# Cultivating Biomedical Innovation

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This is to acknowledge that Kartik Agusala, MD has disclosed that he does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Agusala will not be discussing off-label uses in his presentation.

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Dr. Kartik Agusala is a clinical educator in the Division of Cardiology with a focus on cardiac imaging, serving as medical director of nuclear cardiology. He is a native Texan, having earned his medical degree at Baylor College of Medicine, then completing his medical training at McGaw Medical Center of Northwestern University and then Emory University School of Medicine. His main clinical interests are general cardiology, echocardiography and nuclear cardiology. His background in finance and investment banking prior to medical school led to his interest in health care venture development and biomedical innovation.

Purpose and Overview:

The purpose of this lecture is to introduce the basics of biomedical innovation, including current trends and impact on healthcare. This presentation will also overview the latest developments in cardiovascular clinical innovation and initiatives here at UT Southwestern. The establishment of a Technology Development Network to promote biomedical innovation amongst clinical faculty will also be discussed.

Educational Objectives:

- Understand the basics of biomedical innovation and process of commercialization
- Learn about ongoing trends in healthcare and clinical innovation, particularly within cardiovascular medicine
- Recognize the increasing role of academia in biomedical innovation
- Gain awareness of ongoing projects at UT Southwestern and creation of a Technology Development Network to engage clinical faculty

**Introduction**

The core mission of biomedical innovation is to transform research and ideas into products and services that reduce morbidity and mortality. Invention is the first occurrence of an idea for a new product or process, while innovation is the first attempt to carry it out into practice[1]. More specifically, an invention is a breakthrough in science or technology that extends the boundaries of human knowledge while innovation is the process of translating these new ideas into tangible societal impact through the development of products and services. This enterprise incorporates many research and clinical endeavors.

Advances in computing, digital technology and telecommunications will transform healthcare as they have other major industries and social norms. To what extent and how quickly remains to be seen, but roles of the physician and patient, the delivery of care and overall healthcare experience are already changing.

Here at UT Southwestern (UTSW), this mission is carried out by the Office for Technology Development (OTD), established in 1998. OTD is headed by Frank Grassler and has been successful in its tenure, having generated $194 million in license revenue and $363 million in sponsored research agreements. Approximately 685 patents have been issued on disclosed inventions and 876 license and option contracts have been executed. The year 2017 has set new records with 135 inventions disclosed by faculty leading to 97 patent applications and 38 issued patents, 70 license and option agreements, $11 million in license revenue and $29 million in sponsored research agreements[2]. OTD executes its work through four main divisions: technology commercialization, cooperative and sponsored research, venture development and financial management.


*Figure 1 – The Commercialization Process (from UTSW Office for Technology Development)*

**The Commercialization Process**

After any initial invention discovery, the commercialization process begins with disclosure of the invention by the faculty member to OTD (Figure 1). This initial step begins the ongoing discussion between OTD and the faculty and is an important part of the overall intellectual property (IP) protection strategy. There is an initial interval review in which OTD staff better understand the invention and its context while determining if there is prior art, a patent law term for whether the invention is already known. If an invention has been described in a similar fashion previously, then it may not be patentable. That being said, an invention can have significant commercial potential even if it is not patentable. Similarly, an invention may be patentable but not necessarily have commercial potential. Basic market research and analysis is conducted, the potential for commercialization is assessed and the OTD staff will determine whether to pursue some form of IP protection. Upon securing adequate IP protection, then OTD staff will move forward with commercializing the invention. The most common pathway of commercialization is licensing the invention to existing companies. A license agreement enables the patent rights of an invention to be used by another party in exchange of consideration, such as cash or stock, between the licensor and the licensee. In certain cases, a startup company is created and OTD licenses the technology to the startup company. As broad overview, 69% of the initial disclosures to OTD have been filed for patents with 24% of all initial disclosures resulting in issued patents[2].

The licensure of technologies initiates and sustains collaboration between UTSW and industry, generates revenue and research funding for UTSW and our inventors, facilitates the maturation of the North Texas biotechnology industry and most importantly, allows products and services to benefit society at large.

