Financial Anatomy of Biomedical Research

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Historians and economists have recognized that while scientific innovation has occurred in many settings, it has prospered most when talent, supportive institutions, mobility, free communications, and financing are available in significant measure. The importance of both public and private sectors in fostering science has also been acknowledged. The public’s imagination has been captured by the promises offered by biomedical research. Its commercial value has been readily recognized. Political support in the developed countries of the Americas, Europe, and Asia has gathered behind the hope of assuaging human illness and suffering, as well as expectation of enhanced economic development. Many developing countries also recognize the importance of science to their social and economic welfare and see outside investment as welcome. Much of that investment, both financial and in-kind, comes from the United States. It is difficult to document global investment in biomedical research in detail the picture in the United States is sufficiently challenging to assemble. However, there are strong indications that the United States has seen a sharper growth in research investment in the last decade than has Europe or Asia. For example, the proportion of the global drug development pipeline belonging to organizations headquartered in the United States has increased to 70% in 2003.

Context Public and private financial support of biomedical research have increased over the past decade. Few comprehensive analyses of the sources and uses of funds are available. This results in inadequate information on which to base investment decisions because not all sources allow equal latitude to explore hypotheses having scientific or clinical importance and creates a barrier to judging the value of research to society.

Objective To quantify funding trends from 1994 to 2004 of basic, translational, and clinical biomedical research by principal sponsors based in the United States.

Design Publicly available data were compiled for the federal, state, and local governments; foundations; charities; universities; and industry. Proprietary (by subscription but openly available) databases were used to supplement public sources.

Main Outcome Measures Total actual research spending, growth rates, and type of research with inflation adjustment.

Results Biomedical research funding increased from $37.1 billion in 1994 to $94.3 billion in 2003 and doubled when adjusted for inflation. Principal research sponsors in 2003 were industry (57%) and the National Institutes of Health (28%). Relative proportions from all public and private sources did not change. Industry sponsorship of clinical trials increased from $4.0 to $14.2 billion (in real terms) while federal proportions devoted to basic and applied research were unchanged. The United States spent an estimated 5.6% of its total health expenditures on biomedical research, more than any other country, but less than 0.1% for health services research. From an economic perspective, biotechnology and medical device companies were most productive, as measured by new diagnostic and therapeutic devices per dollar of research and development cost. Productivity declined for new pharmaceuiticals.

Conclusions Enhancing research productivity and evaluation of benefit are pressing challenges, requiring (1) more effective translation of basic scientific knowledge to clinical application; (2) critical appraisal of rapidly moving scientific areas to guide investment where clinical need is greatest, not only where commercial opportunity is currently perceived; and (3) more specific information about sources and uses of research funds than is generally available to allow informed investment decisions. Responsibility falls on industry, government, and foundations to bring these changes about with a longer-term view of research value.
curate appraisal of the challenges facing researchers and their institutions can only emerge when the roles of government, industry, investors, foundations, and universities are understood, because not all sources of financial support afford equal latitude to explore hypotheses having clinical importance. Previous articles have examined specific sectors, but few have done so comprehensively.

**METHODS**

**Scope of Investigation**

We sought to determine the level and trend over the past decade of US biomedical research support from the following 4 major sponsors of biomedical research: (1) federal government, (2) state and local governments, (3) private not-for-profit entities including foundations, and (4) industry. Based on methods developed by the Centers for Medicare & Medicaid Services (CMS) to calculate noncommercial research in the National Health Expenditure Accounts, biomedical research was defined as the life sciences excluding the agricultural science plus the addition of psychology (Aaron Catlin, National Health Statistics Group, written communication, June 6, 2005).

In addition to determining the level of biomedical research funding, we sought to determine the distribution of funds between basic and clinical research, subsidies from endowments and other sources at colleges and universities, and funding for health policy and health services research.

Where possible, publicly available, nonproprietary information sources were used. Public sources were available for federal spending, expenditures by publicly traded companies, and major foundations. For cases in which public sources were not available, we obtained proprietary information from organizations that routinely track such information.

