Digital Innovation in a Regulated Industry: Evidence from Software-Driven Medical Devices

(Preliminary: please do not circulate)

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Abstract

Does technological opportunity enable the rise of new entrants or reinforce the position of incumbents? Research on this classic topic rarely considers the unique features of regulated industries. We offer a novel approach to this question in the context of regulated medical technology, where the introduction of software is of growing importance and has created fresh opportunities for new product development. Pioneering a new application of supervised document classification, we consider over 35,000 new medical devices that came to market in the United States from 2002-2016 in order to identify predictors of digital innovation in this industry. We consider the relative importance of key factors such as geographic and within-firm capabilities and the role of financial resources. We find that location in a region of concentrated expertise and prior firm commercialization experience reinforce one another in predicting digital innovation. While venture capital funding appears to play a role in supporting innovative entrants, closer analysis suggests that this funding selects on other variables that predict digital innovation; in this regulated industry, financial resources do not substitute for existing capabilities. We conclude that incumbent firms have an advantage in innovating in this setting.

Keywords: Innovation; Digitization; Medical Technology; Software

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1 Introduction

In recent years, major industries ranging from manufacturing and inventory management to music to health care have undergone a "digital transformation," in which key aspects of both day-to-day business and new frontiers of product development have migrated to a primarily digital (i.e. software-driven) context. In the health care setting, medical technologies – the devices and equipment used in treating and caring for patients – have become increasingly digitized, as software and networking capabilities have become integrated into a growing number and share of new products. Today, medical devices interface with software for tasks ranging from simple blood pressure monitoring to the processing and analysis of digital radiology images. Digital medical technology is now commonplace and its use is inescapable for health care professionals: a recent report found that U.S. hospitals use an average of 10 to 15 "connected" (networked) digital devices per bed (Newman, 2017).

Like other industries undergoing technological change, this scenario raises questions about how new opportunities for digital product development impact both new entrants and incumbents. Unlike many other settings, however, the medical device industry is strictly regulated: the U.S. Food and Drug Administration (FDA) is the sole regulatory authority with the power to grant marketing approval for medical devices in the United States. The complex regulatory approval process and its associated costs, combined with other resource-intensive features of medical device development, suggest that smaller and less experienced firms are likely to face higher costs of new product commercialization than seasoned incumbents. We explore this phenomenon in a novel dataset and find new evidence to suggest that the existence of entry regulation in health care favors experienced and advantageously located firms and is likely to perpetuate their commercial leadership.

Health care spending now comprises nearly 18% of the U.S. economy (CMS, 2016), representing a large potential market and a variety of opportunities for innovators to grow digital health businesses. Digital health is broadly defined to include companies and products at the intersection of healthcare and technology.[1] The digital health space includes

[1] https://rockhealth.com/what-digital-health-is-and-isnt

health care IT and information systems, as well as a host of companies that build and sell technologies like wireless sensors, software-enabled diagnostic and imaging devices, and artificial intelligence software programs with health care applications. In recent years, there has been dramatic growth in funding for digital health (Tecco and Zweig, 2017) with notable private and public initiatives emerging to fund research and investment in the space.[2]

This study is set in the context of the increasingly software-driven *regulated* medical device industry, an important subset of the digital health ecosystem. Surprisingly, the growth of software in medical devices has not yet been characterized across products or firms, nor has its implications for innovation in this sector been rigorously studied. We therefore begin by documenting a set of trends relating to the growth of software in regulated medical technology. We then explore the factors that predict which types of firms are more likely to pursue software-driven innovations, and under what circumstances.

Previous studies have highlighted the importance of software and digitization in determining how firms innovate (Arora, Branstetter, and Drev, 2013; Branstetter, Drev, and Kwon, 2015) and perform (Brynjolfsson and McElheran, 2016a; Brynjolfsson and McElheran, 2016b). Our study builds in many ways on the literature linking software and networking capabilities to innovative activity; however, unlike previous studies, our primary measure of innovation goes beyond counts of (pre-market) patenting activity to assess the precise and complete set of new products ultimately brought to market. Because new product commercialization in the medical device industry typically occurs well after patenting, this study characterizes software-driven innovation at the very end of the innovation pipeline, focusing on the final phase of new product development in the R&D process. Furthermore, an important distinction from much of the prior literature is that we empirically model digital innovation as a *dependent* variable (whereas others have typically treated the use of software as an independent variable).

[2]For example, Rock Health describes itself as "the first venture fund dedicated to digital health" (https://rockhealth.com/about), and the Massachusetts Digital Healthcare Initiative was launched by Governor Charlie Baker in January, 2016 as "a comprehensive public-private partnership that will advise the administration on the future of the Commonwealth's digital healthcare industry." (http://www.mass.gov/governor/press-office/press-releases/fy2017/governor-establishes-mass-digital-healthcare-council.html)

The first contribution of this paper is to quantify and describe the growth of software in regulated medical devices in the early 21st century. Using detailed data on all new regulated device approvals over the years 2002-2016, we describe the evolution of digital products across medical specialty areas, types of innovator firms, and over time. The second contribution of this paper is to shed light on the determinants of digital innovation in this regulated setting. We find that existing capabilities – both local and within-firm expertise – are by far the strongest predictors of digital innovation. Further, we find that money alone does not compensate for the advantages that are associated with geography and experience; VC funding is associated with digital innovation, but only in the presence of existing capabilities. Interestingly, geographic and within-firm capabilities predict digital innovation separately – that is, there is some amount of firm experience that can compensate for being located in a less advantageous geography (and vice versa). We conclude that this regulated industry strongly favors digital innovation by firms coming from a position of incumbent geographic or experiential advantage.

We proceed as follows: Section 2 provides background on FDA medical device regulation as it relates to the process of bringing new products to market along with a review of related literature. Section 3 presents a conceptual framework for the integration of software into new products given entry regulation and lays out testable hypotheses. Section 4 describes the data employed in the empirical analyses. Section 5 presents estimation results and Section 6 concludes.

2 Background

The FDA is the sole regulatory authority with the power to grant marketing approval for medical devices in the United States. An agency within the U.S. Department of Health and Human Services, the FDA regulates over two trillion dollars' worth of products annually, including all medical technologies (Babiarz and Pisano, 2008). The FDA is organized into centers, each of which focuses on one type of product. Medical devices, including radiation-emitting products such as X-ray and ultrasound machines, are regulated by the Center

for Devices and Radiological Health (CDRH).[3] Within the CDRH, the Office of Device Evaluation reviews new products.[4]

Devices are wide-ranging in their complexity and the risk that they pose to patients. They include products ranging from low-risk devices such as stethoscopes and tongue depressors, to moderate-risk products, such as hearing aids and blood pressure monitors, to complex, high-risk products such as cardiac pacemakers and replacement heart valves. While devices of the lowest risk are subject only to so-called "general controls" of labeling and compliance with the FDA's good manufacturing practices,[5] moderate-risk and high-risk devices must submit applications to the FDA for regulatory clearance or regulatory approval, respectively.[6] The administrative data from these regulatory processes along with each new product's formal description are made publicly available as of the time a device completes regulatory review. These documents constitute the main source of new product data used in the analyses that follow.

As described in detail below, a growing number and share of devices now contain software. Yet despite recognition of the increasingly digital nature of medical devices,[7] the FDA does not formally track the use of software in medical devices in its product-level regulatory data. As a result, the prevalence and growth trajectory of digital products and their prevalence across medical specialty areas have not yet been broadly described. The first portion of this paper is therefore dedicated to using information embedded in the text of medical device summaries to quantify digital medical devices and their growth over time. Using text mining, supervised document classification, and an off-the-shelf natural language processing tool for medical text, we analyze 15 years of medical device product summaries. We then turn to a set of empirical exercises that model the drivers of digital innovation

[3]Other centers are responsible for other product categories. For example, drugs are regulated by the Center for Drug Evaluation and Research (CDER) and biologics are regulated by the Center for Biologics Evaluation and Research (CBER).

[4]Since 1976, the regulation of new medical devices has been governed by the Medical Device Amendments (MDA) to the Federal Food, Drug, and Cosmetic Act of 1938.

[5]https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/315.cfm

[6]https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/

[7]See, for example, the FDA's growing list of guidance documents related to software in medical devices (FDA, 1999; FDA, 2005a; FDA, 2014; FDA, 2016).

across firms in this industry.

2.1 Moderate-Risk Devices and the 510(k) Process

Moderate-risk devices are approved through a process called "premarket notification," which is often referred to as the "510(k) process" – a reference to the section of the law that established this regulatory pathway. The 510(k) is defined as:

> *"a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device...that is not subject to [the more extensive process of Premarket Approval,] PMA [,which is required for devices of the highest risk]."*

One important component of the 510(k) application is the "510(k) Summary," a text document describing the device and published at the time of clearance. The summary includes "a description of the device such as might be found in the labeling or promotional material for the device" along with "an explanation of how the device functions [and] the scientific concepts that form the basis for the device." The summary also describes "significant physical and performance characteristics of the device, such as device design, material used, and physical properties," making it a clear source of information on all of the product's key technological characteristics.[8] It is these summaries (and their equivalents from high-risk devices) that are used to construct the text database, described below. An example 510(k) Summary can be seen in Exhibit 1.

2.2 High Risk Devices and the PMA Process

High-risk (Class III) devices are regulated through a process called Premarket Approval (PMA), which typically requires data from clinical trials in order to establish a device's safety and effectiveness with reasonable certainty.[9] Evidence from trials is presented to the

[8] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=807

[9] See: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/

FDA as one part of the PMA package (Kramer et. al., 2012).[10] Appendix B contains additional detail on the PMA process.

Like the 510(k) process, the PMA process includes a product-specific summary document, which is made publicly available at the time the device is approved.[11] Much like 510(k) summaries, PMA summary documents contain information on indications for use and a detailed device description – "how the device functions, the basic scientific concepts that form the basis for the device, and the significant physical and performance characteristics of the device" – among other components.[12] An example PMA summary can be seen in Exhibit 2.

2.3 Software in Medical Devices

The integration of software into medical devices is a relatively recent phenomenon. The first traces of regulatory interest in software in medical devices go back to 1999, when the FDA first released its first guidance document, outlining expectations and standards for software embedded in new medical technologies (FDA, 1999). The FDA's guidance has been augmented and updated several times since (e.g. FDA, 2005a; 2005b; 2014; 2016) and today, medical devices that not only incorporate software, but also functionally *rely* on it, are commonplace. From imaging devices for radiology, to software-enabled insulin pumps, to implantable heart failure monitors capable of wireless transmission, thousands of patients and their physicians have come to depend on software-enabled medical devices.

2.4 Software in the Health Care Industry

While we are not aware of any studies of the digitization of medical devices, a small but growing body of literature in management and economics explores topics at the intersection of digitization and health care. Most prominently, a number of papers have analyzed the

[10] Detail of the PMA review process can be found at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm047991.htm

[11] These summaries are used along with their moderate-risk device equivalents in the analysis below.

[12] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=814.20

use and adoption of electronic medical records (EMRs), one of the primary ways in which software has impacted health care delivery in the past decade (e.g. Dranove et. al., 2014; Agha, 2014; Adler-Milstein et. al., 2014; Lee et. al. 2013). The studies have documented the ongoing adoption of EMRs along with heterogeneous (and typically limited) impacts on patient outcomes.

This study is also related to a small literature on the use and adoption of software and digital data elsewhere in health care delivery. For example, Athey and Stern (2002) find that basic digitalization of emergency services (911) increased the short term survival rate of patients in cardiac distress. Other researchers have considered subtler regulatory factors such as data privacy laws (Miller and Tucker, 2016) in order to understand how new technologies are adopted and used by patients. Yet beyond these studies, management and economics research at the intersection of digitization and health care is scant and the impacts of digitization on health care innovation have not been rigorously examined.

2.5 Determinants of Innovation

We consider the role of firm capabilities that have been known to impact innovative activity in other sectors and contexts. These factors include the role of geographic clusters as well as firm experience – both inside and outside of a specific R&D area – as well as firm financial resources.

A number of studies have highlighted the role of geography in innovative activity. Forman, Goldfarb, and Greenstein (2016) study the competing effects of colocation and coagglomeration of invention, showing evidence of geographic clustering of patents within the San Francisco Bay Area in information and communication technologies as well as more generally. Earlier research from Jaffe, Trajtenberg, and Henderson (1993) suggests similar dynamics – namely, that local knowledge spillovers lead to geographic clustering of patent citations. In the related health care context of biotechnology, Mariani (2004) highlights the importance of the role of knowledge spillovers and agglomeration economies in research-intensive sectors.

