ABSTRACT

Despite advances in knowledge and technology, approaches to health care discovery and delivery have not broadly kept pace with those advancements. While there have been notable improvements in shaping diagnosis and treatment resulting from knowledge made available through advances in technology, the field generally uses broad population characteristics as the basis for determining the health of, and how to treat, individuals. Today, with the confluence of big data and artificial intelligence (AI), we have an opportunity to tailor diagnoses and treatments precisely as needed for an individual—in other words, to practice precision medicine. The Johns Hopkins University Applied Physics Laboratory (APL) and Johns Hopkins Medicine (JHM), in partnership with the Bloomberg School of Public Health, Johns Hopkins Information Technology, and others across the institution, are working to usher in this new paradigm. These organizations jointly developed the Precision Medicine Analytics Platform (PMAP). This platform pulls data from many sources, aggregates the data, and then provisions needed data to approved researchers in a secure environment where they can apply advanced techniques and other tools to analyze the data. The guiding vision is to create and sustain the ability to accelerate gaining knowledge and value from data and from closing the loop between discovery and delivery, ultimately reducing health care costs and improving patient outcomes.

INTRODUCTION

Today, two decades into a new millennium, the fields of biomedical research and health care stand upon centuries of knowledge about the function of the human body and how to care for the ill or injured. The knowledge that fueled these advancements was gained from what has been the cornerstone of medicine since antiquity: using the scientific method—the hypothesis-driven systematic use of observation to learn. In the earliest days of medicine, practitioners literally used their senses to observe the human body to develop approaches to maintain or restore individuals’ health. As time passed and the field evolved, use of provider senses increasingly became complemented by technology to observe and learn with great resolution, frequency, and accuracy.

Drawing on these technologies, providers mapped individuals into broad classes or populations based on
measures or observables such as age, gender, weight, heart rate, blood pressure, and blood chemistry. These measurements have stood the test of time as very important characteristics (“vital signs”) that provide insight into the health of an individual and serve as a basis for shaping how individuals are treated. Technological advancements have, however, made it possible to consider augmenting this approach by potentially enriching the provider’s insights by revealing aspects of an individual’s health that might otherwise be hidden absent capitalizing on these new technologies.

Today, we stand poised to capitalize on the true promise of precision medicine—the ability to accurately tailor diagnosis and treatments precisely as needed for an individual. Technology-driven disruptive forces will advance and accelerate knowledge faster than ever before, leading to greater insight into clinically relevant and biologically anchored dynamics that define an individual’s health and health state. These technology-driven disruptive forces result from the confluence of primarily two advancements: big data—the ability to rapidly collect torrents of disparate data about individuals and populations—and artificial intelligence (AI)—the ability of computers to perform tasks and actions traditionally performed by humans, such as learning, reasoning, and decision-making at massive scale. The global impact of big data and AI is being felt in diverse industries ranging from defense, intelligence, transportation, consumer economies, and health and health care. APL is harnessing experience with big data and AI in several of these industries to partner with Johns Hopkins Medicine (JHM) to disrupt health care today, just as JHM did in the late 19th century—this time through the power of precision medicine.

THE VISION FOR PRECISION MEDICINE AT JOHNS HOPKINS

Health care has benefited substantially from technological advancements and groundbreaking discoveries. Some cancers can be detected earlier. Previously deadly or severely debilitating conditions can be kept at bay or cured. While these advancements have improved the quality of life for individuals and have, in many cases, reduced the overall cost of care and extended lives, it is widely recognized that the ability to diagnose and treat conditions—ranging from influenza, certain cancers, and chronic conditions such as cardiovascular disease, arthritis, and diabetes—is hindered by inefficiencies and lost learning opportunities in biomedical discovery and health care delivery. After the underlying causes of illness and injury are discovered, it can take decades and enormous sums of human and financial capital to develop effective treatments. Furthermore, individuals often are treated uniformly (e.g., with a single seasonal influenza vaccination or broad-spectrum antibiotics) rather than with treatments tailored to their specific characteristics (see Figure 1). Under the pressure of health care’s growing financial impact, which in the United States is approaching 18% of the gross domestic product with little to show for extended health or life span, the health care field has come to the realization that traditional approaches to biomedical research and health care delivery will only continue the escalation in cost and the toll on human life.