Figures were adjusted for inflation using the biomedical research and development price index (BRDPI). The BRDPI measures how much the National Institutes of Health (NIH) budget must change to maintain the same purchasing power. Information was obtained for the years 1994 through 2004. In some cases, 2003 data were used because data for 2004 are not yet available.

**Federal Funding**

The principal data source for federal support of biomedical research was the National Health Expenditure Accounts. The National Health Expenditure Accounts, published by the US Department of Health and Human Services, are an annual series of statistics presenting total health expenditures. Because the National Health Accounts’ data only provide an aggregate value for federal support, NIH funding was based on federal obligations for research, development, and research and development plans as reported by the National Science Foundation. Other federal funding was calculated as the difference between total federal funding and NIH funding. The total for other federal funding may be an overestimate, due to methodological differences between the National Health Expenditure accounts and the National Science Foundation. In addition to the NIH, federal funding comes from the National Science Foundation, Department of Energy, the Environmental Protection Agency, and the National Aeronautics and Space Administration. Federal spending for biodefense research was included in the NIH total if it was administered through the NIH.

**State and Local Government Funding**

State and local government support for biomedical research was determined from the National Health Expenditure Accounts. Certain support, such as tobacco settlement monies that have been used to fund biomedical research and funds from the recently passed stem cell initiative in California, are not directly captured.

**Private Not-for-Profit Support**

The National Health Expenditure Accounts were also the principal data source for funding support by private not-for-profit entities. Private entities included foundations, public charities, medical research organizations (such as the Howard Hughes Medical Institute) and voluntary health organizations (such as the American Cancer Society, and individual disease groups). Additional data on total health funding beyond medical research were obtained from the Foundation Center. Total health funding was estimated by taking the product of total foundation giving (to all causes) times the estimated proportion of large grants given to health. Our analysis did not account directly for private philanthropy by individuals. Some, but not nearly all, of these funds are given to colleges and universities and thus would be reflected in part in expenditures by these institutions.

**Industry Support**

To capture industry funding of biomedical research, data from the respective trade organizations were used, which rely on information from companies’ audited financial statements. The Pharmaceutical Research and Manufacturers of America (PhRMA) report total costs for all domestic pharmaceutical research and development expenditures by their member companies. Likewise, the Biotechnology Industry Organization (BIO) provides data on research and development expense by the US biotechnology industry. The data for pharmaceutical and biotechnology support reflect some overlap of research and development expenditures by large biotechnology firms that conduct research having both agricultural and human application (such as synthetic plant models), that have company-company research alliances, and that are members of both PhRMA and BIO. For 2003, PhRMA published a figure of $10.5 billion for non-PhRMA member biotechnology research and development. By comparison, BIO’s estimate for biotechnology industry support for 2003 was $17.9 billion. Published data for funding for non-PhRMA members for earlier years are
not available. Finally, NIH funds to biopharmaceutical firms would also be double counted (under federal and industry funding).

The medical device industry’s funding of biomedical research was determined from a 2003 benchmarking study of 31 divisions of medical technology companies. Information about regulatory approval of devices was obtained from annual US Food and Drug Administration (FDA) reports.

**Distribution of Funds Between Basic and Clinical Research**

The distribution of biomedical research funds between basic and clinical science was evaluated for the NIH and the pharmaceutical industry. For the NIH, funds have been historically divided into basic, applied, and development and later condensed into 2 categories, basic and applied (Andrew Baldus, NIH Assistant Director for Budget, unpublished data, 2005). For the pharmaceutical industry, funds were divided into prehuman/preclinical, phase 1 through 3, phase 4, approval and regulatory, and other and unclassified based on data published by PhRMA. Studies deemed phase 4 include both those required by the FDA for approval for safety tracking and those initiated by companies for new indications or entry into additional markets.

The distribution of NIH funds among the most heavily funded investigators and institutions was also determined from the NIH (Andrew Baldus, unpublished data, 2005).

