



PROMOTING BREAKTHROUGH MEDICAL INNOVATION: INSIGHTS FROM AN ANALYSIS OF RECENT TRANSFORMATIVE DRUGS, BIOLOGICS AND MEDICAL DEVICES

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Abstract

Background: Improvements in medical diagnosis and treatment depend on the development of new medical technologies. In recent years, pharmaceutical and medical device industries have been criticized for limited innovative output in many different fields. As a result, there have been a host of new proposals intended to stimulate medical innovation. Unfortunately, there is limited knowledge on how ideas for transformative medical products are generated and much controversy over the best ways to commercialize these technologies. Few empirical studies have been conducted on the catalysts of or obstacles to this process. A better understanding of the medical innovation process would enable policymakers to implement strategies most likely to successfully spur new breakthrough therapies.

Methods: This thesis focused on twelve recent transformative medical innovations spanning a wide range of clinical disciplines. Through qualitative analysis of semi-structured interviews with key individuals (n=143) directly responsible for these innovations, insights and opinions were collected on how the lessons learned from their experiences inform the innovation process today. To explore the innovation process in greater detail, coronary artery stents—a medical device that revolutionized interventional cardiology—was selected for further evaluation. Further in-depth interviews with key stent innovators (n=16) assessed the roles of individuals, institutions and external factors in early stent innovation. To supplement this work, a comprehensive quantitative assessment of the patent literature spanning 10 years prior to FDA approval of the first coronary stent was done to study changes over time in the sources of innovation in this field.

Results: Interviewees emphasized the central role played by forward-thinking individuals and their supporting institutions in driving medical innovation. In addition, respondents discussed the importance of collaboration between individuals and institutions to share resources and expertise. A strong foundation in well-delineated basic science was also cited as a major contributing factor to the eventual success of an innovation. Interviewees agreed on a few obstacles to transformative innovation, including a greater emphasis on patenting in academia, difficulty negotiating the technology transfer process, barriers to open collaboration between industry and academia, and funding constraints. Increased regulatory demands, reimbursement concerns and luck were not commonly described as factors that influenced transformative innovation. The in-depth study of stents corroborated these themes, particularly demonstrating the central importance of physician-inventors who saw the need for coronary artery stents in their clinical practice. These physician-inventors—including Julio Palmaz and Richard Schatz, Cesare Gianturco and Gary Roubin, and Ulrich Sigwart—drove early prototype designs and provided clinical validation. Large companies entered afterwards with engineering support and expertise navigating the regulatory process. In the patent search, 245 patents related to bare metal coronary artery stents were granted from 1984 (when the first patent issued in this field) to 1994 (after the first stents were approved). Each year showed an increase in the number of patent filings, from 1 in 1984 to 97 in 1994. The largest fraction of patents was issued to private companies (44.9% of the total). Public companies, individual inventors, and non-profit institutions represented 31.4%, 18.0%, and 5.7%, respectively. Moreover,

private companies represented the majority of coronary artery patents filed in the earliest 5 years of the field. The top-10 most cited patents in the field also prominently featured two private entities: Expandable Grafts Partnership and Cook Inc. Both stent products developed from these organizations were created by or dependent on the work of independent academic physician-inventors.

Conclusions: Despite the relative heterogeneity of the medical innovations studied, transformative innovation most often originated from the insights and experiences of individuals with direct clinical expertise. External factors either catalyzed (e.g., supportive institutions, strong underlying science and collaboration) or hindered (e.g., technology transfer challenges, lack of funding and onerous conflict of interest rules) the development process. Strategies aimed towards promoting transformative medical innovation should focus on institutional-level policies targeting the earliest stages of innovation. This includes providing individuals with unique expertise with the capacity to pursue innovative work. Technology transfer processes should be simplified to enable meaningful collaboration for individuals between institutions with disparate expertise and resources. Policymakers should continue to support basic science research, which underlies future innovations. By contrast, policies that increase reimbursement or tax breaks for large institutions or extend patent terms are less likely to impact transformative medical innovation.

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Glossary of Abbreviations

EGP: Expandable Grafts Partnership

EPO: European Patent Office

FDA: the Food and Drug Administration

IDE: Investigational Device Exemption

INPADOC: International Patent Documentation Center

NIH: the National Institutes of Health

NYU: New York University

MIT: the Massachusetts Institute of Technology

ORs: Operating rooms

TNF-alpha: Tissue necrosis factor-alpha

UNC: University of North Carolina at Chapel Hill

USPTO: United States Patent and Trademark Office

UTSA: University of Texas at San Antonio

UTSW: University of Texas Southwestern

1.0 Introduction

The Chairman of Stryker Inc.—a Fortune 500 medical technology—explains,¹ “medical device innovation comes from the labs, the engineers, the companies. It also comes from the ORs and surgeons’ experience, academic labs, and universities around the world.” This strikingly broad statement encapsulates the current controversy over the sources of medical product innovation. While innovations certainly could come from all corners, where is it most likely to arise? Who can be counted on for the most critical steps? How can society support medical innovators’ progress from a design on a paper napkin to an assembly line? An in-depth study of recent examples of successful breakthrough medical innovations may reveal valuable insights into this historically opaque process.

1.1 Background

Medical innovation has always been central to delivery of high quality health care. However, there is ongoing concern regarding the current state of medical innovation.^{2,3} The cost of drug development continues to rise while output from the pharmaceutical industry has been criticized for not being “transformative,” that is, offering substantial improvements in patient outcomes over existing therapeutics.⁴ Despite the \$150 billion dollars spent on biomedical research in 2010,⁵ phase 2 trial success is at a 5 year low of 22%.⁶ Venture capital, a traditional source of funding for new breakthrough biomedical innovations, has decreased investment by 50% in the biotechnology and medical device sectors in the past 6 years.⁷ Industry has continued to de-vest from the total funding of early biomedical innovation from 55% in 1998 to 25% in 2010.⁸ Stakeholders question whether the new drugs approved each year by

the FDA—many criticized as marginal improvements over existing therapies—justify the enormous investment.

Some have pointed out that the pace of transformative medical product development in the modern era has been particularly slow when compared with the so-called golden years of pharmaceutical and medical device innovation in the 1980s and 1990s.^{9,10} On the heels of paradigm-changing advances in biotechnology tools such as gene cloning and expression, polymerase chain reaction, and next-generation sequencing, these decades saw an unprecedented rise in new classes of medications offering major improvements in treating cancer,¹¹ heart disease,¹² and infectious diseases,¹³ life-sustaining medical devices including implantable defibrillators¹⁴ and coronary artery stents,¹⁵ and important new diagnostic tests such as magnetic resonance imaging¹⁵ and bone densitometry.¹⁶

In response to the lag in innovation in recent years, policymakers, patients, physicians, and researchers in the private and public sectors have proposed new policies to re-energize medical therapeutic development.^{17,18} For example, medical device industry representatives have argued that reducing the corporate tax burden will attract greater investment in research and development.¹⁹ Both the medical device and pharmaceutical companies contend that the high profit margins they enjoy²⁰ are necessary for re-investment in developing new technologies. Another suite of proposals from representatives from the pharmaceutical industry and patient advocates rely on reducing hurdles to regulatory approval of new products.²¹ For example, the 2012 FDA Safety and Innovation Act included multiple proposals designed to expedite the approval process for new therapies.²² But in the European Union, where regulatory oversight of new medical devices is much less rigorous than in the US, there is no

evidence of better patient outcomes related to expedited treatment with more highly innovative devices overall.²³ The scant regulatory oversight of the device market in the EU also permits many ineffectual or dangerous new devices from being widely used. In 2012, the NIH created a new center devoted to funding translational research in drug development to make possible therapeutic targets more attractive for subsequent development.⁴ However, without a clear understanding of the sources of medical innovation, there is little hope for effective policymaking that will spur new innovation.

1.2 Review of approaches to studying medical innovation

The process of developing breakthrough medical technologies remains poorly understood.²⁴ Although there is evidence that innovation in medical technologies happen at the public/private interface,²⁵ recent studies have illustrated the disproportionate benefit and impact of the public sector in the development of novel pharmaceuticals.²⁶ Furthermore, there is little consensus on the contribution and roles of individual users in the inception and development of these radical technologies.²⁷ A number of different approaches have been employed to study the innovation process.

A qualitative research approach enables the investigation of motivations, reflections, and outcomes in a small cohort of subjects who share a common experience.²⁸ This technique has been used previously to address fundamental questions relating to the development and adoption of new medical technologies.²⁹ Applying qualitative research methods to case study research is appropriate for exploring new technologies, particularly in concerns to the 'how' and 'why' of the process.³⁰ Studies that include multiple cases are considered more robust and intrinsically valid given the ability to make comparisons and identify common themes.³¹

Another strategy to assess the medical device innovation process is through an analysis of the record of patents related to the development of a given product. Because patents are also published, their review can provide evidence of the timing and nature of a participant's contribution to the field. When submitting a patent application to the United States Patent and Trademark Office (USPTO), inventors are required by law to cite previous patents relevant to their work.^{32,33} As a result, patents can provide a useful research tool for identifying and connecting various contributors to the innovative process.³⁴ For example, Trajtenberg collected patent and citation records related to computed tomography (CT) scanner technology, and his analysis of the results found that subsequent citations accurately reflect patent importance.³⁵ Examining the patent literature is a viable way of assessing the origins of technology; information appears earlier in patents than in scientific journals and patents may include information that does not appear in the medical literature.³⁶⁻³⁸

Other methods have employed bibliometric strategies to investigate the innovation process. Agarwal and Searls extracted data from abstracts published in PubMed, literature citations and patent filings to identify drivers of innovation. They postulated that this method is capable of identifying areas of increasing scientific activity and new therapeutic opportunities.³⁹ The FDA also offers online, searchable databases of regulatory information, such as the date of approval and special designations of all approved drugs and devices. Prior studies have used information from the FDA to track recent pharmaceutical approvals and assess which method of drug discovery led to the highest proportion of approved drugs.⁴⁰ Although these above mentioned methods provide an analytically robust method to study macro-innovation, it is unable to capture the human interactions, motivations and insights that underlie discovery and

development. In 2012, the FDA Safety and Innovation Act created a new regulatory designation for breakthrough therapies to facilitate the approval of therapies that address major unmet clinical needs.⁴¹ Studying innovations that qualify under this designation may serve as another strategy to understand how breakthrough therapeutics came about. Ultimately, the complexity of medical innovation likely requires a multi-faceted method approach.

1.3 Prior work

In the business literature, Shane and Venkataraman published a seminal work presenting a conceptual framework of innovation and entrepreneurship; in that article, the authors propose that entrepreneurship opportunities must first exist, which then enables individuals to recognize these opportunities and exploit them.⁴² Later works provide additional support to this conceptual model by highlighting the central roles played by individuals in recognizing and then acting upon sources of opportunity.^{43,44}

Social science methodologies have frequently been applied to answer questions about medical innovation. In a classic work,⁴⁵ Coleman tracked the diffusion of a single class of antibiotics (tetracyclines) in four local markets and highlighted the central role played by early-adopters who then influenced the prescribing habits of colleagues. However, this study and a follow-up work on tetracyclines⁴⁶ focus on the later-stage diffusion of the innovative drug and do not assess how this antibiotic was developed or the key individuals involved.

In another study, Consoli and Mina outlined a conceptual model of medical innovation as an interplay between three major domains: (1) an individual sphere in which interactions between practitioner and physician reveal problems and

opportunities, (2) the technology and science systems in which research advances and clinical testing are done, and (3) the broader scientific domain in which non-application based work is performed. Using coronary artery disease and glaucoma as empirical examples, the authors use a bibliometric-based method to demonstrate the interconnectedness between large industry players and smaller companies and that research hospitals acted as key nodes of innovation.⁴⁷ In a study of 4 medical technologies (3 surgical devices and 1 biocompatible implant) through interviews with key individuals, the authors identified the dominant role played by physician-users in the invention of the technology as well as the establishment of necessary collaborations. The profile of these physician-users included a high motivation to develop new solutions, highly specialized knowledge that provided them insight into the opportunity and clinical need, and supportive development environment. The authors conclude that the starting point of innovation results from an incremental accumulation of knowledge defined by the clinical problem at hand. They postulate that industry did not originate these technologies given the lack of a deep understanding of user needs and an inability to creatively incorporate relevant technologies outside of the domain in question.²⁷

Within the field of ophthalmology, a case study on the development of intraocular lenses focused on understanding the development process. This work also showed the key influence of clinicians on early innovation, selection of promising designs, and further dissemination of the technology to other ophthalmologists.⁴⁸ Although the intraocular lens study and other sociological models are useful to frame the larger context of innovation, these studies were not done with the explicit goals of providing insights or recommendations for present-day innovation. They also remain specific in

regards to specialty areas, limiting the authors' ability to make more generalizable conclusions.

In the clinical literature, publications have highlighted recent breakthrough innovations.^{49,50} Although these studies serve as useful resources to identify what qualifies as a breakthrough medical innovation, they do not provide insights on how these innovations developed. There are examples of specialty-specific publications that track the development of important innovations in greater detail. For instance, in the oncology space, articles and other forms of media have been produced chronicling the development of imatinib (Gleevec),^{51,52} trastuzumab (Herceptin)⁵³ and bevacizumab (Avastin).⁵⁴ Other analogous articles chronicling major advances in otolaryngology (cochlear implants),⁵⁵ psychiatry (chlorpromazine)⁵⁶ and robotic surgery innovations⁵⁷ have also been published. The general goal of these studies is to reveal important historical facts and credit key individuals, not to identify lessons for future innovation.