JHM was at the forefront of an earlier realization about the state of medical research and health care delivery. In the late 1800s, under the leadership of William Welch and with support from leading researchers and providers of that age, JHM pioneered a methodical and systematic approach to using science to understand the human body and the afflictions that impact it. The result was a new era of knowledge, education, training, and policy. Today, JHM has come to a newer realization about the current state of research and health care delivery and has established the Hopkins inHealth initiative (https://www.hopkinsmedicine.org/inhealth/) to harness the emergence of big data and AI as a force to reinvent medicine in the form of precision medicine.

In this precision medicine paradigm, which might actually be thought of as “accurate medicine,” patients realize value from health care’s ability to tailor treatment to the individual. This tailoring is enabled by accumulating enough data from large populations of individuals such that a specific individual can be placed among “peers” in granularly defined subpopulations with like characteristics—characteristics that are far more descriptive and extensive than those used in today’s generalized approach of describing people by gender, age, weight, and even genomics. At JHM, precision medicine

Figure 1. Traditional treatment approach versus precision medicine treatment approach. In the current approach (left), individuals often are treated uniformly (e.g., with a single seasonal influenza vaccination or broad-spectrum antibiotics). In the precision medicine approach (right), treatments are tailored to individuals’ specific characteristics.
means drawing on hundreds or thousands of characteristics far beyond today’s norm of a handful of measures to describe people and their health state.

It is JHM’s vision (Figure 2) to accelerate the cycle of discovery and delivery by fueling it with massive amounts of disparate data that describe the social, behavioral, environmental, and biological characteristics of individuals. The process will also be informed by knowledge of fundamental basic science and the knowledge and wisdom of clinicians. This new paradigm aims to unveil a new era of medicine that is less costly in terms of both financial impact and the toll on human life.

THE PROMISE OF BIG DATA AND PRECISION MEDICINE

Until recently, big data, characterized by its volume, velocity, variety, and veracity, could hardly be used to describe health-related data. Visits to doctor’s offices typically provide the only opportunity to systematically collect data regarding an individual. Aside from routine annual checkups, these visits usually occur when the individual is already ill or injured, and they involve the collection of a limited number of measurements considered indicative of one’s health state. These measures are collected along with laboratory blood and other tests (e.g., swabs and x-rays) if there is some indication of a latent, emerging, or present illness or injury. With the regulatory-driven move to electronic health records in the United States, these intersections (i.e., visits) with providers greatly amplify the volume, velocity, and variety of digitally collected data regarding individuals.

No longer, however, are doctor’s offices visits the only way to gain visibility into the measures traditionally used to define one’s health at a particular time. The near ubiquitous presence and availability of digital health technology—sensors, smartphones, Internet of Things (including the Internet of Medical Things), and wearable devices—enable the ability to gain insight into the social, behavioral, environmental, and biological determinants of an individual’s health and health state continually over time. As a result, the answer to the question “Is this person healthy, ill, injured, or healing?” may be held within the disparate data we can now collect longitudinally over time at massive scale.

Although electronic health record data are often fragmented among providers and are notoriously error prone (i.e., have limited veracity), and the digital health technology industry is in its infancy with wearables being largely considered recreational-grade sensors, the digitization of medical data means that the big data trend is becoming realized in the health domain and is poised only to improve the veracity and clinical utility of collected data.