**Expenditures at Colleges and Universities**

Biomedical research expenditures at universities and colleges were estimated from the National Science Foundation’s report *Academic Research and Development Expenditures: Fiscal Year 2002*, which separates federal and nonfederal expenditures. Nonfederal expenditures include funds from the following 4 sources: state and local government, industry, institutional funds (including endowment income), and all other sources. To estimate the relative contribution of each of the 4 sources to biomedical research, the relative contribution of each to all science and engineering was calculated and then extrapolated using the reported ratio of total science funding to biomedical research.

**Funding for Health Policy and Health Services Research**

Funding for health policy and health services research from foundation and federal sources was estimated from the Foundation Center’s *Update on Foundation Health Policy Grantmaking*, the Agency for Healthcare Research and Quality federal obligations, and NIH funding for health services research (Andrew Baldus, unpublished data, 2005). Data on commercial investment by health insurers in health services research were not available. Estimated funding for health policy and health services research was compared with total US health expenditures as calculated in the National Health Expenditure Accounts.

**RESULTS**

**Overall Funding for Biomedical Research**

Total funding from federal, state, and local governments; private entities; and industry increased from $37.1 billion in 1994 to $94.3 billion in 2003 (Table 1 and Figure 1). Adjusted for inflation by using the BRDPI, total biomedical research funding (in 2003 dollars) nearly doubled from $47.8 billion in 1994 to $94.3 billion in 2003. Industry support from pharmaceutical, biotechnology, and medical device firms account for the majority (57%) of funding for biomedical research. The proportion of biomedical research support that comes from industry has remained relatively constant from the 1994 to 2003 period, ranging from 56% to 61%. The NIH is the next largest funder at 28%. State and local government support and private funds accounted for 5% and 3% of biomedical research funds, respectively.

**Federal Funding**

The NIH is by far the largest federal funder of biomedical research. Adjusted for inflation by the BRDPI, NIH obligations nearly doubled (in 2003 dollars) from $13.4 billion in 1994 to $26.4 billion in 2003. The next largest federal funders of biomedical research (as measured by federal obligations) in 2002 were the Department of Defense ($1.2 billion), the Department of Agriculture (50.5 billion), the National Science Foundation ($0.5 billion), and the Department of Energy ($0.4 billion).

**State and Local Government Funding**

Nonfederal spending on biomedical research (adjusted for inflation) increased by 45% from 1994 to 2003 or roughly half the rate of federal spending. Funding for stem cell research initiatives in California were not included.

**Private Not-for-Profit Support**

Adjusted for inflation, private support for biomedical research increased 36% from $1.8 billion in 1994 to $2.5 billion in 2003 (in 2003 dollars). Private support for biomedical research comes primarily from foundations, voluntary health organizations, and the freestanding research institutes. The Bill and Melinda Gates Foundation gave approximately $236 million in grants for medical research in 2003 and was the largest foundation funder (Table 2).

Medical research only represents a small proportion of total health support from foundations. In addition, foundations give grants to support hospital and medical care, specific diseases, and mental health. Foundation giving for health in total has increased from an estimated $1.7 billion in 1994 to $5.9 billion in 2003.

**Industry Support**

Industry funding from pharmaceutical, biotechnology, and medical device firms increased 102% from $26.8 billion in 1994 to an inflation-adjusted $54.1 billion in 2003 (in 2003 dollars). The growth rate (inflation ad-
justed) for the medical device sector (26%+) exceeded that for either the pharmaceutical (89%) or biotechnology (98%) sectors. The proportion of biomedical research support coming from industry sources remained relatively constant and was 56% for 1994 and 58% for 2003. Figure 2 shows the total financial return to company investors, which reflects increasing divergence since 2000 in the performance of medical device and pharmaceutical companies. In turn, this reflects in part the device companies’ greater productivity, as reflected by the number of new devices brought to market (Table 3).