1.4 Purpose of inquiry

The key goal for this inquiry is to study transformative medical innovation that emerged in the golden era of the 1980s and 1990s to derive lessons for medical innovation today. In particular, I hope to identify and highlight key features of the innovative process that promoted or hindered the development and eventual approval of these technologies. Given the complexity and heterogeneity of the innovation process and a lack of prior works employing both rigorous qualitative and quantitative research methods, I focused on the following specific aims:

- Analyze transcripts of semi-structured interviews with successful biomedical innovators across multiple transformative medical devices and pharmaceutical

products for specific insights and opinions on the differences between the innovation process that led to these discoveries, and key features of the current innovation climate

- Investigate the origins and factors around the early innovation process using one transformative technology as an in-depth case study by interviewing key innovators and gleaning lessons from these interviews relevant to present day innovation
- Demonstrate a novel methodology of evaluating the patent literature as an additional method of identifying the origins around one transformative technology and apply lessons from these results to present day innovation
- Synthesize the lessons learned from these transcripts of innovators and results from an in-depth case study to provide policy recommendations that would most likely spur on future transformative innovation

2.0 Methods

Several methodologies were employed to investigate this topic. Techniques included a qualitative analysis through semi-structured interviews with innovators. Separate corroborating analyses were performed using the available clinical, patent and FDA literature. The ethics review board at Brigham and Women's Hospital approved the study.

2.1 Identifying examples of transformative medical innovation

The first methodological step involved determination of transformative innovations. Although there is no single definition that describes a 'transformative' or 'breakthrough' innovation, these technologies are generally characterized by meeting an

unmet need for the first time generating high user value, inducing a substantial change in current practice and displaying significant differences compared to existing technologies.^{49,50} In 2011, Kesselheim conducted a modified Delphi protocol survey to identify the most transformative drugs and devices approved by the FDA in 14 different medical fields. The survey covered leaders of clinical departments in each of these 14 fields from the top 30 academic institutions in the United States in terms of NIH funding. These participants were instructed to identify the 5 “most transformative” products out of a list of all new molecular entities approved in their fields between 1985 and 2009. “Most transformative” was defined as a drug that was both innovative *and* had a groundbreaking effect on patient care and health care delivery. On the basis of the expert consensus panel process, the list was expanded to include two medical devices as well.⁵⁰

2.2 Qualitative analysis: identifying lessons for innovation today

Kesselheim and his research team used the regulatory, patent, and medical literature to identify key innovators who contributed to the development of the most transformative products identified through the Delphi protocol. Using a qualitative research approach, Kesselheim led semi-structured interviews with 147 of these innovators representing 12 different drugs, devices and biotechnology innovations (median 16 innovators/innovation, range: 3-19). See **Table 1** for a complete list of the innovations studied. 35% of these innovators were industry-based, 63% were academic or government-based and 1% represented either key investors or patient advocates. Interviews involved leading participants chronologically through idea conception, product development, testing, and approval. To identify differences in the innovation

climate from then and now, participants were specifically prompted to provide lessons from their experience for current-day biomedical innovation.

Eighty-one of the 143 interviewees (55%) explicitly discussed current-day challenges to medical innovators and differences between new product development now and during their contributions to the transformative products. Among this cohort of 81 interviews, 31 (38%) were from industry, 48 (60%) from academia/government, and 2 (2%) from other environments (see **Figure 1**). It was this cohort of interviewees who formed the basis for the research conducted for this thesis. Transcripts of these interviews were analyzed using standard coding techniques⁵⁸ and the constant comparative method of qualitative data analysis.⁵⁹ Xu and Kesselheim reviewed a subset of 3 randomly selected interviews, focusing on the sections of the interviews in which current challenges to medical innovation and differences between historical and modern medical product development.⁶⁰ Xu and Kesselheim then independently developed a qualitative coding scheme. The coding schemes were then compared, discussed and reconciled to produce a final coding structure which consisting of 2 broad themes (drivers of innovation and hindrances to innovation) with 22 specific codes. Xu then analyzed these interviews according to this coding scheme using the NVIVO qualitative research software program.

2.3 Qualitative analysis: in-depth case study of bare metal coronary stents

The coronary stent was selected as a case study for more in-depth analysis into the origins of innovation. Bare metal stents for treatment of coronary artery disease,^{61,62} represent transformative devices⁴⁹ that spawned the modern era of interventional

cardiology^{63,64} and became a multibillion-dollar industry,⁶⁵ despite ongoing controversy over who deserved credit for their development.⁶⁶

Through a review of the regulatory, patent, and medical literature, I targeted thirty seven potentially relevant stent innovators, including six high priority targets. Fourteen agreed—including all of our high priority targets—while two declined. Two additional participants were identified through referrals. Both Xu and Kesselheim jointly conducted semi-structured interviews with these fourteen stent innovators. See **Table 2** for a full list of stent innovators who participated in interviews.

Interviewees were asked to proceed chronologically through idea conception, product development, testing, and approval. Next, participants were asked to assess how academic medical centers, various companies they interacted with, and government regulatory authorities were involved with the work at different stages in the development. Third, participants were asked to recall how each phase of the development process was funded (private vs. industry vs. government), and whether patents were sought to protect their intellectual contributions. Finally, participants were asked to consider the roles of individual initiative, environmental factors, serendipity vs. strategic planning, advances in science and technology, and clinical need.

Median time for telephone interviews with stent innovators was 40 minutes (range: 23-75). Interviews were transcribed and then analyzed using the same standard coding techniques as described above.⁵⁹ As before, Xu and Kesselheim conducted independent analysis of three randomly selected interviews and developed separate coding schemes for organizing the data. The coding schemes were then compared, discussed and reconciled (using the NVIVO software package, QSR International, Melbourne, Australia) to produce a final coding structure which consisting

of seven broad themes (with 92 specific codes): (1) antecedents of stent development, (2) timeline of stent development, (3) key contributors to stent development, (4) the role of intellectual property, (5) the role of academic medical centers, (6) the role of device companies, and (7) other key characteristics of the inventive process.

2.3.1 Patent search methodology

To provide a complementary view into the sources of bare metal stent innovation, I conducted a comprehensive review of patents related to the initial development of the stent. To determine the time period for the patent search, a Medline search identified reports of the major clinical events in the development of coronary artery stents. Search terms were (“history” OR “development”) AND (“stent” OR “coronary stent” OR “bare metal stent”). From this search, review papers describing the history of the bare metal coronary stents as well as the earliest clinical validation studies were identified. The FDA on-line database for Pre-Market Authorization (PMA) approvals was used to identify the major regulatory approvals in this field. Based on data from these sources, I concluded that the time period most relevant to the discovery of bare metal stents encompassed the years preceding the publication of the first pivotal studies on the effectiveness of the technology in 1994 and corresponding FDA approval.

To identify patents related to bare metal stents that were approved during this time period, a search was deployed using the Thomson Innovation comprehensive patent database of US patent applications and granted patents.⁶⁷ This tool, updated bi-weekly, includes indexes content from the Derwent World Patents Index and the European Patent Office's INPADOC database. Overall, these records encompass 90 countries with full text documents from seven authorities – the US, Canada, EPO,

Patent Cooperation Treaty, France, Germany, and United Kingdom, and English translations of abstracts from Japanese and Korean applications and granted patents. Patents in this database are searchable by terms of interest within the patent, including the title, assignee (the person or company that owns the inventor's legal patent rights), abstract (short description), claims (list of items on which the applicant is seeking exclusive rights), description (a longer explanation of the elements of the invention and its function) and the classification code (internationally agreed upon hierarchical system of language independent symbols for the classification of patents).⁶⁸

The World Intellectual Property Organization's natural language search engine (TACSY version 2.1.1) was used to locate the appropriate designation for classification of applications related to stents (A61F). Within this patent classification section, A61F2/82 to A61F2/94 were identified as the group subclasses that would have included patents related to bare metal coronary artery stents (see **Table 3**). Thomson Reuter's innovation platform was then used to identify all patents filed under these subclasses until 1994. A total of 532 relevant patents met these criteria. A manual review of each patent was performed to identify the final sample. I excluded patents covering vascular grafts, delivery systems for stents, catheters, stent removal or expansion devices and stents designed for use outside of the vasculature (e.g. urological applications). Patents that covered combination catheter and stent systems were included along with novel methods to manufacturer stents. The final sample consisted of 245 patents.

2.3.2 Patent data extraction

From each patent record, the date of application, the date of approval, the name

of the inventor, the name of the assignee (if any), and the characteristics of the claims covered by the patent were extracted. An assignee is the person or company that owns the inventor's legal patent rights. To determine the rate of patent citations, our sample of patents by their application number were inputted to an electronic database of patents compiled by the National Bureau of Economic Research (NBER).⁶⁹ The NBER database comprises of detailed information on approximately 3 million U.S. patents granted between 1963 and 1999, which includes the time period of our study. The database displays the number of times each patent was cited by another patent ("citations received").⁷⁰ Citation count is a surrogate measure of the value of a patent, and has been linked to patent value and importance in previous economic analyses.^{33,71}

Next, using a methodology from Dr. Kesselheim's prior research,⁷² each assignee was categorized to one of three groups: publicly traded, privately held, or not-for-profit at the time of patent application. Hoover's database (Hoover's Inc., Austin, TX) was used to determine the status of assignees. This database includes records of 65 million companies searchable by name, location or industry. The profiles include overviews, history, financial records and initial public offering status information starting from 1948. Subsidiaries of public companies were categorized as public companies. Assignees without records in the Hoover's database were researched with supplemental Google, Bloomberg, and Elsevier business intelligence searches. For the 20 entities without available data, an assignment as a small, private entity was made. Patents not assigned to a particular entity are legally the property of the named individual inventor(s). Finally, patents that had been abandoned due to delinquent fees or penalized for late upkeep fees required by the USPTO were also identified. Such delinquent patents are more likely to be of minimal value and not contribute

meaningfully to a marketable product.

3.0 Results

The most transformative products identified as a part of this thesis span a wide range of medical specialties from oncology to orthopedics. These products include medical devices, small molecules, and biologic drugs.

3.1 Opinions on innovations

The participants in our study provided a wide variety of opinions regarding the factors contributing to their successful contributions to transformative innovation and the challenges facing modern medical product development (see **Table 4**). The individuals and the institutions in which they worked were most often noted by our respondents as the primary drivers of innovation. Our respondents also cited sound basic science foundation and collaboration as key elements that promoted successful innovation. Issues concerning intellectual property, in particular the challenges of technology transfer, and funding difficulties were identified as the most common hindrances to innovation. Less often, regulatory policies and reimbursement were discussed. Key quotes categorized by common themes are listed in **Table 5**.

3.1.1 Drivers of drug and medical device innovation

3.1.1.1 Individuals

As one innovator of the vascular endothelial growth factor (VEGF) inhibitors that were transformative in the care of ophthalmology and to a lesser extent, cancer, summarized, “I think that individuals really still drive a lot of this.” Specifically, most

innovators pointed to individuals with both the insight to recognize unmet clinical needs and the ability to push forward solutions. For example, Robert Langer started working as a post-doctoral fellow on angiogenesis inhibitors and then went on to develop numerous biomedical innovations in his own career. He attributed the eventual development VEGF inhibitors to Judah Folkman's "original hypothesis that if you stop vascularization, that might be a new approach to cancer therapy" and Folkman's persistence to the field despite skepticism from the existing clinical community. Using bisphosphonates as another example, Rossini (head of research at Isitituto Gentili, a small company at the time) notes, "you often need a physician—scientist involved in these drug discovery programs ... somebody who really knows what's an unmet medical need and what's not."

Inevitably, breakthrough innovation faced skepticism and setbacks requiring champions to continue pushing development forward. Michael Brown, a Nobel Prize winner for his role in describing cholesterol biology and a former member of Pfizer's Board of Directors, stated, "every drug that has ever come to market has had an internal champion." He explains that "every drug gets knocked down somewhere along the way before it finally reaches market. There is some scare that happens, some perceived toxicity in some animal model and turns out not to be relevant or they get the first lead compound and it has horrible pharmacokinetics and somebody has to believe in the project to continue to work and find the right compound." Internal champions were essential to push development forward in spite of clinical challenges and internal politics. In the case of the statin class of drugs, transformative in their impact on lowering cholesterol and reducing incidence of cardiovascular disease, Al Alberts and Ed Scolnick of Merck stood behind the continued development of the first member of

the class, lovastatin (Mevacor), despite concerns of the mutagenicity of the compound in animal models and elevations of liver enzymes in early human trials.