**Intellectual Property Protection**

Intellectual property (IP) is a generic term for the intangible property rights that are the result of intellectual effort. The main forms of IP protection are patents, copyrights and trademarks. A patent is an agreement between the US government and the inventor in which the government gives the inventor an exclusive right to benefit from the invention for a period of time, generally 20 years from the day the patent application is filed[2]. In exchange, the inventor discloses all relevant details of the invention to the public such as make and use. To be patentable, an invention must be novel and non-obvious, legal terms that imply that the new idea cannot be obviously derived from the sphere of public knowledge prior to the patent application date. A copyright is a form of IP protection for original works that are fixed in tangible form such as software, art, painting, literature, photographs and movies. Trademarks are words, symbols, phrases or designs that identify and distinguish sources of goods of one party from those of another. Depending on the particular invention, OTD determines which IP protection is most feasible.

**Ownership and Disclosure**

All inventions of UTSW employees are owned by the Board of Regents of the University of Texas System, as specified in the employment contract. Furthermore, inventions need to be disclosed if they are created using UTSW facilities, on UTSW time or if they relate to employment duties such as patient care, biomedical education or biomedical research. Given that IP protection can be greatly diminished if an invention is discussed in public before a patent application is filed, OTD recommends that all inventions be disclosed to OTD before public discussion or publication. If an inventor is unsure whether their idea constitutes an actual invention as opposed to a research outcome, OTD recommends disclosure of the idea to help with this assessment to help preserve IP protection.

UTSW has one of the most generous distribution policies in academia. UTSW will assume all upfront patent costs. Any revenue generated by the patent is first used to recoup the patent costs, then shared as follows: 50% to the inventor, 25% to the inventor's lab or subledger and 25% to UTSW.

**Biomedical Innovation and Healthcare**

Biomedical innovation can be broadly divided into two basic categories: basic science and clinical science. Basic science innovation involves the diagnostic and therapeutic potential of small molecules, peptides, biologics, nucleic acid therapies, vaccines, gene therapies and stem cells. Clinical science innovation involves medical devices, the broad area of information technology and innovation in healthcare delivery.

**Major Healthcare Trends**

There are several major trends currently shaping the U.S. healthcare system. The Affordable Care Act was designed to start the transition from a traditionally volume driven, fee for service model of care to a value based system that promotes desired outcomes, reduces cost and increases access. Reimbursement models are increasingly rewarding team-based care, such as through Accountable Care Organizations (ACOs), that is driven and measured by quality. Advances in computing are allowing large data acquisition and analytics to better understand patterns on a macro level, known as population medicine. Simultaneously, ubiquitous smartphone technology, advanced telecommunications and wearable sensors are promoting the Internet of Things and a deeper understanding of individual risk and treatment known as precision health. Patients are becoming increasingly empowered as they gain access to medical knowledge, have more direct contact with healthcare providers and own their own medical information. Advancements in machine learning and deep learning have led to the emergence of Big Data, in which large, complex data sets can be studied for patterns and relationships never before seen. These trends are also affecting the methodology and execution of clinical research. For example, the ongoing ADAPTABLE trial, studying the cardiovascular benefit of aspirin 81mg vs 325mg, is a pragmatic clinical trial with data directly obtained from the electronic medical record.

Well known, established technology companies have heavily invested in healthcare. Alphabet Inc. (the parent company of Google LLC) has three healthcare focused companies: DeepMind Health, the health arm of their artificial intelligence company, Verily, a population health data company, and Calico which is focused purely on the science of longevity. Apple, Inc. has released CareKit and ResearchKit which are open source frameworks which allow users to build software applications to manage medical conditions and better enroll patients in research studies, respectively. IBM's Watson is a vast undertaking using artificial intelligence in many areas of healthcare, from interpreting genetics tests to helping an interventional cardiologist choose the best guidewire for an intervention.

To what extent and how quickly these trends actually change the delivery and experience of healthcare for patients and providers remains to be seen. Regardless, numerous products and services have emerged over the last 10 years and have already started changing the traditional landscape.

**Medical Devices**

A medical device is defined as an instrument used to diagnose, prevent or treat disease or affect structure or function in a man or animal where the primary action is not chemical. Medical devices are regulated by the FDA Center for Devices and Radiological Health and are classified into three classes that are subject to progressively more regulatory control. There are several novel implantable and nonimplantable medical devices developed recently in cardiovascular medicine. The CardioMEMs™ HF System, created by St. Jude Medical, Inc., is the first and only FDA approved wireless, implantable pulmonary artery pressure monitor. Use of CardioMEMS™ in 550 NYHA Class III systolic and diastolic congestive heart failure (CHF) patients showed 37% reduction in CHF admissions at 6 months, with 99% of patients free of device complications[3]. The Micra™ transcatheter pacing system, created by Medtronic plc., is the world's smallest pacemaker and is delivered percutaneously into the right ventricular without intracardiac leads. It is 93% smaller than conventional pacemakers, has >99% successful implantation rate and lasts 12 years with fewer procedural complications than traditional pacemakers[4].