Distribution of Funds Between Basic and Clinical Research

Although overall funding for biomedical research has increased significantly since 1994, the distribution among basic and clinical research by the 2 largest funders, the pharmaceutical industry and the NIH, has changed. As shown in Table 3, the proportion of total pharmaceutical research and development expenditures (including those outside the United States) that has gone to clinical trials (phases 1-3) has increased from 28% in 1994 to 41% in 2003. In addition, the proportion of research and development funds that have supported phase 4 trials has increased from 5% in 1994 to 11% in 2003. The changes in NIH funding are much smaller than in the pharmaceutical industry (Table 4). In 1994, 43% of the NIH budget went to support clinical research.
search and by 2004, the percentage increased to 45%.

**Expenditures at Colleges and Universities**

Total biomedical research expenditures at universities and colleges were $19.6 billion for 2002 up from $10.7 billion in 1995. Federal expenditures account for 64% of expenditures. Institutional funds account for the next largest share at 17%. Institutional funds include subsidy from physician practice income, endowments, and hospitals’ support of research.

The distribution of NIH funds among the most heavily funded institutions has remained almost unchanged from 1994 to 2003. In 1994, the 10 most heavily funded institutions received 19% of extramural funding and the top 50 received 55%. For 2003, the percentages were the same. Similarly, the proportion of NIH funds going to the 100 most heavily funded investigators in 1994 was 6.4% and in 2004 the percentage was 6.3% (Andrew Baldus, unpublished data, 2005).

**Funding for Health Policy Research and Health Services Research**

The federal government and foundations spent $1.4 billion on health policy research and health services research in 2002. Federal funding for health services research came primarily from the NIH ($787 million in fiscal year 2002) and the Agency for Healthcare Research and Quality ($299 million in fiscal year 2002). The Robert Wood Johnson Foundation accounted for nearly 63% of the $359 million foundations gave for health policy in 2002. The sum of federal and foundation spending for health services research in 2002 was an estimated 1.5% of biomedical research funding and 0.1% of the total US expenditure on health care.

**Table 2. Top 10 US Foundations Awarding Grants for Medical Research, 2003**

<table>
<thead>
<tr>
<th>Foundation</th>
<th>Amount, US $</th>
<th>No. of Grants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bill and Melinda Gates Foundation</td>
<td>235,764,355</td>
<td>11</td>
</tr>
<tr>
<td>Donald W. Reynolds Foundation</td>
<td>54,513,104</td>
<td>7</td>
</tr>
<tr>
<td>The Starr Foundation</td>
<td>31,810,000</td>
<td>13</td>
</tr>
<tr>
<td>The Whitaker Foundation</td>
<td>25,413,415</td>
<td>112</td>
</tr>
<tr>
<td>The Dana Foundation</td>
<td>18,866,866</td>
<td>41</td>
</tr>
<tr>
<td>Burroughs Wellcome Fund</td>
<td>17,935,462</td>
<td>45</td>
</tr>
<tr>
<td>Avon Foundation</td>
<td>17,018,443</td>
<td>16</td>
</tr>
<tr>
<td>Gordon and Betty Moore Foundation</td>
<td>15,032,532</td>
<td>1</td>
</tr>
<tr>
<td>The Flinn Foundation</td>
<td>15,025,000</td>
<td>2</td>
</tr>
<tr>
<td>The Abramson Family Foundation</td>
<td>13,667,023</td>
<td>9</td>
</tr>
</tbody>
</table>

*Based on grants of $10,000 or more awarded by a national sample of 1010 larger US foundations.

**Figure 2. Cumulative Stock Market Return of Publicly Traded Life Science Companies, 1994-2003**

Stock price and dividend income. Analysis courtesy of the Boston Consulting Group. *Cumulative stock market return is the sum of the change in stock price plus dividend income.