3.1.1.2 Supportive institutions

The institutions in which innovators worked were similarly instrumental to the drug discovery process. The three types of institutions discussed most often were academic centers, large pharmaceutical manufacturers, and small companies. Academia was noted to be an environment conducive to essential scientific investigation, most commonly before large or small companies saw a viable business opportunity. Each of the transformative innovations included in this study had clear and direct ties to work done in academic or government laboratories. Graham Russell, one of the key physician-scientists involved with the testing and recognition of the therapeutic potential of bisphosphonates in bone disease, noted that academic based investigators “kept this field [osteoporosis] going during the first 15-20 years before big pharma really got involved” by pursuing “some fairly wacky ideas” targeting “diseases which really hadn’t been treated” at the time.

Work performed at academic centers for these transformative products frequently extended beyond basic science work and the elucidation of pathophysiologic mechanisms. Predominantly supported by government funding, Jan Vilcek at New York University (NYU) had already developed early polyclonal antibodies to tumor necrosis factor (TNF) and lymphotoxin by the time the fledgling biotechnology company Centocor approached him with a licensing agreement for his work. Neither he nor the company had a clear diagnostic or therapeutic product in mind, but Vilcek’s work ended up forming the basis for the first TNF blocker tested in clinical trials, infliximab (Remicade).

One innovator of the anti-CD-20 targeted cancer therapeutic rituximab (Rituxan) pointed out that “now academia has become more commercial on doing clinical trials” by establishing the necessary “infrastructure development” to test new innovations clinically.

Academic institutions were criticized for lacking resources to translate impactful science to commercial products. Langer explained that he began starting companies as a development vehicle for the research performed in his MIT laboratory in the late 1980s because he “wanted to see that [drug development] process speed up” by getting “the resources to make those things happen” given the “tremendous amount of time and money” required for drug development. In all cases, partnership with industry was necessary to engage larger scale clinical trials, and negotiate the FDA approval process.

However, large companies were often cited as being risk averse and particularly resistant to development of these transformative technologies, because the innovations challenged prevailing opinions at the time about the origins of disease, blazed new therapeutic approaches, or represented unknown risks. Ulrich Sigwart, a pioneer of coronary artery stent designs, noted that after Pfizer acquired the rights to his first stent design in the 1980s, litigation over mechanical failures of their Bjork-Shiley aortic valves compelled the company’s leadership to pull completely out of the implantable cardiac device field, including abandoning Sigwart’s first stent designs. Several years later, Sigwart partnered with Advanced Cardiovascular Systems to develop his stent concepts. Another stent pioneer, Julio Palmaz, endured frequent rejections from multiple different medical device companies before finally negotiating a development agreement with Johnson & Johnson after 5 years of validation studies. He recalled,

“people hated the stent; they hated it. It was incredible. When you would go to a company and would show them the stent in the early ‘80’s ... immediately you can see their face, they start rolling their eyes, and kind of making scowls.” Our respondents note that in the modern day climate, industry has grown to direct more of its attention and resources towards less risky products. One statin innovator complained that in industry, “the major change has been a switch from looking for cures to looking for marginal advantage.”

Predicted reimbursement—largely related to expected market size of the therapeutic—was often the leading factor in the industry’s interest—or lack thereof—in investing in new technologies. Nearly all of the innovations we studied faced skeptical industry investors along the way because estimated market size was inappropriately perceived to be limited. When Ciba-Giegy and Sandoz merged to form the Novartis in 1996, management reviewed existing programs. By this time, the tyrosine kinase inhibitor imatinib (Gleevec) was a relatively mature compound ready for formulation and toxicity testing. According to Brian Druker, the oncologist primarily responsible for proving the therapeutic potential of imatinib in chronic myelogenous leukemia (CML), priority for imatinib’s program at Novartis suffered because it was “so low on the priority list” given that CML “by their market estimate” would never be able to “make back their investment.”

In the cases where large pharmaceutical manufacturers demonstrated lack of interest, small start-up entities performed the initial commercialization work for innovations originated in the academic setting. Small companies were noted to have the benefits of a singular focus on one product, capital efficiency and a less bureaucratic structure. Isaac Kohlberg, a technology transfer expert who mediated the

NYU-Centocor relationship that ultimately led to the discovery of infliximab, commented that small companies represents “the development vehicles” best able “to take a project up to Phase I and Phase II” given that “in a large company because of the turnover of people, and the many other projects that they are developing and the not-invented-here syndrome things may fall between the cracks.” Rituximab represents another example of the advantages of a small company, which was developed for a total budget estimated by one innovator to be \$17 million dollars “which is unheard of, but that’s because we were a small company.”

3.1.1.3 Collaboration

Many respondents viewed that open relationships among innovators, particularly between scientists in academia and industry, contributed to innovation. In the development of VEGF inhibitors, one innovator emphasized that “if you were collaborative with things, a lot can be accomplished and so we were able to accomplish a lot more in this field and area because various groups were collaborating so that we could have ever have done if that wasn’t the case.” Collaboration allowed scientists with different expertise to focus on separate, equally critical components of innovation. Druker noted, “we’ve got to figure out ways for companies and academics to work together quickly, efficiently and effectively. That’s what we did” in developing imatinib. He went further by explaining that as an academic based researcher, “I’m not going to do the formulation. I’m not going to do the toxicology. Drug companies do that really well. I’m going to set up the model systems to test their drugs. I’m going to run the clinical trials. That’s what I do really well.”

Some respondents felt that collaboration in recent years among academia and industry had diminished due to shifts in focus of industry to 'safer' drug targets and change towards less mutual trust. One statin innovator wished "some of these 'me-too' drugs were not occupying the attention of the drug companies when they could be looking for new drugs." Several respondents discussed a change in scientific culture where, as one HIV therapeutic innovator put it, "everyone's a lot cagier than they used to be." When anesthesiologist John Sear, who conducted some of the early clinical trials on propofol, was asked how information exchange between academia and industry has changed, he answered, "the fact that there was a considerable degree of trust on both sides meant that information was freely available for discussion. I think today you know you can't get anything unless you sign three pieces of paper and almost swear that you'll shoot yourself if you ask the wrong question." Increasing concern surrounding academic based conflict of interest policies was the most commonly cited sub-theme that deterred collaboration and free information exchange. Thomas Fogarty, who contributed to the development of stents and several other catheter based medical devices, noted, "conflict of interest has been carried to a point where you can't work with some of these companies. Well the fact is, we as physicians cannot do anything without our companies. Companies can't do anything without us ... Stanford and Harvard both view industry as the evil empire. Well, they can be if you let them ... they're throwing the baby out with the bath water."

3.1.1.4 Strong underlying science

More than a quarter of our respondents believed that transformative innovations had their foundation in a strong understanding of basic biologic processes and

pathophysiology. Well-delineated basic science was key to increasing the likelihood that breakthrough therapeutic innovation would be successful clinically. Alexander Wlodawer, who contributed to the development of HIV protease inhibitors by first studying a protease isolated from Rous sarcoma virus, stated “you cannot simply try to develop drugs in a practical way with insufficient basic understanding of the system.” Jan Mous, an industry based innovator involved with HIV protease inhibitor, added, “the best combination to be successful and to be productive and fast is to have a strong interest in the basics and the physiology of the disease or in this case, of the infection. Through a deep understanding of these mechanisms, and the target, that will increase the likelihood that a specific compound will end up becoming a successful drug.” Indeed, the ultimate development of HIV proteases drew on years of background research on the protein structures of retroviral proteases without the explicit goal to develop drugs.

In the case of VEGF, Judah Folkman’s initial hypothesis and work on angiogenesis factors of tumors started as early as the 1960s. The first VEGF inhibitors approved by the FDA more than thirty years later was built on robust underlying research and tens of thousands of publications in the peer-reviewed literature describing the biology of the various regulatory molecules of angiogenesis, *in vivo* cloning of capillary endothelial cells and polymer science. In regards to stents, Richard Schatz, a cardiologist who contributed to increasing the flexibility of the original Palmaz stent, explains that much of their success was because “we spent a lot more time on the design and a lot more time proving that it worked. All the others were just kind of wham-bam. ‘Let’s get it out there as fast as we can’ but without any data.”

3.1.2 Hindrances to innovation

3.1.2.1 Intellectual property

Interviewees who discussed intellectual property agreed that the culture in academia has shifted toward greater legal protection of scientific discoveries by seeking and obtaining more patents. Jonathan Leis, who developed the first effective assay systems for a key HIV enzyme that helped catalyze discovery of antiretroviral therapy, explained, “I was trained to seek the knowledge [as a basic research scientist] and publish it and work out as much of it as you can.” Leis noted that patenting was not a part of the process neither he nor his university considered at the time. However with the changing culture, Leis remarked that today “we set up screens for small molecules ... if we find it then we would patent it and talk to the drug companies for developing.” The opinions were mixed in regards to whether this cultural shift promotes or hinders innovation. Some reported that patenting by academic institutions is a fair way to ensure some of the windfall from new drugs was re-invested into research. For example, one rituximab researcher reasoned, “I don’t think it would be a barrier to have interposed patents and licenses and some royalty flow to the university from this success ... it’s too bad the university didn’t benefit from this, and that Genentech and IDEC [now Biogen Idec] were the only beneficiaries.” However, others were frustrated by the change. Russell, involved with the discovery of bisphosphonates, described that this shift does not necessarily protect meaningful innovations: “it’s gone too far. There’s a lot of rubbish that gets patented out of universities.” Many innovators believed that the new focus on patenting hindered the core mission of academic institutions to conduct research and share freely. Nobel laureate, Mike Brown, explained that early clones of HMG-CoA reductase were shared between academia and industry much

more easily because “back in the 1980’s, our university didn’t insist that we patent it and we didn’t patent anything. So the legal things were obviously totally different from today.” Patents relating to research tools were identified as more likely to hinder to innovation, as compared those covering potential therapeutics and devices.

Technology transfer offices were often cited for complicating the innovation process. The administrative burden and inefficiency of the system precludes efficient translation of scientific discoveries to commercial products. Phil Romano, an angel investor in Palmaz’s coronary artery stent, helped negotiate a technology release from the University of Texas San Antonio, remarked that such a release would be more difficult in the present climate and has generally avoided seeking out university-based technology in his post-stent medical entrepreneurial ventures because “we tried going to universities and universities come to us but they are so damn hard to deal with I mean it’s ridiculous ... we don’t bother with them.” Both academic- and industry-based innovators agreed that the current process of transferring technologies patented by universities to commercial entities was more time intensive and difficult than it used to be. Stuart Schlossman, a scientist who helped describe the CD20 antigen attacked by rituximab, explained that now “technology transfer probably protects the hospitals to better extent” with the drawback that process can be “intrusive in the relationship that you might be able to have with a pharmaceutical company because many of them have very good scientists. And, many of them would be complementary to the work that you could do.” Russell lamented, “you can’t work in a university these days without them wanting to patent you opening the door for them” and when patents are applied for by technology transfer offices “they don’t really have much to offer, they have a problem passing them on to licensees.” In order to facilitate innovation, one physician-innovator

noted, “the first thing we do when we get a great idea now is get it outside [the academic setting] and get it commercialized.” Richard Stack, a physician-scientist at Duke University, explained that in the early days of the stent he and his team were among the first to conceive and patent the concept biodegradable coronary stents⁷³—this has only recently become translated into a promising new class of stents.⁷⁴ Stack explains that difficulty navigating the technology transfer process was a key reason why he and his team abandoned further investment in the biodegradable stent during the 1980s.

A minority of interviewees specifically pointed to the current need for material transfer agreements (MTAs) in sharing reagents and other products between academic and industry scientists, whereas open sharing was commonplace in the 1980s and 1990s. Tony Adamis, who helped develop ophthalmologic uses of VEGF inhibitors while at Boston Children’s Hospital, explained that discovery of the drug was greatly aided by his cooperative relationship with Genentech-based Napoleone Ferrara. Ferrara “made it move fast” with the mindset of “let’s figure out the truth here, what’s the science.” Adamis recalls that Ferrara would “send me packages on dry ice every few months, just was extremely generous. We couldn’t do those experiments without him.” Imatinib pioneer Druker supported a universal MTA to facilitate collaboration and interaction because “then it would take a week to get these agreements implemented instead of six months to a year with everybody negotiating over all the same things, publication rights, intellectual property, all these things.”

3.1.2.2 Funding challenges

Several respondents commented that supporting the research critical to breakthrough innovation is growing increasingly difficult given stagnant government funding. Patricia D'Amore, who worked as a vascular biologist on angiogenesis in the eye, explained that in the present climate it is difficult to pursue the basic research that could uncover new therapeutic options when "government funding is so uneven and unpredictable." Nora Heisterkamp, key in uncovering the science of the Philadelphia chromosome translocation ultimately targeted by imatinib, noted that it is now difficult for a researcher to "go off onto a tangent and discover things. That wouldn't be possible based on the very restrictive NIH granting system." Given the requirement to procure NIH funding to cover an investigator's salary, she found that there is now less security to "develop new avenues of research" than when she was cloning the breakpoints of the Philadelphia chromosome.

Criticism on funding challenges extended beyond government sources to private sources as well. Venture capital was cited as becoming more risk averse in terms of investing in medical technologies. One academia-based stent innovator pointed out that the "venture capitalists don't want to invest in new ideas because they may never get paid for it." Another early stent innovator on the industry side remarked on the increasing burden of proof required by venture capitalists, "now the venture capitalists want human data before they'll plunk any money in." Industry sponsorship was not cited as a significant form of funding for our academic-based researchers.

