

The undiscovered country: the future of integrating genomic information into the EHR

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The articles in this special issue take advantage of the research and experience of the Electronic Medical Records and Genomics (eMERGE) Network and are designed to provide operational and academic leaders with a “getting started” guide for integrating genomic information into the electronic health record (EHR). As noted in the article by Gottesman et al.,¹ the eMERGE network has been actively researching issues that shed light on the integration of genomic information into the EHR. However, as the authors in this special issue have indicated, many questions and challenges remain. We have completed mapping of terra incognita and have now arrived at the shores of the undiscovered country.

Additional discussion, education, and research need to occur in order to determine the placement and role of genomic results in the EHR. One challenge is that guidelines for the interpretation and use of genomic results in clinical care need to be established. In addition, provider education on the interpretation and value of genomic results in clinical care is sorely needed. Previously, germline genetic results were the province of geneticists and involved extensive counseling, whereas genomic results, which have the potential to impact care in multiple specialties, involve providers who are not geneticists. How much education is then required? Enough to interpret results and, if necessary, facilitate referral to experts for further evaluation of the test and treatment such as an echocardiogram and cardiology, or more like lab test results for which providers know what the result is and are given reference ranges that guide action on it? There is the added wrinkle of direct-to-consumer (DTC) testing, which will require additional provider understanding and education.² As Hartzler et al.³ noted in their article, there are many discussions that need to take place among the various stakeholders. The complex ethical issues among the stakeholders were well covered by Hazin et al.⁴

Hartzler et al.³ also touched upon genomic results being available in personal health records (PHRs) or patient portals. Will genomic information obtained at medical centers be available in the PHR? Test results in PHRs can either be manually released, in which case the provider must release the result to the patient, or autoreleased, in which case the result is automatically sent to the patient after a fixed interval of time. Most sites have found that autorelease of lab test results is well accepted by patients and does not generate excessive phone calls or PHR messages.⁵

The underlying assumption is that the patient will ask questions and/or the provider will contact the patient to discuss any abnormal results. Can the same approach for release of lab results in the PHR be used for genomic results? Are genomic results more equivalent to sensitive tests such as that for HIV? In New York State, HIV test results require counseling, which precludes autorelease. Current standards for the reporting of single-gene test results recommend genetic counseling,⁶ and certain extremely sensitive test results such as presymptomatic testing for Alzheimer or Huntington diseases require extensive pre- and posttest counseling.^{7,8} Alternatively, are genomic results more akin to radiology results, which many centers are wrestling with given that the reports are written for providers and are not easily interpretable by the lay public? These reports also include incidental findings that may or may not have been discussed with the patient by the ordering clinician. Radiology results and pathology results are not routinely autoreleased at many sites,⁵ although one of the authors (M.S.W.) notes that radiology reports as well as patient-controlled image downloads are now available at Geisinger Health System.

It is difficult to prognosticate how much direct access to genomic test results patients will have because of two developments. Unlike the diagnostic testing discussed above, (i.e., laboratory, imaging, and pathology) patients can order and view their own results through DTC genomic testing. How DTC testing will interact with provider-ordered testing, viewable in the PHR, is unclear. It also remains an open question of whether or not there will be widespread uptake of DTC genomic testing. Nevertheless, companies involved in the DTC space have developed innovative ways to represent genomic test results that have been shown to be comprehensible and accessible to consumers.^{9,10} These methods may be instructional to PHR designers. The appropriately named Open Notes research project, is releasing all progress notes to the patient, and the initial results are encouraging.¹¹ This would make any discussion of which test results to autorelease in the PHR potentially moot as progress notes may contain test interpretations by providers.

It remains unclear which diagnostic tests genomic results are most analogous to in terms of provider reporting and interpretation.^{12,13} Articles in this issue have discussed delivering the raw data, the result, and the interpretation. Genomic education

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Submitted 8 July 2013; accepted 18 July 2013; advance online publication 26 September 2013. doi:10.1038/gim.2013.130

of both providers and patients remains a pressing need because results and interpretation of results may be confusing or meaningless to many providers¹⁴⁻¹⁸ as well as to most patients.¹⁹ To date, other than the specialty of genetics and the need for counseling, few providers seem to want to see the raw genomic data, let alone have the means to understand it.²⁰ As in the setting of other complex tests, most providers want interpreted reports, although, as noted earlier, challenges remain with education. Laboratory tests are generally stored in EHRs as discrete, interpreted results. The raw data are not presented, as health-care providers do not want to read spectrograms to determine the patient's electrolyte levels. By contrast, imaging presents the raw data, images, and interpretation to EHR users. Imaging uses links to a picture archival communication system and the interpretation is stored as a text blob. In the case of imaging, specialists prefer reading their own imaging with assistance available as needed from, for example, radiologists. Pathology is somewhere in between in that the interpreted free text reports are always stored in an EHR, but viewing pathology specimens requires going to the pathology department to view them.

Like pathology results, genomic test results are returned as unstructured text. The near future evolution of pathology reporting may be a guide to what could happen to genomic test reports. To improve the utility of the reports, the College of American Pathologists has recommended the use of synoptic reporting for certain cancers.^{21,22} Synoptic reporting incorporates free text into a structured format that allows for the data to be represented also as discrete elements. This concept has been expanded to create documents that are both human and machine readable through the use of clinical document architecture (CDA). In their 2006 article, Dolin et al.²³ state, "CDA is a ... standard that specifies the structure and semantics of a clinical document ... for the purpose of exchange. A CDA document is a defined and complete information object that can include text, images, sounds, and other multimedia content. It can be transferred within a message and can exist independently, outside the transferring message."²³ Some have suggested that CDA documents could be used for genetic and genomic test reporting, and the Health Level Seven clinical genomics workgroup has created a CDA implementation guide for genetic testing reports.²⁴ This prototype is now available for testing, and the model is being extended to support genomic data. Chute et al.²⁵ discuss this in more detail. Is this the solution to the reporting conundrum?