Firm experience and incumbency have also been shown to drive innovative activity in contexts ranging from biotech (Henderson and Cockburn, 1996) and pharmaceuticals (Scott Morton, 1999; Nerkar and Roberts, 2004) to computer and IT hardware (King and Tucci, 2002; Bayus and Agarwal, 2007). In various settings and competitive environments, research has shown that a firm's experience in an industry is important for predicting when and how it enters new markets. Explanations for the enduring role of incumbent firms are numerous, but include organizational experience in specific types of markets (Scott Morton, 1999), productivity spillovers in R&D activities (Henderson and Cockburn, 1996), complementarities among technological and product-market experience (Bayus and Agarwal, 2007), and experience with the process of new market entry *itself* (King and Tucci, 2002). Using detailed commercialization histories, we are able to revisit this set of questions in the medical device setting.

Finally, firm financial resources are thought to explain firms' innovation activities. Cohen (2010) reviews the literature on this topic and concludes that in many (but not all) settings, cash flow is associated with higher levels of R&D spending, noting that at least for smaller firms, the causality is thought to run from the former to the latter (Hao and Jaffe, 1993). Thus, we consider firms' access to capital (in particular, public markets and VC funding) as specific financial resources that may drive digital innovation.

3 Conceptual Framework

We outline a simple conceptual framework for considering how firms make decisions to pursue new product development projects, given heterogeneous past experiences and resources. In particular, we emphasize that the *existence of entry regulation* and the costs and institutional know-how required for regulatory approval generate differences in the relative costs of commercialization activities across different types of firms.

A typical feature of digital products is low (or zero) marginal cost of provision to additional customers (Goldfarb, et al., 2015). We build on this intuition, noting that in the case of a multi-purpose technology such as software (e.g. for digital data transmission, imag-

ing, or data display), the marginal cost of applying the technology to subsequent products within a firm's portfolio will fall as the firm acquires experience. These differences in costs may be mitigated by the availability of financial resources, which are known to shape R&D investments at the firm level (Kortum and Lerner, 2000; Cohen, (2010; Hall and Lerner, 2010; and many others).

3.1 Framework for firm decision-making

A simple framework for considering firm investments can be seen in the following stylized 2-period model: consider a firm, f, facing a decision in period 1 ($t = 1$) regarding commercialization of a product in class, c. Commercializing each product involves costs, C_{fct}, which include manufacturing/production costs, M_{fct}, and investment costs, I_{fct} – e.g. for product design and R&D. That is, $C_{fct} = M_{fct} + I_{fct}$.

Commercialization of a product results in expected revenues in period 2, r_{fct+1}. Firms will invest in commercializing new products when $C_{fct} < r_{fct+1}$, that is, whenever net expected profits from a given product are positive:[13] $r_{fct} - C_{fct} = \pi_{fct} > 0$.

Investment costs required to commercialize a new product, I_{fct}, in turn, will be shaped by both the firm's financing costs, K_{ft}, and the firm's existing capabilities, E_{fct}, in period 1, such that $I_{fct} = f(K_{ft}, E_{fct})$, where the first derivative of I_{fct} with respect to both K_{ft} and E_{fct} is negative. Therefore, we can re-write total cost as a function of manufacturing costs, financing costs, and capabilities in period 1:$C_{fct} = f(M_{fct}, K_{ft}, E_{fct})$.

3.2 Hypotheses

In plain terms, our conceptual framework predicts that the costs of commercializing a new product will vary with firm capabilities as well as financial inputs to R&D activities. Then, C_{fct} will be decreasing in E_{fct} and increasing in K_{ft}. As a direct corollary, expected revenues

[13] A more detailed model could also account for the relevant discount rate. This stylized 2-period model does not incorporate the fact that it may take more than one period for an investment to realize positive profits, which could also be included in a more detailed model, however we note that since the average product lifecycle is just 1.5-2 years (Wizemann, 2010), it is realistic to assume that products should achieve profitability on a very short time horizon in order to justify commercialization.

in period 2 for firm f commercializing a given device in period 1, π_{fct+1}, would be increasing in E_{fct} and decreasing in K_{ft}, leading firms with more experience and/or lower financing costs to be more likely to pursue innovation. In this setup, three further assumptions, which are consistent with both the theoretical and empirical literature, are required in order to take into account variation in firm investment and commercialization decisions over time. All cross-partial derivatives of C and π can then be signed, leading to a set of testable hypotheses.

Assumption 1: We assume that all firms can access the same local labor and raw materials markets so that the remaining variation in the cost of manufacturing *after* controlling for location is only related to differences in financing costs and capabilities, both of which can vary across firms and over time. Thus differences in product commercialization costs, C_{fct}, vary only as a function of financing costs and firm capabilities: $C_{fct} = f^*(K_{ft}, E_{fct})$.

Assumption 2: We allow E_{fct} to include both local geographic capabilities, γ, and within-firm capabilities, α, and assume these capabilities can be both general (e.g. general experience with software-driven products) or specific (e.g. expertise related to a certain class of digital products such as radiology devices). Local capabilities include the local labor market and specific capabilities related to software device commercialization in a region.

The importance of regional expertise and geography in predicting innovative activity has been well established (Delgado, Porter, and Stern, 2014; Forman, Goldfarb, and Greenstein, 2016; Mariani, 2004; Jaffe, Trajtenberg and Henderson, 1993, and many others) as has the role of within-firm capabilities (Henderson and Cockburn, 1996; Scott Morton, 1999; King and Tucci, 2002; Bayus and Agarwal, 2007; Nerkar and Roberts, 2004, and many others). We can then write E_{fct} as a function of local and within-firm capabilities, h, where $E_{fc} = h(\gamma_{fc}, \alpha_{fc})$ such that $\frac{\delta E}{\delta \gamma}$ and $\frac{\delta E}{\delta \alpha} > 0$. That is, a firm's total capabilities are increasing in both local geographic capabilities and within-firm capabilities.

We further assume that there is a hierarchy in applicability of the above capabilities such that class-specific experience is the most relevant followed by general experience. This hierarchy applies to both local capabilities and within-firm capabilities. Hence, we can

write the equation for E_{fc} with more granularity such that $E_{fc} = h(\gamma_f, \gamma_{fc}, \alpha_f, \alpha_{fc})$, where we consider both general and class-specific components to local and firm capabilities. The hierarchy in applicability implies a hierarchy of impact, such that more specific experiences drive down implied commercialization costs more than general experiences. Thus, $\frac{\delta E_{fc}}{\delta \gamma_f} < \frac{\delta E_{fc}}{\delta \gamma_{fc}}$ and $\frac{\delta E_{fc}}{\delta \alpha_f} < \frac{\delta E_{fc}}{\delta \alpha_{fc}}$.

- **Hypothesis 1**: $\frac{\delta C_{fct}}{\delta E_{fc}} \frac{\delta E_{fc}}{\delta \gamma fc} < \frac{\delta C_{fct}}{\delta E_{fc}} \frac{\delta E_{fc}}{\delta \gamma f} < 0$.
  - **1a:** Local capabilities decrease commercialization costs
  - **1b:** And do so in a way that is increasing in the specificity of those capabilities
- **Hypothesis 2**: $\frac{\delta C_{fct}}{\delta E_{fc}} \frac{\delta E_{fc}}{\delta \alpha fc} < \frac{\delta C_{fct}}{\delta E_{fc}} \frac{\delta E_{fc}}{\delta \alpha f} < 0$.
  - **2a:** Within-firm capabilities decrease commercialization costs
  - **2b:** And do so in a way that is increasing in the specificity of those capabilities

Assumption 3: We assume that a firm's financing cost, K_{ft}, correspond largely to a firm's access to external capital, either through public capital markets or via venture capital investments. This assumption is consistent with literature linking firm performance and innovation to access to finance and financial constraints (Hao and Jaffe, 1993; Cohen and Klepper, 1996; Cohen, 2010; Stern, 2017). As such, we can write K_{ft} as a decreasing function of a) being publicly listed (i.e. having access to public capital markets), ϕ_{ft} and b) being VC-funded, v_{ft}, where T≥1. We can then define K_{ft} as a function g where $K_{ft} = g(\phi_{ft}, v_{ft})$ and $\frac{\delta K}{\delta \phi}$ and $\frac{\delta K}{\delta v}$ <0.

The next set of hypotheses therefore address the implications of financial resources for patterns of commercialization, as smaller and more capitally constrained firms will have reduced incentives to pursue digital innovation:

- **Hypothesis 3**: $\frac{\delta C_{fct}}{\delta K_{fc}} \frac{\delta K_{fc}}{\delta \phi_{ft}} < 0$. The cost of new product development will be lower for publicly listed companies, leading these firms to be more likely to engage in software-driven innovation.

- **Hypothesis 4**: $\frac{\delta C_{fct}}{\delta K_{fc}} \frac{\delta K_{fc}}{\delta v_{ft}} < 0$. The cost of new product development will be lower for firms with venture capital funding, leading these firms to be more likely to engage in software-driven innovation.

We test each of these hypotheses in the analyses described below.

4 Data, Classification, and Summary Statistics

4.1 Summary

This project draws on four main sources of data. We begin with administrative data on the universe of FDA-regulated moderate-risk and high-risk medical devices that came to market over 15 recent calendar years (2002-2016, inclusive). For each device, we collect and analyze the text of the accompanying product summary or statement. Using an automated script and two different types of supervised document classification, we identify and characterize digital (i.e. software-driven) devices. First, we document the incidence and frequency of keywords related to software and networking capabilities in products and track these keywords over time. Subsequently we use the National Library of Medicine's Medical Text Indexer (MTI)[14] – a set of document classification algorithms that take free text and provide subject indexing recommendations based on the Medical Subject Headings ("MeSH®" vocabulary) established by the National Institutes of Health (NIH) – to validate the keyword-driven classification exercise. Using the commercializing firm's identity along with historical data about the location of a given product application and firm-level financial data, we characterize commercializing firms at the time each medical device in our dataset came to market.

4.2 Administrative Data on New Medical Devices

The first dataset for this project comes from combined regulatory clearance documents associated with all new moderate-risk and high-risk medical devices that came to market in the

[14] https://ii.nlm.nih.gov/MTI

United States after 1996. Moderate-risk devices, such as hearing aids, blood pressure monitors and echocardiograph devices, are the largest category of devices regulated by the FDA, while high-risk devices, such as pacemakers and drug eluting stents represent a smaller share of new products. Moderate-risk device clearance happens through a process called "510(k)," while high-risk device approval occurs through the PMA process. Both processes are described briefly above (Section 2) and in detail in Appendix A and Appendix B, respectively. These processes represent the final step of the research and development process, after which a cleared/approved product can be legally marketed in the United States. The FDA has historically received approximately 4,000 applications for new 510(k) devices annually, compared to fewer than 100 PMA Applications (Maisel, 2004).

The FDA's 510(k) clearance database[15] and PMA approval database[16] include the full set of device names, product codes (specific 3-letter classifications that categorize devices according to site of use and purpose), and submission and FDA decision dates for all products historically cleared/approved for marketing. The top eight medical specialty areas (classes) account for over 75% of all new product approvals and are the focus of this study (Table 1). Each of these classes experienced over 2,000 unique new device approvals between January 1, 2002 and December 31, 2016.[17] Due to availability of product descriptions (see the next sub-section), this represents our period of analysis. Over this period, a total of 35,794 new regulated devices came to market in the United States. Each class of devices includes multiple product codes and (typically) multiple unique devices within each product code. Figure 1 presents a simple example of the hierarchy of the classification system.

4.3 Rich Text Data

The second source of data is a novel database of text files comprised of the device summaries (standardized product descriptions). At the time of 510(k) clearance or PMA approval, a "summary" or "statement" is published for each device. As noted above, the summary must

[15] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm

[16] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm

[17] These eight classes are defined using the full set of FDA clearance records available and therefore represent the universe of newly-approved, FDA-regulated devices.

contain: "a description of the device...including an explanation of how the device functions, the scientific concepts that form the basis for the device, and the significant physical and performance characteristics" (e.g. design and physical properties).[18] In less than 10% of cases in our sample years, a related document called a "statement" was published in lieu of a summary[19]. When this was the case, we used the text from the product statement instead. While typically somewhat less detailed than summaries, statements can and do contain relevant information about the content of products (e.g. several included use of the word "software") and therefore provide the type of text information that is relevant for product classification in this study.[20] We use the term "summary" broadly below to refer to both types of documents.

Device summaries and statements are published as online PDFs following a standardized URL-format and we use an automated script to batch download all posted documents. These documents began to be digitized in May 2001 and we begin our study sample in 2002, the first full calendar year with digitized documents available. Using Abbyy FineReader optical character recognition (OCR) software, we convert downloaded documents into machine-readable text files. In total, 98% of product summaries could be converted to a machine-readable format for a total of 35,794 device-text pairs.[21] We have no systematic concerns regarding selection or time trends in missing text data: the machine readability of online PDFs is not statistically different across medical specialties overall, in any year(s), or over time. For all years, at least 97% of all digital documents were machine-readable following OCR document processing. Appendix C, Table I presents the total number of machine readable summaries in our sample by calendar year.

The use of text-based data – e.g. categorizing phrases to document firm extensions

[18]https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/ PremarketSubmissions/PremarketNotification510k/ucm142651.htm; as noted above, Exhibits 1 and 2 present examples of 510(k) and PMA summaries, respectively.