3.1.2.3 Regulation and innovation

Opinions were mixed on the role of government regulation in innovation. Some criticized the FDA as being a hindrance to innovation. Romano (stents) specifically identifies the unpredictability of FDA examiners in evaluating approval applications—“there is probably so much technology and so many good things that could come out and help people that because one examiner doesn’t think it’s going to do what it’s supposed to do or set up the testing properly and whatever, it gets railroaded, it gets smashed.” Numerous innovators have noted that the FDA has required higher levels of efficacy and safety. Holloway (HIV) noted that in the case of new antivirals “you have to demonstrate that you’re better than whatever’s out there, especially. We’re moving toward having AIDS medications that are going to be generic so you’re going to have to have a much higher barrier to show that your compound is significantly better.” Michael Brown mentioned that the first statins were approved based on “a 2,000 patient two year trial” while new cholesterol medications now would be required “to do a 30,000 patient, 5 year trial. Instead of just measuring cholesterol in the blood, they have to actually count heart attacks.” Thus, “the FDA has become much, much more conservative and demands much, much higher levels of safety and efficacy.” Although the majority of respondents felt that the FDA has become more demanding in its requirements to prove safety and efficacy, there are others who wonder whether there is sufficient rigor required in the approval of high-risk medical devices. However, it is important to note that the device regulatory process differs significantly from the drug approval process in that there is greater variation in the regulatory requirements of devices based on its function and risk.

3.2 Origins of innovation: in-depth analysis of the coronary artery stent

To further explore the medical innovation process, the next section of the thesis focuses on the coronary artery stent and the results emerging from qualitative interviews with key innovators as well as a quantitative review of the early patent literature. See **Table 6** for illustrative quotes regarding the development of the coronary artery stent.

3.2.1 Precedents for coronary artery stent innovation

Interviewees pointed to three antecedent developments that set the stage for the development of coronary artery stents. The first was the practice of dilating arteries using percutaneous angioplasty, pioneered by Charles Dotter, a radiologist at the Oregon Health and Science University in the 1960s. Dotter developed his early catheter prototypes with the aid of Cook Inc, a small company founded by an early medical entrepreneur, Bill Cook. The second major antecedent was the development of percutaneous transluminal coronary angioplasty (PTCA). Andreas Gruentzig, a German cardiologist who came to Emory University in 1980, helped pioneer angioplasty in the coronary arteries. A final key development mentioned by participants was improvement in the manufacturing of catheters required to deliver stents to the coronary arteries. Several innovators cited John Simpson, a cardiologist at Stanford University, who introduced a new catheter system that vastly improved steerability. He founded ACS, a privately held medical device company, to commercialize catheters and guidewires.

3.2.2 Coronary artery stent development

The first coronary artery stents emerged from three teams. Two were US-based, with one led by Julio Palmaz and Richard Schatz, and another by Cesare Gianturco and Gary Roubin. The third was European-based led by Ulrich Sigwart. **Table 7** outlines key stent development milestones.

3.2.2.1 Palmaz-Schatz stent

Argentina-trained radiologist Julio Palmaz attended a talk by Gruentzig at the Society of Interventional Radiology Meeting in New Orleans in 1978. On the taxicab ride back to the airport, Palmaz drafted his initial concept of the stent. Palmaz soon began fashioning his slotted tube stent design in his garage. Palmaz moved to the University of Texas-San Antonio in 1980 to continue his work. With dedicated research time and laboratory space, Palmaz finished animal studies of his stent, which he presented at the Radiological Society of North America annual meetings in 1984 and 1985. In 1985, Palmaz met Richard Schatz, an interventional cardiologist conducting research at the Southwest Research Institute in San Antonio. Schatz made a modification to Palmaz's design to improve the stent's flexibility and introduced Palmaz to his friend Philip Romano, a restaurateur. Romano provided \$250,000 in seed money and the three formed Expandable Grafts Partnership (EGP) in late 1985 and then filed the first patent application on the technology.

Prior to EGP, Palmaz unsuccessfully sought company partners. However, with more mature technology and a business partner, EGP licensed its intellectual property to Johnson & Johnson in 1986 for \$10 million and a royalty percentage (6-9% on use in the coronaries and 3-6% for peripheral use based on gross sales). Johnson & Johnson provided engineering support for Palmaz and Schatz and organized and funded the

pivotal trials for US premarket approval. Human experiments with the Palmaz-Schatz stent occurred in peripheral arteries in 1987 and coronary arteries in 1988. First sales of the stent came in Europe by 1988. The FDA initially rejected the first Palmaz-Schatz stent application in 1993. However, the team quickly reapplied and gained FDA approval in August 1994 for the elective use of the Palmaz-Schatz stent for restenosis on the basis of two pivotal trials (BENESTENT and STRESS).

3.2.2.2 Gianturco-Roubin stent

Cesar Gianturco was an accomplished innovator in interventional radiology who did much of his work at the Carle Clinic in Urbana, Illinois before becoming a professor of experimental diagnostic surgery at the University of Texas MD Anderson Hospital.⁷⁵ Gianturco had a long history working with Cook Inc. having developed balloon-deployable metallic stents and intravascular filters for peripheral vessels.⁷⁶ With funding and engineering support from Cook, Gruentzig collaborated with Gary Roubin, then a cardiologist at Emory, to develop a coronary stent based on Gianturco's initial wire coil designs. After Gruentzig's untimely death in a plane crash, Roubin continued the development, and after about a year started testing a balloon-expandable flexible coil stent (Gianturco-Roubin Flex-Stent). This stent was tested to treat acute vessel closure, a medical emergency, following balloon angioplasty, and gained FDA approval in early 1993 for this indication.

3.2.2.3 Wallstent and Multilink stent

Ulrich Sigwart was a cardiologist working at the Centre Hospitalier Universitaire Vaudois in Lausanne, Switzerland. In the early 1980s, Sigwart built self-expanding

stents from an elastic wire braid, inspired by cylindrical Chinese finger traps made from woven strips of bamboo. The University's experimental surgery department and a grant from the Swiss National Fund supported initial prototypes and animal studies. In 1985, Sigwart partnered with MedInvent, a small private medical device company in Switzerland, to provide additional supplies and manufacturing and engineering support for the stent, which was later named the Wallstent. This work led to the first stent placement in the coronary arteries of patients in Europe.⁶⁴ In 1986, MedInvent was acquired by Schneider, a subsidiary of Pfizer, but the company put development of the Wallstent on hold due to liability concerns.

With Wallstent development at a standstill, Sigwart began to work in 1989 with a small team at ACS, a private catheter focused company, to pursue a balloon-expandable stent, leading to the MultiLink stent. In 1993, the first Multilink stent was implanted in a patient in London. In 1997, it was approved by the FDA and quickly gained market dominance due to its improved steerability.

3.2.2.4 Other stents

A second wave of coronary artery stent designs were commercialized more expeditiously due in part to regulatory approval pathways blazed by the earliest innovators. For example, whereas the FDA required the Palmaz-Schatz stent to be tested in the peripheral circulation before being applied to coronary arteries, this hurdle was not imposed on any other designs. Independent US-based inventor Dominic Wiktor developed a stent with Medtronic that was FDA-approved in June 1997. Advanced Vascular Engineering's stent was approved in December 1997; Medtronic subsequently acquired the company in 1998. European interventional radiologist Ernst

Strecker developed stents for peripheral use in the 1980s and partnered with Boston Scientific—which went public in 1992—to create a self-expanding coronary artery stent (approved late 1998). More recently, stent innovation has prioritized drug-eluting stents and bio-absorbable stents, which can be traced to work by Richard Stack at Duke University in the early 1980s.

3.2.3 Role of individuals

We found wide agreement that individual inventors played the primary role in early development (Table 2). When describing the origins of this transformative device, respondents commonly pointed to the key contributions of Drs. Palmaz, Schatz, Gianturco, Roubin, and Sigwart.

These key innovators were early adopters of coronary artery angioplasty and had first-hand exposure to clinical problems related to the technique, most notably post-angioplasty restenosis. In interviews with all (Gianturco was deceased), they conceived of the stent as an alternative to angioplasty or as a way of preventing abrupt artery closure, a medical emergency. As Sigwart noted, “I found that balloon angioplasty was unpredictable, and I said, we must find some sort of endo-luminal support.”

The inventors also did substantial work in developing the technology. After failing to secure industry partners in the early 1980s, Palmaz progressed through animal studies himself and filed the Investigational Device Exemption to begin human testing. Similarly, Sigwart engaged in prototype development and animal testing of the Wallstent on his own time.

All of these innovators faced substantial skepticism. As Palmaz said, “People hated the stent; they hated it. It was incredible. When you would go to a company and

would show them the stent in the early '80's ... immediately you can see their face, they start rolling their eyes, and kind of making scowls. There was something about stents that everybody disliked." This skepticism was shared by others outside of industry. The Veterans Administration's rejections of Palmaz's grant applications to fund his work compelled him to find private funding through Romano and Schatz.

3.2.4 Role of industry

Most interviewees described the entry of large medical device companies after stent prototypes had been sufficiently developed and tested in laboratory and animal trials. Risk was cited as a primary factor that hindered earlier industry involvement. According to interviewees, companies believed it was physiologically incompatible to implant prosthetic material in the coronary circulation. Companies also had legal concerns. The Bjork-Shiley mechanical heart valve had been recalled around that time for safety reasons prompting Pfizer to halt development of Sigwart's first stent product. Cook Inc. was concerned about legal risks related to the potential failure of implantable cardiac devices, necessitating Roubin to personally file the first Investigational Device Exemption application to begin testing his stent in humans. Given the invasiveness of the technology, there was also significant concern regarding the FDA approval process and the "difficult regulatory environment." Finally, according to interviewees, many companies perceived substantial business risks. According to Palmaz, consultants from McKinsey & Co. provided a strong recommendation to Johnson & Johnson against investing in the Palmaz-Schatz stent believing the market size to be too small.

When they became involved, medical device companies provided financial resources and engineering to test design hypotheses of physician-innovators. The

company's engineers also supported manufacturability. However, individual inventors reported that they accounted for ease of manufacturing in their initial prototype designs. The Palmaz-Schatz laboratory-produced prototype was essentially manufacture-ready when Johnson & Johnson became involved.

Second, medical device companies provided necessary support in organizing clinical trials and negotiating the FDA approval process. Organizing the randomized trials and FDA premarket authorizations took seven to eight years to complete. The inventors estimated that the companies invested in the range of \$100-\$500 million in the processes leading to device approval, earning revenues surpassing that investment within a year or two after the devices were approved. Supporting a key result from our multi-innovator analysis, internal champions at Johnson & Johnson were cited by Schatz, Romano and Palmaz as crucial in pushing the stent project forward. Lastly, device companies provided existing sales channels to deploy the technology, although innovators such as Schatz helped convince other clinicians to adopt the technology.

3.2.5 Role of intellectual property

We found that ownership of intellectual property played a minimal role in incentivizing early innovation in this field. No key inventors initially sought out patents after developing their stents citing a combination of a lack of expertise, funding limitations and a philosophical commitment to research dissemination. Our interviewees each said that the potential profitability of the resulting products was not an

important consideration. They indicated that a pressing unmet clinical need was what drove their work.

The key innovators in our study considered themselves uninformed about patents. Sigwart said, “I was completely naive in the area and the only thing I wanted was to get the scaffold into the angioplasty.” Palmaz first broached the subject of patenting with the University of Texas in 1984, six years after he first conceived of his stent, but reports that he was told by university officers that his work was not patentable. Without patent protection, Palmaz presented his work that year to the public at a national conference of radiologists later leading to a loss of European rights. In Roubin’s case, he recalled no involvement with patenting at all, leaving that to his colleagues at Cook. Sigwart did not initially apply for a patent on his work; rather, intellectual property protection was sought first by MedInvent only after he signed a contract releasing the technology rights to them.

Patents ultimately became paramount in the context of the larger corporations that later became involved in stent commercialization. Upon forming EGP, Romano required Palmaz and Schatz to explicitly extricate the University of Texas’s possible ownership of the technology. The partnership then applied and paid for its own patent. Johnson & Johnson later expended substantial resources, in the words of one interviewee, “expanding the patent limits.” The patent record became crucial as these larger companies engaged in litigation with one another. By 2002, multiple lawsuits between Johnson & Johnson, Cordis, Medtronic and Boston Scientific about which company had priority to overlapping designs of their different versions of coronary artery stents resulted in billions of dollars in damages and fees.⁶⁶ In one judgment, Medtronic

and Boston Scientific paid Johnson & Johnson \$1.2 billion for patent infringement on the Palmaz-Schatz stent.

A lax posture towards patents excluded some inventors and key contributors from financial rewards. For example, the University of Texas San Antonio, which financially supported and provided laboratory space for important early proof-of-concept experiments conducted by Palmaz, declined to invest the resources to patent the discovery. Ultimately, Palmaz offered them a 3% share of his royalties, which has since led to an estimated \$10-\$30 million in total payments to the university. Roubin and Emory University similarly received no royalties from his work or the testing that occurred in university laboratories, although Cook later provided Roubin with a financial gift to recognize his contribution. Without patents, Sigwart and his institution received no royalties from his original innovations, even after the technology was sold to Pfizer. This negative experience led him to change his approach towards intellectual property in his subsequent collaboration with ACS.