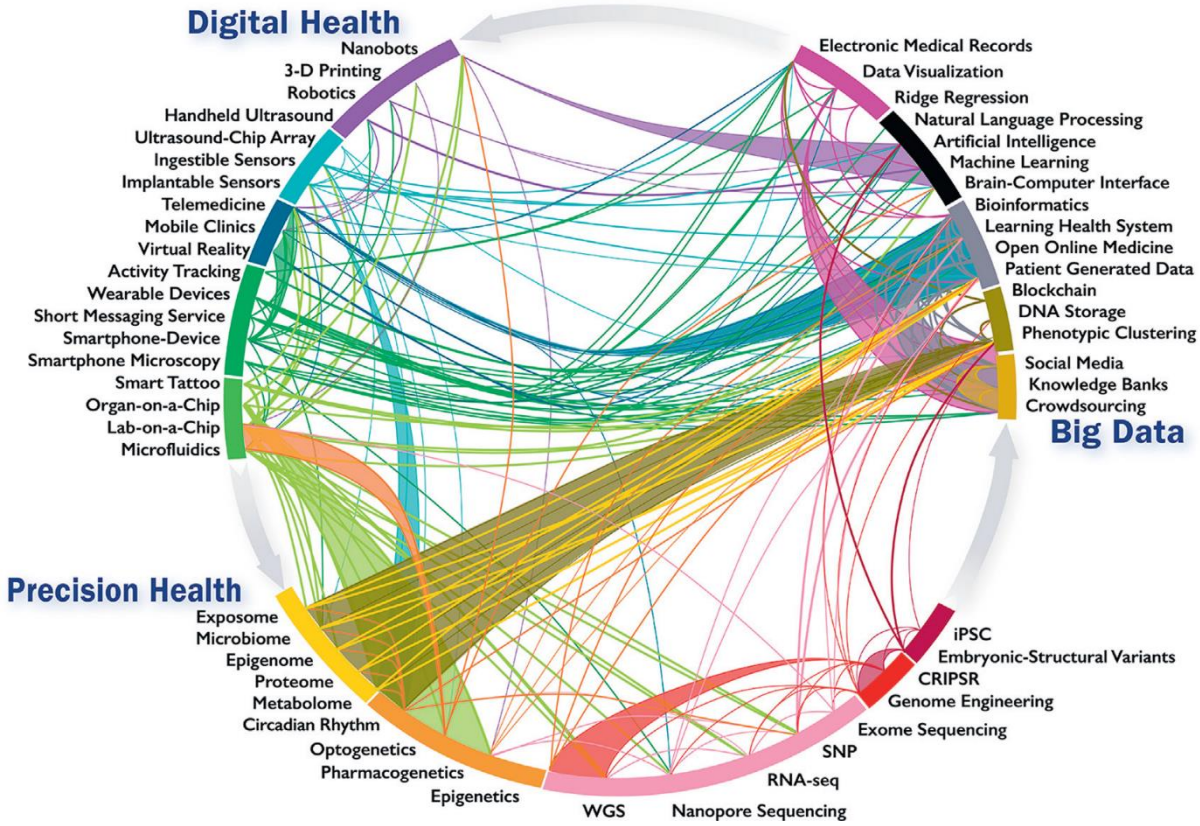


*Figure 2 – Digital Health vs Big Data (from Bhavnani, S.P., et al., 2017 Roadmap for Innovation, JACC 2017)*

**Digital Health**

Perhaps the fastest growing field in clinical innovation is digital health, as indicated by the recently termed digital health revolution. Digital health includes mobile health (mHealth), health information technology (IT), wearable devices, telehealth and telemedicine (Figure 2). The FDA has created a new Digital Health Program to help regulate this rapidly expanding area. These fields are steadily extending the healthcare experience outside of the traditional clinic and hospital setting, allowing patients to gather and communicate biometric data, communicate electronically with physicians and experience virtual medical encounters.