**Table 3. US Pharmaceutical Research and Development by Function, 1994-2003**

<table>
<thead>
<tr>
<th>Year</th>
<th>Prehuman and preclinical†</th>
<th>Phase 1-3</th>
<th>Phase 4</th>
<th>Approval and regulatory</th>
<th>Other and uncategorized</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>6.3 (67)</td>
<td>3.1 (28)</td>
<td>0.6 (5)</td>
<td>0.4 (4)</td>
<td>0.7 (7)</td>
<td>11.1 (100)</td>
</tr>
<tr>
<td>1995</td>
<td>6.5 (55)</td>
<td>3.5 (30)</td>
<td>0.5 (5)</td>
<td>0.4 (4)</td>
<td>0.8 (7)</td>
<td>11.7 (100)</td>
</tr>
<tr>
<td>1996</td>
<td>7.3 (53)</td>
<td>4.0 (30)</td>
<td>0.9 (6)</td>
<td>0.5 (4)</td>
<td>0.9 (7)</td>
<td>13.6 (100)</td>
</tr>
<tr>
<td>1997</td>
<td>8.1 (52)</td>
<td>4.1 (27)</td>
<td>1.0 (6)</td>
<td>0.7 (4)</td>
<td>1.6 (11)</td>
<td>15.4 (100)</td>
</tr>
<tr>
<td>1998</td>
<td>9.25 (54)</td>
<td>4.9 (28)</td>
<td>2.1 (11)</td>
<td>0.8 (4)</td>
<td>1.4 (8)</td>
<td>17.35 (100)</td>
</tr>
<tr>
<td>1999</td>
<td>8.1 (44)</td>
<td>5.1 (28)</td>
<td>1.9 (9)</td>
<td>0.7 (4)</td>
<td>2.4 (13)</td>
<td>18.4 (100)</td>
</tr>
<tr>
<td>2000</td>
<td>8.4 (30)</td>
<td>5.5 (26)</td>
<td>3.3 (11)</td>
<td>0.6 (5)</td>
<td>5.0 (24)</td>
<td>21.4 (100)</td>
</tr>
<tr>
<td>2001</td>
<td>9.6 (32)</td>
<td>9.3 (31)</td>
<td>3.9 (12)</td>
<td>2.3 (8)</td>
<td>5.2 (17)</td>
<td>29.7 (100)</td>
</tr>
<tr>
<td>2002</td>
<td>10.5 (34)</td>
<td>10.7 (35)</td>
<td>4.1 (12)</td>
<td>2.5 (8)</td>
<td>3.5 (11)</td>
<td>31.1 (100)</td>
</tr>
<tr>
<td>2003</td>
<td>11.0 (32)</td>
<td>14.2 (41)</td>
<td>3.7 (11)</td>
<td>4.1 (12)</td>
<td>1.4 (4)</td>
<td>34.4 (100)</td>
</tr>
</tbody>
</table>

*Percentages may not sum to 100 due to rounding. Includes bioavailability and process development.

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medical device companies are spending on clinical trials and other research infrastructure, rather than buildings, equipment, and programs, rather than buildings, laboratory instrumentation, clinical databases, and other research infrastructure. This is a growing problem for teaching hospitals and universities, which must rely on endowments and gifts for those investments. Changes in clinical reimbursement and other pressures on operating margins in academic medical centers limit the amount of cross-subsidy available for research. Our analysis indicates that this subsidy was 17% of academic medical centers’ research funding in 2003, which is midway between the 6% and 28% reported by others using different data sources in 1996 and 1999, respectively. There is also evidence that state and local government funding of programs will become more important, even in traditionally private universities. Similarly, universities have limited ability to support promising activities, such as investigators who are striking out in unexplored directions, changing focus, or involving colleagues from other scientific fields. As these are unlikely to initially win NIH or industry funding, university funds and foundation support will be important to sustain them. The many small family foundations and disease charities are a growing and important source of such funding.

The parallel growth of public and private spending suggests a strong interrelationship between the sources of funds and their use. But does funding follow scientific opportunity, or does opportunity arise when funds are available?

New drugs, medical devices, and diagnostic tests are more dependent on publicly funded academic research than other industries. In one comprehensive analysis, this dependence was especially marked for identification of entirely new classes of drugs. This dependence was in contrast to equally rapidly moving fields, such as electronics, computing, energy, and chemicals, for which industry-sponsored research is also conducted in universities. Aerospace, given its military tie, was another exception. Moreover, publicly funded research contributed equally to initiation of new projects and the completion of those already under way. This interdependence of public and private sponsors has many implications for enhancing the productivity of research.