3.2.6 Innovator characteristics

Key inventors were all physicians directly exposed to the clinical problems they were seeking to address. Most interviewees specifically remarked on these inventors' aptitude and vision, such as their ability to recognize potential innovative solutions to emerging clinical problems such as coronary artery restenosis. Interviewees also pointed to the inventors' resiliency despite considerable resistance from the medical community. Another common quality was that inventors were seen as risk-takers, in contrast to the widespread perceptions that the companies were risk-averse. Interestingly, a background in engineering was not necessary. All individual inventors

were able to directly develop prototypes from raw materials and deploy them in animal models.

3.2.7 Collaboration

Collaborative work was central to the early development process. For the Palmaz-Schatz and Gianturco-Roubin stents, each inventor brought different contributions to building the device. Interviewees cited the importance of collaborations between the academic inventors and their colleagues in medical device companies for engineering support. Other unofficial collaborations also helped move the development process forward. For example, Palmaz received early assistance from an engineer not affiliated with his academic medical center in learning about manufacturing processes such as laser etching that he could use to produce a prototype of his stent concept. Interviewees also recalled the inventors discussing their work at national professional meetings, and the importance of these open brainstorming sessions in facilitating progress of the individual projects.

3.3 Patent literature analysis of the coronary artery stent

Accounts of coronary artery stent development date back to the late 1970s, although the first clinical report did not appear until 1985 (Table 2). Until 1994, there were a number of key preclinical, clinical, and regulatory steps leading to the approval of bare metal stents for use in coronary arteries, which quickly became widely used after that point. In an analysis of 12 US hospitals (detailed in the next section), stent use as a percentage of percutaneous transluminal coronary angiography procedures increased from 5.4% in 1994 to 69% by 1997.⁷⁷

3.3.1 Overall patent data

We identified 245 patents relating to coronary artery stents during the years 1984-1994 that involved 107 unique assignees. Private companies were assigned the most patents (110, 44.9%), followed by public companies (77, 31.4%), individual inventors (44, 18.0%) and non-profit entities (14, 5.7%). See **Table 8**. Twenty entities that were not identified within our database searches were designated as private. Public companies had the greatest ratio of patents filed to assignees (4.3) among all the different assignee subtypes, suggesting that public companies were the most likely to seek multiple patents in this area. Average citation count was similar across individual inventors, non-profits, private companies or public companies.

Individual inventors (19, 43%) and non-profit entities (5, 36%) were more likely to be associated with patents that were delinquent in fees or expired due to a lack of payment. This is consistent with the fact that individual inventors and non-profit entities have less funding for the purposes of filing and maintaining a patent. Removing these patents from the database did not substantially change the average patent citation count for any of the assignee subtypes.

3.3.2 Most influential patents

To identify the key sources of intellectual property contributed to coronary artery stent development, we then focused on the most highly cited patents, and found that the share of patents belonging to privately held companies increased compared with the overall sample. Among the top 25% most highly cited patents, privately-held companies

contributed a larger proportion (51%, 31 patents), publicly traded companies contributed 16 patents (26%), individuals contributed 12 (20%), and non-profit entities contributed 2 (3%).

The top ten cited patents in our sample are even further skewed towards privately held companies (**Table 9**). Expandable Grafts Partnership, started by the physician co-inventors of the Palmaz-Schatz stent, owned the most highly cited patent (1,857 subsequent cites), as well as 4 out of the top ten. Cook Incorporated, which commercialized the Gianturco-Roubin stent, owned the third most highly cited patent (1,017 subsequent cites) and fifth most highly cited (966 subsequent cites). The Gianturco-Roubin stent and Palmaz-Schatz stent were the first two stents approved in the US market, in 1993 and 1994, respectively (**Table 7**). By contrast, Medtronic, a public company, owned the second most highly cited stent (1,039 subsequent cites), although its Wiktor stent was relatively late to the US market and was not approved by the FDA until June 1997.

3.3.3 Temporal trends in patenting

Starting in 1984, the total number of stent-related patents filed per year steadily increased (**Figure 2**). The largest percentage increases in patent counts were in 1992 (68%) and 1994 (97%). Privately held companies dominated patenting early in the study period, contributing to the majority of patents in every year from 1984 through 1989. Publicly traded companies did not control a majority of patents until the final two years (1993 and 1994), although the increase in public company patenting rose substantially over the last 5 years of the sample. Rates of patents owned by individuals and non-profit entities stayed generally constant throughout the time period studied.

4.0 Discussion

Although our interview subjects developed groundbreaking advances in disparate fields, similar themes emerged from their insights on transformative innovation today compared to their past experiences. The core components of transformative medical innovation continue to center on the roles of individuals and the institutions they represented. Reflections from our respondents suggest that a host of factors either hinder or catalyze transformative innovation. Meaningful collaboration and strong underlying science were cited as consistent catalyzers. Major obstacles to transformative innovation currently included an increasing lack of early stage funding, and intellectual property and other challenges that prevent collaboration. Our results also showed that changes to the regulatory and reimbursement environment were not as influential to transformative medical innovation. From our in-depth study of stents, the results generally support the findings from the multi-innovation analysis with some caveats, in particular with regards to the role of FDA regulation.

4.1 Individuals and innovation

Our results are consistent with tenets of entrepreneurial theory, which emphasizes the central role individuals play in identifying and acting upon opportunities.^{42,44} As seen in the innovations sampled in this paper, these individuals acted as either visionaries who recognized meaningful unmet clinical needs, scientists and engineers who were experts on the underlying pathophysiology and science or internal champions who remained persistent despite naysayers and setbacks. Often

times, these individuals crossed institutional boundaries, made personal and professional sacrifices in order to push forward their respective innovations.

Another secondary finding is the interconnectedness of innovators to one another in regards to mentorship and counseling, a phenomena that has been reported in the field tissue engineering.⁷⁸ In the case of statins, both Brown and Goldstein had an existing relationship with Scolnick at Merck, in that they all were residents at Massachusetts General Hospital together. Goldstein worked previously in Scolnick's laboratory at the NIH before moving on to the University of Texas Southwestern. Nadler, an innovator involved in the development of Rituxan, was a mentor to Druker (imatinib) at Dana-Farber Cancer Center. Prior work has shown that academic scientists were more likely to engage in commercial activities when their colleagues were highly-regarded scientists who engaged in commercial activities prior.⁷⁹ From our results, strategies focusing on supporting and connecting these highly skilled individuals would likely support transformative innovation.

Our in-depth study of the stent found that much of the early work was also pioneered by individual inventors, not only in generating ideas in the face of substantial skepticism, but also in prototype development and early testing. These individual inventors were motivated by the desire to address a pressing clinical problem. Moreover, the clinical imperative arose from complications of the emergence of balloon angioplasty, as well as from the desire to apply existing experimentation with peripheral artery stents to relieve coronary artery blockages. The fact that many of the key innovators were physicians who could draw on their direct experience with patients turned out to be central to recognizing and addressing this clinical need. Important parallels have been shown in the case of electron microscopes—Riggs and von Hippel

also found that the majority of innovations with the highest scientific importance were developed by the users of the instruments.⁸⁰ Physician-innovators provided the driving force behind overcoming concerns about legal risk and limited market potential that arose from risk-averse established companies. The inventors' scientific know-how allowed them to move their projects forward, with some innovators reporting even building their own prototype stents in their garages. Their experiences in dealing with patients with coronary artery disease provided them with motivation to push their ideas forward.

The stent patent results also support the findings that individuals played a critical role in the early innovation process. Prior work shows that individual physicians account for almost 20% of all medical device patents during 1990-1996 with compelling evidence that patents filed by physicians have higher impact as measured by citation number compared to patents originating from industry only.⁸¹ Our analysis of stents is consistent with this as individual inventors accounted for 18% of all patents granted for stents between 1984 to 1994, behind only private and public companies. Within both of these private companies, individual physicians operating in academic medical centers drove the underlying product design and development.

4.2 Institutions and innovation

All of the individuals included in this study operated within institutions with separate strengths and weaknesses. In the case of drug development, there has been a long-standing belief that the pharmaceutical industry's research leads to most new medicines,⁸² while public institutions like NIH support medical innovation separate from drug development.⁸³ This sentiment is also expressed in the device market, as industry representatives have pointed to themselves as the primary sources of new products.⁷⁶

Others point to the primacy of small companies in the device innovation process.⁸⁴ Our results challenged some of these traditional beliefs.

From our cohort, academia was generally credited with offering the freedom to pursue new avenues of research while large industry boasted significant resources, manufacturing expertise and regulatory experience. In some instances, small companies served as effective commercialization engines. Small companies represented an attractive acquisition for larger, better-funded entities to further develop promising technologies. For instance in the case of coronary stents, Medtronic purchased Arterial Vascular Engineering in 1998.⁸⁵ Johnson & Johnson licensed stent technology from Expandable Grafts Partnership in 1988, while Schneider Inc., then a subsidiary of Pfizer and now a part of Boston Scientific, purchased MedInvent, a small private Swiss company, in 1986 to gain access to an early stent design pioneered by Ulrich Sigwart, then an interventional radiologist working at the Centre Hospitalier Universitaire Vaudois in Switzerland. More importantly, our results show that there is no clear demarcation between institutional roles in developing transformative innovation. Work in academia would extend beyond simply idea generation or basic science research into prototype development and regulatory work. In a minority of cases, small companies and industry also conducted and supported critical underlying science that only later became breakthrough products. Indeed, new models for drug development are showing a more integrated model where industry is increasing its upstream work and academia is conducting more commercialization activities.^{86,87}

In the case of stent development, the institutional roles played by academia, small and large companies generally supported the findings from the broader multi-innovation analysis. Individual innovators supported by academic medical centers were

the primary source of transformative device development. Schatz, Sigwart, Gianturco and Roubin all operated within academic institutions during the preliminary phases of their work. Moreover, these researchers often times extended into areas of development that included manufacturing considerations and validation studies for regulatory approval. Under the chairmanship of Stewart Reuter in the UTSA Department of Radiology, Palmaz was able to develop his stent prototypes to the point of being nearly manufacture-ready. Roubin at Emory submitted his own investigational device exemption (IDE) to the FDA in order to clinically evaluate his stent design. An industry executive commenting specifically on our stent work, argues that large companies play in the success of a medical breakthrough by lending expertise in product development and iterative refinement, even though the early ideation came from physician-innovators.⁸⁸ Even though industry plays a significant role in funding medical device development, the high-risk and early stages of development requires continued support from public funding.⁸⁹

The patent data supported the findings derived from the interviews. The earliest and most impactful patents were attributed to individual physician-inventors who formed or worked with smaller private companies. Only after more clinical validation and development occurred did larger public companies become more involved in the patenting space. Often times, larger public companies would use their considerable resources to acquire intellectual property developed by smaller private companies or physician-inventors including the instance where Johnson & Johnson licensed technology from Expandable Grafts Partnership or Medtronic and Arterial Vascular Engineering. Non-profit entities (e.g. hospitals and universities) only represented a minority of patent holders for stent technology, despite the fact that academic based

physician-inventors were identified as the primary driver of stent innovation. There are at least two possible explanations derived from our results. The first is that in the 1980s and 1990s, universities and hospitals were less interested in investing resources and time to file patents. A further discussion on the implications of the growing interest of patenting by non-profit for innovations is detailed in later sections. A second explanation for a lack of patenting from non-profit institutions is that physician-inventors who develop a commercially valuable product may simply chose to work with private companies or form their own rather than working with their academic employers—this is less likely given the existence of invention disclosure policies among employers, academic or industry-based.

4.3 Promotion of innovation: underlying science and collaboration

A key finding of this study is that areas of innovation where the best underlying science was done were more likely to lead to game changing diagnostics and therapeutics. Investigators noted that insights and hypotheses responsible for eventual therapies depended on insights gained from prior, basic science work. Strong underlying science also provided a better understanding of the mechanism of action and risks of a potential therapeutic, thus lowering the risk of failure in later, larger scale studies. A recent quantitative study investigating how new molecular entities were discovered between 1999-2008 suggests that target-based approaches without an optimal determination of the underlying molecular mechanism were less likely to lead to new therapies.⁴⁰ Others have postulated that areas of high scientific activity and publications precede the development of novel drugs that draw on these new discoveries.³⁹ As the NIH turns more towards translational science, there is

considerable uncertainty surrounding support of basic research. From our results, basic research is critical to the wellspring of future transformative therapeutics.

In the case of stents, Palmaz and Schatz explicitly highlight the importance of rigorous underlying science. Palmaz first conceived the stent as early as 1978, sixteen years before the first FDA approval. Both Palmaz and Schatz believe that the extensive animal and pre-clinical testing they invested at UTSA before eventual commercial launch was critical to their eventual early market dominance over less-proven and less-rigorously tested competitors. A rigorous bibliometric review of patent citations for early patent stents was beyond the scope of this thesis. From our interview results, these early patents did explicitly borrow from earlier research done in related fields such as peripheral and urological stenting.

