FDA's Critical Path Initiative and Approach to Personalized Medicine

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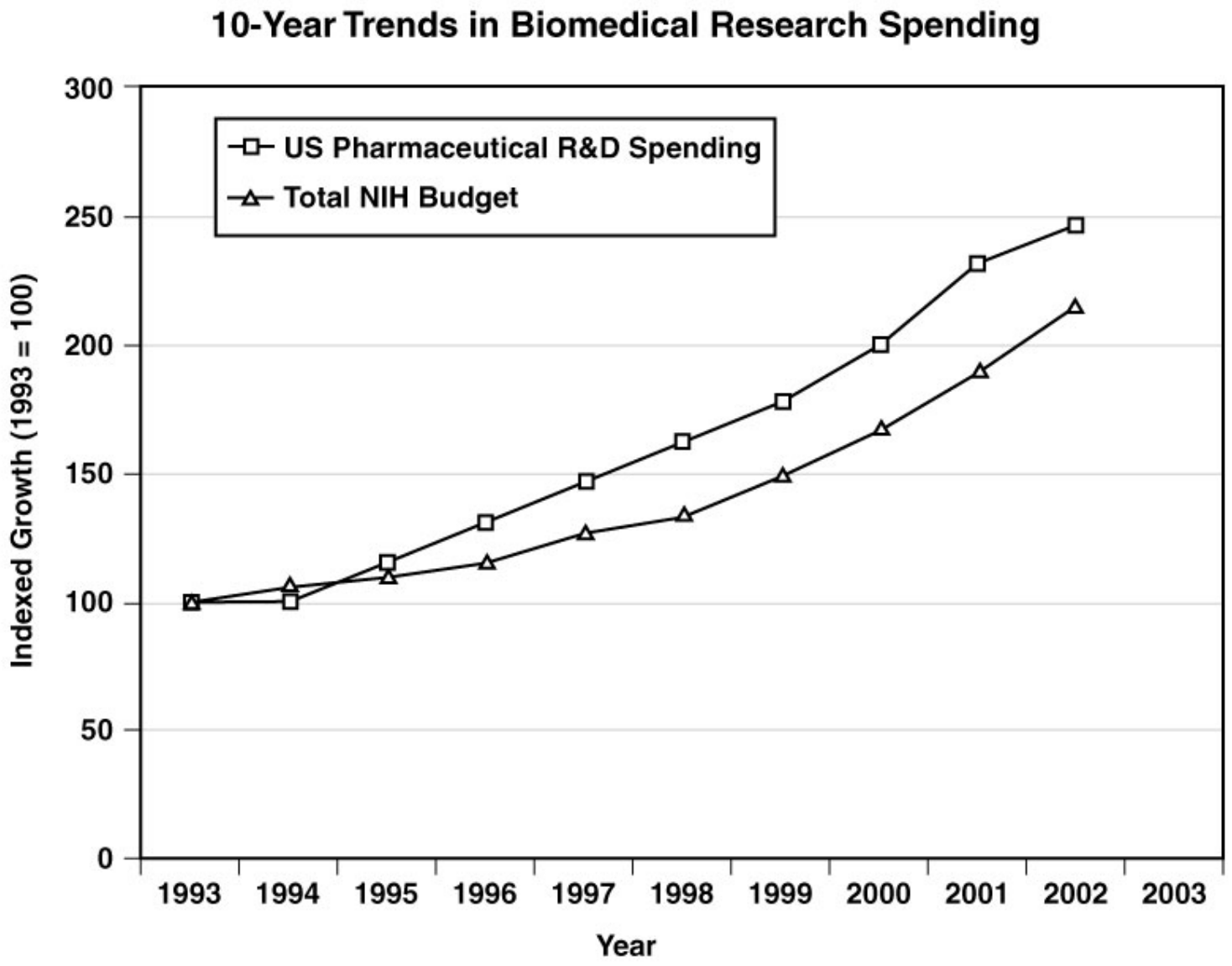
This is a “Golden Age” for Biomedical Discovery