What does this big data emergence mean for precision medicine? It means that if we explicitly believe that the data collected about an individual hold the answer to their health state, then if we collect enough similar data from large populations of other people, we can discern where an individual resides relative to others in terms of their individual health state. With enough population-level data accumulated, we can define treatments and care pathways for an individual based on what we learn from the treatments and care pathways of other like individuals. This is equivalent to what Netflix, Amazon, and other tech-driven firms are doing today with consumer behavior—that is, they monitor the purchases an individual makes, along with their clickstream digital exhaust, to tailor the presentation of

Figure 2. JHM’s precision medicine vision. Precision medicine seeks to use big data, knowledge of basic science, and wisdom of clinicians to speed up the cycle of discovery and delivery, ultimately reducing health care costs and improving outcomes.
content and offerings (i.e., to give the consumer what they want/need). These companies’ value proposition is to further their bottom-line revenue. For the health domain, the value proposition of accumulating these data is improved outcomes at lower cost.

Achieving this value proposition in a field that still has remnants of its cottage industry age will not be easy. Just a few of the paradigm shifts the domain will need to implement to realize the power of big data for precision medicine are policy changes related to data access; rethinking legacy information technology (IT) infrastructure that tends to put data into inaccessible silos; and a change in mind-set away from the traditional “small data” mentality of the past to a realization that more health data may be collected outside the walls of a clinic, hospital, or research laboratory than inside.

THE PROMISE OF AI AND PRECISION MEDICINE

Collection of massive amounts of disparate data is a necessary enabler for precision medicine, but collection alone is not sufficient to fully realize the promise. Generating meaningful value from these data is also necessary, and that can only be done through analytics. In the age of small data in health care, traditional statistical analysis proved to be adequate to discern mean- ing from data collected during clinical encounters and research studies. Today, however, with the abundance of complex and highly dimensional data, these statistical analysis techniques—and the ability to perform these analyses at massive scale—are quickly being outpaced by more advanced methods of AI. (See the article by Piorkowski, in this issue, for more on APL’s data science contributions.)

Traditional statistical analysis techniques have formed the basis for the scientific method applied to biomedical and health research for centuries. This analysis approach involves establishing a hypothesis and then using well-defined mathematical methods to arrive at conclusions that either prove or disprove the hypothesis, along with confidence measures to characterize the strength of the proof. AI techniques such as random forests, convolutional neural networks, and other deep learning and machine learning techniques are ushering in a new age of analytic approaches into biomedical and health research. These AI techniques—coupled with big data, which provides the high dimensional- ity of today’s health analytics—offer a complementary approach to the traditional hypothesis-driven approach. That is, the AI/big data approach affords a means to “let the data inform the hypothesis” rather than having to rely solely on the wise clinician/researcher to define the hypothesis; this is perhaps better characterized as “hypothesis generating research.” These complementary approaches are an example representation of human–machine teaming, which capitalizes on the relative strengths of humans and machines (i.e., AI) and compensates for the weaknesses of each. Figure 3 illustrates the process.

As with the application of any new technology to a new domain, there are fits and starts in terms of successes and failures. The highly visible misstep of the IBM Watson initiative at MD Anderson is an example of the fate many early adopters encounter. Yet there are lower-profile examples of successes in focused areas. Among these breakthroughs are CE Mark, Paige’s computational pathology AI-based decision support for pri- mary diagnosis of prostate cancer, announced in 2019, the Google, University of California, San Francisco, and Stanford collaboration demonstrating the power of deep learning applied to electronic health records, and many others.

At Johns Hopkins, as part of Hopkins inHealth precision medicine research, we are beginning to see early indications of value from AI applied to health data associated with a variety of clinical conditions. While our approach has been focused within condition-centric centers of excellence, we have undertaken development of analytical tools and methods with an eye toward

Figure 3. AI/big data in precision medicine. Incorporating AI techniques complements the traditional hypothesis-driven approach to biomedical and health research. With the AI/big data approach, the data can inform the hypothesis rather than the clinician/researcher being required to define the hypothesis at the outset.
generalizability across conditions. Accordingly, we have developed, for example, a natural language processing (NLP) toolbox that provides researcher- and clinician-facing means for bringing meaning to unstructured text—nearly all our centers of excellence have a need for such NLP capabilities.

