The Inclusion of Economic Variables in Case Studies of Biomedical Research Impact

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Overview of Presentation

- Components of public funding of research & NIH goals
- Standard BCA information model for health care
- Evaluating economic ROI of research funding
- Information framework for retrospective BCA
- NIH case study approach for retrospective outcome analysis
- Framework applied to case studies
- Findings: deficits in documentation of research and attribution
- Considerations about research costs and attribution analysis
- Conclusions
- Future research

Introduction

Public funding of research includes many discrete components

- Setting research priorities
- Determining allocations of appropriated funds
- Funding research infrastructure
- Selecting and funding meritorious projects
- Conducting research
- Monitoring research progress
- Communicating research findings
- Training researchers
- Developing policies relating to funding (e.g., data sharing, human subject protections)

Evaluation of research, particularly the outcomes of biomedical research, has entered a period of intense demand for rigorous methods and actionable results. Challenges and opportunities exist in meeting this demand.

Mission & Goals of the NIH (Knowledge, Health, Society)

- NIH's mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability.
- Goals of the agency:
  - Foster fundamental creative discoveries, innovative research strategies, and their applications as a basis for ultimately protecting and improving health
  - Develop, maintain, and renew scientific human and physical resources that will ensure the Nation's capability to prevent disease
  - Expand the knowledge base in medical and associated sciences in order to enhance the Nation's economic well-being and ensure a continued high return on the public investment in research
  - Exemplify and promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science

Retrospective CBA in Health Care

- Analyze existing health condition
  - Epidemiology, costs, utilization
- Analyze an existing intervention (prevention or treatment)
  - Utilization, cost
- Analyze the development and implementation of an improved or new intervention
  - Clinical trials, manufacturing, marketing, utilization, cost
- Predict (model) changes in health care costs and utilization resulting from an improved or new intervention

An Information Framework for BCA of Biomedical Research

Please See Handout

- Information Categories
  - Research related to health condition
  - Health conditions prior to or concurrent with research
  - Development of new or modified health intervention
  - Attribution of research to health outcomes
    - Causal link between research and health intervention
- Key Topics are associated with each Information Category
- Potential data sources are identified for each Key Topic

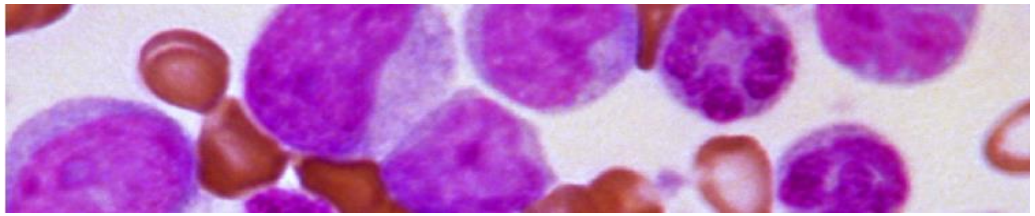
Case Study Method to Conduct Outcomes Analysis of Biomedical Innovations

- Combine narrative with numbers to produce stories of impact with a strong data backbone
- Trace the chain of evidence between scientific discoveries to impact
- Identify types of impact, including knowledge, health, and other societal impacts
- Document data sources and identify high value data
- Provide clear attribution by describing the contributions of NIH and other players in the biomedical enterprise

Case Study Example: Gleevec®

Please see handout

- Gleevec® (imatinib) is a kinase inhibitor approved in 2001 to treat Chronic Myelogenous Leukemia (CML), a rare form of blood cancer
- One of the first targeted, molecular-based cancer treatments
- Before Gleevec®, a patient with CML:
  - received chemotherapy as the standard of care - not highly effective & with many side effects.
  - had a 5-year survival rate of less than 30%.
- The 5-year survival rate for CML patients taking Gleevec approaches 90%.
- As CML is a rare disease, industry had diminished incentive to in invest in drug discovery



RESEARCH-TO-PRACTICE MILESTONES FOR GLEEVEC®

For more information on the supporting evidence and research sponsors for the following milestones, see the Web appendix table.