Use of mobile health devices is steadily increasing as providers and patients become more aware and comfortable with these technologies. In particular, use of pocket echocardiography (Figure 3) is a major advent that can reduce the time to assess cardiac structure and function. This advantage was demonstrated by Bhavnani et al where pocket echocardiography and smartphone connected devices (EKG, blood pressure monitor and pulse oximeter) reduced the time to percutaneous valvuloplasty or surgical valve replacement for patients with rheumatic heart disease[5]. The REHEARSE-AF study demonstrated that use of AliveCor's Kardia device (Figure 4), an FDA approved medical grade mobile EKG monitor, was significantly more effective (hazard ratio of 3.9) compared to routine care in all patients greater than 65 years of age with

CHADS2vasc score of 2 [6]. KardiaBand™ from AliveCor (Figure 4), is also FDA approved and replaces the Apple Watch wristband to more seamlessly capture user's data.


*Figure 3 - VScan Pocket Echocardiography (from GE Healthcare)*

The use of mobile communication technologies to improve health, known as mHealth, has dramatically risen since 2008 when the term gained widespread use, with approximately 318,000 mHealth apps now available[7]. However, health technology evidence supporting their use is very limited with recent data demonstrating no significant improvement in patient outcomes[7]. Nonetheless, the ubiquitous and ever increasing use of smartphone technology positions mHealth as a major opportunity to effect better patient care. For example, the Corrie Health application, developed at Johns Hopkins using Apple's CareKit open source framework, engages patients who have suffered a myocardial infarction in the post-discharge period to improve diet, exercise, medication compliance and other fundamentals of health. A small pilot study of 60 patients showed a cost savings of $262,000 achieved by preventing readmissions (CorrieHealth.com). More broadly, a smartphone based method of cardiovascular data collection and analysis was proven feasible through the MyHeart Counts Cardiovascular Health Study in which nearly 50,000 people used the MyHeart Counts iPhone application to record physical activity and fill out health questionnaires. Machine learning algorithms were then applied to cluster participants and associations to better identify patterns and behaviors[8].


*Figure 4 - KardiaMobile™ and KardiaBand™ (from AliveCor)*

**Artificial Intelligence**

Artificial intelligence (AI) is defined as a computer system that can perform human intelligence-like tasks such as logical reasoning, problem solving, decision making, natural language processing, visual perception, speech recognition and object manipulation. Over the last three decades, machine learning (ML), which uses self-improving and self-learning algorithms based on large data set analysis, has significantly advanced the application of AI to healthcare. Moreover, in the last several years, deep learning, which uses multi-layered neural networks to more efficiently process data, has significantly advanced application of AI to healthcare. For example, ML was applied to research methodology in a novel way by phenomapping the classification of heart failure with preserved ejection fraction. In this study, machine learning analyzed numerous phenotypical characteristics, including many clinical metrics, EKG and echo criteria, to develop a new classification of heart failure with preserved ejection fraction into three distinct phenotypes. These phenotypes not only reflected different patient populations but also had statistically different cardiovascular outcomes, which may be an opportunity in the future for targeted therapies[9].

Several recent studies have demonstrated the power of ML to accurately predict future cardiovascular risk. ML was superior to traditional risk scores, such as the Framingham Risk Score (FRS), in predicting 5-year all-cause mortality when applied to cardiac CTA findings in the CONFIRM registry (AUC ML: 0.79 vs. FRS: 0.61, $p< 0.001$)[10]. When ML was applied to a combination of echocardiographic and clinical variables, it more accurately predicted 5-year all-cause mortality than FRS and ACC/AHA guidelines (AUC ML: 0.89, FRS: 0.61, ACC/AHA guideline: 0.74)[11].

ML is also being used to improve the interpretation of cardiac images. The FAST-EF study demonstrated the feasibility, consistency and accuracy of using ML to automatically trace the endocardial borders on echocardiography to determine LV ejection fraction. The process took an average of 8 seconds and correlated well with manually traced LV ejection fraction with essentially no variability[12]. While the FAST-EF study required users to first identify the proper image before applying ML, research is already being done to automate this step as well. A recent study demonstrated that deep learning neural networks are highly accurate in classifying numerous echocardiographic images into the 15 standard imaging views. The overall accuracy was 98% and for single low-resolution views, the ML algorithm performed better than board certified echocardiographers (92% vs 70-84%)[13].

