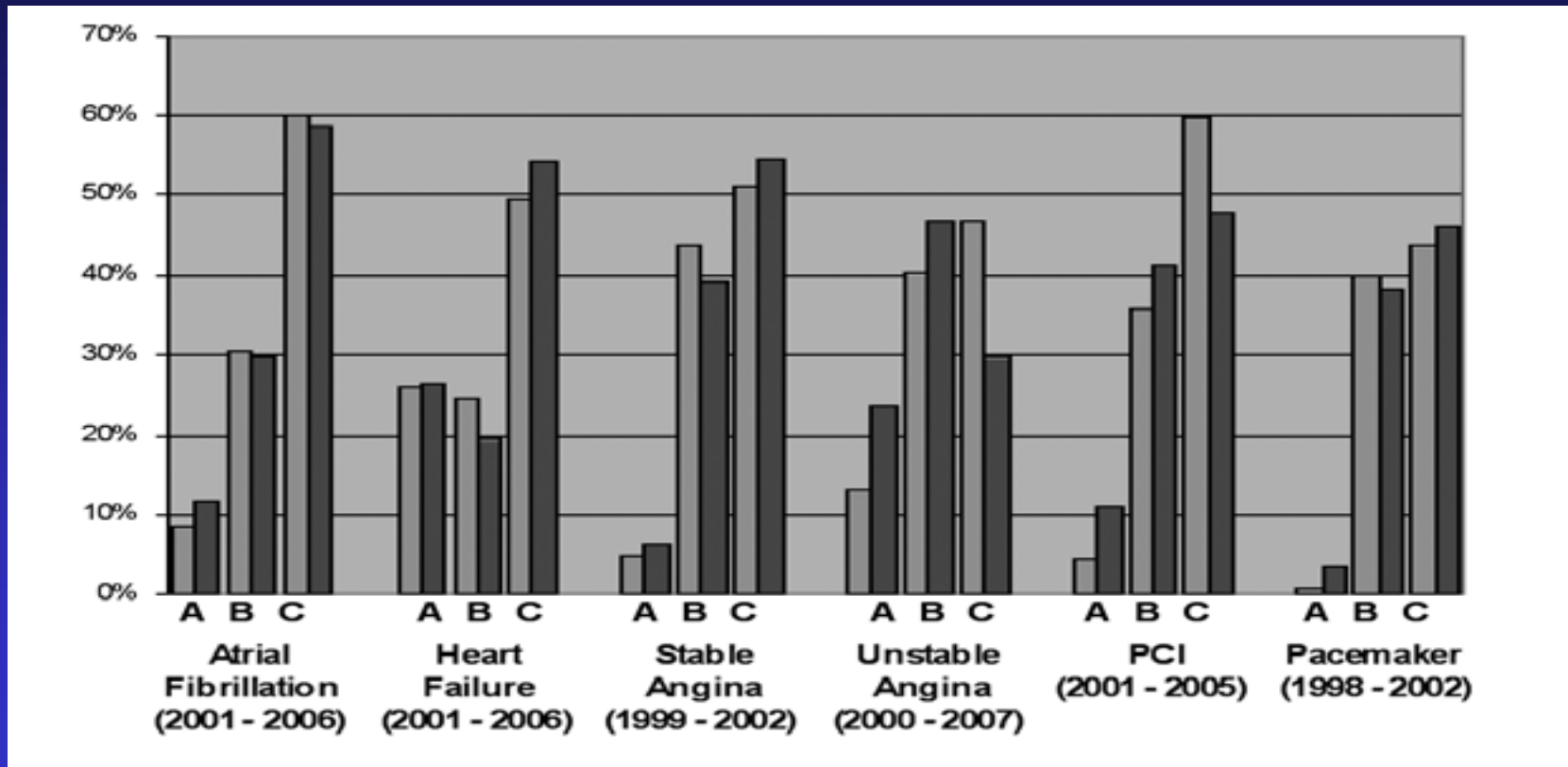
Disparate Growth In Per Capita Medicare Expenditures Over Time