Beyond strong science that elucidated new pathways and targets, the success of transformative innovation depended on the ability for individuals from different institutions to collaborate. Given that no single entity can claim end-to-end responsibility for the transformative innovations in our cohort, collaboration remained essential for knowledge exchange, research tools and resource pooling. On an individual level, academic based researchers with less than two-thirds of their total research support from industry were as productive academically while also engaging in more commercialization activities compared to faculty without any industry collaboration.^{90,91} Universities and departments with established collaborations with industry have been shown previously to be better able to realize commercial opportunities.^{92,93} Currently, industry is becoming increasingly active in establishing closer relationships with academic institutions to explicitly develop new breakthrough therapies.⁸⁷ Although collaboration itself was a positive driver towards innovation, further work still needs to

determine the optimal degree in order to preserve intellectual freedom and the distinct expertise of separate institutions.

As a medical device technology, the importance of collaboration is underscored in the case of stents. Although physician-innovators operating in academic institutions represented the early drivers of technology ideation and development, larger companies played an important role in manufacturing and organization of large-scale clinical trials. Palmaz, Schatz and Romano enjoyed the regulatory expertise and additional funding for necessary clinical studies from Johnson and Johnson. Sigwart and Khosravi, a project manager at ACS, enjoyed a fruitful relationship where ACS engineers refined and developed Sigwart's vision. Physician-innovators with existing relationships with companies were able to more speedily advance their work (Gianturco/Roubin and Cook Inc.) as compared to those who did not (Palmaz). This is supported by other empirical work which shows that relationships between academic researchers and industry facilitates the uptake of transformative ideas and nascent technologies.^{94,95} To attract industry interest, Palmaz had to demonstrate more clinical efficacy in animal studies and human case studies than did the innovators allied with Cook Inc., who already had a longstanding relationship. This ultimately led to a delay in the availability of coronary artery stents by several years.

4.4 Hindrances to innovation: intellectual property and funding challenges

Transformative medical innovation is rare for many reasons both societal and scientific. The culture surrounding intellectual property has shifted to emphasize patenting discoveries in academia. Between the years 1995 and 2000, twenty of the top fifty patent entities were assigned to institutions whose primary mission was non-

commercial.⁹⁶ A historical concern from academia is that an interest in patenting and commercial activity leads to undermining of information sharing.⁹⁷ Others have argued that a focus on patenting and commercialization creates conflicts that take away from the true social purpose of biomedical research to publish scholarship.⁹⁸ Although more recent evidence suggests that publishing scholarly articles and commercialization activity are not necessarily mutually exclusive,⁹⁹ our respondents were conflicted about the implications of patenting in academia. On one hand, patenting enables academia to recoup its investment on new discoveries and fund more research. On the other hand, patenting in academia may limit individuals and institutions from interacting with one another as freely as before and publishing data freely.

Specifically within the general area of intellectual property, innovators in both academia and industry strongly agreed that technology transfer in academic institutions acts as a major bottleneck to innovation today. Since the Bayh-Dole Act in 1980 was enacted, the technology transfer process at academic institutions has been criticized for a lack of sufficient processing capacity, poor return on investment, and inability to efficiently commercialize technology.^{100,101} Our results concur with prior reports calling for simplification of the academic-industry licensing process in order to facilitate commercialization of breakthrough technologies.¹⁰² The University of North Carolina at Chapel Hill (UNC) offers an interesting test case. UNC recently introduced a standard agreement (the Carolina Express License) available to any member of the university interested in commercializing inventions with a particular focus on the life sciences.¹⁰¹ In the subsequent years following its implementation, UNC went from forming an average of 3 new companies per year to 7.6 with 79% of these entities choosing to accept the standard agreement.¹⁰³ In agreement with prior single innovation studies,¹⁰⁴

none of our respondents from industry or academia suggested increasing patent terms as a method to promote transformative innovation.

The coronary artery stent has a complex litigious history including direct issues with the technology transfer process. Tracing this history to the early origins of the stent, presentations made at medical conferences by Palmaz about the design of their stent jeopardized EGP's ability to claim intellectual property rights outside the US.

Finally, we found that concerns and focus on patenting played a very limited role in the early stages of the coronary artery stent. Notably, in recent years, physician-innovators and academic medical centers have shown greater propensity towards obtaining patents.¹⁰⁵ Some reports have suggested that the proliferation of patents might hinder transformative innovation,¹⁰⁶ pointing to specific examples where this has been the case in the medical device market.¹⁰⁷ For example, innovators of the stent agreed with innovators from our multi-innovation cohort—they pointed to current-day patenting trends as harmful to the essential collaborative relationships they developed during their work on coronary artery stents, and blamed these trends on certain university technology transfer offices seeking greater control over patent rights or insisting on burdensome licensing agreements.¹⁰⁷ However, inattention to patents in the stent case also led to inequitable distribution of royalties, with some important early innovators and institutions being excluded from deserved royalties. Although Sigwart developed early designs of the stent, his lack of experience in the role of patents and commercialization allowed MedInvent to own all intellectual property rights—MedInvent was eventually acquired by Pfizer for an estimated \$80 million USD (\$159 million adjusted for inflation), while Sigwart did not enjoy any financial reward. Further research is required to determine whether increased attention to patents and revenue

generation on the part of physician-innovators and academic research centers in modern times does indeed contribute to reduced innovation, and if so, whether alternative mechanisms for identifying key contributors to transformative innovation and their proper compensation are necessary.

The patent literature is able to lend some corroboration to an inequitable distribution of windfall. The early literature does show that MedInvent was an assignee of some of the earliest patents in the stent space. Cook Inc. was noted to be the assignee from the intellectual work done by Roubin and Gianturco. Roubin noted that at the time, he did not have a formal royalty agreement with Cook Inc. Unfortunately, the patent literature is unable to show the existence of agreements between inventors and outside institutions with the assignee listed.

Beyond intellectual property issues, financing new, transformative research with limited preliminary data remains a challenge. As venture capital, public and industry sponsored investment in biomedical research continues to decline, there is considerable uncertainty on future streams of early-stage funding. Often times, such research goes against prevailing opinions of the time. Comments from our respondents suggest that the present-day funding climate limits the ability for researchers, particularly non-established individuals, to follow new areas of high-risk, high-reward work. Our results show that although industry was noted to have significant resources for drug and device development, very few members of our cohort describe significant industry funding of the underlying science and early validation work behind transformative innovations. This finding is supported by empirical work describing a continued decline in industry's investment in academic based research over the past 20 years.⁹¹ Expansion of more

risk-tolerant funding strategies from both public and private sources is necessary to fill this gap.

In the development of the stent, funding challenges represented a major barrier. Palmaz found significant difficulty winning grant funding for his work. Both Palmaz and Sigwart depended on discretionary department funds from their respective academic institutions to fund their early work—these innovators used their own funds to pay for necessary research tools. In some respects, the lack of funding pushed both innovators to reach out to small companies (MedInvent) or form new entities (EGP). In the case of Sigwart, this led to a highly unfavorable agreement. Given the perception of the innovators we spoke with that established companies and venture capitalists were—and remain—generally risk-averse regarding highest risk and most innovative medical technology, funding for such work outside of these channels is critical. This suggests that supporting research in new devices through entities such as the NIH and facilitating the efforts of innovators like Palmaz who seek to move their discoveries out of the academic setting are likely to have the greatest impact in generating breakthrough discoveries.

4.5 Regulation, reimbursement and other factors

Our results suggest that regulatory and reimbursement considerations were less likely to be factors in the development of transformative technologies. The majority of individuals who did discuss regulation agreed that the regulatory requirements for demonstrating safety and efficacy have increased today. One possible explanation for this higher burden of proof is that the transformative innovations in this cohort

represented a new paradigm that future drugs had to meet where before there were no therapeutic options.⁶

In the case of stents, interviewees were more critical of the FDA as a hurdle to innovation compared to interviewees involved in pharmaceutical and biotechnology innovations. The reasoning behind this most likely lies with the inherent differences in device and drug regulation. A more detailed description of the regulatory process of medical devices is outside of the scope of this thesis.¹⁰⁸ Briefly, approval for medical devices most often occur through the 510(k) approval pathway—this pathway requires considerably less testing and clinical validation before approval. It is offered to devices that are deemed low risk or can cite an existing technology previously approved by the FDA to match equivalency. Life sustaining devices such as stents or artificial heart valves generally qualify as Class III devices and undergo a regulatory approval process similar to pharmaceuticals. Specifically for devices, the FDA approval process has been criticized as overly burdensome in that it requires demonstration of safety and effectiveness, as compared to performance only regulatory systems like the EU.¹⁰⁹ A systematic review completed in part by this author compared the regulatory system of the United States and European Union. The results showed no evidence that reducing the burden of regulation improves clinical outcomes.²³ In fact, the FDA's increased burden of proof has safeguarded American patients from the diffusion of now recalled unsafe or ineffective devices, which were originally approved in Europe and used on European patients. High profile examples include the PIP breast implant, Watchman left atrial appendage ablator, the Watchman left atrial ablation device and PleuralSeal™ lung sealant.¹¹⁰ The regulatory environment does impact innovation and there remains a tradeoff between the FDA's responsibility to public health and the potential benefit of

early access to new medical technologies—our results from the stent suggest that this is a downstream consideration that may affect devices more so than pharmaceuticals or biotechnology innovations.

Concerns with eventual market size and reimbursement were a deterrent to innovation, particularly from industry actors. Our results suggest that early estimates of market size in the case of both imatinib and the coronary stent were significantly under-inflated. McKinsey and Company, a global consultancy, advised Johnson and Johnson to pass on the Palmaz and Schatz's stent product given the limited future market size. Coronary stents now represent a multi-billion dollar market. Imatinib was considered by Novartis executives to be a niche market product. In 2012, imatinib represented an estimated \$4.2 billion in sales, which translates to approximately 13% of Novartis's total yearly pharmaceutical revenues.¹¹¹ In the end, predicted market size for nascent innovations was unreliable in predicting the final commercial value.

5.0 Limitations of Work

There are both qualitative and quantitative limitations that exist with this investigation.

5.1 Qualitative Limitations

As a predominantly qualitative study, the sample size remains small and may introduce biases. Our cohort of 81 innovators derived from the total analysis group of 143 respondents exhibited similar percentage breakdown of academics and industry representatives. For each of the innovations described in this study, opinions from both industry and academic innovators were analyzed. Academics represented a higher proportion, which may skew the results in favor of the roles played by non-profit institutions. However, the selection of these innovators was based on a clinical

literature review as well as referrals from other innovators in order to minimize this potential bias.

5.2 Quantitative Limitations

In regards to our patent analysis, it is possible that the entirety of patents in the field were not captured. To reduce the likelihood that patents were missed, manual and automated inspections were performed. However, patents classified under different codes would not have been included in our cohort. Finally, our analysis of the early development of coronary artery stents used patent documents, so if other essential contributions were made and not patented in the US or if the patent application were rejected by USPTO examiners, we could have missed them. We remain confident in our results, in part because the USPTO ultimately grants patents from 85% of all applications¹¹² and because the two private companies that emerged as key to the field through our patent search were also the companies behind the first coronary artery stents approved by the FDA. Still, the role of intellectual contributions not captured by patents in the development of coronary artery stents and other transformative medical devices bears further study.

Although the stent represents a clear example of a transformative innovation, it represents a single case, which may not be generalizable. However, our results are consistent with case histories of other transformative medical devices¹¹³ such as coronary balloon catheters¹¹⁴ and bone densitometry scanners.¹¹⁵ More importantly, the insights gleaned from an in-depth study showed strong agreement with the exception of the role of FDA regulation from our multi-innovation cohort.

6.0 Conclusion and Policy Implications

Policymakers face a myriad of proposed strategies to spur medical innovation. Strategies include both upstream and downstream strategies to promote transformative innovation such as new funding mechanisms for research,¹¹⁶ creation of more public-private partnerships,⁵ repealing excise taxes for medical device companies,¹¹⁷ extending patent protection to the pharmaceutical industry¹¹⁸ and modification of the regulatory system.²¹ Our results derived from the opinions of prior successful innovators suggest that strategies that act on the local and institutional level are most likely to spur next generation breakthroughs.

Early idea generation most often happens at the physician-innovator level. This is exemplified in the case of stents. Policies aimed to promote innovation should focus on enabling expert individuals to act upon the opportunities they identify. These individuals should be provided the institutional support to collaborate with other individuals from separate institutions to develop their work. This development depends on a source of high-risk, high-reward funding. Given the perception of the innovators in our cohort felt that established companies and venture capitalists were—and remain—generally risk-averse regarding highest risk and most innovative medical technology, funding for such work outside of these channels is critical. Both government and industry must continue to support the critical basic science underlying future breakthroughs. Unfortunately, government funding for science has slowed in recent years, and faces substantial budget cuts in the future as well.¹¹⁹

Collaboration between institutions with separate expertise and resources supersede challenges related to intellectual property concerns. Policies on the institutional level should directly promote collaboration. This enables academia to potentially enjoy the resources and regulatory expertise of industry, while offering

industry the opportunity to engage with thought leaders and invest in breakthrough science.