[19]https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/510kClearances/ucm089452.htm

[20]However, the use of statements could, in theory, lead to under-counting of digital products if their text files are less detailed. Therefore, in robustness tests, we repeat all results to show that they hold when considering the sample of product summary documents only.

[21]These include 35,495 510(k) summaries and 299 PMA summaries.

into new products and services, as in Greenstein (2000) – has a well-established history in empirical analysis, however the automation of these exercises is a relatively nascent phenomenon. Gentzkow, Kelly, and Taddy (2017) describe several techniques for parsing and analyzing text data and highlight the fact that "the information encoded in text is a rich complement to the more structured kinds of data traditionally used in research." In recent years, text data has been used in studies ranging from sentiment analysis of policy uncertainty (e.g. Baker, Bloom, and Davis, 2016) to labor economics (e.g. Deming and Kahn, 2018) and in the analysis of patent data (e.g. Moser, Ohmstedt, and Rhode, 2017). Here, we demonstrate the utility of automated classification of product types at scale for understanding the content and functionality of new medical devices.

We process text files in two ways, each of which leads to a similar classification of digital medical devices. Our first approach is a form of supervised document classification in which we identify the incidence and frequency of keywords related to software and networking capabilities in each device description. These terms were selected in advance using two online glossaries of computer related terms[22] (a list of the 36 most frequently used keywords – each of which were found in over 100 unique product descriptions – can be found in Appendix C, Table II). Unsurprisingly, "software" and several related keywords have increased in their frequency of use over time (Appendix C, Figure I). Because "software" is the most common among our search terms and is highly correlated with others, we rely on inclusion of the keyword "software" in a product's description as our first indicator to identify digital products.

Categorizing products as including "software" represents our first application of simple document classification to identify digital devices. This classification method has the advantage of being simple and highly transparent, but the disadvantage of being somewhat *ad hoc*. However, this method has a high rate of success in identifying products of interest. In particular, since the product descriptions included in FDA clearance documents are standardized and parsimonious, there is no reason, and indeed no option, to include extraneous words related to features that are not included in the device itself. To put it simply, keywords

[22]composite list from http://www.math.utah.edu/∼wisnia/glossary.html and https://pc.net/glossary

such as "software" will not appear in the product description if they do not relate to aspects of the device's functionality (See Exhibits 1 and 2). Nevertheless, we performed several manual inspections to confirm that incidents of keywords found were indeed references to the technology in the device: we drew a random sample of 120 devices (8 per calendar year) that had been flagged for including general "software" capabilities and manually inspected each of these devices' summaries. In this sample, 100% of devices flagged as including "software" were found to be correctly coded (i.e. a 0% rate of type I error in this random sub-sample).

We validate our *ad hoc* supervised document classification using the National Library of Medicine's MTI algorithm. As noted above, the MTI takes free text as an input to provide subject indexing recommendations based on the MeSH vocabulary established by the NIH. Since our primary measure of digitization is the incorporation of software into new products, we classify device descriptions using the MTI and generate an indicator for whether the algorithm assigned the MeSH code for *software* to the product.[23] The MeSH code for "software" broadly covers "sequential operating programs and data which instruct the functioning of a digital computer" – a slightly higher bar for classifying digital products than searching for the keyword "software" alone.

The MTI algorithm has the advantage of being externally validated by the NIH and through several years of use by the National Library of Medicine, but has two clear disadvantages: First, as noted above, we believe that the bar may be higher for flagging product descriptions for software inclusion (i.e. identifying digital devices), since the MTI will require a *discussion* of software programs in the text, beyond simply invoking the keyword "software." For this reason, our expectation is that the MTI may identify a more software-intensive subset of products in our sample. Second, the MTI is non-transparent in how it assigns concepts to text, since the algorithm itself is not published.[24]

Comparing the MTI output to our own keyword-based document classification method, we find high degree of overlap: 100% of the devices flagged by the MTI as describing software

[23]In the MeSH Tree, "Software" takes the Tree Number L01.224.900. We identify all products that are classified as being anywhere on the "Software" branch of the MeSH Tree.

[24]The MTI algorithm is not directly observable/open source; we batch process text files through the algorithm and record the subject headings that the MTI returns as output.

are also identified by the keyword method as being about the subject of software. However, as expected, not all summaries using the keyword "software" are identified by the MTI. The rightmost column of Appendix C, Table I presents a cross-tabulation of our *ad hoc* keyword-based document classification vs. the MTI's classification. Notably, the actual keyword "software" has the highest degree of overlap with the MTI-based definition. Because we care primarily about digitization in the sense of incorporation of *any* software, we focus on the keyword-based definition for our primary analysis, however for all regression models, we test the alternative (MTI-based) definition and present alternative versions of tables in Appendix C. The choice of definition does not appear to change the sign or statistical significance of the main results below, however magnitudes are attenuated roughly proportionally to the decrease in the number of software devices that are included in the MTI-defined sample.

Figure 2 presents the growth of new digital devices over our period of observation at the firm-product-year (F-P-Y) level.[25] Figure 3a shows the growth in digitized product codes – i.e. unique *types* of devices – over time, while Figure 3b shows growth in the number of *firms* pursuing digital innovation. Through these figures, we see that the growth in digital devices has been a result of the entry of both new products and new firms. Figure 4a shows that the number of digital product codes grew by over 400% over this period, while non-software product codes grew by only about 150% (albeit off of a higher baseline). Figure 4b breaks down the growth of digital devices across medical specialty classes, revealing interesting heterogeneities. Although all classes show growth in digital products, the share of new products that are digital varies dramatically across medical specialty classes.

4.4 Firm Financial Data

Each device is linked by its commercializing entity to detailed firm financing data. We first link commercializing entities to a panel of firm acquisitions created using data from *EvaluateMedTech*[26] in order to account for subsidiary ownership and introduce the notion of *child* (acquired) and *parent* (acquirer) firms. These child and parent firms are then separately

[25] Where "product" specifies a unique FDA product code.

[26] A market intelligence database that tracks public and private firms in the medical device industry

linked to data on each firm's public listing status and venture capital data. In order to link firm-level datasets, we use the software program *matchIT*, which performs fuzzy matching of company names (or addresses) between (or within) datasets and grades the text match quality by score. We used this software because it is highly flexible, fully parameterized, and deals effectively with foreign names. Firm names were cleaned using a consistent set of rules to account for suffixes and abbreviations.[27]

Data on venture capital funding are assembled from *EvaluateMedTech* and *Preqin*, with precedence given to the latter.[28] We observe deal dates and funding amounts for each linked firm, which we use in creating both lagged binary indicators for whether a firm was ever venture-funded or venture-funded prior to product commercialization, as well as running totals for dollar values of venture funding.

Data on firm public listing were collected from *EvaluateMedTech* and *Capital IQ*, with precedence given to the *former*, as it has broad coverage of the medical device industry.[29] These data allow us to create a binary indicator for whether the commercializing firm was publicly listed at the time a given product came to market. Figures 5 and 6 show the share of digital devices that were commercialized by venture capital-funded firms (in the sample of all privately-held firms) and by public firms, respectively.

4.5 Classifying Innovation and Accounting for Firm Geography and Experience

In the final data assembly, we collapse our dataset to the F-P-Y level. This only impacts firms that commercialized multiple devices within a single product code in a given calendar year (for example, a firm that brought two carotid artery stents to market in 2010 would only be counted once in the product code for carotid artery stents in that year. This coding is consistent with observing a firm doing a certain *type* of product innovation in a given year).

[27]This method is similar in nature to work done for the NBER Patent Data Project by Bessen.

[28]Preqin is widely considered the best publicly available dataset for venture funding and has been used in a variety of recent studies (e.g. Korteweg and Nagel, 2016 and Harris, Jenkinson, and Kaplan, 2013).

[29]We validate *EvaluateMedTech* data using *Capital IQ*, long considered a primary source for detailed firm financials. See, for example, Sheen (2014); Acharya and Xu (2016); Booth and Salehizadeh (2011).

We always take the maximum of our indicator for digital innovation at the F-P-Y level. For example, if a firm brought two blood pressure monitors to market in 2010 and only one of those devices was digital, the firm would be characterized as having done digital innovation in blood pressure monitors in 2010. Collapsing the data to F-P-Y level creates a standard unit of innovation by which we can compare firms over time. This yields a data set of 27,310 observations of firm-product-year level commercialization activity over our study period.[30]

With respect to geography, we characterize firms as to whether or not they are in a "digital cluster" in three (increasingly specific) ways. Each of these definitions requires limiting the sample to U.S.-based applications only in order to operationalize a consistent definition of state-based geographic clusters. Notably, many of these applications are from U.S. offices non-U.S.-headquartered firms, so many large, international firms are represented in the final sample.

First, we consider local labor market expertise. Using annual data from the U.S. Bureau of Labor Statistics (BLS), we compile data on each state's share of software engineers in the labor force in order to consider whether there is a relationship between the characteristics of the skilled IT workforce in a state and the likelihood of digital innovation emerging from that state. Because each application includes an address, we can see the location of the facility from which a device application was submitted. Figure 7 presents a set of example states. While there is some variation over time within states, the primary source of variation in the share of software engineers is across states.

Next we consider two types of state clusters for digital innovation as defined by where device commercialization took place in preceding years. We define digital clusters by identifying the top 10 states for software device commercialization, based on a 5-year moving average of the number of digital products brought to market leading up to the year

[30]In order to collapse the full set of new product data, we cleaned commercializing firm names using the same set of rules as used in the firm financial data construction. In addition, we hand-checked all firm names to capture instances in which similar, non-subsidiary firms were recorded differently due to either misspellings or omission/addition of words that would not have been identified by *matchIT*, our fuzzy matching software program. For instance, "BD" was hand replaced with Beckton Dickinson and *Medartis Medizinprodukte und Forschung* ("Medartis Medical Products and Research") was replaced simply with *Medartis*. This allows us to properly aggregate firm experience with the regulatory approval process and within specific product types and medical device classes (as described below).

of observation. We then consider a class-specific version of this definition, in which we define the top 10 states for software device commercialization within each medical specialty class. We create an indicator variable for whether or not a device originated from a cluster, based on each of these definitions. The sample used in regression analysis is limited to the years 2006-2016 (inclusive), to facilitate a 5-year look-back on regional product expertise. Figures 8a and 8b show the share of digital devices in states located in clusters vs. those not located in clusters using these two definitions.

Finally, we characterize firms' digital device experience along two dimensions. First we calculate the count of total digital devices the firm has commercialized up to, but not including, the year of observation. Second, we calculate the total count of digital devices within each *class* that the firm has commercialized up to, but not including, the year of observation. Table 2 presents summary statistics of all variables used in regression models and Table 3 presents additional summary statistics and t-tests for digital vs. non-digital products.

5 Estimation and Results

In the estimation exercises that follow, we test the hypotheses outlined in Section 3.2. First, we explore evidence for Hypotheses 1 and 2 by modeling the relationship between capabilities (external and internal, respectively) and the likelihood of a firm engaging in digital device innovation. Next, we explore evidence for Hypotheses 3 and 4 by modeling the relationship between firm financial resources (public capital and VC funding, respectively) and the likelihood of engaging in digital innovation. In combined models, we consider all factors simultaneously and explore mechanisms.

5.1 Overall estimates

Trends in digital innovation in medical technology and observed variation across medical specialty class are seen in Figures 2-4. Notably, there is significant heterogeneity across

classes in the volume (Figure 2) and share (Figure 4b) of digital innovation. There are also clear time trends, with new digital products growing over time. These descriptive findings point to the importance of using class and year controls in empirical models. At the F-P-Y level, we therefore model the likelihood of digital innovation, D, as:

$$D_{fpct} = f(\beta \mathbf{X})$$

Where **X**s include:

- Indicators of capabilities (geographic and within-firm), ranging from general to class-specific.
- Indicators of firm financial resources, including whether a product emerged from a publicly listed firm or a VC-funded firm.
- Controls for:
  - Clearance year, in order to capture time trends in software inclusion over time
  - Medical specialty class, in order to account for persistent differences in the relative ease or applicability of software in a given area of medicine and medical technology

In the regression models that follow, all specifications therefore include year and class fixed effects, with standard errors clustered at the product code level in acknowledgement of potential differences across product types (e.g. as a result of differences in innovation behavior or regulatory burden). All tables report marginal effects from Logit models, facilitating a more direct interpretation of statistical relationships.[31]

Table 4 presents a full set of controls. As expected, there are statistically significant differences across classes and over time. Column 1 uses year fixed effects, while Column 2 includes a time trend. Notably, the coefficients on sample controls are very similar across the two samples. The pseudo-r-squared values are trivially higher in the models using year fixed

[31] A full set of corresponding linear probability models (excluded due to length and redundancy) lead to the same conclusions as those presented below.

effects rather than a time trend, so we use the full specification in Column 1 as controls in all subsequent regressions (however results are stable regardless of the convention chosen).