Age-sex-race adjusted, in 2006 Dollars

Quality of Evidence in Clinical Guidelines

AHA/ACC Heart Disease Recommendations



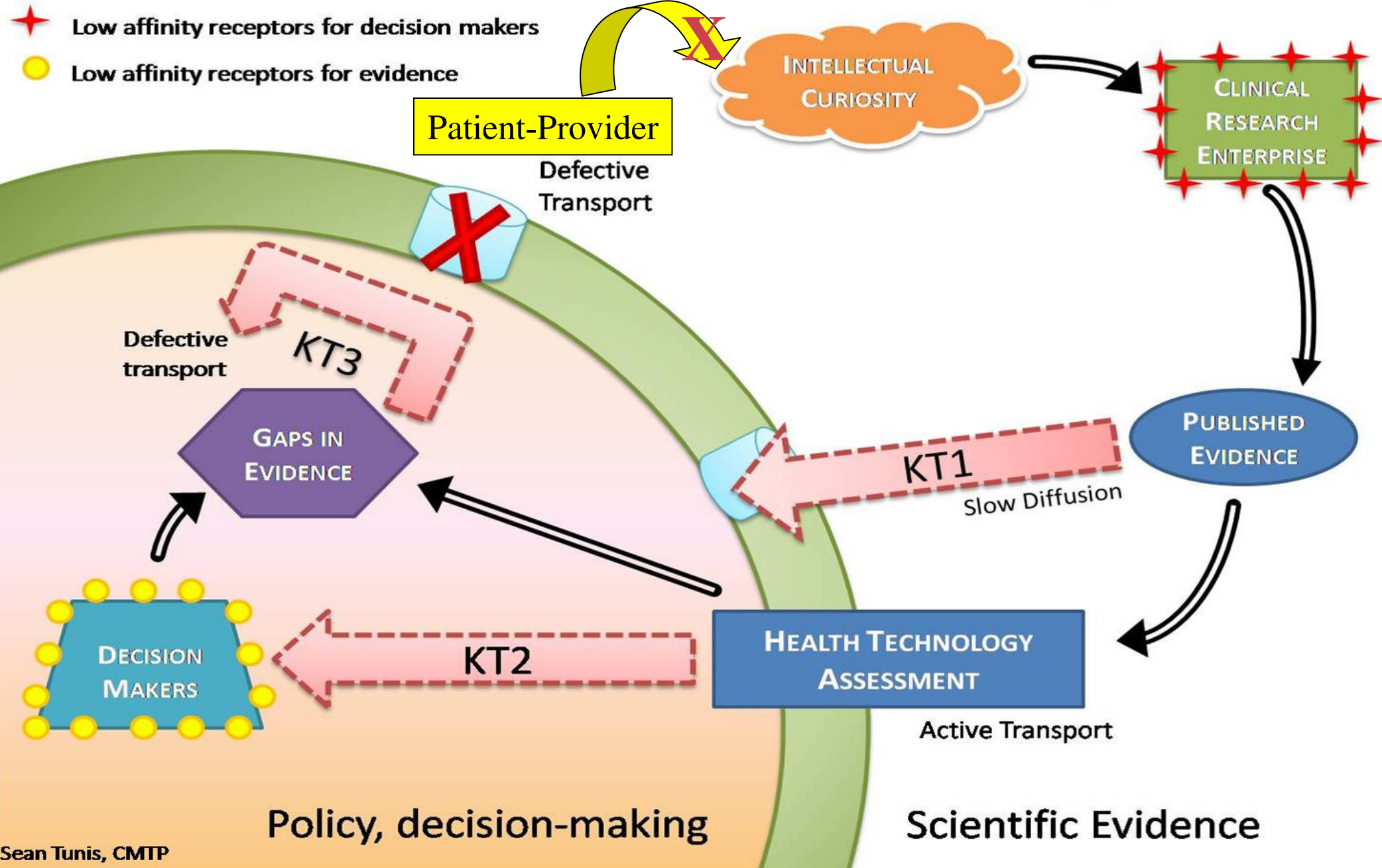
Source: Robert Califf, IOM Meeting on Evidence-based Medicine, December 2007

Why so many “C’s”?

- The paradox
 - 18,000 new randomized controlled trials published in 2007
 - “Available evidence is limited or poor quality”

Are we asking the right questions?

Molecular Basis of Uncertainty



The Obvious Policy Issue

We need to generate new data on what works best for whom, under what circumstances.

Recovery Act's \$1.1B for Patient-Centered Health Research

Implementation Update:

- Federal Coordinating Council established
- Institute Of Medicine (IOM) Report commissioned
- Reports from IOM & Council delivered June 30, 2009
- FY09 spending plans to Congress July 30, 2009
- RFAs from National Institutes of Health and Agency for Healthcare Research and Quality announced and under review
- \$200-300 million per year for 10 years in health reform

Efficacy versus Effectiveness Trials

	Efficacy Studies	Effectiveness Studies
Objective	Does it work under optimal circumstances?	Does it work under usual circumstances?
Motivation	Regulatory approval – FDA	Formulary approval
Intervention	Fixed regimen / forced titration	Flexible regimen
Comparator	Placebo; Arbitrarily chosen comparator	Usual Care, Least expensive/most efficacious
Design	RCT-strict control	RCT or open label-minimum control
Subjects	Selected or “eligible” subjects; high compliance	Any subjects; low compliance
Outcomes	Condition-specific; Strong link to mechanism; Short-term horizon	Comprehensive (for example, QoL, utilities); Weak link to mechanism of action; Short- and long-term horizon
Analysis	Protocol adherers	Intent to treat