We have applied machine learning methods that process highly dimensional input data, including electronic health records, imaging, and patient-reported outcomes, to produce and define clusters of subpopulations among patients with multiple sclerosis, along with methods to discern which features are most important in defining these subpopulations. Further, we have developed tools that map health-state trajectories of patients within each of these subpopulations, thus defining the basis for predicting how a given individual patient with multiple sclerosis may progress based on the cohort of other patients with similar characteristics across the highly dimensional space.

While AI applied to health is still in its early days, we can see bright spots of promise in today's state of the art. Looking toward the future, we can see the potential to realize value from data that have historically landed “on the cutting room floor,” such as data from failed drug trials. In fact, we can see the potential to radically change the approach to how clinical trials are performed today. We can see the potential to improve diagnosis for patients who have a variety of illnesses or injuries. However, we will not see any of this value without a new approach to how data are collected, organized, and provisioned.

WHERE WE STAND TODAY—THE PRECISION MEDICINE ANALYTICS PLATFORM

The hallmark of JHM's revolution in medicine in the late 19th century was the coupling of discovery and the delivery of medicine. This pairing has produced remarkable breakthroughs that have improved the lives of many worldwide. While this connection continues today, it is not as robust as needed to realize the promise of precision medicine. Team approaches to translational biomedical discovery and clinical care exist; however, many areas in the research domain operate in a loosely coupled manner. That is, each research effort operates independently—each researcher undertakes their hypothesis-driven study, independently accesses clinically obtained data from the electronic health record, and gathers study-specific data via stand-alone databases, repositories, and registries. The researcher creates software tools to access, manipulate, process, and visualize these data using independently developed, maintained, and updated approaches—institutional review and approval of requests for access to these data are also handled on a case-by-case basis. Data and tools are shared only in limited cases and, more important, sharing of lessons learned and cross-pollination related to clinical insights are limited within narrow channels of communication.

This approach to biomedical discovery is unsustainable—it cannot withstand the disruption created by the confluence of big data and AI. Legacy health IT, principally the electronic health record, which had been the source for many research studies, is suitable for coding and billing but not a sustainable basis for clinical research in the age of big data. Further, disaggregated registries and repositories are also contrary to the needs of AI-based approaches, which thrive on highly dimensional data. A new approach is needed if the power of these disruptive forces to revolutionize the practice of medicine is to be realized. See Figure 4 for an illustration of the traditional approach versus the precision medicine approach.

This existential need is what drove the partnership between JHM and APL to jointly develop the Precision Medicine Analytics Platform (PMAP). From the inception of PMAP development in 2016, the guiding vision

![Figure 4. Traditional biomedical discovery process versus precision medicine discovery process. In the traditional discovery process (left), each researcher independently accesses clinically obtained data from the electronic health record and gathers study-specific data via stand-alone databases, repositories, and registries. In the precision medicine discovery process (right), disparate, high-velocity, high-volume data are aggregated into a single repository.](image-url)
was to create and sustain the ability to accelerate gaining knowledge and value from data and from closing the loop between discovery and delivery in this new era of big data and AI.

PMAP handles the “dirty work” of creating pipelines to access disparate, high-velocity, high-volume data (i.e., big data). It aggregates these disparate data into a harmonized and normalized single Data Commons to facilitate access, obviating the existence of multiple researchers independently creating different tools to access the same data and storing them separately. The Data Commons affords a single repository that combines the transactional data of the electronic health record with other sources of data while also providing a single point of storage from which secure study-specific projections of data can be provisioned to researchers with institutional approval to access them. See Figure 5 for an illustration.

Figure 5. The PMAP platform. PMAP pulls data from many sources and aggregates the data into the Data Commons. The data can then be provisioned to approved researchers in a secure Research Environment where they can access needed data and a suite of tools and capabilities built for other studies to capitalize on a build-once-and-reuse-many-times paradigm. Much of the development since the platform’s 2016 inception has focused on building PMAP’s infrastructure. In 2021, the team is focused on the analytics and delivery components of the platform.