Basic, foundational research

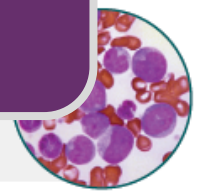
Targeted, preclinical research

Clinical research

IDENTIFYING THE MOLECULAR TRIGGER OF CML (1914-1990)

1914 Biologist Theodor Boveri first had the idea that chromosomal abnormalities might play a role in tumor development, but no tools existed at that time to test his hypothesis.[8]

1950s New scientific techniques helped researchers link chromosomal abnormalities to specific diseases.[9]



chromosome," after the city in which it was discovered.[10] NIH

1983-1984 NCI researchers determined that ABL1, a gene that was known to be involved in some cancers, was altered by the chromosomal translocation.[12,13] NIH

1985 The protein (BCR-ABL) created from the cancer-causing gene was determined to be a protein kinase, a class of cell-signaling molecules. The BCR-ABL protein constantly signals to a cell that it is time to divide, leading to cancer.[14] This finding inspired researchers to look for ways to inhibit BCR-ABL signaling as a treatment for CML. NIH

DEVELOPING A TARGETED BCR-ABL KINASE INHIBITOR (1990-1996)

1990 NIH-funded r… began develo… study BCR-AL… explore ways to …

1993 Dr. Druker and his colle… partnered with Ciba-Geigy to study their collection of compounds for signs of anti-cancer activity.[18] NIH

1996 Imatinib (Gleevec®) was shown to kill cancerous cells without harming healthy ones by blocking BCR-ABL kinase signaling.[19] NIH

TESTING AND APPROVING A LIFE-CHANGING DRUG (1997-2015)

1997 The Food and Drug Administration Modernization Act[20] allowed the FDA to create a "Fast Track" mechanism that makes important new drugs available to patients more quickly.[21]