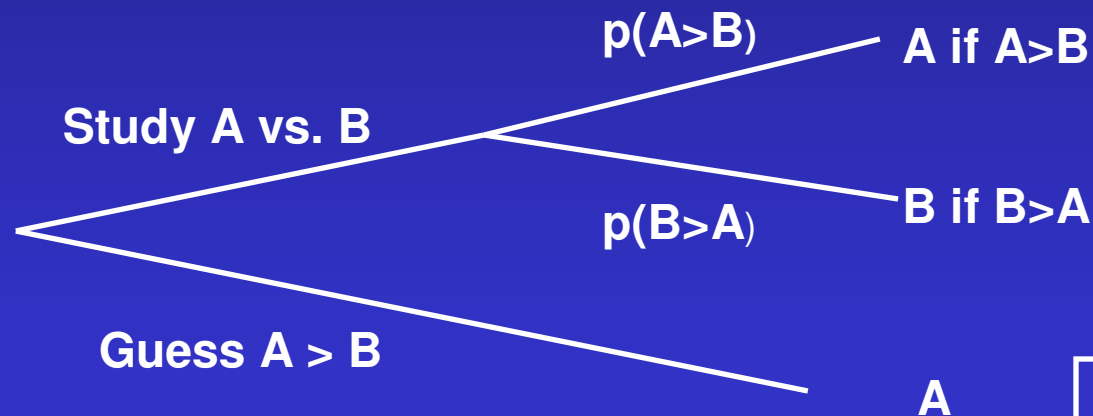
Committee's Definition of CER

The generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care.

The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels.

Guiding Principle: The Value of Information (VOI)

- **Definition:** Difference between the value of the outcome given the decision one would make in the absence of additional information and the value of the outcome of the decision that would be made as additional information became available as a result of research