5.2 Geographic and within-firm capabilities

Table 5 presents results predicting digital innovation at the F-P-Y level, specifically evaluating Hypotheses 1 and 2. Controlling for medical specialty class and year, we find that although a state's share of software engineers is not a strong predictor of digital innovation, other measures of geographic expertise meaningfully increase the likelihood of digital innovation. Dummy variable indicators for being in either a general digital device cluster (Column 2) or being in a class-specific digital device cluster (Column 3) are both strongly associated with higher probabilities of digital innovation in new products – both individually and jointly (Column 4). In the combined model, which suffers less from potential omitted variable bias, we observe that being in a general digital device cluster is associated with a 3.2 percentage point increase in the likelihood of digital innovation, while being in a class-specific cluster increases that probability by a further 12.9 percentage points. These findings lend support for Hypotheses 1a and 1b, respectively.

These coefficients are also of meaningful economic significance; consider cardiovascular devices, which were roughly 40% digital in 2016. These estimates imply that a firm located in a digital device cluster would be 8% more likely to innovate digitally if it were in a general digital device cluster and a further 32% (or a total of 40%) more likely to innovate digitally if that firm were located in a class-specific cluster. Further, the magnitude of these coefficients is not significantly diminished in models that include additional independent variables, further evidence of a robust and persistent relationship between geographic expertise and digital innovation in the U.S. medical device industry.

Columns 5-7 of Table 5 consider the role of within-firm capabilities (accumulated firm experience) in commercializing digital products. Column 5 shows a strong, positive statistical relationship between past digital device experience and current likelihood of digital innovation. Column 6 shows that this relationship is driven entirely by within-class

experience. Indeed, experience outside the focal product class is negatively predictive of digital innovation in the focal class. The estimates in Column 6 indicate that a doubling of a firm's class-specific experience with digital device commercialization is associated with an 8.5 percentage point increase in the likelihood that a firm subsequently innovates digitally in that class. These results suggest that with respect to within-firm capabilities, only accumulated experience that is relevant to a specific product area is positively predictive of digital innovation. That is, the results support both Hypothesis 2a and 2b, but also reveal that Hypothesis 2b is the dominant factor at play.

The results in Column 7 are highly similar when all potential geographic capabilities are accounted for simultaneously (Column 8). The similarity of the estimated coefficients across specifications in Table 5 indicates that geographic and within-firm capabilities are mostly independent of one another and have largely orthogonal impacts in these predictive models.

5.3 Firm financial resources

Table 6 presents results from regressions designed to evaluate Hypotheses 3 and 4. We first consider whether public firms (Column 1) and VC-funded private firms (Column 2) are more likely to engage in digital innovation. We find that while both indicators have positive coefficients, only VC funding is a statistically significant predictor of digital innovation, with VC-funded firms roughly 2.9 percentage points more likely to innovate digitally. Column 3 presents results when using the natural logarithm of the cumulative total of venture capital funding up to the year of commercialization as a predictor. These results indicate that a doubling of a firm's VC funding is associated with a 1.2 percentage point higher likelihood of digital innovation. Columns 4 and 5 present results from combined regression models that consider public status and VC funding (amounts) simultaneously, finding again that only venture capital funding (both as a binary status and a cumulative funding total) are significant predictors of new digital commercialization. Across all models, the coefficient on the public dummy is estimated to be positive, but never statistically significant.

With respect to Hypotheses 3 and 4, all coefficients in Table 6 are of the predicted sign, but only Hypothesis 4 is broadly supported by the data. In the next section, we consider the relationships between the various factors that predict digital innovation in order to understand how they interact in practice.

5.4 Further regression analysis and mechanisms

Table 7 presents a set of combined models in which Hypotheses 1-4 are evaluated simultaneously, with further extensions to test interactions between venture funding and geographic and within-firm capabilities. Differences between the results presented in Table 7 and those seen in Tables 5 and 6 therefore indicate the size and direction of any omitted variable bias unintentionally introduced by assessing individual hypotheses separately.

We also use this set of estimation models to ask how venture capital – the only financial variable that has a statistically significant relationship with digital innovation – interacts with firm geography and internal capabilities. This exercise tests whether venture capitalists are investing in firms based on attributes that are separately correlated with digital innovation.

Columns 1 and 2 of Table 7 reproduce the fully specified models in Tables 5 and 6, with Column 3 corresponding to a combined model. The results established thus far are remarkably stable even when estimated in the context of this "all-in" model. Columns 4 through 7 consider the primary factors that predict digital innovation and how they interact in our sample. In particular, we interact our measures of capabilities (geographic and within-firm) with an indicator for the running total of VC funding. All results point to *selection* in the flow of VC funds, rather than any separate, additive relationship between VC funding and digital innovation. Specifically, we find that VC funding, while predictive of digital innovation when considered alone, is flowing into firms in class-specific digital device clusters (Column 5) as well as those with prior digital device commercialization experience – both general (Column 6) and class-specific (Column 7).

Notably, unlike the coefficient on VC funding, the estimated coefficients on indicators

for geographic clusters and within-firm commercialization experience continue to be positive and statistically significant predictors of digital innovation. These results simultaneously bolster support for the importance of geographic and within-firm capabilities in driving digital innovation and eradicate the evidence that financial resources such as VC funding can separately support digital innovation in their absence.

6 Discussion and Conclusions

In this study, we document several trends in the digitization of medical technology and its implications for firms in the industry. We characterize the growth of digital devices over time and across medical specialty classes, finding important differences. For example, by 2016, there were over twice as many digitized product codes and more than three times as many new product approvals in cardiovascular devices as compared to orthopedic devices. These descriptive findings are novel; to our knowledge, no other studies have comprehensively characterized the digitization of regulated medical devices. Along the way, we develop and validate a method for using supervised document classification to analyze the contents of new product descriptions. We use multiple methods to collect indicators of the use of software in product descriptions of new medical devices.

We then turn to unpacking which types of firms have been driving digital innovation in medical technology and find several pieces of evidence that point to significant incumbent advantages. Specifically, we observe a strong relationship between both geographic clusters and prior commercialization experiences in predicting digital innovation. The importance of commercialization experience is evocative of other studies of the medical device industry such as Chatterji (2009) that emphasize the importance of regulatory knowledge, marketing knowledge, and and understanding of market opportunities in the medical device industry. The results are also similar to those seen in other settings, where the important role of "complementary know-how" in a changing industry has been well-documented (Helfat, 1997). More broadly, the findings are consistent with the evidence that acquired capabilities have positive spillovers not only within firms, but also across firms in a local labor market, as

summarized by Azoulay and Lerner (2012).

These relationships exist across various levels of specificity in defining geographic clusters, but within-firm capabilities appear to be driven by class-specific experience. This may be due to the limited applicability of existing capabilities to different classes of products. For example, a firm that has developed general purpose technology for displaying digital images from a radiology device is likely to have several applications of that technology *within* radiology, but may not have any reason to try to incorporate that technology into orthopedic devices.

We also consider a number of financial resources that may support digital innovation, but find little evidence that such resources are a driving force in innovative activity. While VC funding appears to play a role in funding innovative entrants, a closer look at the data suggests that the relationship is entirely driven by selection on other variables that predict digital innovation. In other words, money alone does not appear to compensate for geography and experience in this industry: VC funding in the absence of local or within-firm expertise does not predict higher rates of digital innovation.

Taken together, our results include several pieces of evidence in support of within-region and within-firm positive spillovers from past digital innovation into future digital innovation. Interestingly, these factors work largely orthogonally to one another, indicating that some amount of firm experience can compensate for being located in a less advantageous geography and vice versa. We conclude that this regulated setting favors firms coming from a position of incumbent geographic and/or experiential advantage.

Our results further suggest that understanding and supporting digital innovation in health care will necessitate a nuanced understanding of how different types of firms enter new markets. In particular, the existence of entry regulation may mean that incumbent firms play a more significant role in digitizing products than may be true in settings with fewer entry hurdles, such as consumer technology. Further, to the extent that new regulatory policies emerge to either streamline or complicate the use of software in new medical technologies, these policies could have differential effects across geographies and could differ-

entially impact incumbents vs. (potential) new entrants. As regulators increasingly devote attention to digital devices – for example, through the FDA's new "digital health software precertification" program,[32] – it will be important to keep such considerations in mind.

[32]https://www.fda.gov/MedicalDevices/DigitalHealth/DigitalHealthPreCertProgram/Default.htm

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Figures

Exhibit 1: Extract from 510(k) Statement

510(K) SUMMARY JAN 1 1 2008

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR §807.92.

The assigned 510(k) number is: K073198

1. **Submitter's Identification:**

   Microlife Intellectual Property GmbH, Switzerland

   Espenstrasse 139
   9443 Widnau / Switzerland

   Date Summary Prepared: October 30, 2007

2. **Name of the Device:**

   Microlife Upper Arm Automatic Digital Blood Pressure Monitor, Model WatchBP Home (BP3MX1-1).

3. **Information for the 510(k) Cleared Device (Predicate Device):**

   Microlife Upper Arm Automatic Digital Blood Pressure Monitor, Model BP3AC1-1 PC, K#060686.

4. **Device Description:**

   Microlife Upper Arm Automatic Blood Pressure Monitor, Model WatchBP Home is designed to measure the systolic and diastolic blood pressure and pulse rate of an individual by using a non-invasive technique in which an inflatable cuff is wrapped around the Upper arm. Our method to define systolic and diastolic pressure is similar to the auscultatory method but uses an electronic capacitive pressure sensor rather than a stethoscope and mercury manometer. The sensor converts tiny alterations in cuff pressure to electrical signals, by analyzing those signals to define the systolic and diastolic blood pressure and calculating pulse rate, which is a well - known technique in the market called the "oscillometric method".
   The device has <DIAG> and <USUAL> measurement mode. In additional, the device can be used in connection with your personal computer **(PC)** running the WatchBP 1.0 software. The memory data can be transferred to the PC by connecting the monitor via cable with the PC.

Exhibit 2: Extract from PMA Statement

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Continuous Glucose Monitoring (CGM) System
Device Trade Name:	iPro2 Continuous Glucose Monitoring (CGM) System
Device Procode:	MDS
Applicant's Name and Address:	Medtronic MiniMed 18000 Devonshire Street Northridge, CA 91325
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P150029
Date of FDA Notice of Approval:	June 17, 2016
Priority Review:	*Not Applicable*

II. INDICATIONS FOR USE

iPro2 CGM System (MMT-7745)
The iPro2 Recorder is to be used with either Enlite sensor or Sof-Sensor and is intended to continuously record interstitial glucose levels in persons with diabetes mellitus. This information is intended to supplement, not replace, blood glucose information obtained using a standard home glucose-monitoring device. The information collected by the iPro2 Recorder may be uploaded to a computer (with Internet access) and reviewed by healthcare professionals. This information may allow identification of patterns of glucose level excursions above or below the desired range, facilitating therapy adjustments which may minimize these excursions.

VI. Software

The current software version for the iPro2 CGM system is v1.1A. Software verification and validation were carried out in accordance with the FDA guidance document *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices: General Principles of Software Validation: Final Guidance for Industry and FDA Staff (2002).* Software development activities included establishing detailed software requirements, linking requirements with associate verification tests, software code reviews, unit testing, system level testing and defect tracking and dispositioning to ensure the software conforms to patient needs and intended uses. Software was previously reviewed under P980022/S071.

VII. Human Factors Testing

The sponsor referenced human factors testing from previous submissions (P980022 and P120010) and provided new testing to support the proposed system configuration. New testing included the following:

- Evaluation of tasks regarding the removal of the iPro2 recorder from the Enlite sensor and inspection of fluids on the recorder before initiating contact with the iPro2 docking station.
- Evaluation of specific tasks performed in the software.

