The Implementation Chasm Hindering Genome-informed Health Care

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For the last two decades, the incorporation of genomics into clinical care has promised prevention of disease, diagnosis of patients with uncommon diseases, and treatments tailored to each individual's innate susceptibilities and characteristics. That vision is beginning to be realized. For example, organizations like the Undiagnosed Disease Network are now identifying the underlying genomic etiology of approximately 35% of patients presented to them.[1] Academic medical centers like Vanderbilt University Medical Center and Northwestern Medicine are routinely using drug-genome interactions within the electronic health record (EHR) to recommend tailored drug therapies for thousands of patients.[2] Many major health systems are applying genomic sequencing to screen their patients or employees for latent genetic susceptibilities in cancer, cardiac disease, and other heritable conditions.

Along with rapid progress in demonstrating that genomic medicine is possible and practical, geneticists and researchers exploring the ethical, legal, and social implications (ELSI) of genomics are developing frameworks and policies to responsibly return genetic data to patients and providers.[3] Emerging approaches to returning results are addressing the unique characteristics of genomic data; for example, investigators at the University of Michigan have demonstrated an approach to recontacting a research participant when previously non-actionable genomic variants become actionable.[4] Multiple practical challenges remain in

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The Journal of Law, Medicine & Ethics, 48 (2020): 119-125. © 2020 The Author(s)
DOI: 10.1177/1073110520916999

effectively communicating genomic results to patients and their providers; many of these challenges are rooted in how genetic data is stored, represented to health care providers, and associated with clinical guidance.[5]

To outside observers, the path from exemplar cases of implementation to a world where these services are routinely available may seem clear. However, the widespread adoption of promising clinical applications of genetics is hindered by health system characteristics and fraught with misconceptions about the readiness of the technology. Together, these issues negatively impact the diffusion of innovations in health care. Each of these hindrances will be discussed below.

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I. Characteristics of the Health Care System that Impact Genomic Integration

We are in the midst of a revolution in our understanding of what it means to be healthy and in our delivery of care to prevent disease or to optimally manage symptoms. For example, through the lens of genomics, we have completely transformed our understanding of the etiology and treatment of seizure disorders[6] and screening for or characterizing breast cancer.[7] These discoveries have fueled our belief in precision medicine as integral to the future of health care. Importantly, these advances are fueled by the meteoric rise in the generation of digital data related to health and disease. The volume of health care data has multiplied 8-fold since 2013 and is projected to grow at a compound annual rate of 36% between 2018 and 2025.[8] However, these advances require overcoming key issues that characterize today's health care system, including delays in translating evidence-based medicine into practice, challenges related to accountability and burnout, and uneven technical capability across health care systems.

A. Delays in Translating Innovative Care Delivery from Research into Practice

When a groundbreaking change in the thinking about disease management appears in the highest impact journals in medicine, it is almost always followed by concerted, investigator-led efforts to publicize the impact of the discovery through editorials, press releases, and various presentations. Sometimes, patients advocate for the adoption of the innovation and extol the value to each other and to their providers. Yet we know that, on average, more than a decade is needed to change practice, despite these efforts.[9] For example, in 2005 it was discovered that patients who smoked cigarettes benefit from even simple counseling using a method known as the 5 A's (ask, advise, assess, assist, arrange follow up).[10] However, 10 years later, in a national study examining lung cancer screening, less than 25% of people still smoking received this intervention.[11]

There are a number of reasons for the slow uptake of evidence-based medicine into practice.[12] Adoption of change must first overcome the fact that clinicians are ethically bound to *primum non nocere* (first do no harm). Patients in research studies are carefully selected and often differ in subtle ways from the average patient in routine care. Clinicians must be convinced that a pioneering study is replicable and that novel interventions do not have unintended consequences or distract from higher priority tasks. This skepticism is ingrained in health care.[13] As a consequence, changing the practice of medicine at a local level requires attention to knowledge about the change, attitudes toward the change, and behaviors that facilitate the new processes.[14]

B. Accountability and Wellness Issues Impede Experimentation

As a result of important work summarized by the National Academy of Medicine beginning with *To Err is Human*,[15] there have been two fundamental changes in the U.S. health care system. First, there has been an surge in the adoption of EHRs, in large part motivated by federal regulation and incentives.[16] Physicians using federally approved (certified) EHRs subjectively report mixed results in terms of their own satisfaction and the impact on the quality of care.[17] Adoption of