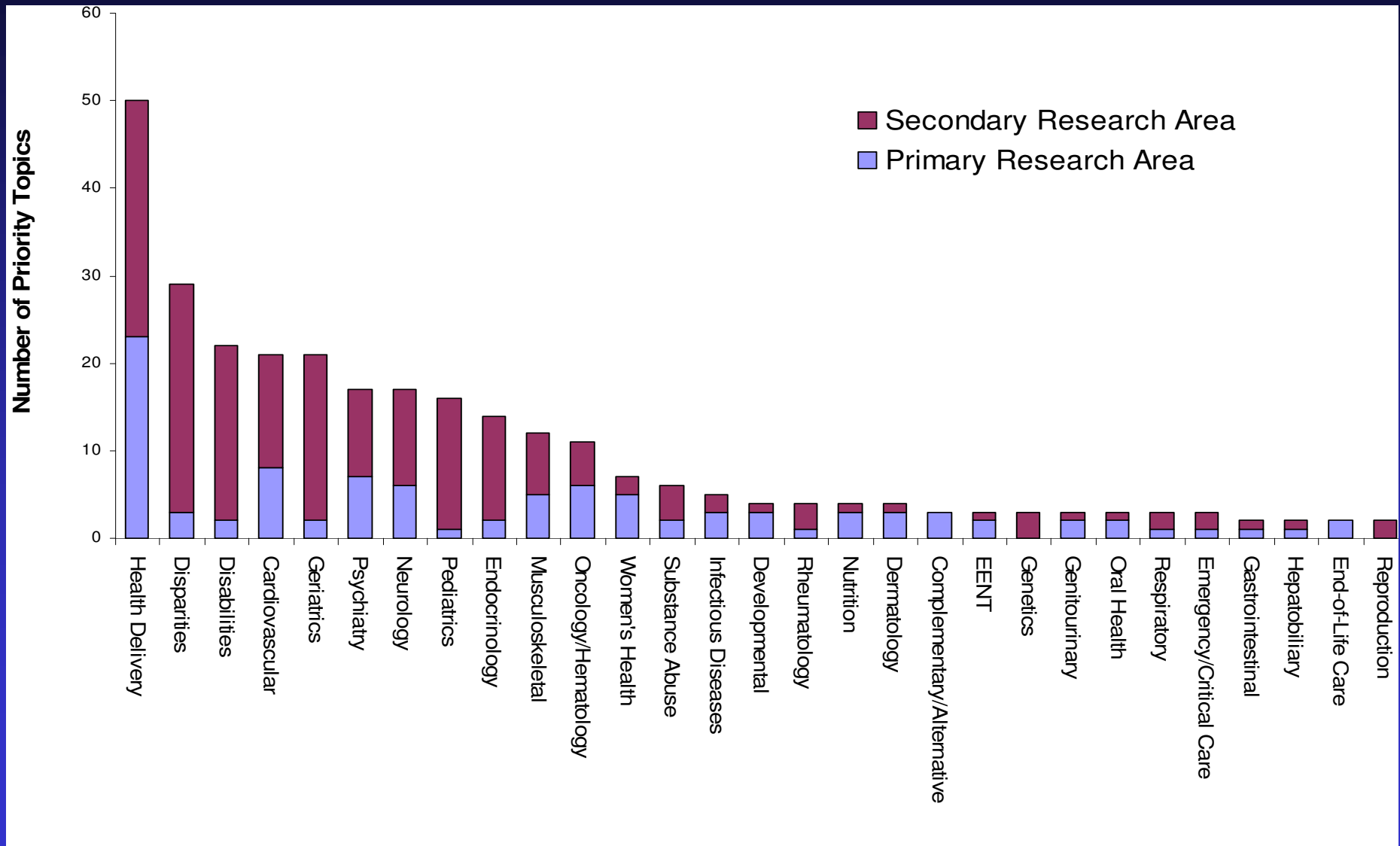


Value of Research is :
 $(B-A) \text{ if } B > A = p(B > A) (B-A)$

Inputs into VOI Calculation

- **Choice to be Made:** Identification of the relevant set of alternatives to be compared
- **Value of Outcomes:** Construction of an outcome measure to compare benefits across interventions
- **Potential Findings of Research:** Characterization of how additional research might change uncertainty of the outcomes of an intervention
- **Probability of Change in Choice:** Prediction of the probability that clinical choices will change in response to research results

Distribution of the recommended research priorities by primary and secondary research areas



- Compare the effectiveness and cost-effectiveness of conventional medical management of type 2 diabetes in adolescents and adults, versus conventional therapy plus intensive educational programs or programs incorporating support groups and educational resources.
- Compare the effectiveness of comprehensive care coordination programs, such as the medical home, and usual care in managing children and adults with severe chronic disease, especially in populations with known health disparities.

- Compare the effectiveness of accountable care systems and usual care on costs, processes of care, and outcomes for geographically defined populations of patients with one or more chronic diseases.
- Compare the effectiveness of different benefit design, utilization management, and cost-sharing strategies in improving health care access and quality in patients with chronic diseases (e.g., cancer, diabetes, heart disease).
- Compare the effectiveness (including resource utilization, workforce needs, net health care expenditures, and requirements for large-scale deployment) of new remote patient monitoring and management technologies (e.g., telemedicine, Internet, remote sensing) and usual care in managing chronic disease, especially in rural settings.

- Compare the effectiveness of traditional behavioral interventions versus economic incentives in motivating behavior changes (e.g., weight loss, smoking cessation, avoiding alcohol and substance abuse) in children and adults.
- Compare the effectiveness of strategies for enhancing patients' adherence to medication regimens.
- Compare the effectiveness of different disease management strategies for activating patients with chronic disease.

- Compare the effectiveness of shared decision making and usual care on decision outcomes (treatment choice, knowledge, treatment-preference concordance, and decisional conflict) in children and adults with chronic disease such as stable angina and asthma.
- Compare the effectiveness of patient decision support tools on informing diagnostic and treatment decisions (e.g., treatment choice, knowledge acquisition, treatment-preference concordance, decisional conflict) for elective surgical and nonsurgical procedures—especially in patients with limited English-language proficiency, limited education, hearing or visual impairments, or mental health problems.

- Compare the effectiveness of strategies for enhancing patients' adherence to medication regimens.
- Compare the effectiveness of different disease management strategies for activating patients with chronic disease.
- Compare the effectiveness of alternative redesign strategies—using decision support capabilities, electronic health records, and personal health records—for increasing health professionals' compliance with evidence-based guidelines and patients' adherence to guideline-based regimens for chronic disease care.

- Compare the effectiveness of various strategies (e.g., clinical interventions, selected social interventions [such as improving the built environment in communities and making healthy foods more available], combined clinical and social interventions) to prevent obesity, hypertension, diabetes, and heart disease in at-risk populations such as the urban poor and American Indians.
- Compare the effectiveness of school-based interventions involving meal programs, vending machines, and physical education, at different levels of intensity, in preventing and treating overweight and obesity in children and adolescents.