Figure 1: Device classification (example)

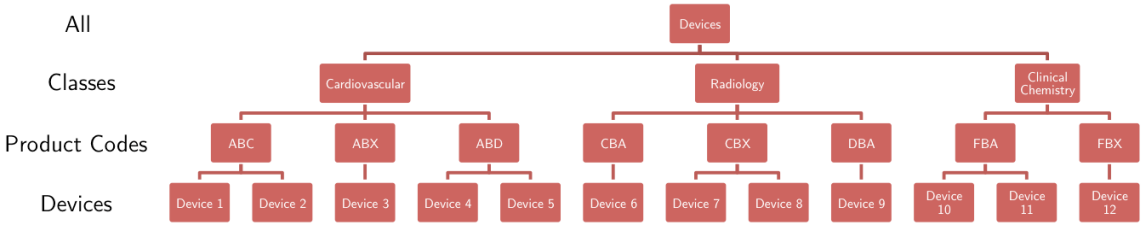


Figure 2: Number of newly approved digital devices (F-P-Y level)

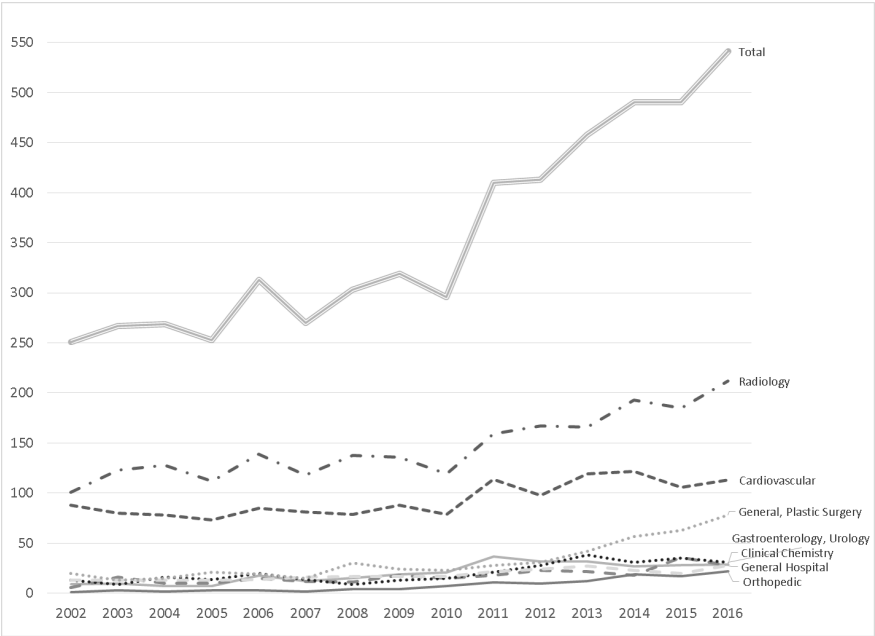


Figure 3a: Cumulative number of digital device product codes

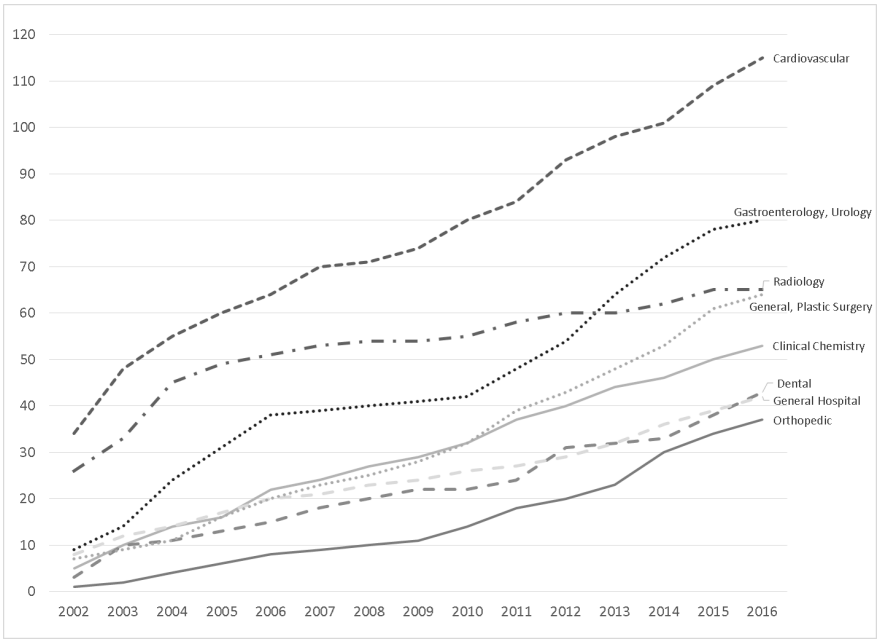


Figure 3b: Cumulative number of firms digital devices (F-P-Y level)

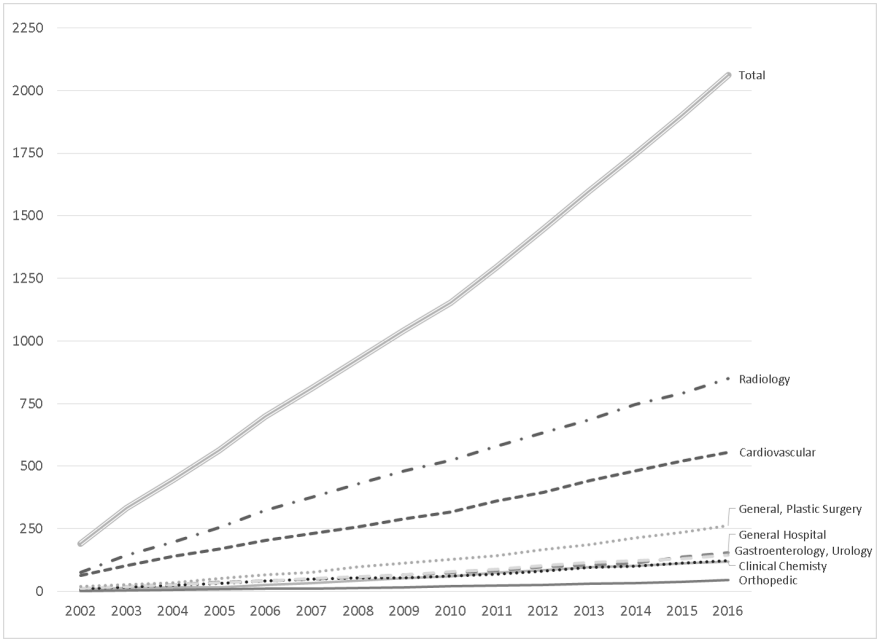


Figure 4a: Cumulative growth of digitized product codes (base year = 2002)

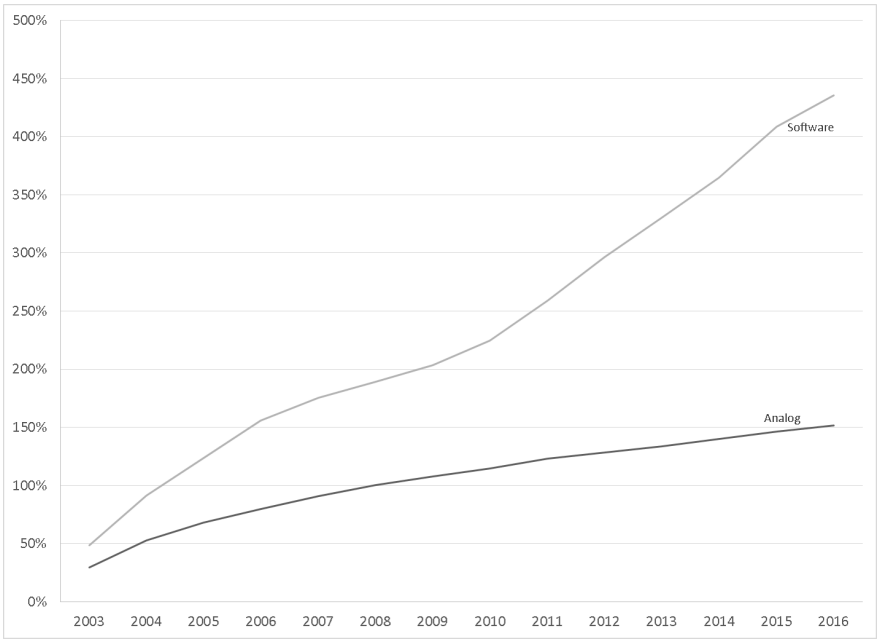


Figure 4b: Share of newly-approved digital devices (F-P-Y level)