Another major development in information technology is large data analytics, known as Big Data (BD). Big data is defined as an extremely large data set that can be analyzed to reveal patterns and interactions, only recently possible with advances in computing speed and capacity. With further advances in BD, the hope is to move from simple descriptive analytics (*what happened?*) and diagnostic analytics (*why did it happen?*) to predictive analytics (*what will happen?*) and prescriptive analytics (*how can we make it happen?*). Prescriptive analytics in healthcare is currently offered through automated clinical decision support tools which aim to

maximize value for effort by helping providers adhere to optimal clinical pathways and reduce practice pattern variability. For example, MayoExpertAdvisor is an application which leverages patient data using natural language processing and data analysis of the electronic medical record to generate specific management recommendations, along with supporting data, relevant calculations and risk scores[14]. A recent study demonstrated that use of MayoExpertAdvisor to assess cardiovascular risk to guide cholesterol management saved primary care physicians significant time, clicks and keystrokes and improved risk score accuracy and guideline-consistent treatment recommendations from 60% to 100%[15]. SMARTCare (Figure 5), funded by a $15.8M grant from the Center for Medicare and Medicaid Innovation, is a novel clinical decision support tool for the management of stable ischemic heart disease. It provides a variety of embedded tools along the care continuum that leverage registry and other databases to assist providers and patients at each decision point, such as the appropriate of stress testing, cardiac catheterization, stenting, procedure quality and follow-up.

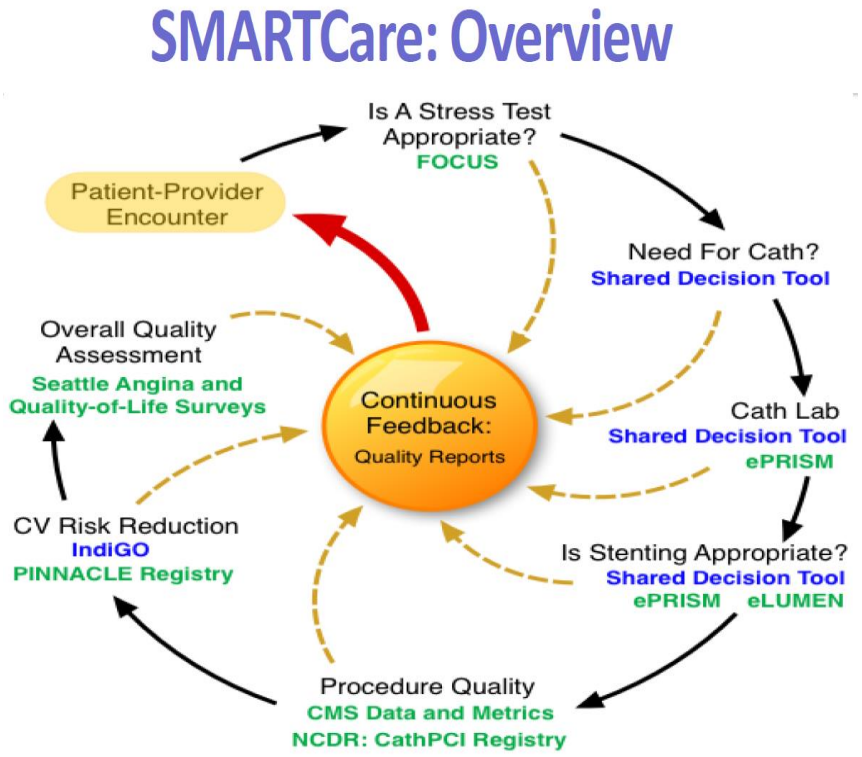


*Figure 5 - SMARTCare Overview (from Brindis, R. ACC CV Summit Presentation, 2016)*

These innovations in clinical medicine have the potential to fundamentally change the delivery of healthcare. As illustrated in the utopian "Digitized Cardiovascular Physician Visit" (Figure 6), technology can liberate both patients and providers from the many inefficient and impersonal aspects of the current healthcare paradigm and allow a more meaningful, direct connection with truly shared decision making and health empowerment.