- Compare the effectiveness of treatment strategies for obesity (e.g., bariatric surgery, behavioral interventions, pharmacologic treatment) on the resolution of obesity-related outcomes such as diabetes, hypertension, and musculoskeletal disorders.
- Compare the effectiveness of interventions (e.g., community-based multilevel interventions, simple health education, usual care) to reduce health disparities in cardiovascular disease, diabetes, cancer, musculoskeletal diseases, and birth outcomes.

An interactive file of the list of priority topics is available on the project website at:

www.iom.edu/cerpriorities

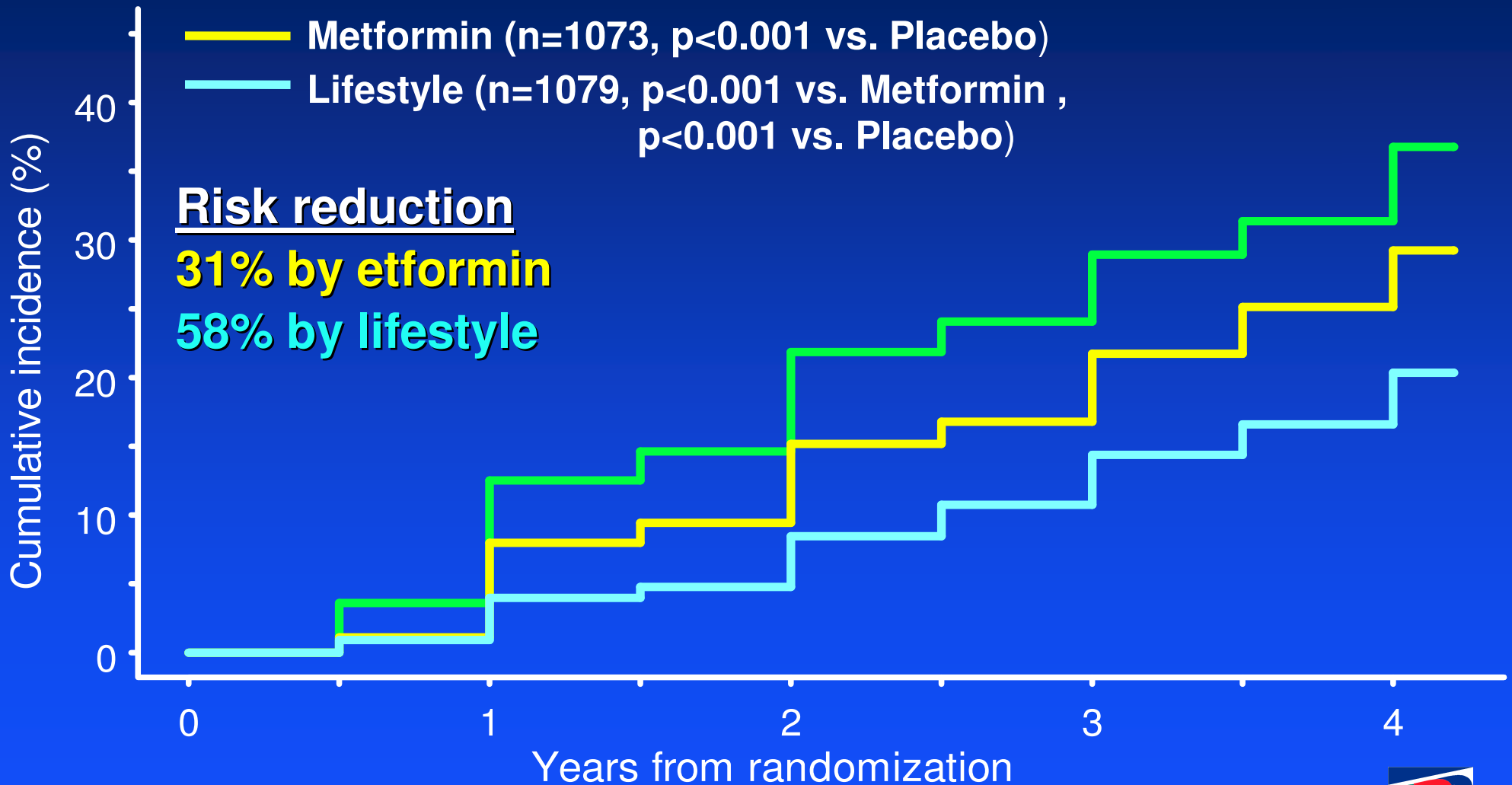
Categories of CER Methods

- Systematic reviews of existing research
- Decision modeling, with or without cost information
- Retrospective analysis of existing clinical or administrative data
- Prospective non-experimental studies, including observational epidemiologic studies and registries
- Experimental studies, including randomized clinical trials (RCTs)