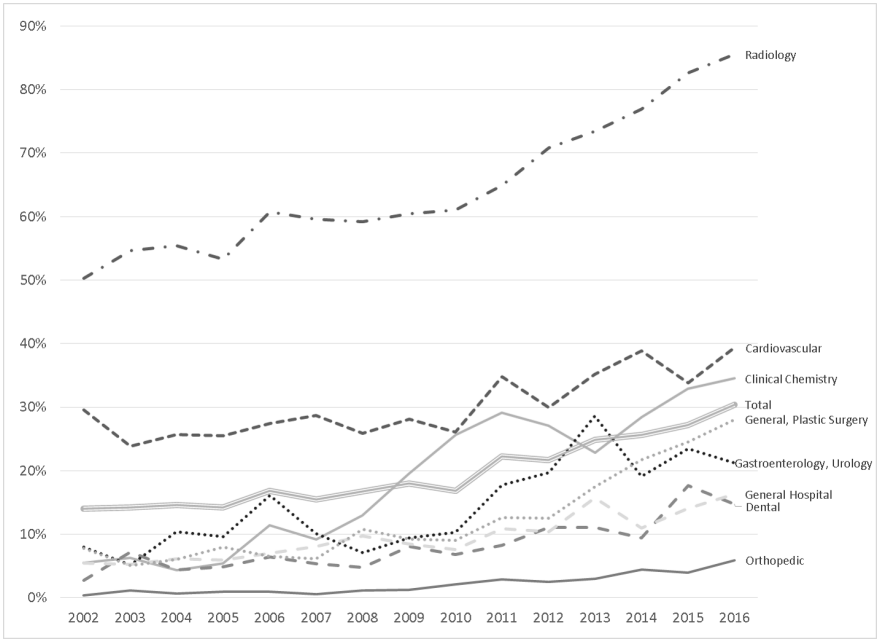


Figure 5: Share of digital devices: VC vs. non-VC-funded private firms

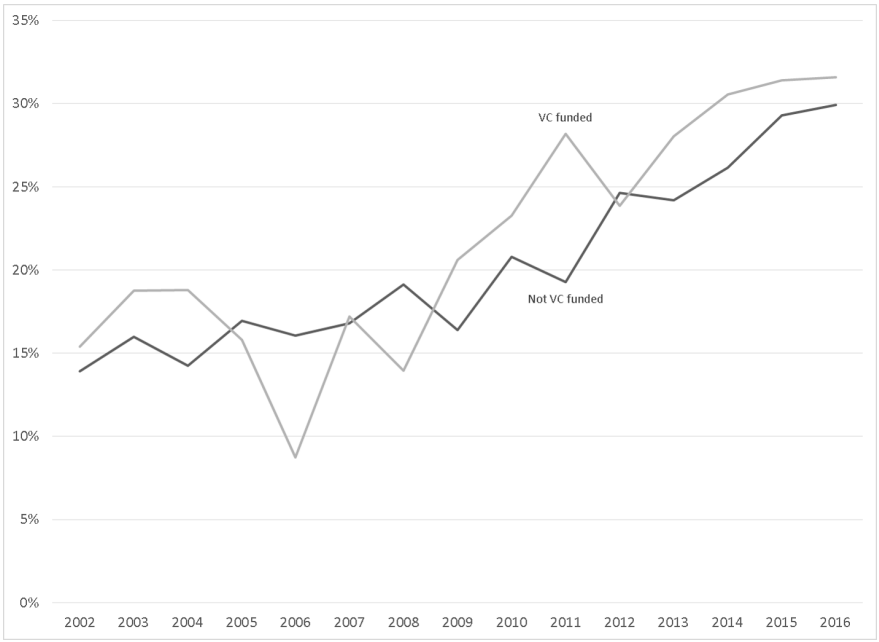


Figure 6: Share of digital devices: publicly-listed vs. private firms

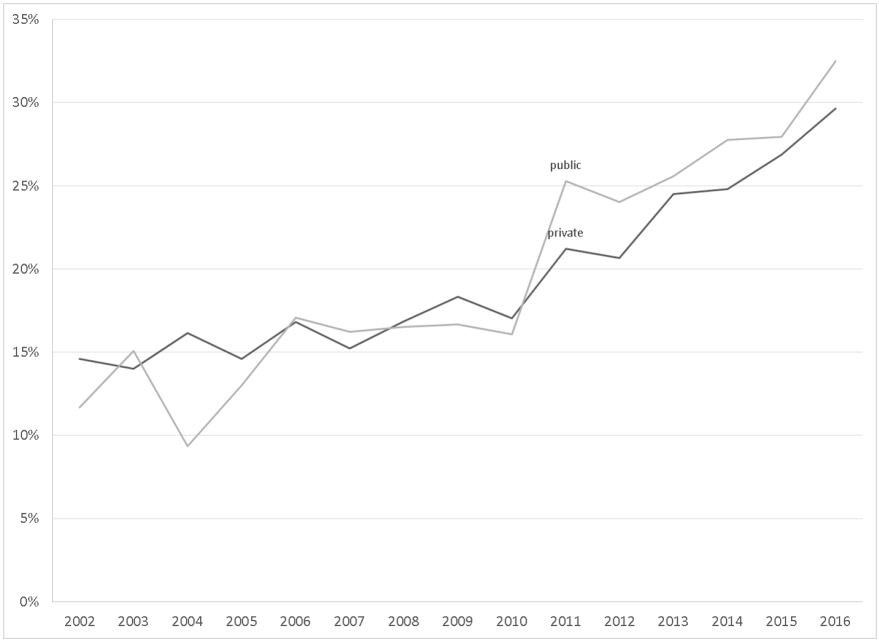
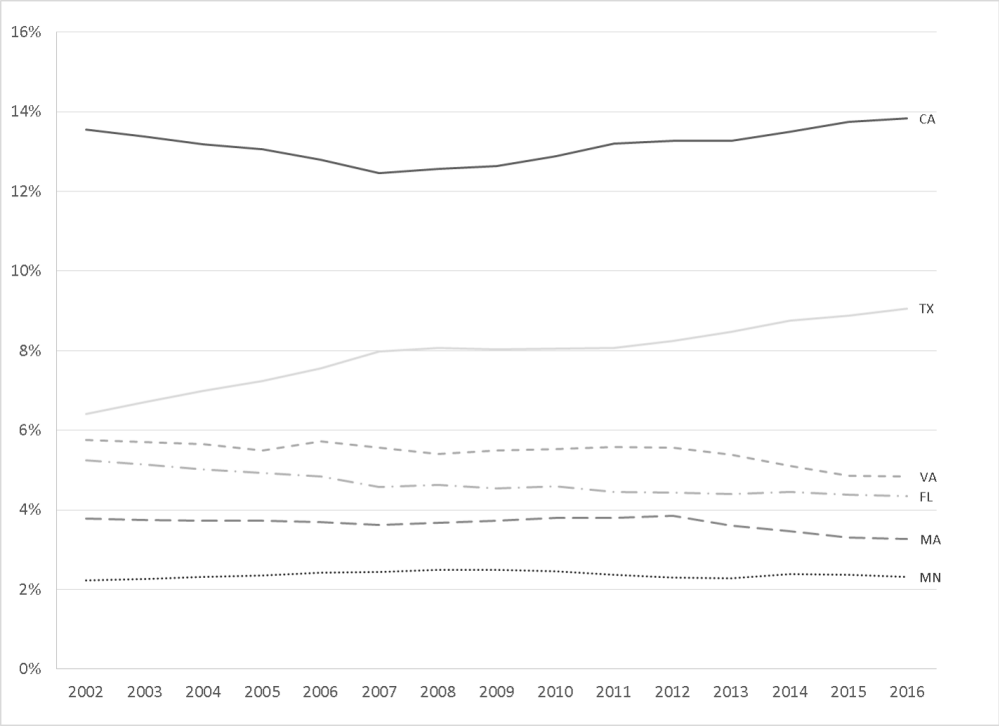


Figure 7: Variation in state share of software engineers*



*linear imputation for years 2002-2004 and 2016

Figure 8a: Share of digital devices in *general* clusters vs. rest

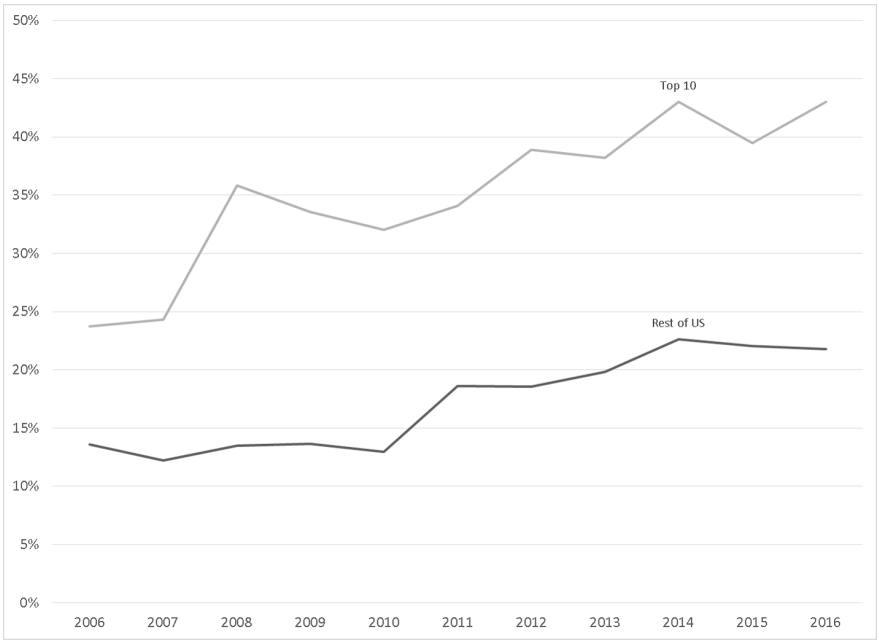
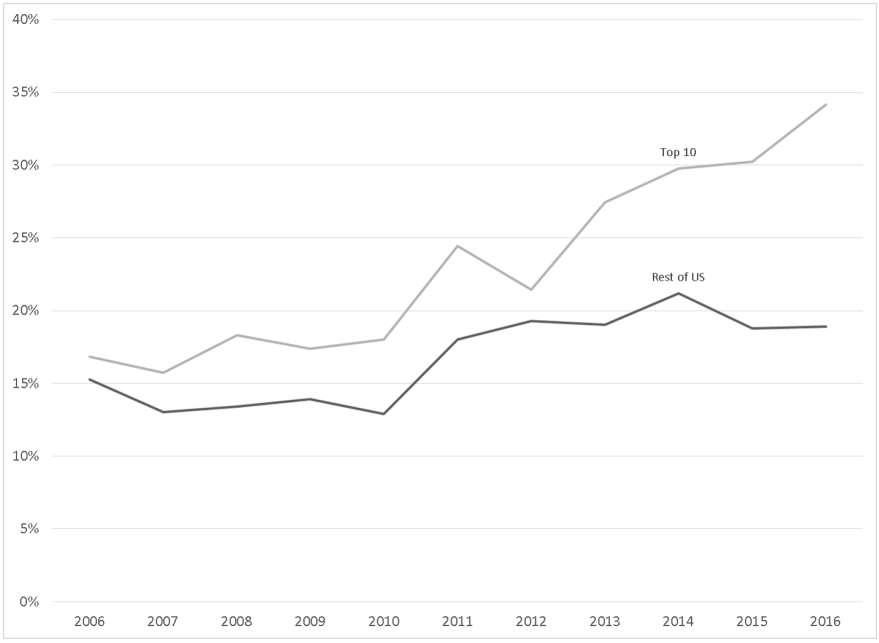


Figure 8b: Share of digital devices in *class-specific* clusters vs. rest



Tables

Table 1: Total counts of products by medical specialty (class) and overall

	Unique devices at p-y* level		Unique devices at f-p-y* level		Unique devices at f-p-y level**	
	n	%	n	%	n	%
Cardiovascular	6,092	17.0	4,643	17.0	2,761	17.6
Clinical Chemistry	2,353	6.6	1,845	6.8	956	6.1
Dental	3,942	11.0	3,207	11.7	1,718	10.9
Gastroenterology, Urology	2,571	7.2	2,156	7.9	1,281	8.1
General Hospital	3,779	10.6	3,037	11.1	1,432	9.1
General, Plastic Surgery	4,959	13.9	3,851	14.1	2,285	14.5
Orthopedic	7,228	20.2	5,194	19.0	3,566	22.7
Radiology	4,870	13.6	3,377	12.4	1,732	11.0
Total	35,794	100.0	27,310	100.0	15,731	100.0

*f=firm, p=product, y=year

**post 2005, US only

Columns 1-2 present the full sample of products observed. Columns 3-4 present the same data collapsed to the firm-product-year level; these data are used to generate measures of firm experience, but not all observations are used in regression models. Columns 5-6 present summary statistics for the analysis sample used in estimation.

Table 2: Summary statistics

Metric	Sample Mean (± SD)
Share of software engineers in state	0.053 ± 0.043
Prior digital devices (all)	4.23 ± 14.53
Prior digital devices (class-specific)	2.19 ± 8.52
Total venture funding, cumulative	5.96 ± 22.98
In digital device cluster (general), %	14.36
In digital device cluster (class-specific), %	47.57
Publicly listed, %	28.95
VC funded (applicant), %	16.17

Non-binary variables are given as mean ± SD
n=15,731
Prior digital devices calculated using keyword-based definition

Table 3: Firm experience summary statistics by product type

	Analysis sample (Full)	Non-Digital Devices	Digital Devices	T-Statistic (Digital vs. Non)
Software	(n=15,731)	(n=12,673)	(n=3,058)	(n=15,731)
Prior digital devices	4.23	2.71	10.51	-17.17
Prior digital devices (same class)	2.19	1.05	6.93	-19.54
Prior digital devices (different class)	2.04	1.66	3.58	-8.94

Notes: Digital devices defined using keyword-based classification. T-statistic is from a difference-in-means t-test with unequal variances comparing the non-digital vs. digital samples. All tests have a corresponding p-value of < 0.000.

Table 4: Control variables: year and product class

Logit model: digital device innovation		
	(1)	(2)
Clearance year=2007	-0.008	
	(0.009)	
Clearance year=2008	-0.002	
	(0.012)	
Clearance year=2009	-0.003	
	(0.011)	
Clearance year=2010	0.000	
	(0.013)	
Clearance year=2011	0.050***	
	(0.012)	
Clearance year=2012	0.046***	
	(0.013)	
Clearance year=2013	0.069***	
	(0.013)	
Clearance year=2014	0.099***	
	(0.016)	
Clearance year=2015	0.104***	
	(0.017)	
Clearance year=2016	0.115***	
	(0.016)	
Clearance year		0.014***
		(0.001)
Cardiovascular	0.075	0.073
	(0.072)	(0.072)
Dental	-0.127*	-0.129*
	(0.061)	(0.061)
Gastroenterology, Urology	-0.056	-0.058
	(0.060)	(0.060)
General Hospital	-0.085	-0.087
	(0.065)	(0.065)
General, Plastic Surgery	-0.080	-0.082
	(0.061)	(0.061)
Orthopedic	-0.190***	-0.192***
	(0.055)	(0.055)
Radiology	0.451***	0.449***
	(0.091)	(0.092)
N	15,731	15,731
Pseudo R^2	0.2225	0.2208

* p<0.05, ** p<0.01, *** p<0.001

Logit model results for years 2006-2016, inclusive. Column 1 includes year fixed effects; Column 2 includes a linear time trend. Omitted class = Clinical Chemistry; omitted year (Column 1) = 2006, marginal effects reported. Digital devices defined based on keyword method.

Table 5: Geographic and within-firm capabilities

Logit model: digital device innovation							
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
State software employees (Ln)	0.007			0.005			0.005
	(0.005)			(0.004)			(0.004)
In digital device cluster		0.068***		0.032**			0.025*
		(0.012)		(0.010)			(0.010)
In digital device cluster for prod. class			0.136***	0.129***			0.112***
			(0.010)	(0.009)			(0.007)
Prior digital devices, internal (Ln)					0.045***		
					(0.006)		
Prior digital devices in class, internal (Ln)						0.085***	0.074***
						(0.009)	(0.008)
Prior digital devices in diff. class, internal (Ln)						-0.033***	-0.028***
						(0.007)	(0.006)
N	15,731	15,731	15,731	15,731	15,731	15,731	15,731

* p<0.05, ** p<0.01, *** p<0.001

All models include full set of time and product class fixed effects, marginal effects reported. Standard errors are clustered at the product code level. Digital devices defined based on keyword method. Firm experience and clusters are defined using data from the prior five years.

Table 6: Financial resources

Logit model: digital device innovation					
	(1)	(2)	(3)	(4)	(5)
Publicly listed firm	0.009			0.011	0.010
	(0.011)			(0.011)	(0.011)
VC-funded firm		0.029*		0.030*	
		(0.012)		(0.013)	
Total VC funding, $ (Ln)			0.012**		0.013**
			(0.004)		(0.004)
N	15,731	15,731	15,731	15,731	15,731

* p<0.05, ** p<0.01, *** p<0.001

All models include full set of year and product class fixed effects. Standard errors are clustered at product code level, marginal effects reported. Digital devices defined based on keyword method.

Table 7: Combined models and interaction terms

Logit model: digital device innovation							
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
State software employees (Ln)	0.005		0.002	0.002	0.003	0.003	0.003
	(0.004)		(0.004)	(0.004)	(0.004)	(0.004)	(0.004)
In digital device cluster	0.025*		0.024*	0.024*	0.024*	0.024*	0.024*
	(0.010)		(0.010)	(0.010)	(0.010)	(0.010)	(0.010)
In digital device cluster for prod. class	0.112***		0.112***	0.112***	0.106***	0.112***	0.111***
	(0.007)		(0.007)	(0.007)	(0.008)	(0.007)	(0.007)
Prior digital devices in class, internal (Ln)	0.074***		0.076***	0.076***	0.075***	0.072***	0.067***
	(0.008)		(0.008)	(0.008)	(0.008)	(0.008)	(0.008)
Prior digital devices in diff. class, internal (Ln)	-0.028***		-0.027***	-0.027***	-0.026***	-0.030***	-0.025***
	(0.006)		(0.006)	(0.006)	(0.006)	(0.006)	(0.006)
Publicly listed firm		0.010	-0.017	-0.017	-0.017	-0.017	-0.018
		(0.011)	(0.009)	(0.009)	(0.009)	(0.009)	(0.009)
Total VC funding, $ (Ln)		0.013**	0.012***	0.012***	0.006	0.004	0.000
		(0.004)	(0.003)	(0.003)	(0.004)	(0.004)	(0.004)
VC $ (Ln) * In cluster				-0.001			
				(0.007)			
VC $ (Ln) * In cluster for prod. class					0.012*		
					(0.005)		
VC $ (Ln) * Prior digital devices (Ln)						0.010***	
						(0.003)	
VC $ (Ln) * Prior digital devices in class (Ln)							0.017***
							(0.003)
N	15,731	15,731	15,731	15,731	15,731	15,731	15,731

* p<0.05, ** p<0.01, *** p<0.001

All models include full set of year and product class fixed effects. Standard errors are clustered at product code level, marginal effects reported. Digital devices defined based on keyword method. Firm experience and clusters are defined using data from the prior five years.