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https://doi.org/10.1177/1073110520916999 Published online by Cambridge University Press

EHR technology happened at the same time as the second major change in the system, which Berwick has called the "accountability era" — when regulations and reporting requirements consume more resources and require more non-clinical work from care providers than ever in our history.[18] These changes are still very new and need to be incorporated more systematically into the workflow of busy professionals to alert them to deficiencies in the quality of their care. In their present form, the burden of documenting additional information, or copying and pasting information from one encounter to the next,[19] compounds the stress on health care personnel.[20]

Job-related stress has led to an epidemic of burnout and its sequelae among health care providers. Suicide rates are now consistently higher among physicians than in the rest of the population, and have been attributed, at least in part, to job stress.[21] The EHR has been portrayed as more of a curse than a blessing, with publications citing issues related to system usability[22] and record usefulness[23] now commonplace. All of this combines to create a health care workforce more reticent than ever to experiment with innovation.[24] This reticence is pervasive and in no way limited to innovation in precision medicine and genomics. Local and national health care leaders must approach any change by first recognizing impact of this stress on the willingness of care providers to change.[25]

C. Technical Capability Variance Forces less Aggressive Practice Change

The third major change in the national health care environment relates to the ever-expanding chasm between digital natives — people who were born or assimilated into the digital era — and digital immigrants — people who have been asked (or forced) to develop new skills.[26] While some industries, such as the airline and ride-share industries, have quickly evolved a "mobile first" business strategy, health care has been obligated to develop a solution for all levels of digital literacy and data privacy concerns,[27] which radically slows the pace of change in the field.

The root causes for lags in technical capability stem from both the provider and patient side of health care. From the provider side, there is variation between provider comfort with technology that has been shown to impact ability to use and recommend technology in some settings.[28] From the patient perspective, there continues to be a wide variation in the level of comfort with technology.[29] There is, as Ammenwerth has noted, a compounding challenge when both the capabilities of the people and the capabilities of the technology need to be transformed.

II. Fundamental Misconceptions

In addition to the structural and individual impediments above, there are a number of misconceptions about the ease with which the widespread adoption of genomics applications in medicine can occur. First, genomic results are not easily integrated into the EHR in a way that facilitates decision making. Second, genomic results are costly to sequence, store, and retrieve, depending on the technical approaches used for each of these tasks. Coupled with the relative novelty of genomic medicine and lack of widespread comfort with genomic data, these challenges will take time to overcome. The paragraphs that follow provide detail about each of these misconceptions.

A. Genomic Information and Readiness for EHR Use

Today's EHR is capable of accepting patient information in a variety of forms, ranging from images (photographs, radiographic test results, scanned text) to unstructured text, to highly structured individual data items, such as a code for a test name and a result and reference range in standardized units. As information becomes more structured, it is generally more capable of becoming computable (i.e., understandable by computer software).

In the case of genomic information, multiplexed panels or sequencing tests are able to identify thousands to millions of variants in hundreds of genes — far more than a human health care provider can be expected to manually review and act on. To maximally impact patient care and decision making, patient-specific genomic variation that impacts clinican decision making should exist in the EHR in a structured form that can drive clinical decision support available at the time of medication ordering, diagnostic evaluations, or patient risk assessments.[30] However, at this time, most genomic results arrive as a document image, with results that are not encoded and thus not directly computable, analyzable, or sharable except as a copy of the image. Authors have called on reference labs to support delivery of structured data and for EHRs to accept computable results,[31] but this deficiency persists.

There are a number of technical barriers to closing this gap. First, many health systems outsource genetic testing to external laboratories, most of which do not transmit back machine-readable results. EHRs are able to integrate results fully only when they are transmitted in a standard messaging format that facilitates use by computer algorithms. These standards are still in evolution, and their use is limited.[32] Second, there is more than one standard for identifying gene variants and the reference sequence. Without a universal lexicon of gene variants, any attempt to recognize characters in a PDF file and to extract specific genomic

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information from these reports is fraught with the potential for error and patient safety risk. In addition, these reports often contain some results based on assays of questionable quality, which is not conveyed on the report itself. Finally, the industry is beset with inertia; most laboratories do not prioritize improving the sharing of discrete, encoded data unless there is health system or regulatory demand. Moreover, vendors of EHRs react to customer demand, rather than proactively anticipating innovation.