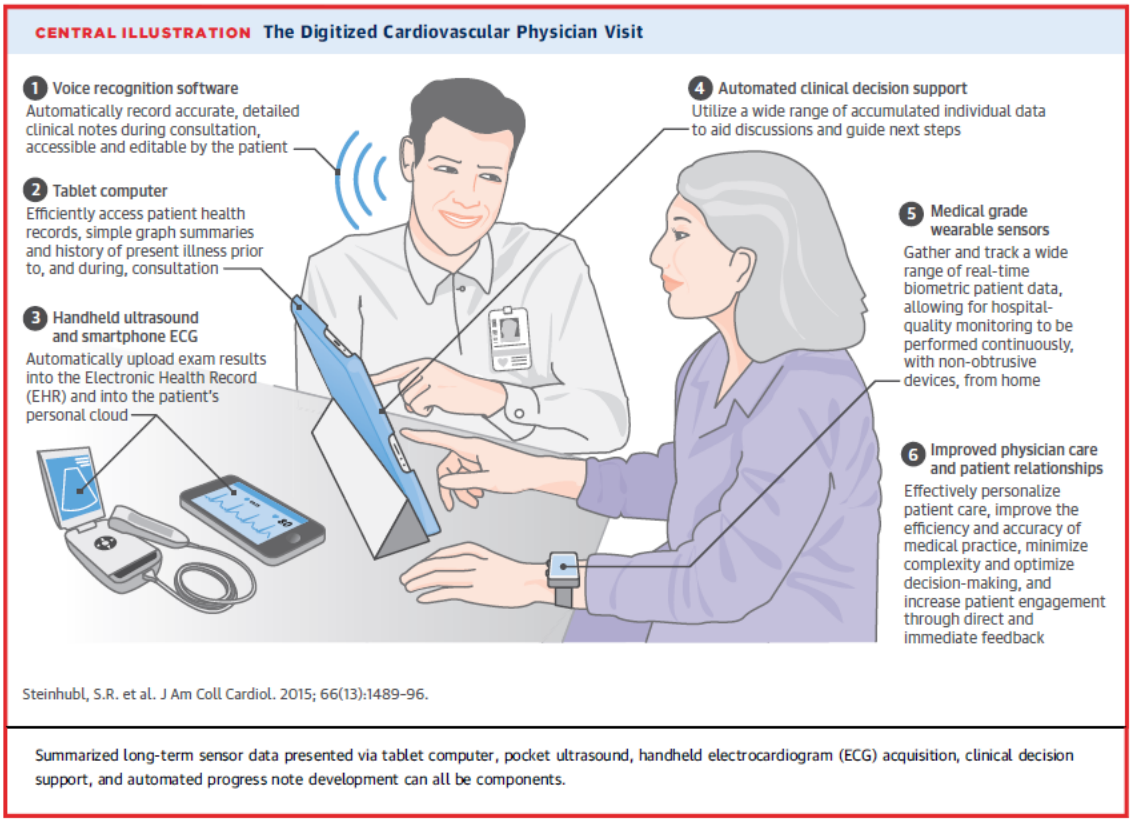


*Figure 6 – The Digitized Cardiovascular Physician Visit*

**Barriers to Healthcare Technology Adoption**

Despite their vast potential, there are significant barriers to the adoption of these novel technologies. Traditionally, a clinical need drives the development of a valuable product or service. Critics argue that many of these novel technologies are developed hastily outright and then unsuccessfully applied to a clinical need, which has led to many low value products and services. Probably most important, health technology evidence demonstrating improvement in outcomes is lacking for most of these novel technologies. Furthermore, there are numerous barriers to integration into the existing healthcare infrastructure and workflow such as technology, cost, time, billing, and reimbursement. Apart from potential provider burnout of assimilating the large amount of patient data provided by these technologies, there are legitimate medicolegal and responsibility concerns as well.

FDA regulatory approval is often a lengthy and rigorous process that has difficulty keeping pace with these rapidly progressive technologies. In an era of major international data breaches, patient data security and privacy is of utmost importance and earning social trust is necessary and appropriate. And more fundamentally, many fear that as these technologies continue to empower patients, they will lessen the scope and relevance of healthcare providers.