Appendix A: The 510(k) Process

The information in this appendix is taken directly from the FDA's official description of the 510(k) (premarket notification) process (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/)

Introduction

Each person who wants to market in the U.S., a Class I, II, and III device intended for human use, for which a Premarket Approval (PMA) is not required, must submit a 510(k) to FDA unless the device is exempt from 510(k) requirements of the Federal Food, Drug, and Cosmetic Act (the Act) and does not exceed the limitations of exemptions in .9 of the device classification regulation chapters (e.g., 21 CFR 862.9, 21 CFR 864.9). There is no 510(k) form, however,21 CFR 807Subpart E describes requirements for a 510(k) submission. Before marketing a device, each submitter must receive an order, in the form of a letter, from FDA which finds the device to be substantially equivalent (SE) and states that the device can be marketed in the U.S. This order "clears" the device for commercial distribution.

A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device (21 CFR 807.92(a)(3)) that is not subject to PMA. Submitters must compare their device to one or more similar legally marketed devices and make and support their substantial equivalency claims. A legally marketed device, as described in 21 CFR 807.92(a)(3), is a device that was legally marketed prior to May 28, 1976 (preamendments device), for which a PMA is not required, or a device which has been reclassified from Class III to Class II or I, or a device which has been found SE through the 510(k) process. The legally marketed device(s) to which equivalence is drawn is commonly known as the "predicate." Although devices recently cleared under 510(k) are often selected as the predicate to which equivalence is claimed, any legally marketed device may be used as a predicate. Legally marketed also means that the predicate cannot be one that is in violation of the Act.

Until the submitter receives an order declaring a device SE, the submitter may not proceed to market the device. Once the device is determined to be SE, it can then be marketed in the U.S. The SE determination is usually made within 90 days and is made based on the information submitted by the submitter.

Please note that FDA does not perform 510(k) pre-clearance facility inspections. The submitter may market the device immediately after 510(k) clearance is granted. The manufacturer should be prepared for an FDA quality system (21 CFR 820) inspection at any time after 510(k) clearance.

What is Substantial Equivalence

A 510(k) requires demonstration of substantial equivalence to another legally U.S. marketed device. Substantial equivalence means that the new device is at least as safe and effective as the predicate. A device is substantially equivalent if, in comparison to a predicate it:

- has the same intended use as the predicate; **and**
- has the same technological characteristics as the predicate;

or

- has the same intended use as the predicate; **and**
- has different technological characteristics and the information submitted to FDA;
  - does not raise new questions of safety and effectiveness; **and**
  - demonstrates that the device is at least as safe and effective as the legally marketed device.

A claim of substantial equivalence does not mean the new and predicate devices must be identical. Substantial equivalence is established with respect to intended use, design, energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, labeling, biocompatibility, standards, and other characteristics, as applicable.

A device may not be marketed in the U.S. until the submitter receives a letter declaring the device substantially equivalent. If FDA determines that a device isnotsubstantially equivalent, the applicant may:

- resubmit another 510(k) with new data,
- request a Class I or II designation through thede novoprocess
- file areclassification petition, or
- submit a premarket approval application (PMA).

Who is Required to Submit a 510(k)

The Act and the 510(k) regulation (21 CFR 807) do not specify who must apply for a 510(k). Instead, they specify which actions, such as introducing a device to the U.S. market, require a 510(k) submission.

The following four categories of parties must submit a 510(k) to the FDA:

1. Domestic manufacturers introducing a device to the U.S. market;

Finished device manufacturers must submit a 510(k) if they manufacture a device according to their own specifications and market it in the U.S. Accessories to finished devices that are sold to the end user are also considered finished devices. However, manufacturers of device components are not required to submit a 510(k) unless such components are promoted for sale to an end user as replacement parts. Contract manufacturers, those firms that manufacture devices under contract according to someone else? s specifications, are not required to submit a 510(k).

2. Specification developers introducing a device to the U.S. market;

A specification developer develops the specifications for a finished device, but has the device manufactured under contract by another firm or entity. The specification developer submits the 510(k), not the contract manufacturer.

3. Repackers or relabelers who make labeling changes or whose operations significantly affect the device.

Repackagers or relabelers may be required to submit a 510(k) if they significantly change the labeling or otherwise affect any condition of the device. Significant labeling changes may include modification of manuals, such as adding a new intended use, deleting or adding warnings, contraindications, etc. Operations, such as sterilization, could alter the condition of the device. However, most repackagers or relabelers are not required to submit a 510(k).

4. Foreign manufacturers/exporters or U.S. representatives of foreign manufacturers/exporters introducing a device to the U.S. market.

Please note that all manufacturers (including specification developers) of Class II and III devices and select Class I devices are required to follow design controls (21 CFR 820.30) during the development of their device. The holder of a 510(k) must have design control documentation available for FDA review during a site inspection. In addition, any changes to the device specifications or manufacturing processes must be made in accordance with the Quality System regulation (21 CFR 820) and may be subject to a new 510(k). Please see our guidance, "Deciding When to Submit a 510(k) for a Change to an Existing Device."

When a 510(k) is Required

A 510(k) is required when:

1. Introducing a device into commercial distribution (marketing) for the first time. After May 28, 1976 (effective date of the Medical Device Amendments to the Act), anyone who wants to sell a device in the U.S. is required to make a 510(k) submission at least 90 days prior to offering the device for sale, even though it may have been under development or clinical investigation before that date. If your device was not marketed by your firm before May 28, 1976, a 510(k) is required.

2. You propose a different intended use for a device which you already have in commercial distribution. The 510(k) regulation (21 CFR 807) specifically requires a 510(k) submission for a major change or modification in intended use. Intended use is indicated by claims made for a device in labeling or advertising. Most, if not all changes in intended use will require a 510(k). Please note that prescription use to over the counter use is a major change in intended use and requires the submission of a new 510(k).

3. There is a change or modification of a legally marketed device and that change could significantly affect its safety or effectiveness. The burden is on the 510(k) holder to decide whether or not a modification could significantly affect safety or effectiveness of the device. Any modifications must be made in accordance with the Quality System regulation, 21 CFR 820, and recorded in the device master record and change control records. It is recommended that the justification for submitting or not submitting a new 510(k) be recorded in the change control records.

A new 510(k) submission is required for changes or modifications to an existing device, where the modifications could significantly affect the safety or effectiveness of the device or the device is to be marketed for a new or different indication for use. SeeIs a new 510(k) required for a modification to the device?for additional information.

When a 510(k) is Not Required

The following are examples of when a 510(k) is not required.

1. You sell unfinished devices to another firm for further processing or sell components to be used in the assembling of devices by other firms. However, if your components are to be sold directly to end users as replacement parts, a 510(k) is required.

2. Your device is not being marketed or commercially distributed. You do not need a 510(k) to develop, evaluate, or test a device. This includes clinical evaluation. Please note that if you perform clinical trials with your device, you are subject to theInvestigational Device Exemption(IDE) regulation (21 CFR 812).

3. You distribute another firm's domestically manufactured device. You may place a label on the device, "Distributed by ABC Firm" or "Manufactured for ABC Firm," (21

CFR 801.1) and sell it to end users without submission of a 510(k).

4. In most cases, if you are a repackager or a relabeler you are not required to submit a 510(k) if the existing labeling or condition of the device is not significantly changed. The labeling should be consistent with the labeling submitted in the 510(k) with the same indications for use and warnings and contraindications.

5. Your device was legally in commercial distribution before May 28, 1976 and you have documentation to prove this. These devices are "grandfathered" and havePreamendment Status. You do not have to submit a 510(k) unless the device has been significantly modified or there has been a change in its intended use.

6. The device is made outside the U.S. and you are an importer of the foreign made medical device. A 510(k) is not required if a 510(k) has been submitted by the foreign manufacturer and received marketing clearance. Once the foreign manufacturer has received 510(k) clearance for the device, the foreign manufacturer may export his device to any U.S. importer.

7. Your device is exempted from 510(k) by regulation (21 CFR 862-892). That is, certain Class I or II devices can be marketed for the first time without having to submit a 510(k). A list of the Class I and II exempted devices can be found onMedical Device Exemptions 510(k) and GMP Requirements. However, if the device exceeds the limitations of exemptions in .9 of the device classification regulation chapters (e.g., 21 CFR 862.9, 21 CFR 864.9), such as the device has a new intended use or operates using a different fundamental scientific technology than a legally marketed device in that generic type of device, or the device is a reprocessed single-use device, then a 510(k) must be submitted to market the new device.

Preamendment Devices

The term "preamendments device" refers to devices legally marketed in the U.S. by a firm before May 28, 1976andwhich have not been:

- significantly changed or modified since then;and
- for which a regulation requiring a PMA application has not been published by FDA.

Devices meeting the above criteria are referred to as "grandfathered" devices and do not require a 510(k). The device must have the same intended use as that marketed before May 28, 1976. If the device is labeled for a new intended use, then the device is considered a new device and a 510(k) must be submitted to FDA for marketing clearance.

Please note that you must be theownerof the device on the market before May 28, 1976, for the device to be grandfathered. If your device is similar to a grandfathered device

and marketedafterMay 28, 1976, then your device does NOT meet the requirements of being grandfathered and you must submit a 510(k). In order for a firm to claim that it has a preamendments device, it must demonstrate that its device was labeled, promoted, and distributed in interstate commerce for a specific intended use and that intended use has not changed. SeePreamendment Status for information on documentation requirements.

Third Party Review Program

The Center for Devices and Radiological Health (CDRH) has implemented a Third Party Review Program. This program provides an option to manufacturers of certain devices of submitting their 510(k) to private parties (Recognized Third Parties) identified by FDA for review instead of submitting directly to CDRH. For more information on the program, eligible devices and a list of Recognized Third Parties go toThird Party Review Program Informationpage.

Appendix B: The PMA Process

The information in this appendix is taken directly from the FDA?s official description of the Premarket Approval process (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm).

Overview

Premarket approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury. Due to the level of risk associated with Class III devices, FDA has determined that general and special controls alone are insufficient to assure the safety and effectiveness of class III devices. Therefore, these devices require a premarket approval (PMA) application under section 515 of the FD&C Act in order to obtain marketing clearance. Please note that some Class III preamendment devices may require a Class III 510(k). See “Historical Background” for additional information.

PMA is the most stringent type of device marketing application required by FDA. The applicant must receive FDA approval of its PMA application prior to marketing the device. PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s). An approved PMA is, in effect, a private license granting the applicant (or owner) permission to market the device. The PMA owner, however, can authorize use of its data by another.

The PMA applicant is usually the person who owns the rights, or otherwise has authorized access, to the data and other information to be submitted in support of FDA

approval. This person may be an individual, partnership, corporation, association, scientific or academic establishment, government agency or organizational unit, or other legal entity. The applicant is often the inventor/developer and ultimately the manufacturer.

FDA regulations provide 180 days to review the PMA and make a determination. In reality, the review time is normally longer. Before approving or denying a PMA, the appropriate FDA advisory committee may review the PMA at a public meeting and provide FDA with the committee's recommendation on whether FDA should approve the submission. After FDA notifies the applicant that the PMA has been approved or denied, a notice is published on the Internet (1) announcing the data on which the decision is based, and (2) providing interested persons an opportunity to petition FDA within 30 days for reconsideration of the decision.

The regulation governing premarket approval is located in Title 21 Code of Federal Regulations (CFR)Part 814, Premarket Approval. A class III device that fails to meet PMA requirements is considered to be adulterated under section 501(f) of the FD&C Act and cannot be marketed.

When a PMA is Required

PMA requirements apply to Class III devices, the most stringent regulatory category for medical devices. Device product classifications can be found by searching the Product Classification Database. The database search provides the name of the device, classification, and a link to the Code of Federal Regulations (CFR), if any. The CFR provides the device type name, identification of the device, and classification information.