Our cohort of stent innovators specifically pointed to current-day patenting trends as harmful to the essential collaborative relationships they developed during their work on coronary artery stents. Some reports have suggested that the proliferation of patents might be hindering transformative innovation,¹⁰⁶ and provided specific examples where this has been the case in the medical device market.¹⁰⁷ As physician-innovators and academic medical centers have shown greater propensity towards obtaining patents,⁹⁹ academic technology transfer offices must find improved methods to convert those patents into licenses for commercial development. The significant proportion of our innovators pointed to the academic technology transfer process as a major bottleneck to transformative innovation. Even delays measured in months can equate to significant revenue lost for a commercial entity given the finite terms imposed on patents. Standardized agreements organized by category (e.g. biotechnology product, small molecule or significant risk medical device) and with preset royalty payments, licensing fees and milestones for biotechnology innovations would potentially eliminate costly and lengthy one-off negotiations for promising, but still nascent technologies.

Although, federal policymaking on regulation and reimbursement do influence innovation, our work suggests that these changes would be less impactful. There is no evidence from our results that taxation reductions for the medical device and pharmaceutical industry and patent extension will have a direct effect on transformative innovation. These policies would more likely benefit only established devices and businesses.

7.0 Suggestions for Future Work

There are numerous directions for future work. The first step is to extend the in-depth analysis of stents to the other transformative innovations in this cohort. Specifically, a study on the origins of all of the innovations in our cohort would allow the determination of descriptive statistics on the relative contributions of industry, academia, government and individuals. In addition, in-depth patent analyses of more cases of transformative medical innovation enable similar comparisons. This would also allow validation of this methodology as a robust and repeatable method of understanding and studying the innovation process. Using the patent literature, a detailed study of co-inventors could be undertaken to uncover interconnections between individuals and institutions.

In this study, we grouped transformative drugs and medical devices together. There are inherent differences to these two classes in regards to development, product lifecycle and regulation—these issues extend beyond the scope of this thesis. However, a comparison between results between drugs and devices may identify specific recommendations for the pharmaceutical and medical device industries.

Although our cohort represents clinically relevant medical advances, there have been more recent innovations in the past 10-15 years that represent breakthroughs in their own right. Given the rapidly evolving environment of innovation, an updated analysis of a more recent cohort may provide valuable insights as well. Examples of more recent transformative innovation can be identified through the FDA's new special designation categories, which recognize new entities targeting major unmet clinical needs.⁴¹

Another potential direction is a failure analysis. This study focused on transformative successes. However, many innovators also described instances of failed

innovations. Nonetheless, the opinions and thoughts of innovators who did not ultimately succeed in developing medical technologies may provide additional insight.

8.0 Summary of Work

Medical innovation is critical to healthcare systems by providing solutions to unmet clinical needs. Given the recent concern from multiple healthcare stakeholders that the pipeline of medical innovation is slowing, this thesis attempts to provide insights on how to spur breakthrough medical innovation in present day. First, recent examples of transformative medical innovations were identified. Second, key innovators responsible for these innovations were selected, contacted and interviewed using a semi-structured script. Third, an exemplary case (coronary artery stent) was selected for an in-depth analysis, which included a detailed recounting of the development of the stent and an exhaustive analysis of the patent literature surrounding the stent. Fourth, a qualitative and quantitative analysis was undertaken to specifically glean insights for present day innovation. This thesis derives its findings and recommendations from one of the largest and most comprehensive collections of interview transcripts from biomedical innovators responsible for developing the most important devices, drugs and diagnostics used in medicine today to identify themes and improve generalizability. The major findings include the following policy suggestions:

- Support the physician-innovator, more often operating in an academic center and with direct exposure to the clinical need, to pursue high risk, high reward research

- Develop a supportive institutional environment that fosters collaboration with other individuals in outside institutions in order to share resources, expertise and research material
- Continue funding basic science as the best preliminary work improves the chances that transformative innovation occurs
- Reform the academic intellectual property transfer process to enable breakthrough science to become breakthrough commercial entities
- Increasing reimbursement or patent terms and reducing regulatory burden are downstream considerations with policies aimed at these factors less likely to spur transformative medical innovation

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10.0 List of Figures and Tables

Table 1: List of transformative drugs and devices

Technology	Application
<i>Medical devices</i>	
Bare metal coronary stents	Post-angioplasty restenosis
Bone mineral density scanner	Diagnosis of osteoporosis
<i>Small-molecules</i>	
Anti-retroviral drugs	Human immunodeficiency virus
Bisphosphonates	Osteoporosis, other diseases of bone loss
Paclitaxel (Taxol)	Ovarian and breast cancer
Propofol (Diprivan)	Anesthesia
HMG-CoA reductase inhibitors ("statins")	Hyperlipidemia
Imatinib (Gleevec)	Chronic myelogenous leukemia
<i>Biologic drugs</i>	
Rituximab (Rituxan)	Non-Hodgkin's lymphoma
TNF-alpha inhibitors	Autoimmune disorders
Trastuzumab (Herceptin)	<i>HER2</i> -positive breast cancer
VEGF inhibitors	Various solid tumors, retinal neovascularization and macular degeneration

Figure 1: Institutional roles of individuals in the total cohort and the cohort commenting specifically on lessons for innovation

Total Cohort (n=143)

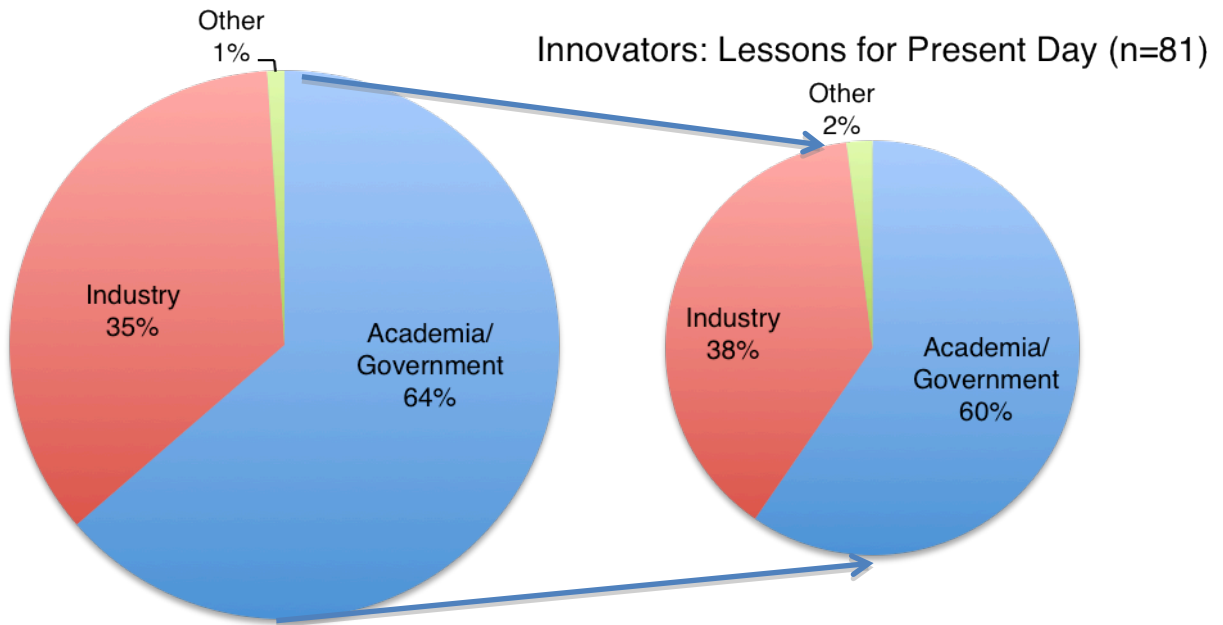


Table 2: List of stent interviewees†

Name	Source	Background	Summary of role
Brian Bates	Referral	Business development at Cook Medical	Collaborator with Gianturco in stent engineering
Andrew Cragg, M.D.	Patent search	Medical trainee at the University of Minnesota	Developed early nitinol stent prototype
Thomas J. Fogarty, M.D.	Patent search	Cardiac surgeon at the University of Oregon	Developer of a catheter system and collaborator of Dotter
Richard A. Hillstead	Patent search	Engineer at Cordis	Early stent developer at Cordis
Farhad Khosravi	Patent search	Engineer at Advanced Cardiovascular Systems	Developed Multi-Link stent with Sigwart at ACS
Julio C. Palmaz, M.D.*	Patent search and medical literature	Interventional radiologist at University of Texas-San Antonio	Lead inventor and developer of the Palmaz-Schatz stent
Leonard Pinchuk	Patent search	Entrepreneur	Licensed stent-related intellectual property to Cordis
Stewart Reuter, M.D.	Medical literature	Chief of Radiology at University of Texas-San Antonio	Mentor of Palmaz; provided research funding, lab space during early stent research
Phillip Romano	Referral	Restauranteur	Financial investor, partner with Palmaz, Schatz
Gary Roubin, M.D.*	FDA records and medical literature	Cardiologist at Emory University	Developed and validated the Gianturco-Roubin stent
Richard Schatz, M.D.*	Patent search and medical literature	Cardiologist in San Antonio	Co-inventor of the Palmaz-Schatz stent
Ulrich Sigwart, M.D.*	Medical literature	Cardiologist at the University of Lausanne (Switzerland)	Developed the Wallstent and the Multi-Link stent
Edward L. Sinofsky, Ph.D.	Patent search	Engineer at Bard	Early stent developer at Bard
Richard Stack, M.D.*	Patent search	Cardiologist at Duke University	Early stent developer at Duke

	and medical literature		
Ernst-Peter Strecker, M.D.*	Patent search	Interventional radiologist at the Freiburg University Clinics (Germany)	Developed the Strecker stent and later contributor on stent development with Boston Scientific
Sidney Wallace, M.D.	Medical literature	Interventional radiologist at MD Anderson Cancer Center	Collaborator with Gianturco in stent design and application

† In alphabetical order. The identification of an interview source on this list does not imply endorsement of the article or its findings.

* Pre-determined “high priority” interview target

Table 3: Search strategy used to identify coronary artery stent patents

International classification	Category description
A61F2/82	Devices providing patency to, or preventing collapsing of, tubular structures of the body
A61F2/84	Instruments specially adapted for their placement or removal
A61F2/86	Stents formed from wire-like elements
A61F2/88	Formed as helical or spiral coils (nets formed from intersecting coils)
A61F2/90	The wire-like elements forming a net structure
A61F2/92	Stents in the form a rolled-up sheet expanding after insertion into the vessel
A61F2/94	Stents retaining their form after locating in the predetermined place

Table 4: Percentage of Respondents Discussing Specific Categories

Major Categories	n (%)	Sub-Categories	n (%)
Role of Institutions	36 (44)	Industry	24 (29)
		Academia/government	22 (27)
		Small Companies	14 (17)
Role of Individuals	30 (37)	Clinical Scientists	16 (20)
		Internal Champions	11 (14)
		Basic Scientists	4 (5)
		Translational Scientists	2 (2)
Intellectual Property	25 (31)	Focus on Patenting	16 (20)
		Academic Technology Transfer	14 (17)
		Material Transfer Agreements	3 (4)
		Litigation Concerns	2(2)
Collaboration	21 (26)	Conflict of Interest	9 (11)
		Academia/Industry Relationships	8 (10)
		Change in Openness	5 (6)
		Cultural Differences	2 (2)
		Greed	1 (1)
Strong Underlying Science	21 (26)		
Funding Limitations	12 (15)		
FDA	7 (9)		
Reimbursement	6 (7)		
Luck	3 (4)		
Technology Improvements	2 (2)		

Table 5: Representative Quotations in Key Subject Areas

Categories	Selected Quotes
Role of Individuals	<p data-bbox="630 254 1365 294">“I think that individuals really still drive a lot of this.”</p> <p data-bbox="630 327 1365 401">“Every drug that has ever come to market has had an internal champion.”</p> <p data-bbox="630 434 1365 621">“You have to have the courage to say yes to a certain idea, a certain therapeutic target and say ‘we’ll go for it’ instead of trying to tackle 10 or 15 in the hope that one of those will be successful in the end.”</p>
Role of Institutions	<p data-bbox="630 621 1365 737">“I think that the major change has been a switch from looking for cures to looking for marginal advantage.”</p> <p data-bbox="630 770 1365 877">“So I wish some of these “me-too” drugs were not occupying the attention of the drug companies when they could be looking for new drugs.”</p> <p data-bbox="630 911 1365 984">“Often pharma companies are overwhelmed with the opportunities they might work on.”</p> <p data-bbox="630 1018 1365 1136">“More academic centers are working on things that have translational and practical impact. It’s quite hard. It’s quite expensive.”</p>
Intellectual Property	<p data-bbox="630 1136 1365 1283">“When you are talking about research tools like patenting and enzyme, which can be used as a target by companies, the patenting of research tools has hindered progress.</p> <p data-bbox="630 1283 1365 1390">I don’t think it would be a barrier to have interposed patents and licenses and some royalty flow to the university from this success.”</p> <p data-bbox="630 1423 1365 1570">“We tried going to universities and universities come to us but they are so damn hard to deal with I mean it’s ridiculous. It’s terrible. We don’t bother with them.”</p> <p data-bbox="630 1604 1365 1711">“You can’t work in a university these days without them wanting to patent you opening the door for them.”</p> <p data-bbox="630 1745 1365 1829">“There’s a lot of rubbish that gets patented out of universities. They all have their tech transfer office.”</p>
Collaboration	<p data-bbox="630 1829 1365 1900">“Biggest hurdle right now is how do you get ‘em out of the lab and into clinical trials and that’s the</p>