Barriers to the discovery of new drugs have received much attention over the past decade. Despite the doubling of biomedical research funding and the shift toward clinical research by pharmaceutical companies, the number of new molecular entities approved by the FDA has fallen. For example, from 1994 to 1997, the number of new molecular entities approved averaged 35.5 per year. From 2001 to 2004, the number of new molecular entities averaged 23.3 per year. As a consequence, pharmaceutical productivity decreased over the last 10 years, and it is lagging behind that of the biotechnology and device sectors (Table 5). Financial return to investors has paralleled those changes in productivity, as shown in Figure 2.

Three factors are commonly cited by industry observers to explain the productivity differences: increasing costs of clinical trials, the evolution of the mix of targets to more complex categories, and the adoption of riskier development strategies. As our analysis shows, clinical trial costs have increased faster than early stage, discovery, and preclinical research funding, driven both by expansion of the numbers of participants per trial and by the average treatment duration. The degree to which these changes are driven by marketing factors (proving advantages against competitive treatments) as opposed to...
posed to regulatory requirements is difficult to determine.

We believe a major factor in decreasing productivity stems from pharmaceutical companies’ frequent determination that compounds approvable from a regulatory standpoint are not worth bringing to the market because the intensity of competition is so high that it is not worth challenging existing drugs that are safe and effective. This highlights the need to invest in clinical areas with few effective treatments and for which novel mechanisms or entirely new classes of drugs are possible. The willingness of biotechnology companies to do this may, in part, account for their greater relative productivity.

Observers differ sharply on the role of regulation in driving the decline in pharmaceutical productivity. Time elapsed from submission of trial results to FDA action has diminished, and the FDA maintains that it has not tightened its regulatory standards. However, it does seem indisputable that there have been shifts in the acceptable threshold for risk/benefit for many diseases as the depth of scientific understanding increases and as information about the effects of drugs on large patient populations is more readily available. There is also no doubt that simpler FDA requirements for devices adds to their commercial attractiveness and willingness of companies to support research. Device trials are typically shorter, involve fewer participants, and interpret risk and benefit differently.18

Given trends in financing, the application of emerging scientific knowledge to new therapeutic avenues will continue to be problematic. This critical function is often referred to as translational research. Industry’s funding of translational research has not kept pace with the increase in total spending. Industry’s shift to favor late-stage clinical trials, the stable distribution of NIH spending on basic and applied research, and the growing preference of venture investors for companies having products that are close to market reflect this “translational gap.” There have been increasingly strident calls for creative remedies, including shifting the relative proportion of public and private monies to translational research.36 Past investment has produced prodigious new basic knowledge in molecular biology, the genome, neuroscience, immunology, and other areas. Their full clinical promise is yet to be realized.39 The NIH’s Roadmap Initiative is aimed at alleviating translation as a rate-limiting step. We believe the private sector should also mirror those actions.

Foundations will likely play an even more important role in funding biomedical research in the decade to come. In addition to their direct support of biomedical research, foundations contribute 20% of their dollars to other health-related organizations. A 1998 Institute of Medicine report advocated that foundations fill visible gaps by funding research that is speculative scientifically, politically risky or unpopular, and where commercial value is low or not readily apparent.33 Especially identified were reproductive and international health, substance abuse, behavioral or social interventions, education, and health services research related to outcomes, clinical utility, and new care models. Translational research was also identified. Our analysis indicates that foundations are following suit and improving their ability to identify gaps on which they can have most effect, as well as increasing their ability to make scientifically informed grant awards and be more selective. Many have shortened the application and decision process to allow more flexibility to fund rapidly moving scientific fields.