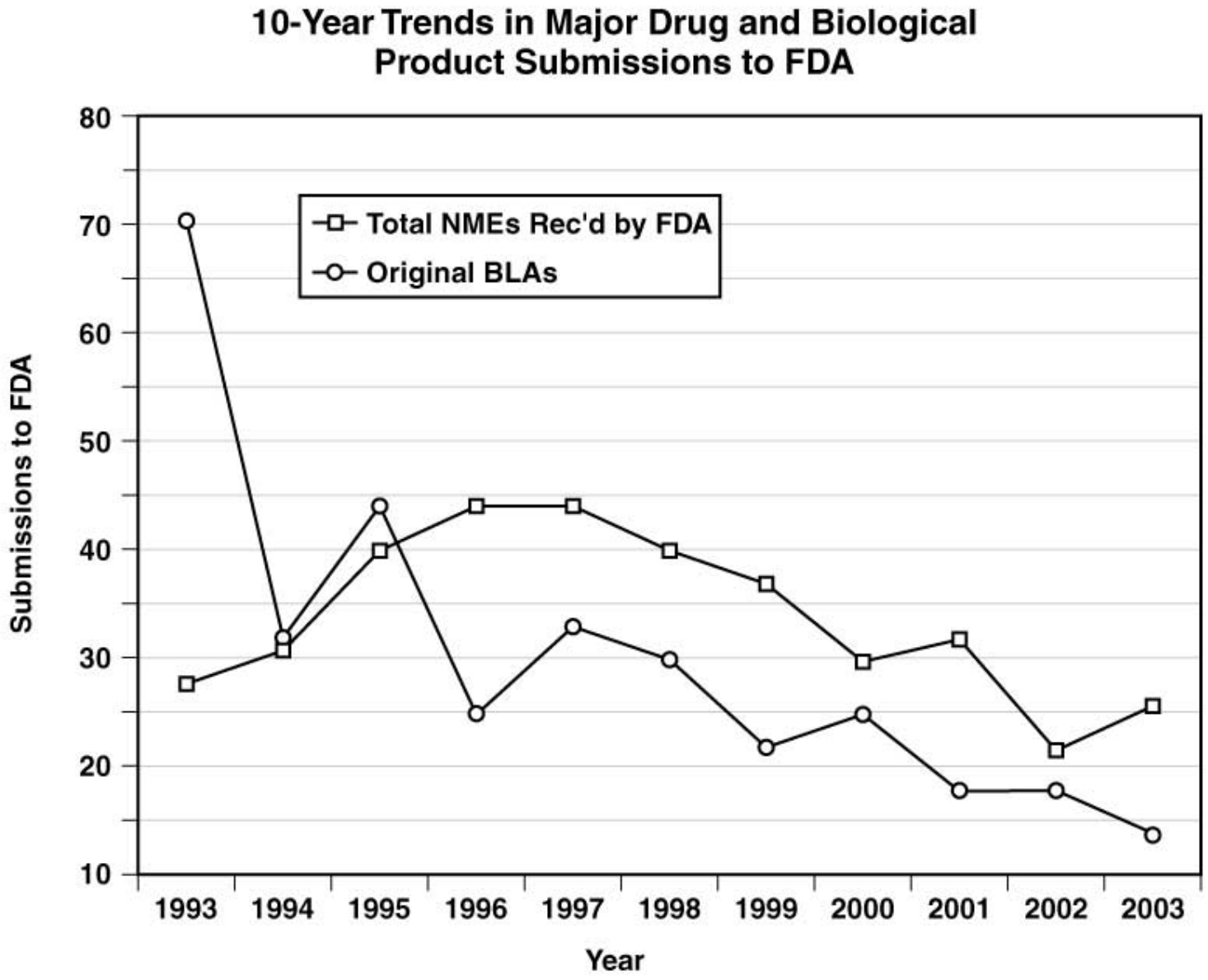
- Sequencing of human genome reveals new candidate targets
- Combinatorial chemistry, high throughput screening, biosynthesis provide thousands of candidate drugs
- Electronics innovations, nanotechnology, materials science drive device innovation
- Transgenic animals, new technologies (e.g., RNAi) for evaluating activity

Ten Year Investment in U.S. Biomedical Research

- Increased from $37B in 1994 to $94B in 2003 (doubling when inflation-adjusted)
- 57% of funding from industrial sector
- 33% of funding from government (28% NIH)
- 10% private sources


10-Year Trends in Biomedical Research Spending
US Pharmaceutical R&D Spending
Total NIH Budget
Indexed Growth (1993 = 100)
300
250
200
150
100
50
0
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
Year