Overby's²⁶ and Marsolo's²⁷ articles address the use of clinical decision support (CDS) to facilitate the use of genomic information in health care as well as the current state of CDS in eMERGE sites. Many sites have focused their CDS work on pharmacogenomics, which provides prescribing recommendations based on genomics and for which there are published guidelines.²⁸ Use of this information has become increasingly routine. For clopidogrel, the Food and Drug Administration has a black box warning that recommends genomic testing be considered as "an aid for determining therapeutic strategy."²⁹⁻³⁴ For abacavir, the Food and Drug Administration has a black

box warning requiring HLAB*5701 testing.³⁵ Denny's³⁶ article in this special issue describes pharmacogenomics in an internally developed EHR. Besides clinical utility and focused use, CDS for pharmacogenomics has one other advantage, which is the use of structured data: drug information such as name and dose. Use of structured data also lends itself to capture of outcomes data, which is critical to the development of robust evidence of utility.

CDS will require actionable discrete data that can be stored and represented in the EHR.¹³ Articles in this issue and others have noted that representation and storage of genomic information in the EHR has remained challenging because most commercial EHRs are not up to the task. Although the data need to be stored in a structured form, the article by Kho et al.³⁷ summarizes where we are today with the storage of discrete phenotypic data that can be linked to genomic data, which is equally important to CDS. The article by Tarczy-Hornoch et al.³⁸ highlights the needs for standard representation in test results in addition to CDS. Even when sites used the same sequencing technology and commercial EHR, customized solutions were required at each site. As Chute et al.²⁵ note, the standards to make this happen are still evolving, and as a result commercial EHR vendors have been slow to incorporate genomic results.

By its very nature, CDS depends on a knowledge base and rules engine.^{39,40} This makes CDS challenging for genomic test results in that both the knowledge and the rules around this knowledge are rapidly changing.⁴¹ As a result, both the knowledge base and the rules engine require frequent and rapid revisions. Ury,⁴² in his article, explores this problem. It is the long-held belief of the authors that interpreted results residing in the EHR, the CDS rules, and the knowledge itself will need to be "versioned." This article defines the term "versioning" as the creation of a standardized and systematic methodology for dating and numbering the rules and knowledge in a consistent way, as well as systematically recording changes in content. Older versions of the CDS rules and knowledge would be archived indefinitely in a yet to be developed knowledge maintenance schema. Without versioning, it will be impossible to tell why possibly contradictory actions were taken on what seems to be the same genomic results at different times. Versioning would tie the decision to the knowledge available to the clinician at that specific point in time, which is critical for liability and quality improvement purposes.

Because challenges remain for storing genomic results in an EHR as discrete data, as well as the need to rapidly update the knowledge base and the decision rules, several sites have begun developing external CDS. In external CDS, the knowledge base and rules engine reside outside of the EHR. This methodology has begun to be used to help standardize knowledge and implementation of rules across multiple sites^{39,43} and has the potential to accelerate implementation. Efforts to facilitate the adaptation of external CDS have focused on producing agnostic extensible CDS that could be shared by multiple sites.^{44,45} The challenge with external CDS for genomic results is to make the genomic CDS actionable. Without standards, many sites are

challenged with presenting little more than recommendations at the point of care that ask the user to consider the information and take action if the user feels appropriate. The approach of presenting CDS as FYI (For Your Information) is not desirable, as David Bates and others have noted.⁴⁶ Chute et al.'s²⁵ article calls attention to the need for standard representation and notes that taxonomy and development of these standards as well as others might solve this conundrum. It is the belief of the authors that within the next few years we will see researchers develop external CDS capable of generating messages that trigger specific actionable items in a commercial EHR. Until standard representation of genomic results occurs, widespread adaptation of CDS by commercial EHRs will continue to be challenging regardless of value propositions by providers and patients.

CDS for genomic testing will also have to address issues of confidentiality and privacy. In contrast to other forms of diagnostic testing (i.e., laboratory, imaging, pathology), genomic testing is somewhat unique regarding its privacy and confidentiality issues.^{17,47} There remains significant concern about the impact of genomic test results on a patient's health insurance and perhaps even employment,⁴⁸ despite the passage of the Genetic Information and Nondiscrimination Act.^{49,50} Although both Hartzler³ and Hazin⁴ address this, much still needs to be discussed and done. The age of whole-genome sequencing is rapidly approaching, and patients will be presented with results that they neither want nor understand and which providers struggle to interpret.^{20,51} Unless we provide a secure and trustworthy environment for the storage of genomic information and combine this with public policies that protect against the misuse of this information, there will be concern about the routine use of this information for health care, even when it has been shown to improve outcomes.

In conclusion, we have completed an initial mapping of terra incognita with this special issue summarizing the knowledge, experience, and wisdom of eMERGE consortium members. Although much has been learned, many questions remain. A concerted and collaborative effort involving all groups working on these daunting problems will help to generate solutions that will allow genomics to move into clinical care. We have arrived on the shores of the future, the undiscovered country, and although much remains to be resolved, the future looks so bright we ought to be wearing shades.

DISCLOSURE

The authors declare no conflict of interest.

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