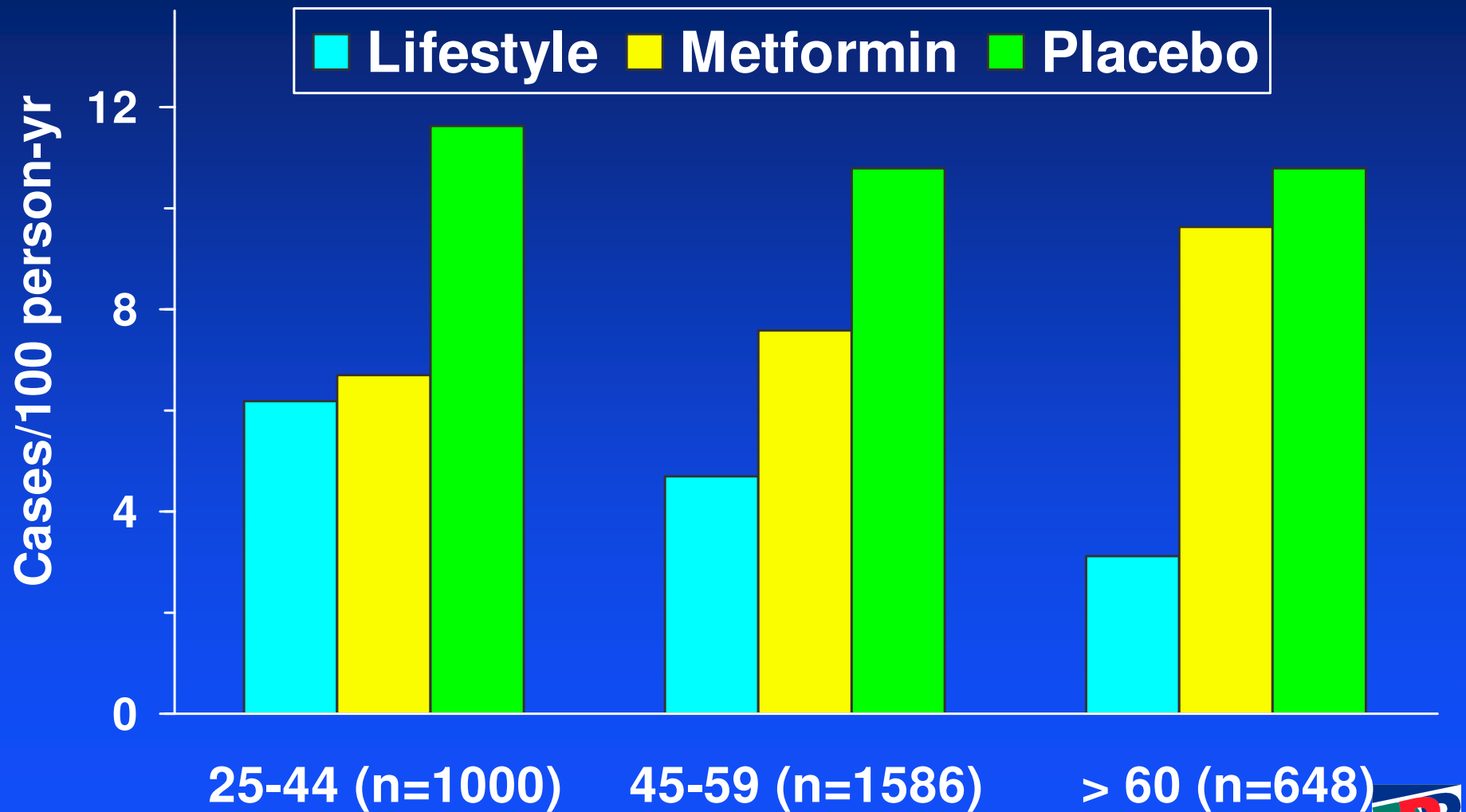
Incidence of Diabetes

- Placebo (n=1082)
- Metformin (n=1073, $p < 0.001$ vs. Placebo)
- Lifestyle (n=1079, $p < 0.001$ vs. Metformin, $p < 0.001$ vs. Placebo)