Matching Acceleration of Product Development Has Been Expected


10-Year Trends in Major Drug and Biological Product Submissions to FDA
Total NMEs Rec'd by FDA
Original BLAs
Submissions to FDA
80
70
60
50
40
30
20
10
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
Year

Ten Year Trends Worldwide

- 2004 marked a 20-year low in introduction of new medical therapies into worldwide markets
- DiMasi, et al. (2003) estimated that the capitalized cost for self-originated NMEs developed by multinational pharma & approved in 2001 would be about $1.1 B per NME.
- Disincentive for investment in less common diseases or risky, innovative approaches

Predictability Problem

- Product development success rate has declined:
  - New compounds entering Phase I development today have 8% chance of reaching market, vs. 14% chance 15 years ago.
  - Phase III failure rate now reported to be 50%, vs. 20% in Phase III, 10 years ago.

Problem: Biomedical Discoveries are Not Effectively Translated

- Huge Investment in U.S. Biomedical Research
- Lack of corresponding new products available to patients
- Major increases in medical product development costs
- Major rise in healthcare costs

Speculation on Causes of Translational Problems

- Genomics & other new science not at full potential (10-15 yrs)
- Easy targets taken; chronic disease harder to study
- Rapidly escalating costs & complexity decrease willingness and ability to bring many candidates forward into the clinic
- Mergers and other business arrangements
- Some people blame FDA

What's the Diagnosis?

- Investment and progress in basic biomedical science has far surpassed investment and progress in the *medical product development process*
- The *development process* – the critical path to patients – becoming a serious bottleneck to delivery of new products
- We are using the evaluation tools and infrastructure of the last century to develop this century's advances

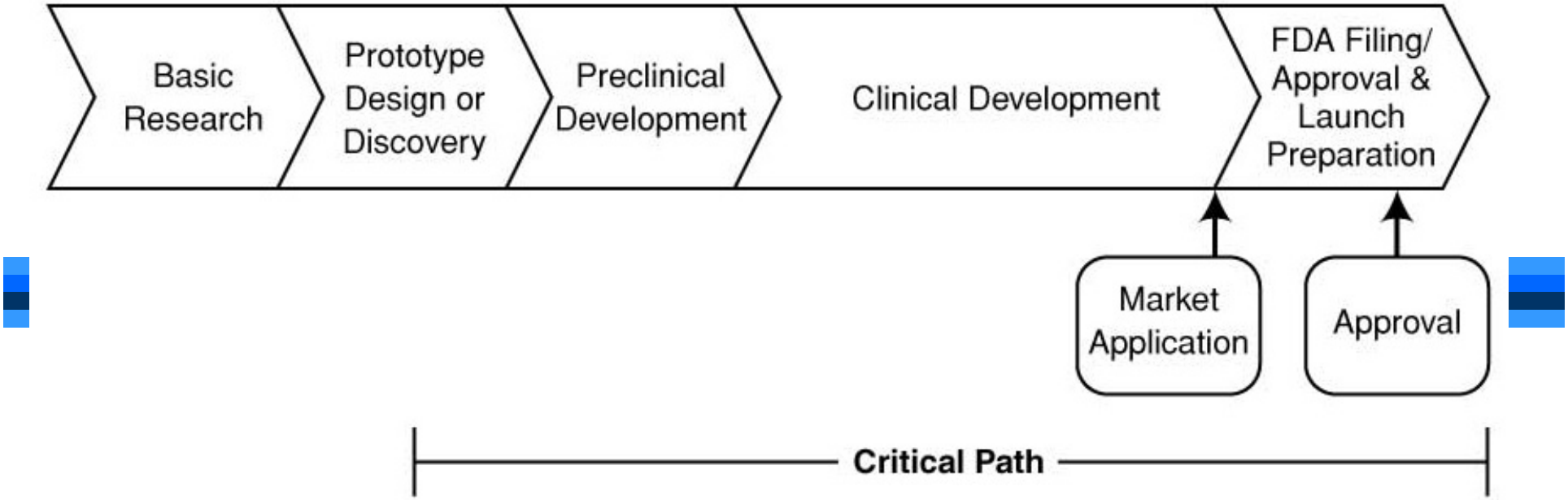
Beyond Discovery: Root Cause of Problem?