Accelerating research with PMAP is only one aspect of the platform. Its real purpose is to impact clinical care in a way that realizes value for the health care system, the provider, and the patient—without realizing this value, PMAP has failed to deliver. While the bulk of the development since 2016 has been targeted at the “shovel and spade” work of building PMAP’s infrastructure, as we enter 2021, the team is pivoting to squarely focus on the analytics and delivery components of the platform. This is the beginning of where we expect the full force of big data and AI to be its most disruptive to precision medicine.

THE PERILS OF BIG DATA AND AI

We are early in the emergence of the disruptive transformation underway in biomedical research and health care delivery. Though there are promising indicators of the future, there are also concerns: about ethics associated with computers making decisions with life/death consequences,22 security and privacy,23 bias in models and training data,24 reproducibility of results,25 and more. While it is very true that these factors also impact application of big data and AI to other domains, data related to health and health care are considered extremely personal and sensitive, and people are naturally concerned about who and/or what is making decisions that potentially impact their health. It is conceivable that any number of these challenges may conspire to plummet precision medicine into the Gartner Hype Cycle’s “trough of disappointment”;26 however, we are hopeful that all fields will collectively advance both the science and policy27 associated with big data and AI while cultural acceptance of degrees of human–machine teaming evolves to a stage where precision medicine’s promise reaches the “plateau of productivity” and value.

WHERE WE WILL STAND IN THE NEXT QUARTER CENTURY

Polio and HIV/AIDS are examples of illnesses that once ravaged individuals, but decades of research and clinical trials resulted in cures or therapies that
significantly dented the impact of symptoms. Polio was first described clinically in 1789, and it took until 1955–1957 to see an 85–90% drop in the incidence of the disease.28 HIV/AIDS, which escalated in the 1980s, is an example from more modern times.10 Thirty-plus years of substantial research led to today, when antiretroviral therapy (ART) medications can drive the viral load to undetectable levels with little to no risk of transmission. These are monumental accomplishments of biomedical discovery and health care delivery, yet in both cases, it took decades and enormous tolls on quality of life and life span as well as tremendous financial impact to individuals, communities, and governments.

Now in 2021, we can look to the ongoing transformation driven by the Hopkins inHealth precision medicine initiative. We are hopeful that the collaborative efforts of APL and JHM to develop and deploy PMAP across the institution will accelerate the development of cures and treatments for other illnesses and injuries. Even at this early stage of PMAP’s deployment, we are seeing a groundswell of interest and adoption among researchers and clinicians—they are gravitating to the platform to conduct their research and to provide value to their patients. They see how PMAP can streamline their ability to access diverse data and discover heretofore hidden or unknowable insights leading to better care for individuals. These insights will lead to ways to help individuals stay healthier longer, to detect and diagnose illnesses and injuries sooner, and to apply accurate treatments sooner—reducing the overall cost of maintaining and restoring health.

Since its founding in 1942, APL has collaborated many times with its older sibling Johns Hopkins University institutions. These collaborations are described in more detail in the article by Palmer et al., in this issue. APL’s involvement in JHM’s thrust into precision medicine is representative of a new era of strategic teamwork. The two organizations chose precision medicine as an initial focus of this partnership because of JHM’s existential necessity to reinvent its approach to discovery and delivery of medicine and APL’s experience in technical areas relevant to the transformation necessary to realize the benefits of precision medicine. Collectively, we are building the technical, policy, and institutional foundation that will sustain JHM’s leadership through the next 25 years and beyond. With this transformation, all stakeholders—patients, providers, family members, payers, and others—will benefit from the disruptive forces of big data and AI and the power of precision medicine.

**ACKNOWLEDGMENTS:** The accomplishments discussed here are the fruits of visionary leadership from Antony Rosen, Sezin Palmer, Dwight Raum, Chris Chute, Alan Coltri, Dan Ford, Peter Green, Paul Nagy, and Scott Zeger and the dedicated efforts of Diana Gumas, Aalok Shah, Suma Subbarao, and their respective teams across Johns Hopkins University composed of countless faculty, staff, students, and administrators steadfastly committed to making the promise of precision medicine a reality.

**REFERENCES**


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