Health services research is much less well funded than that of biologically based disciplines. Although the biotechnology, pharmaceutical, and medical device industries are among the largest investors in research and development (between 14% and 21% of their sales are invested in research and development),40 investments in health care outside the life sciences sector are much smaller. In 2002, federal and foundation support for health services and policy research represented less than 0.2% of US health expenditures on hospital and physician services and less than 0.1% of total health expenditures. This limited investment in health services research has occurred despite growing concern about the cost (eg, double digit growth in health insurance premiums41) and quality (eg, errors in medicine42,43 and failure to implement best practices44) of health care in the United States.

Moreover, investments to evaluate the clinical and economic value of new technologies have not kept pace with the significant investments in biomedical research, which spawn new therapeutics. To change health services research funding requires a shift in the perceived value of such research.44 Efforts to improve patient safety, disseminate best practices, and secure the greatest value for investments in biomedical research will all require additional investments. Some evidence exists that this is occurring, for we are aware of 60 new regional coalitions and several dozen venture capital–backed companies based on this premise.

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Table 5. New Drugs and Devices Approved by US Food and Drug Administration by Sector, 1998-2004

<table>
<thead>
<tr>
<th>Firm</th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
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<tr>
<td>Pharmaceutical</td>
<td>24</td>
<td>22</td>
<td>22</td>
<td>19</td>
<td>16</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Biotechnology</td>
<td>11</td>
<td>8</td>
<td>11</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>Device*</td>
<td>10453</td>
<td>9676</td>
<td>9835</td>
<td>9064</td>
<td>10238</td>
<td>9570</td>
<td>9182</td>
</tr>
</tbody>
</table>

*Includes instruments, implantables, patient monitoring, diagnostic devices, and in vitro tests.
Although our focus has been on domestic US spending, biomedical research is truly international. Despite the shift of company research and development to the United States, US-based companies of any appreciable size have laboratories in other countries; and even smaller companies typically have research alliances abroad. Likewise, venture capital and private equity investors view international diversification positively. Perhaps most evidently, an increasing number of private foundations that support health research, such as the Gates Foundation, the Rockefeller Foundation, and the Wellcome Trust, operate internationally to achieve their goals. The rationale for international scope in research funding is growing if productivity is to be enhanced. Science has always been an international undertaking, and the most successful scientific communities operate globally.

In this regard, the predominantly domestic focus of the NIH and other public sources may seem anomalous. However, the policy to increase US public spending has not been mirrored in most other countries, with the exception of Australia, South Korea, and Singapore. Our analysis indicates that in 2003, the United States spent 5.6% of its total health care spending on biomedical research. No other country approaches this amount in relative or absolute terms.

Researchers have confirmed the importance of preserving the mobility of talented researchers and the free and open interchange of ideas. The importance of regional geographic clusters for enhancing research productivity has also been documented. Notably, successful clusters have greater scientific value (as measured by citation analysis) and commercial relevance (judged by the number of company alliances or decisions on where to locate new laboratories). Such research confirms the successful alchemy of institutions, talent, mobility, communications, and funding. Although this does not imply futility of the efforts of the geographically isolated researcher or institution, it does indicate that their mobility and free communication must be ensured.

Biodefense and domestic security concerns since 2001 have produced about $4.5 billion in additional federal spending, primarily through the NIH and Centers for Disease Control and Prevention (CDC). Industry spending and that of the Department of Defense cannot be readily estimated, but presumably exceeds that amount. Biodefense research will likely have growing importance, not only because of the overt threat to public health, but because its secondary benefits to medicine generally are now being recognized. Previous comparable federal and industry investments (such as those through the National Aeronautics and Space Administration, National Science Foundation, military, and Energy Department) have spawned new instrumentation, monitoring devices, materials, and computing. Also, benefits to research in vaccines, antimicrobials, and public health infrastructure, outbreak detection, and data sources have already been realized in part due to growing awareness of the parallel specter of avian influenza and severe acute respiratory syndrome. Anecdotally, the venture capital community has taken particular interest in this field.