	<p>hardest point.”</p> <p>“They’re just getting up to it but they’re doing it the wrong way, they’re throwing the baby out with the bath water.”</p> <p>“It has to do with the fact that even with the cultural differences between industry and academia we have to work together. I think it’s actually wonderful to work together.”</p> <p>We’ve got to figure out ways for companies and academics to work together quickly, efficiently and effectively. That’s what we did. what has happened in the intervening decade or 15-odd years is that it’s become much more difficult to form these relationships”.</p> <p>“Everyone’s a lot cagier than they used to be.”</p>
<p>Strong Underlying Science</p>	<p>“Follow the science, number one.”</p> <p>“I think just that good science prevails.”</p> <p>“The main lesson is that drug development is not possible without basic research.”</p> <p>“The thing that comes highest up on the food chain is the thing where the best preliminary work has been done.”</p>
<p>Funding Challenges</p>	<p>“It’s very hard to support research just on government funds these days because the government funding is so uneven and unpredictable.”</p> <p>“Investment what you can see is that the pharma industry hasn’t even just been flat since the 50s. It’s actually been declining in terms of efficiency and productivity in terms of what goes on the market.”</p> <p>“Venture capitalists don’t want to invest in new ideas because they may never get paid for it.”</p>
<p>FDA</p>	<p>“The FDA has become much, much more conservative and demands much, much higher levels of safety and efficacy.”</p> <p>“The FDA is a big issue and big problem. There is probably so much technology and so many good things that could come out and help people that</p>

	<p>because one examiner doesn't think it's going to do what it's supposed to do or set up the testing properly and whatever, it gets railroaded, it gets smashed."</p> <p>"If you think our budget is messed up take a close look at our FDA and how they approve products. I mean we don't really prove things the way we should. There are too many little ways to get around."</p>
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Table 6. Stent Representative Quotations in Key Subject Areas

Thematic area	Illustrative remark
Motivation	<p>“My involvement was driven purely and simply by a clinical imperative at the time.” [<i>Physician-innovator</i>]</p> <p>“It was clear ... that we had a huge shortcoming with [Gruentzig’s] method and that was his acute closure that led to tremendous amount of myocardial infarction emergency surgery.” [<i>Physician-innovator</i>]</p> <p>“I felt very strongly being an operator. I wasn’t just an inventor. I was an operator.” [<i>Physician-innovator</i>]</p>
Obstacles to progress	<p>“We had to be very hard headed to accept all that rejection because it was systematic and relentless.” [<i>Physician-innovator</i>]</p>
Contributors to early success	<p>“We spent a lot more time on the design and a lot more time proving that it worked. All the others were just kind of wham-bam. ‘Let’s get it out there as fast as we can’ but without any data.” [<i>Physician-innovator</i>]</p> <p>“We are more aggressive with filing patents today than we were back then, but in those days, we didn’t file any patents. We just kept our nose to the grindstone and kept things moving.” [<i>Company-based innovator</i>]</p>
Risk and investment	<p>“When the thing is disruptive and totally outlandish, the companies stay away from it.” [<i>Physician-innovator</i>]</p> <p>“So my first reaction when I was told what it was and what I should be thinking about designing was well that’s a stupid idea. We’ve got diseased arteries that are full of stuff already, why would we want to put in a piece of a metal that’s going to be lifetime liability for us?” [<i>Company-based innovator</i>]</p>
Collaboration	<p>“So many, many months and changes and design went by working with the engineers from [company]” [<i>Physician-innovator</i>]</p> <p>“From an engineering product development perspective, they are extraordinary.” [<i>Physician-innovator</i>]</p> <p>“When [company] took over we just basically showed the engineers what we wanted and that was it.” [<i>Physician-innovator</i>]</p> <p>“I mean he had a lot of clinical issues that he saw that needed to be solved and he needed some help in doing that, and we helped him in any way we could. It was just</p>

	a nice partnership.” [<i>Company-based innovator</i>]
Role of intellectual property	<p>“The impetus was to publish and it seems quaint now and maybe stupid, but we didn’t give much thought to patenting.” [<i>Physician-innovator</i>]</p> <p>“The patents of course are critical because no company wants to invest unless they have some IP.” [<i>Company-based innovator</i>]</p> <p>“In those days, we were for a couple of years the number one patenting company in the nation, if not the world.” [<i>Company-based innovator</i>]</p>

Table 7. Timeline of major pre-clinical, clinical, and regulatory events in the early development of coronary artery stents.

Date	Event	Event type
1976	Earliest description of balloon angioplasty for use in the coronary arteries by Gruentzig ¹²⁰	Pre-clinical
1978	Gruentzig presents his angioplasty technique at the 1978 Society of Interventional Radiology Meeting in New Orleans, and concern about restenosis. Palmaz is in attendance ^{121, 122}	Clinical
1985	Gruentzig initiates a collaboration with Gianturco to develop a stent to reduce restenosis ¹²³	Pre-clinical
1985	Palmaz and Schatz describe the use of balloon-mounted slotted-tube stent in the peripheral arteries ¹²⁴	Clinical
Mar 1987	First experimental coronary stent implantation in human patients by Sigwart using WallStent design ⁶³	Pre-clinical
May 1987	Strecker describes a new flexible intravascular stent at the Cardiovascular and Interventional Radiological Society of Europe and the Society of Cardiovascular and Interventional Radiology ¹²⁵	Pre-clinical
Feb 1991	FDA approval of Palmaz-Schatz balloon-expandable stent (Expandable Grafts Partnership, Johnson & Johnson) for the biliary system	Regulatory
1992	Studies report efficacy and utility of Gianturco-Roubin (Cook Inc.) stent to prevent emergency bypass surgery after angioplasty ⁶²	Clinical
May 1993	FDA approval of Gianturco-Roubin stent for coronary procedures, specifically emergency management of coronary closures during angiography	Regulatory
1994	BENESTENT study demonstrating efficacy of Palmaz-Schatz stent in patients with new coronary lesions in the main coronary arteries (n=520) published ¹²⁶	Clinical
1994	STRESS study demonstrating efficacy of Palmaz-Schatz stent (n=410) published ¹²⁷	Clinical
Aug 1994	FDA approval of Palmaz-Schatz stent for elective coronary artery stenting ⁴⁹	Regulatory
1997	Stent use found in 69% of angioplasty procedures ⁴⁹ Error! Bookmark not defined.	Clinical
1998	Restenosis Stent Study Group reported a major benefit of stenting for patients who experienced restenosis of a coronary vessel after balloon angioplasty	Clinical

Table 8. Counts of coronary artery stent patents by assignee type (1984-1994)

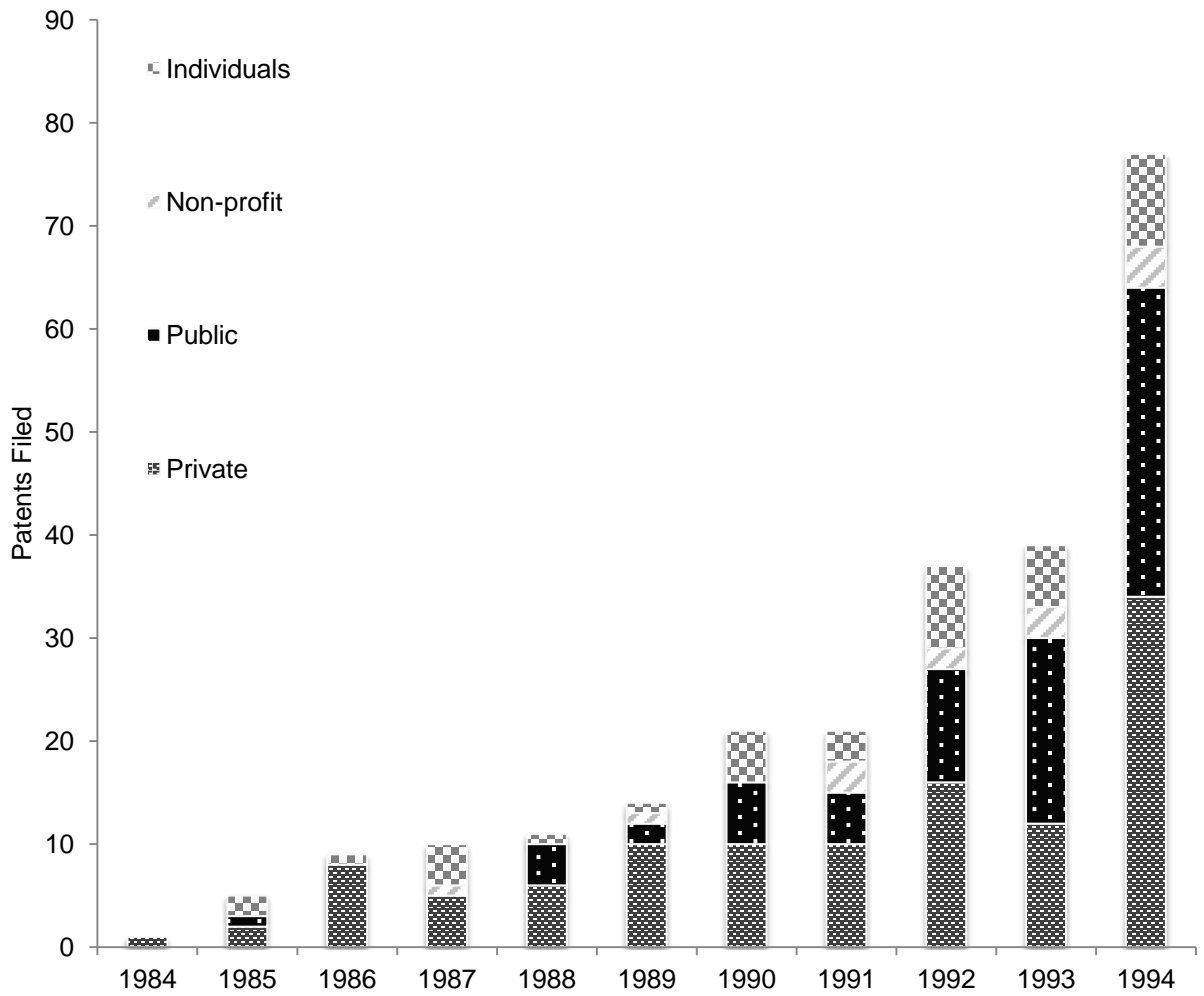
	Unique Assignees	Patents Filed (n, %)	Patents per Assignee	Average Citation Count	Average citation count standard deviation
Non-profit entities	10	14 (5.7)	1.4	235	100
Private companies	43	110 (44.9)	2.6	279	273
Public companies	18	77 (31.4)	4.3	241	197
Individual inventors	36	44 (18.0)	1.2	256	150
Total	107	245	2.3		

Table 9. Top ten cited patents related to coronary artery stents (1984-1994)

Patent	Assignee	Assignee type	Filing Date	Title	Citation Count
US4733665 A	Expandable Grafts Partnership	Private company	11/7/1985	Expandable intraluminal vascular graft has tube formed of thin rectangular section bars which expand to fit lumen	1,857
US4886062 A	Medtronic Inc.	Public company	10/19/1987	Intra-vascular radially extendable stent comprises zigzag wire wound into helix and made of low memory metal	1,039
US4800882 A	Cook Incorporat ed	Private company	3/13/1987	Endo-vascular stent for delivery system comprises wire formed into serpentine shape with alternating loops and bent into cylinder	1,017
US4776337 A	Expandable Grafts Partnership	Private company	6/26/1986	Expandable intraluminal vascular graft using angioplasty balloon associated with catheter to dilate and expand lumen of blood vessel	986
US4580568 A	Cook Incorporat ed	Private company	11/13/1984	Percutaneous endo-vascular stent has zigzag stainless steel wire which is compressed for insertion	966
US4739762 A	Expandable Grafts Partnership	Private company	12/12/1985	Expandable intraluminal graft has thin walled tube with slots parallel to longitudinal axis	919
US5064435 A	Schneider Inc.	Public company	6/28/1990	Self-expanding prosthesis having stable axial length has slidable connected stent	848

				segments of open weave constructions which are elastically deformable to reduce radius dia.	
US4994071 A	Cordis Corporation	Private company	5/22/1989	Bifurcating stent device has balloon-deflatable for withdrawal from vessel and used to expand stent	838
US4856516 A	Cordis Corporation	Private company	1/9/1989	Endo-vascular stent structure has cylindrical form expandable by applying radially outward force	736
US5102417 A	Expandable Grafts Partnership	Private company	3/28/1988	Implanting expandable vascular graft involves number of expandable and deformable grafts expanded within blood vessel	688

Figure 2. Yearly counts of coronary artery stent patents, by assignee type (1984-1994)

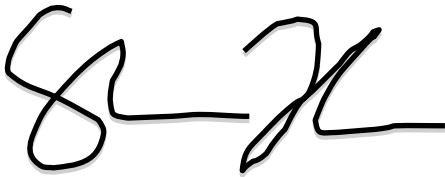


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