A regulation number for Class III devices marketed prior to the 1976 Medical Device Amendments is provided in the CFR. The CFR for these Class III devices that require a PMA states that the device is Class III and will provide an effective date of the requirement for PMA. If the regulation in the CFR states that "No effective date has been established of the requirement for premarket approval," a Class III 510(k) should be submitted.

Please note that PMA devices often involve new concepts and many are not of a type marketed prior to the Medical Device Amendments. Therefore, they do not have a classification regulation in the CFR. In this case, the product classification database will only cite the device type name and product code. If it is unclear whether the unclassified device requires a PMA, use the three letter product code to search thePremarket Approval (PMA) database and the 510(k) Premarket Notification database. These databases can also be found by clicking on the hypertext links at the top of the product classification database web page. Enter only the three letter product code in the product code box. If there are 510(k)?s cleared by FDA and the new device is substantially equivalent to any of these cleared devices, then the applicant should submit a 510(k). Furthermore, a new type of device may not be found in the product classification database. If the device is a high risk device (supports or sustains human life, is of substantial importance in preventing impairment of human health, or presents a potential, unreasonable risk of illness or injury) and has been found to be not substantially equivalent (NSE) to a Class I, II, or III [Class III requiring 510(k)] device, then the device must have an approved PMA before marketing in

the U.S. Some devices that are found to be not substantially equivalent to a cleared Class I, II, or III (not requiring PMA) device, may be eligible for the de novo process as a Class I or Class II device. For additional information on the de novo process, see the guidance "New section 513(f)(2) - Evaluation of Automatic Class III Designation: Guidance for Industry and CDRH Staff" as well as the Evaluation of Automatic Class III Designation (De Novo) Summaries webpage.

Devices Used in Blood Establishments

The Center for Biologic, Evaluation, Research (CBER) has expertise in blood, blood products, and cellular therapies as well as the integral association of certain medical devices with these biological products. To utilize this expertise marketing and investigational device submissions (Premarket Notification, Premarket Approval, and Investigational Device Exemption) for medical devices associated with the blood collection and processing procedures as well as those associated with cellular therapies are reviewed by CBER. Although these products are reviewed by CBER, the medical device laws and regulations still apply. Thelist of medical devices reviewed by CBERare available on the Internet. In addition to CDRH guidance on Premarket Approval,specific medical device guidance for devices reviewed by CBERis available at online or by contacting:

Center for Biologics Evaluation and Research
Office of Communication, Training and Manufacturers Assistance (HFM-43)
1401 Rockville Pike, Room 200N
Rockville, MD 20852-1448 U.S.A.
Telephone Number: 301-827-2000 or 800-835-4709
Fax Number: 301-827-3843

Data Requirements

A Premarket Approval (PMA) application is a scientific, regulatory documentation to FDA to demonstrate the safety and effectiveness of the class III device. There are administrative elements of a PMA application, but good science and scientific writing is a key to the approval of PMA application. If a PMA application lacks elements listed in the administrative checklist, FDA will refuse to file a PMA application and will not proceed with the in-depth review of scientific and clinical data. If a PMA application lacks valid clinical information and scientific analysis on sound scientific reasoning, it could impact FDA's review and approval. PMA applications that are incomplete, inaccurate, inconsist, omit critical information, and poorly organized have resulted in delays in approval or denial of PMA applications. Manufacturers should perform a quality control audit of a PMA application before sending it to FDA to assure that it is scientifically sound and presented in a well organized format.

Technical Sections: The technical sections containing data and information should allow FDA to determine whether to approve or disapprove the application. These sections

are usually divided into non-clinical laboratory studies and clinical investigations.

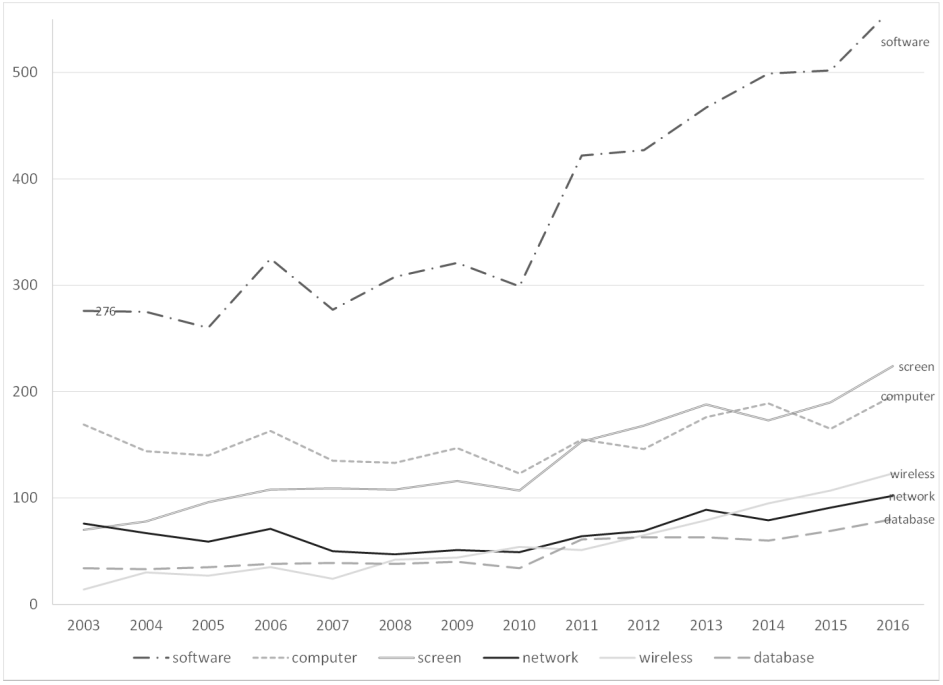
Non-clinical Laboratory Studies Section: Non-clinical laboratory studies section includes information on microbiology, toxicology, immunology, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests. Non-clinical studies for safety evaluation must be conducted in compliance with21CFR Part 58(Good Laboratory Practice for Nonclinical Laboratory Studies). To assist you in determining the appropriate preclinical bench studies for your device, refer to the applicable guidance documents and standards identified in theProduct Classificationdatabase for your device. You may also seek input from the review branch via thePre-Submission Program.

Clinical Investigations Section: Clinical investigations section includes study protocols, safety and effectiveness data, adverse reactions and complications, device failures and replacements, patient information, patient complaints, tabulations of data from all individual subjects, results of statistical analyses, and any other information from the clinical investigations. Any investigation conducted under anInvestigational Device Exemption (IDE)must be identified as such.

Like other scientific reports, FDA has observed problems with study designs, study conduct, data analyses, presentations, and conclusions. Investigators should always consult all applicable FDA guidance documents, industry standards, and recommended practices. Numerous device-specific FDAguidance documents that describe data requirements are available. Study protocols should include all applicable elements described in the device-specific guidance documents.

Appendix C: Additional tables and results

Appendix Figure I: New digital devices (F-P-Y level)



Appendix Table I: Machine readable documents by sample year

Year	Readable Documents	Total Products	% Readable
2002	2,573	2,587	99.5
2003	2,565	2,579	99.5
2004	2,476	2,505	98.8
2005	2,338	2,364	98.9
2006	2,430	2,450	99.2
2007	2,245	2,318	96.9
2008	2,333	2,382	97.9
2009	2,287	2,333	98.0
2010	2,168	2,242	96.7
2011	2,405	2,452	98.1
2012	2,466	2,502	98.6
2013	2,404	2,428	99.0
2014	2,509	2,552	98.3
2015	2,334	2,408	96.9
2016	2,261	2,328	97.1
Total	35,794	36,496	98.1

Based on 8 most common medical specialty areas (classes).

Appendix Table II: Keywords and overlap of each with MTI classification of software devices

Keyword (& acronyms thereof)*	Total devices	% Flagged by MTI as "software"
data	18,894	20%
internet	9,840	17%
software	6,788	73%
imaging	5,470	49%
display	5,107	50%
interface	3,728	40%
digital	3,249	47%
computer	2,779	58%
screen	2,278	49%
transmission	1,798	41%
platform	1,361	47%
network	1,187	62%
wireless	906	48%
database	757	57%
server	731	70%
programmable	714	48%
microprocessor	593	33%
digitally	464	27%
bit	418	58%
processor	381	48%
analog	359	39%
digitalimage	312	54%
ethernet	291	58%
bluetooth	287	35%
cpu	277	50%
LAN	232	66%
datastorage	223	57%
datacollection	221	45%
informationsyste	193	69%
touchscreen	183	31%
download	180	59%
online	161	48%
IT	133	39%
digitaldata	125	54%
harddisk	116	73%
bandwidth	110	63%

This list includes all keywords found in >100 unique product descriptions.

Appendix Table III: Firm experience summary statistics by product type, MTI

	Analysis sample (Full)	Non-Digital Devices	Digital Devices	T-Statistic (Digital vs. Non)
Software-MTI	(n=15,731)	(n=13,557)	(n=2,174)	(n=15,731)
Prior digital devices	3.36	2.22	10.47	-15.48
Prior digital devices (same class)	1.76	0.90	7.11	-16.90
Prior digital devices (different class)	1.60	1.32	3.37	-8.57

Notes: Digital devices defined using MTI-based classification. T-statistic is from a difference-in-means t-test with unequal variances comparing the non-digital vs. digital samples. All tests have a corresponding p-value of < 0.000.

Appendix Table IV: Geographic and within-firm capabilities, MTI

Logit model: digital device innovation							
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
State software employees (Ln)	0.004			0.005			0.005
	(0.004)			(0.004)			(0.004)
In digital device cluster		0.047***		0.025**			0.017*
		(0.010)		(0.008)			(0.008)
In digital device cluster for prod. class			0.087***	0.082***			0.071***
			(0.009)	(0.008)			(0.006)
Prior digital devices, internal (Ln)					0.034***		
					(0.005)		
Prior digital devices in class, internal (Ln)						0.061***	0.054***
						(0.009)	(0.008)
Prior digital devices in diff. class, internal (Ln)						-0.024***	-0.022***
						(0.006)	(0.006)
N	15,731	15,731	15,731	15,731	15,731	15,731	15,731

* p<0.05, ** p<0.01, *** p<0.001

All models include full set of time and product class fixed effects, marginal effects reported. Standard errors are clustered at the product code level. Digital devices are defined based on MTI method. Firm experience and clusters are defined using data from the prior five years.

Appendix Table V: Financial resources, MTI

Logit model: digital device innovation					
	(1)	(2)	(3)	(4)	(5)
Publicly listed firm	-0.009			-0.008	-0.008
	(0.008)			(0.008)	(0.008)
VC-funded firm		0.020		0.019	
		(0.010)		(0.011)	
Total VC funding, $ (Ln)			0.009*		0.009*
			(0.004)		(0.004)
N	15,731	15,731	15,731	15,731	15,731

* p<0.05, ** p<0.01, *** p<0.001

All models include full set of year and product class fixed effects. Standard errors are clustered at product code level, marginal effects reported. Digital devices are defined based on MTI method.

Appendix Table VI: Combined models and interaction terms, MTI

Logit model: digital device innovation							
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
State software employees (Ln)	0.005		0.003	0.003	0.003	0.003	0.003
	(0.004)		(0.003)	(0.003)	(0.003)	(0.003)	(0.003)
In digital device cluster	0.017*		0.015	0.014	0.015*	0.016*	0.016*
	(0.008)		(0.008)	(0.008)	(0.008)	(0.008)	(0.008)
In digital device cluster for prod. class	0.071***		0.071***	0.071***	0.063***	0.070***	0.070***
	(0.006)		(0.006)	(0.006)	(0.007)	(0.006)	(0.006)
Prior digital devices in class, internal (Ln)	0.054***		0.057***	0.057***	0.056***	0.054***	0.051***
	(0.008)		(0.008)	(0.008)	(0.008)	(0.008)	(0.008)
Prior digital devices in diff. class, internal (Ln)	-0.022***		-0.023***	-0.023***	-0.022***	-0.025***	-0.021***
	(0.006)		(0.006)	(0.006)	(0.006)	(0.006)	(0.005)
Publicly listed firm		-0.008	-0.022**	-0.022**	-0.022**	-0.023**	-0.023**
		(0.008)	(0.007)	(0.007)	(0.007)	(0.007)	(0.007)
Total VC funding, $ (Ln)		0.009*	0.009**	0.008**	0.001	0.003	0.001
		(0.004)	(0.003)	(0.003)	(0.004)	(0.003)	(0.003)
VC $ (Ln) * In cluster				0.003			
				(0.006)			
VC $ (Ln) * In cluster for prod. class					0.014**		
					(0.005)		
VC $ (Ln) * Prior digital devices (Ln)						0.008**	
						(0.003)	
VC $ (Ln) * Prior digital devices in class (Ln)							0.012***
							(0.004)
N	15,731	15,731	15,731	15,731	15,731	15,731	15,731

* p<0.05, ** p<0.01, *** p<0.001

All models include full set of year and product class fixed effects. Standard errors are clustered at product code level, marginal effects reported. Digital devices are defined based on MTI method. Firm experience and clusters are defined using data from the prior five years.