**The Role of Academic Medical Centers**

Academic medical centers have traditionally focused on the tripartite mission of education, research and patient care. The role of biomedical innovation in the academic mission was unclear. However, innovation and technology transfer from academics to industry has been an important contributor to economic and societal advancement. From 1996 to 2016, academic research in the U.S. led to the formation of 12,000 new startup companies, 4.3M jobs and $1.3 trillion in U.S. gross industrial output[16]. Due to multiple factors including research funding pressures, academic medical centers have invested into biomedical innovation, as evidenced by the significant increase in the number and depth of biomedical innovation programs at top-tier institutions. Major academic medical societies have also increased their support of this initiative. A statement from the American Heart Association (AHA) advocates for the creation of a Clinician Innovator pathway, a new career pathway in academic medicine for those physicians focused on the intersection of healthcare and emerging technologies[17]. The AHA also created the Center for Health Technology and Innovation in 2016 to improve collaboration between industry and healthcare providers in digital health initiatives. The American College of Cardiology (ACC) released a health policy statement on biomedical innovation in 2017 that focused on digital health, big data and precision health and also created a new Innovation Member Section[18]. There are numerous major collaborations between academia and industry to bolster biomedical innovation such as the Apple Heart Study (Apple and Stanford), Health eHeart (Apple and University of California, San Francisco), Project Baseline (Google, Verily, Duke, Stanford) and JLABS (Johnson&Johnson, Texas Medical Center).

There are valid concerns regarding the motivation for academic medical centers to engage in the commercialization of biomedical innovation, including conflict of interest and profit maximization. However, if the underlying motivation is to move forward products and services that advance healthcare in the right direction and commercialization helps translate those discoveries into therapies that can benefit patients and providers worldwide, then biomedical innovation is simply an extension of the academic mission of patient care. Given that government and private industry are already active in this space, academic medical centers and societies are now appropriately prioritizing this endeavor to ensure that the future of healthcare represents the interests of patients and providers.

**Technology Development Network**

Clinical care is fertile ground for biomedical innovation. The various obstacles that clinical faculty routinely face are opportunities to innovate and improve the delivery of care for both providers and patients. Creating a product or service to practically address an existing clinical need leads to high value improvements that provide greater societal benefit.

At UTSW, many clinical faculty are unaware of OTD, its mission and its resources. Given the vast opportunities for biomedical innovation that arise from clinical workflow, increasing clinical

faculty involvement is already a focus of many top tier academic medical centers and is a major growth opportunity at UTSW.

Increasing UTSW's clinical faculty involvement in biomedical innovation will lead to increased patent submissions, licensing opportunities, sponsored research agreements and new venture startup companies. Clinical faculty will directly benefit from any revenue streams generated by their ideas, from consulting opportunities with startup companies and venture capital firms and the greater societal impact of their ideas.

An effective way to increase clinical faculty involvement is to create a Technology Development Network, comprised of clinical faculty across campus, with three main goals:

- Promote biomedical innovation and increase awareness
- Support the innovation process with development teams
- Increase UTSW's external presence

Interested faculty will promote biomedical innovation on a division and department level and raise awareness of OTD and its resources. They will give initial feedback to colleagues with innovative ideas, help channel invention disclosures to OTD, evaluate other faculty's patent submissions and mentor UTSW medical students in the biomedical innovation elective.

Clinical faculty face significant time pressure and often lack knowledge on how to move an innovative idea towards a patentable product. Because it is a standalone academic medical center, UTSW lacks an established business, engineering, computer science or law school, which naturally creates a need to partner with local institutions for development support. Work is ongoing to establish such a support system by partnering with local institutions such as the University of Texas at Dallas and Southern Methodist University. These teams, comprised of engineering, computer science, legal and business personnel, will provide product planning, business development, regulatory and funding guidance and mentorship to UTSW clinical faculty to help progress ideas towards patentable prototypes.

This technology development network requires significant collaboration with local institutions and, over time, will benefit and grow the North Texas venture ecosystem while increasing UTSW's presence and brand recognition regionally and nationally. Startup companies and venture capital firms often seek expert consultation from the academic community when developing new products or evaluating new investments. Members of this technology development network will be given consulting opportunities as they arise, which will also broaden UTSW's external presence. These same venture capital and industry partners can be leveraged for funding and collaboration for future UTSW ventures.

**Conclusion**

Advances in telecommunications, computing power, and the digital health revolution have set the stage for fundamental changes in the healthcare experience for patients and providers.

Clinical care is fertile ground for innovation as demonstrated by the numerous advances mentioned. Clinical innovation is a growing priority for major academic medical centers and societies and is important to help shape the future of healthcare.

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