- Science used to predict and evaluate product performance has not advanced at the same pace as basic science
- Continuing to use the tools and methods of 19th and 20th century to evaluate 21st century technology: development is now the bottleneck
- Huge opportunity to improve product development with new science
- Requires major paradigm shifts

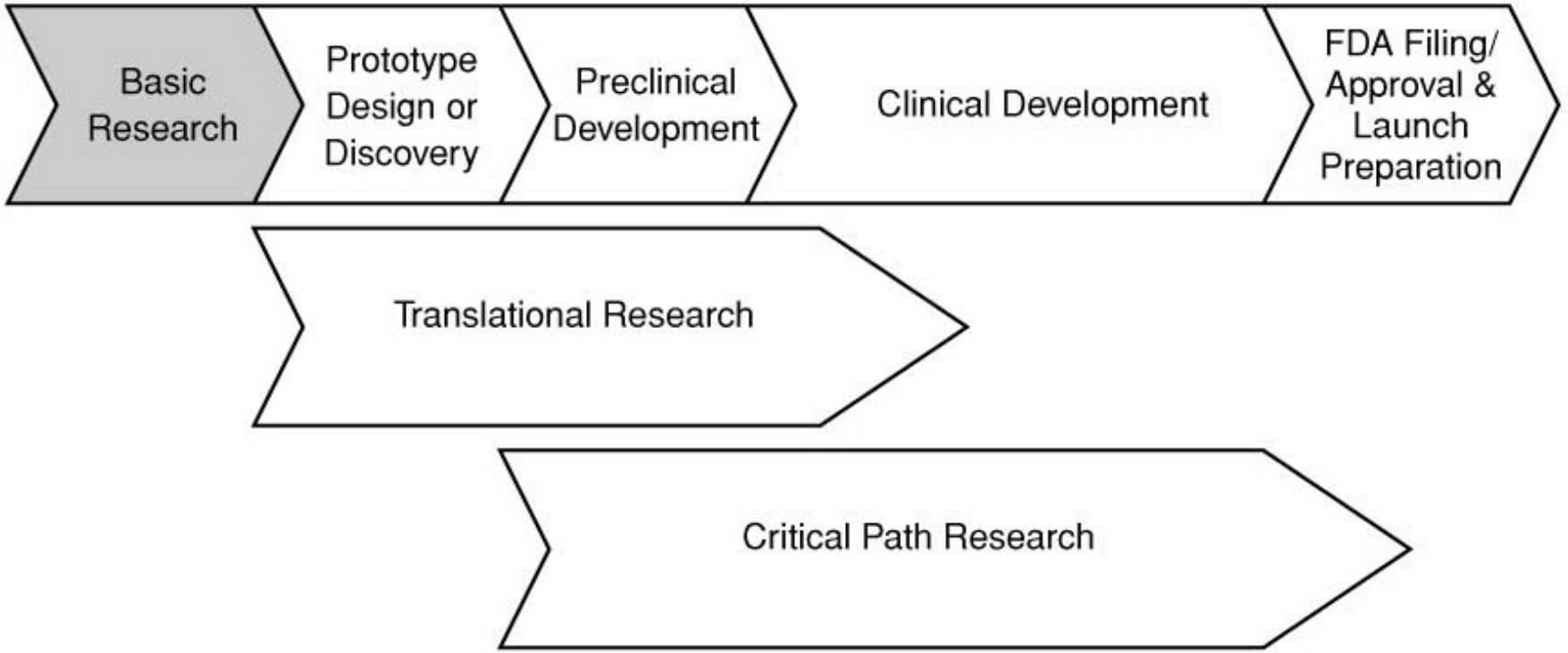
What is the “Critical Path”?

- There is a “critical path” stretching from candidate identification to commercial product
- Involves serial evaluation of product performance through preclinical testing and clinical evaluation
- FDA’s Critical Path Initiative focuses on the science used for these evaluations

The Critical Path for Medical Product Development Is Now the Bottleneck



Evaluative Science Underlying The Critical Path



Science to predict and evaluate safety & efficacy performance of new products, and enable manufacture, is different from basic discovery science

"Critical Path" Dimensions

Evaluative science to address 3 key product performance dimensions:

- Assessment of Safety – how to predict and asses the risks of a potential product?
- Proof of Efficacy -- how to predict and demonstrate that a potential product will have medical benefit?
- Industrialization – how to manufacture a product at commercial scale with consistently high quality?