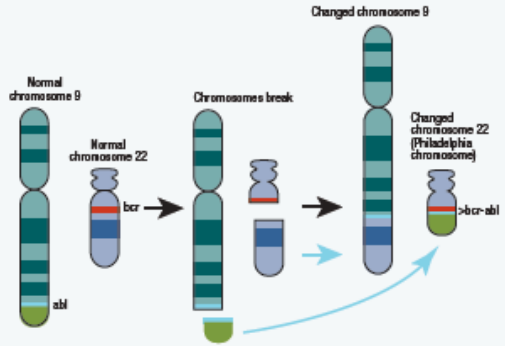
1998 …se in …ial …nts

…tion … 10 …s

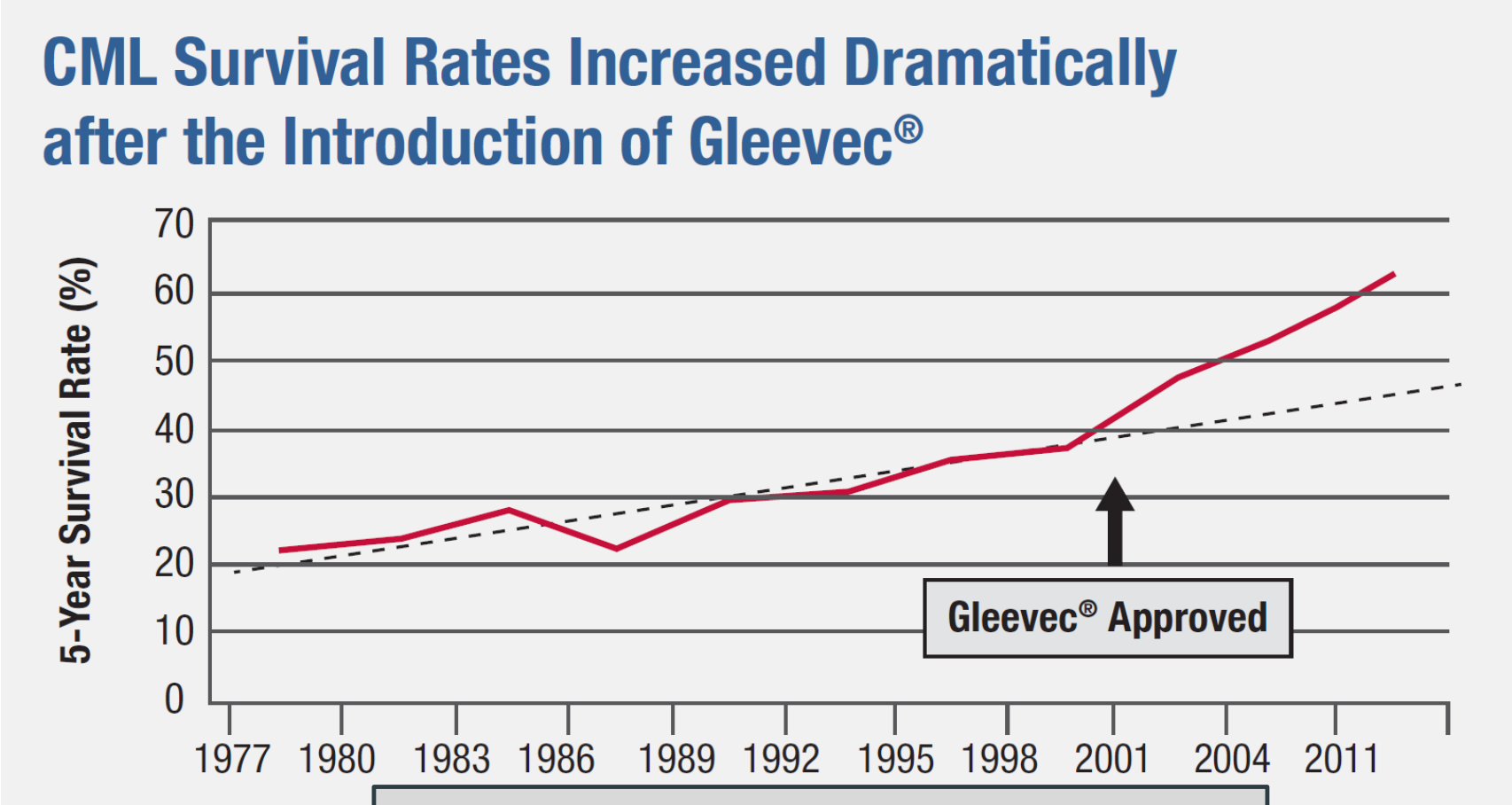
2006 A follow-up clinical study found that after five years of continuous treatment, the vast majority of CML patients receiving Gleevec® remained cancer-free.[24]

NIH *indicates NIH-funded milestones*

SCHEMATIC OF THE PHILADELPHIA CHROMOSOME FORMATION



Population Health Effects of Gleevec®



Source: National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Database

Case Study Data Compared to Information Framework

- Research Category
  - Overlapping key topics: purpose, method, findings
  - Potentially overlapping key topic: utility of research findings to researchers
  - Non-overlapping key topic: cost data (basic or targeted research)

- Attribution Category
  - Overlapping key topic: dissemination of research findings (targeted and clinical)
  - Potentially overlapping key topics: durability of data, environmental scan, face and temporal validity
  - Non-overlapping key topic: causal analysis (e.g.,progression discontinuity)

Case Study Data Compared to Information Framework, cont.

- Commonly accepted research to practice model
  - Government funds basic science research not known to be linked to health condition
  - Government funds basic science research apparently linked to health condition
  - Government funds some targeted or pre-clinical research & some clinical research, especially for rare diseases
  - Government hands off to pharma or other private sector for late stage clinical testing and development

This model was not observed. Although the case study illustrates the federal government's targeted efforts in supporting and providing incentives for rare disease research, NIH was not the sole participant at any stage. There was no clear demarcation of public vs private funding at any stage.

Case Study Data Compared to Information Framework, cont.

- Durability of data
  - No single quantitative or qualitative model exists
  - Expert opinion is important
  - Citation analysis is state of practice
    - Empirical data show citations peak within 5 years

The case study traced milestones over a century.