Can the rate of growth in funding of biomedical science be sustained? Will another doubling occur over the next decade? One can only turn to recent history to speculate. The continuously upward trend from the mid 1990s onward obscures the cyclical nature of research increases of earlier decades. Today, the NIH and other federal science agencies certainly face competing claims on their budgets, during a time when deficit spending, aversion to tax increases, and limited economic growth are likely to prevail. The pharmaceutical industry will continue to face pressures to favor later-stage clinical trials over early, discovery-stage research. Although biotechnology companies have the same set of regulatory and investor scrutiny as the large pharmaceuticals, the historical focus of biotechnology firms on large molecules, of known activity, and with narrower therapeutic indications makes their hurdle somewhat lower. Venture capital investment remains cyclical and its preference for later stage investments (for products closer to market) makes it unlikely that venture capital support of research occurring in early stage companies will grow.

Our analysis revealed the difficulty of assembling a complete picture of all public and private sources of research support. This presents a potent barrier for those wishing to use reliable information for ongoing decisions about investment policy or to make choices of research strategy. Currently, public and proprietary databases do not capture information comparably about stage of research (basic, translational, and clinical) or type of recipient (inside or outside the sponsoring organization); neither is it possible to answer questions readily about specific diseases or areas of biology although individual disease associations and interest groups compile such data selectively. Our experience in reconciling different databases makes us skeptical about comparability of those estimates, due to variability in definitions of research and accounting methods. Furthermore, much information can only be obtained from management- and industry-database suppliers that are usually unfamiliar or unavailable to scientists. Therefore, an ongoing, accurate compilation of such information is needed.

From an economic perspective, can the productivity and effectiveness of research investment be enhanced? During a time of financial constraint, and when scientific opportunity has never been greater, this becomes a pressing question. Almost certainly the answer is yes, but how is it to occur?

Scientific, organizational, public policy, and financial remedies are all required. Scientists must more successfully identify areas of particular clinical need and potential, for which key advances are technically feasible, and within reach of existing knowledge. They must also improve the ability to
determine where new knowledge is most needed and where a push will have disproportionate effect in advancing a clinical field. There is a growing call for investment to be directed to fields of greatest clinical need, where there are refractory, but potentially answerable problems. Creative and flexible organizational arrangements will be important so that talent, instrumentation, and material, whether in companies or academic settings, can be more easily applied to pressing scientific questions. As we have proposed elsewhere, this calls for experimentation with a variety of alternative organizational models, including freestanding research institutes.

Public policy changes will be critical to resolve lingering questions over intellectual property ownership that inhibit the free flow of ideas while also streamlining private investment. Policy should create more incentives for investing in the research of diseases that have limited commercial attraction. Financial remedies are important. The NIH has a particular role to play by more actively identifying areas of scientific opportunity for which answerable scientific questions meet pressing clinical need and to direct funding to them. Because many will not fall within the purview of any single NIH institute, the political challenge may be considerable. Likewise, foundations will be critically important to fill the gaps between public and private support, especially in those areas that are scientifically speculative or high risk, that are politically unattractive, or for which the market has failed.

For all sponsors, the challenge is patience. Biomedical research is an inherently high risk and lengthy process. It would be helpful to remind those making financial decisions that the promise of earlier advances in the basic understanding of physiology in the 1920s and 1930s or of biochemistry and microbiology in the 1940s, 1950s, and 1960s took decades to unfold. By the same token, placing more bets (by spending more on research) will be less effective than changing the odds of the game (by directing it to areas for which science meets clinical need).

None of these remedies will be easy to accomplish, given current competitive and political constraints. All will be necessary if the full potential of the collective investment in biomedical science is to be realized.

Author Contributions: Drs Moses and Dorsey had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Moses, Dorsey, Matheson.

Analysis and interpretation of data: Moses, Dorsey, Matheson, Thier.

Drafting of the manuscript: Moses, Dorsey, Matheson, Thier.

Critical revision of the manuscript for important intellectual content: Moses, Dorsey, Matheson, Thier.

Statistical analysis: Moses.

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Study supervision: Moses, Thier.

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