Lack of encoded and computable results has many downstream effects. For example, because all variants that are identified are typically reported together in one report, it is virtually impossible to help providers or patients interpret individual findings; such interpretive help is usually accomplished via hyperlinks to external knowledge sources linked to individual findings in more structured reports. This is not a new problem, as noted by Guttmacher in 2007,[33] yet it continues to be unsolved and is arguably more significant in the era of consumer-centric care.[34] Another challenge related to the result's lack of structure is how to manage updating results. For example, if a variant is initially in the report as actionable, but subsequently found to be clinically insignificant, the report can be reissued, but it may not be clear which results have changed on that report. The University of Michigan has explored ways to address this, but that work is very much in its infancy.[35]

As we move to a future where genomic test results are delivered in computable form, it will be critical to confront the challenge of accurately interpreting the genomic information in the patient's particular clinical context. It is often the case that genetic variation alone is not the most significant risk factor, and is best evaluated by combining genomic with other clinical data or family history. This combination of information is vital to manage patients with cancer predisposition variants, such as those with positive family histories, and those patients with social/behavioral risk factors (e.g., smoking history). This issue is equally important in non-cancer risk prediction. Warfarin (blood thinner) dosing is one example of non-cancer risk prediction requiring genomic and clinical data. A well-studied algorithm for warfarin dosing incorporates two genes, four demographic parameters, three clinical factors, and four other medications.[36] Although this calculator is not integrated with an EHR, similar tools do exist within EHRs, and have achieved acceptance among clinical users.[37]

B. Genomic Information Availability

There are two major factors associated with the availability of genomic information. The first of these factors relates to the cost associated with this new data source and its integration into health care. A detailed discussion about the costs of implementing and managing genomic information is beyond the scope of this paper, but is reviewed elsewhere.[38] In brief, however, organizations involved with utilizing information must confront costs associated with identifying labs that provide high quality genetic results; performing sequencing, storing results, and sharing results through electronic interfaces that must be built and maintained as source and destination systems change; and increasing institutional insurance to cover any liability associated with breaches that compromise the privacy of genomic data. These costs can easily mount to millions of dollars to initiate such a program.

The second major factor impacting availability is the need for technology standards and guidance for decisions about how best to manage genomic information. The impact of this factor cannot be overstated. Although most EHRs are capable of accepting health data in many formats, most EHR systems currently support neither the volume nor the complexity of genomic data that is needed to optimally impact patient care.[39]

Genomic data come in many forms, ranging from individual variant names to raw data from various types of tests. The largest datasets come from whole genome sequencing and can require as much as 90 gigabytes per report, which equates to 80 terabytes of data for every 1000 patients. Data files of this size or larger are commonplace in radiology, where the response has been to store those raw data in a separate departmental computer system called a Picture Archiving and Communication System (PACS). These systems are designed to support browsing of information; expert interpretations are sent to the EHR as reports that can be used to generate alerts and reminders for providers, while the volumes of raw data remain sequestered. In the case of genomic data, the science of interpretation is very new. In some cases, findings with uncertain significance become actionable overnight. This discovery makes what should or should not be stored in the EHR less certain, especially since patients increasingly are relying on 2014 regulatory changes to demand access to "raw" or uninterpreted genomic data, which limits the role of sequestration.[40] The complexity and volume of the data and changing interpretation have contributed to the slow response to requests by experts to incorporate genomic data into the EHR. New strategies are being proposed to address this, such as the omics ancillary system by Starren,[41] but as of now, this challenge remains unresolved.

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C. Patient and Provider Interaction

For centuries, patients have relied on clinicians as an authoritative source to explain medical facts and disease probabilities.[42] This influence has increasingly been questioned with the emergence of the Internet; surveys demonstrate the challenges doctors face as patients use the Internet to seek answers tor medical questions.[43] With the explosion of information about the importance of genomics and the provision of direct-to-consumer testing, this problem has escalated. Questions related to privacy risks,[44] direct-to-consumer testing value,[45] and appropriate indications for provider-initiated testing may be posed to physicians and advanced practice nurses, with the unfounded assumption that these professionals are experts in this area.[46] In addition to requiring significant foundational knowledge to which many providers have not been exposed,[47] the knowledge itself is evolving too quickly to be easily summarized, making the time investment to stay current virtually impossible in general practice.[48]