FDA's Critical Path Initiative

A serious attempt to bring attention and focus to the need for targeted scientific efforts to modernize the processes and methods used to evaluate the safety, efficacy and quality of medical products as they move from product selection and design to mass manufacture.

Guiding Principles of FDA Initiative

- Collaborative efforts among government, academia, industry and patient groups
- Infrastructure and “toolkit” development, not product development
- Build support for academic science bases in relevant disciplines
- Build opportunities to share existing knowledge & database
- Develop enabling standards

Steps to Date

- Published Initial Report 5/04
- Opened Docket for public comment
- Discussed with FDA Science Board and other Advisory Committees
- Initiating multiple public-private partnership consortia with non-profit conveners
- Published “Critical Path Opportunities Report and List” 3/06
- Working to form multiple consortia to perform research

Major Opportunities for Modernization

- Biomarker Qualification
  - In-vitro diagnostics
  - Imaging
  - Preclinical toxicogenomics
- Clinical Trial Modernization
- Bioinformatics
- Modernizing Manufacturing
- Pediatric Treatments
- Public Health Emergencies

Biomarker Qualification

- “Biomarkers” are quantitative measures of physiology or pathophysiology or pharmacological/physical etc. effect
- Examples: liver function tests, ECGs, radiographs, psychological tests
- Biomarker discovery is fast, but understanding of clinical meaning develops very slowly
- New biomarkers key to personalized medicine
- Consortia needed to develop them

Why Public-Private Biomarker Consortia?

- Successful biomarker qualification is quite uncommon
- New biomarkers are critical to clinical medicine and efficient product development
- No single entity charged with accomplishing qualification
- All parties (government, industry, insurers, academia, patients) have a big stake however

New Biomarkers: Example

- Pharmacogenomic markers
  - Drug metabolism polymorphisms: avoiding serious side effects—first tests have been approved
  - Predictors of drug response or nonresponse (to target treated population)
  - Genetic basis of adverse events—avoid treating those at risk—prevention is preferable to warnings

New Biomarkers

- Advanced Imaging Technologies
  - Distinguish disease subgroups for therapy
  - Rapidly evaluate response to treatment on an individual basis
  - Use as response measure in clinical trials

The Current Clinical Development Model

- The randomized controlled clinical trial represented a scientific triumph over anecdotal medicine in the 1960s
- Used to control for bias and the impact of “random” (unexplainable) variability—but this variability is a the heart of personalization
- Basis for many of the advances of modern medicine

Limitations of Controlled Trials

- Theoretically can answer any and all questions via controlled experiments
- Can answer one or a few questions per trial
- There are an unlimited number of questions about the appropriate use of medical products and the outcomes of such use, and these questions evolve over time
- There is a decidedly limited universe of funding, patients, investigators, time and resources to conduct trials to answer these questions

Limitations of Controlled Trials

- Fact: at the end of most drug development programs, after huge expenditures of time and resources, we don't know a great deal about the drug
- We're quite confident it has a measurable beneficial effect in a described population-but the overall treatment effect is often small. Did few people respond a lot or did a lot of people respond a bit?
- Often many of the people who take the drug do not benefit

Limitations of Controlled Trials as Currently Conducted

- Binary outcome—success or failure--determined by p value—limits information gain and often results in misinterpretation of data (e.g., estrogen trials)
- Large time expenditure—and may find out at the end that the wrong question was being asked
- Little flexibility

Healthcare Consequences of Current Development

- Health care cost controversy: Debates about value of products: we can't quantify
- Health care policy community believes that increased technology=greater expense, and usually lower productivity
- Safety controversies: Products are "Safe" or "Unsafe"
- Health care quality: Confusing results and conflicting reports lead to anecdotal approach to care

More Informative Clinical Trial Designs

- Pair diagnostic(s) with therapeutic in development to identify responsive subgroup(s), or prevent toxicity
- Adaptive designs to answer series of questions—i.e, what dose is correct for which group

Critical Path Payoff for Development Process

- More predictable process; higher success rate, lower development costs
- More information about product performance
- Continuous improvement of development science and processes

Critical Path: Payoff for Patients: More Personalized Treatment

- Much larger treatment effects via more targeted therapy
- Stopping ineffective therapy faster
- Avoidance of side effects and injury through prevention
- Better/earlier product availability
- Higher quality healthcare

Strategies for Improving Health Care