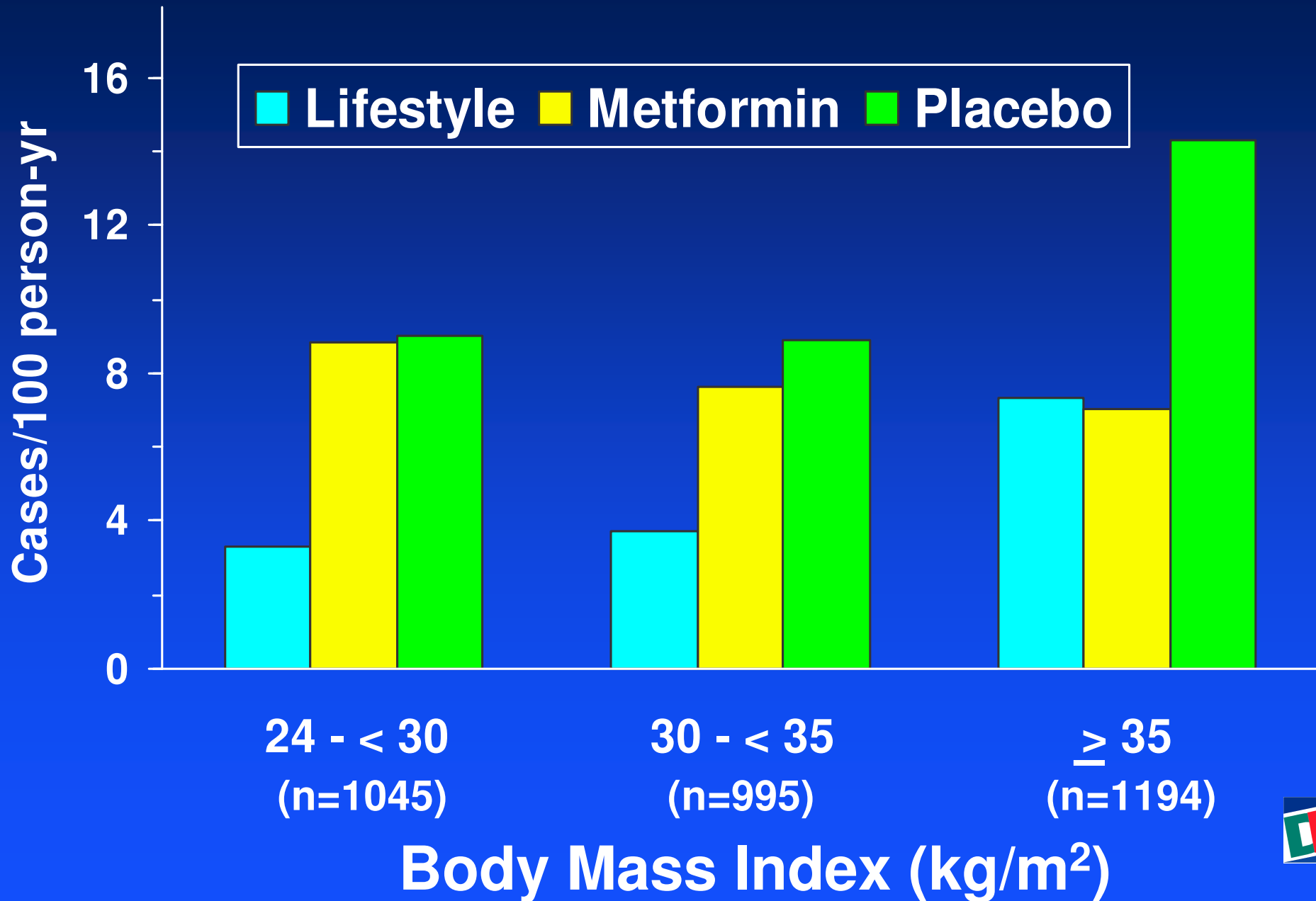
Risk reduction
31% by metformin
58% by lifestyle



Diabetes Incidence Rates by Age



Diabetes Incidence Rates by BMI



Pragmatic Clinical Trials - Definitions

Schwartz D and Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. *J Chron Dis* 1967; 20:637-648.

“Should one prefer the goal of immediate applicability with a sacrifice of true understanding, or the more distant goal which may lead to greater enlightenment and which may prove more fertile for the future?”

Pragmatic Clinical Trials

- Use a pragmatic design for the study:
 - If outcome is relevant to patients
 - If outcome has little mechanistic importance
- Choose outcomes of clinical relevance including patient-reported outcomes and Quality of Life
- Heterogeneous populations with co-morbidities are desirable, regardless of the impact on withdrawal

What Are Adaptive Trials?