Decision making in the genomic era is fraught with its own misconceptions. For example, patients incorrectly believe that a lab report identifying a variant and offering the interpretation that this variant makes a particular drug "less likely to be effective" means that that drug should never be prescribed to them. In fact, this interpretation itself is subject to debate.[49] Labs vary in their quality and lack consistency in their ability to identify a variant. The variants themselves may confer minimal risk of inappropriate drug response, but many people (including physicians) have deficiencies in their understanding of probability and risk.[50]

Finally, other patient-specific factors, including an allergy to other more effective medications, may make the "less effective" medication the best choice.[51] In short, medical decisions made on the basis of the specific test that was ordered and these patient factors may differ substantially from decisions made without that information.[52]

III. Necessary Steps to Achieve A Global Vision for Automation

As is apparent from the discussion above, although there are technically feasible opportunities to improve the integration of genomic information in care delivery, much work remains to be done to create systems that store and interpret genomic data, often in combination with other clinical and social information, to provide effective and accessible guidance to providers and their patients in ways that improve health. These approaches will be costly to develop in both time and resources. It will be necessary to prove that these approaches not only are cost-effective, but also meet the needs and preferences of patients and clinicians.[53]

Once created, these opportunities will in no way be simple or seamless to implement, let alone adopted by all providers. The field of implementation science, which focuses on approaches to promoting the uptake of interventions that have proven effective into routine practice,[54] will be a necessary, but perhaps insufficient foundational science to guide our strategy toward a better integrated solution. These strategies will need to lead to a major evolution in clinical thinking. We will need to change the attitude of care providers. They will need to believe that this new behavior adds value to the care delivery system above and beyond the educational cost (time), risks of harm to the patient, and financial cost to the patient and health care system. We will need to make providers aware of the social pressures to accept the value of precision medicine and the importance of genomics. Providers will need to believe that they are capable of mastering the behaviors related to this new field and deserve to be considered experts at a level that society would expect of them. This will need to know which basic tests to order and to whom a patient should be referred who has questionable results. This level of acceptance will require changes in the core competencies required for physician and nursing board certification, additional opportunities for continuing education, and widely publicized definitive evidence supporting the value of this education and this discipline.

As with any field in its infancy, the incorporation of "precision thinking" into care delivery at a national scale will require a comprehensive change management strategy. One recent publication[55] identified seven challenges that need to be overcome to improve the adoption rate of clinical genomics: producing clear evidence about the cost-effectiveness of genomic testing programs; developing a standard and engrained response to consumer concerns about the risks and benefits of genomic testing; ensuring that the interpretation of genomic results is based on research that takes gender and ethnic diversity into account; creating and managing guidelines for appropriate preventive or diagnostic genomic testing; determining best practices for the communication of initial, as well as revised results from genomic testing; and generating reproducable evidence of the relationship between variants and disease risk. The seventh challenge to be overcome — navigating the various patient and provider preferences to testing and sharing genomic information — is arguably dependent on many of the other challenges.

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IV. Conclusion

Genomic medicine is already making inroads in the clinic, and we are constantly told of our bright genomic future. But to improve patient access to this advanced paradigm of health and disease management, we will need to integrate both new knowledge and new care processes into existing workflows — change that will be onerous, time-consuming, inconsistent, but hopefully valuable to the provision of high quality, economically feasible care worldwide. Advances in both policy and the legal framework supporting the widespread integration of genomic medicine into the EHR should address these challenges in setting achievable quality standards and imposing liability.

Note

Dr. Starren reports a grant from NIH/NHGRI 1U01 HG008673-01 during the conduct of this study. In addition Dr. Starren has a Provisional Patent related to the design of Ancillary Genomic Systems pending. The other authors have no conflicts to disclose.

Acknowledgements

The authors acknowledge the assistance of Susan Wolf, J.D. in vetting the concepts summarized in this manuscript, and in suggesting numerous constructive changes. This paper was supported in part by National Institutes of Health (NIH), National Human Genome Research Institute (NHGRI), National Cancer Institute (NCI) grant 1R01HG008605 on "LawSeq: Building a Sound Legal Foundation for Translating Genomics into Clinical Application." All views expressed are those of the authors, not the funders.

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The Journal of Law, Medicine & Ethics, 48 (2020): 119-125. © 2020 The Author(s)