Estimating NIH Research Costs

- Known costs of individual NIH projects (last 20 years)
  - awarded funding, research management (est)
- Possibly known: intellectual property rights, patenting, and licensing (possible income, too)
- Individual NIH projects linked to other NIH projects can be identified
- Unknown: opportunity costs

- Costs not typically assumed by NIH
  - Grantee organization associated costs
  - Late stage clinical testing (Phase II &Phase III clinical trials)
  - Manufacturing costs
  - Marketing costs (some public health campaigns are federally funded)

Estimating NIH's Research Costs: Potential Business Rules

- Inclusion and exclusion rules for the NIH funding estimate
  - Relevant NIH grants could be identified from acknowledgments in milestone publications (citation analysis)
  - Per grant funding estimate could be determined (total annual funding amount for that grant during the year of publication and up to four years prior to the publication year)
  - For larger program project grants
    - Funding from sub-projects that were directly relevant would be included
    - Funding for cores (e.g., administrative cores, data analysis cores) would not be included

Estimating NIH's Research Costs: Application of Potential Business Rules

Research Phase Supported	NIH Grant Number	Principal Investigator	Institution	Active Fiscal Years Included	Estimated Funding
Pre-clinical	T32GM08243*	Kedes, Laurence	Cedars-Sinai Medical Center	n/a	n/a
Pre-clinical	T32GM07185*	Clarke, Steven	University of California, Los Angeles (UCLA)	n/a	n/a
Pre-clinical	K08CA001422	Druker, Brian	Dana-Farber Cancer Institute; Oregon Health & Science University	1990-1994	$413,035
Clinical	R01CA65823	Druker, Brian	Oregon Health & Science University	1995-2001	$1,765,938
Clinical	P01CA032737**	Sawyers, Charles	UCLA	1997, 1999, 2000	$525,719
			Total Estimated NIH Support		$2,704,692

Progression Discontinuity Design for Big Science, Scriven 2008

Method for attribution analysis for large research centers

Interrupted time series analysis, similar to regression discontinuity

- Step 1(macro): Panels of experts, external to the center, international
  - Meet 3-4 years after start-up and again 3-4 years later
  - Assess the progress of big research centers to determine if there has been "significant acceleration in the rate or excellence of the production of significant or high-quality research…since the center was created"
- Step 2 (meso): Panels of experts, external to the center, international & domestic
  - Meet 3 years after start-up and then every 2 years
  - Look for discontinuities in the outputs of leading scientists working at the centers
  - "… discontinuity in the level of research production – quality or quantity- is the sign that the center paid off"

Progression Discontinuity Design, cont.

- Step 3 (micro):
  - individual and group interviews of senior staff of the centers
  - individual and group interviews of comparable personnel not in centers
  - to identify features of their center, such as structure, infrastructure, or personnel composition, that led to improvements in their own professional activities
  - "…if the best researchers in the field report a major difference in the amount of what they believe to be valuable input or in a net reduction of frustrations…brought about by the center arrangement, and if those in the centers judge that their own work has improved accordingly, it's plausible to infer that this did indeed have some benefits for their work, at least as long as the macro- and meso-level approaches do not indicate the contrary."
  - => what is the economic return of an additional dollar of spending?

Conclusions

- Interest in BCA for federal investments will continue
- New data capture and data analytic tools are being developed
  - Linking of multiple data sets
  - Data mining
  - Big data sets are becoming available
- Federally-funded researchers have a new requirement for data sharing
- BCA applied to health care is complex
- BCA applied to biomedical research is more complex
- BCA is only one of many methods to evaluate biomedical research outcomes

Future Research

Key research questions

- What data must be available to conduct valid and reliable retrospective cost-benefit analysis in the evaluation of biomedical research?
- What data must be available to conduct valid and reliable prospective cost-benefit analysis in the evaluation of biomedical research?

Continuing near-term research

- Development of guidelines for determining federal research costs
- Articulation of the state of the art and state of the practice in attribution analysis

Case Study Contributor Acknowledgments & Web Locations

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- Web materials for the Gleevec® case study can be found @ https://www.nih.gov/sites/default/files/about-nih/impact/fighting-cancer-case-study.pdf
- Additional case studies tracing the involvement of NIH in knowledge, health, and other societal outcomes can be found @ https://www.nih.gov/about-nih/what-we-do/impact-nih-research/our-stories. Topics include:
  - Childhood vaccines against Haemophilus influenzae type b (Hib) infection
  - Restorative neurotechnologies (e.g., cochlear implants, deep brain stimulation)
  - Novel treatments for rare autoinflammatory diseases

Author Disclaimers

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