- Trials that change based on prospective rules and the accruing information:
 - Adaptive sample sizes
 - Adaptive randomization
 - Adaptive accrual rate
 - Drop/Re-enter arms or dose groups
 - Combination therapies
 - Stop early for success or terminate early for futility
 - Adapt to responding sub-populations
 - Adaptive borrowing of information
 - Seamlessly combine phases of development

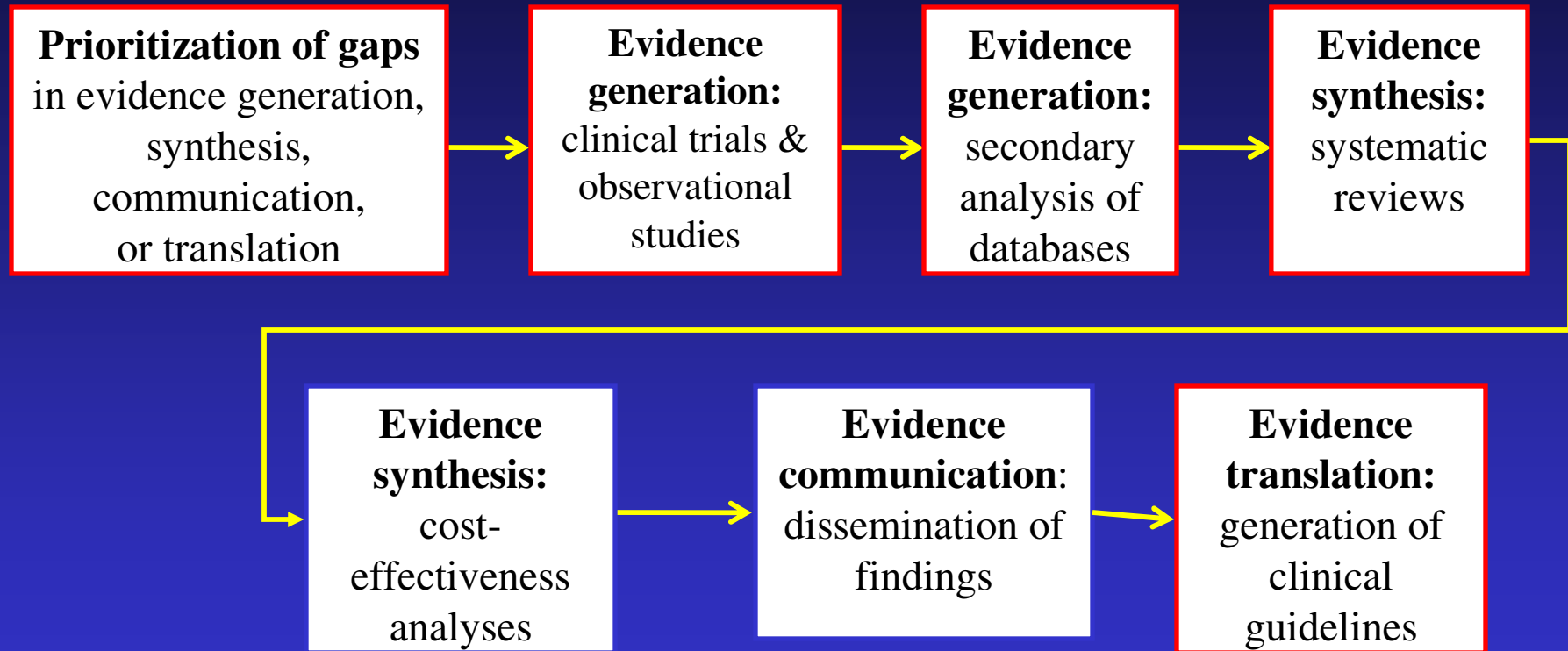
What Does Bayes Add to CER?

- Synthesis
 - Bayes is ideal for combining information
 - Meta-analysis or combining past studies with new data
- Prediction
 - Uses longitudinal models within trials
 - Produce predictive probabilities of trial success
 - Predict individual patient result on different treatments
- Personalized Medicine
 - Bayes conditions on all known data
 - Combines patient-specific information and known historical data
 - Probabilities average over uncertainty in historical estimates

All Methods Have a Role

- Inevitable trade-off between internal validity and feasibility, generalizability, cost, time
- The nature of the research question, and the decision maker will influence best practices
- Experimental studies will have a crucial role in CER, and there is need for improving design and implementation
- Non-experimental methods hold great promise, particularly as methods are refined and data infrastructure is improved

What is Included in Comparative Effectiveness Research?



Requires clinical input

BMJ

**Parachute use to prevent death and major trauma related to gravitational challenge:
systematic review of randomised controlled trials**

Gordon C S Smith and Jill P Pell

BMJ 2003;327:1459-1461

doi:10.1136/bmj.327.7429.1459



Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

What This Study Adds

- No randomized controlled trials of parachute use have been undertaken
- The basis for parachute use is purely observational, and its apparent efficacy could potentially be explained by a “healthy cohort” effect
- Individuals who insist that all interventions need to be validated by a randomized controlled trial need to come down to Earth with a bump!