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PERSPECTIVE

Electronic medical records and personalized medicine

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Abstract If the dream of personalized medicine is to be realized, tremendous amounts of data specific to each individual must be captured, synthesized and presented to clinicians at the time this information is needed to make care decisions for the patient. This can only be accomplished through the use of sophisticated electronic medical record (EMR) systems that are designed to support this function. This article will define two important aspects of a fully functional EMR the ability to: present patients or clinicians with high quality context specific information at the point of care (so-called "just-in time" education) and to combine clinically relevant information from disparate sources in order to guide the clinician to the optimized intervention for a given patient (clinical decision support). Personalized medicine examples are used to illustrate these concepts. As implemented most EMR systems are not being used to assimilate the information needed to provide personalized medicine. A description of necessary enhancements to currently available systems that will be needed to create a "personalized medicine enabled" EMR is provided.

Introduction

> "Personalized health care is information-based health care. It is health care that works better for each patient, based partly on scientific information that is new and partly on technology to make complex information useful…personalized health care is about a transformed role for information in health care."

This quotation by former Secretary of the United States Department of Health and Human Services Michael O. Leavitt (DHHS 2007) captures the central tenant regarding successful delivery of personalized medicine. Personalized medicine by necessity requires the generation and consumption of immense amounts of information specific to the individual including significant portions of the human genome. While it is important not to conflate personalized medicine with genomic medicine, given that currently most information relevant to health care is not genomic, the sheer volume of genomic data has led to the recognition that the capacity of the human brain to analyze all relevant data elements has been exceeded. To illustrate, Ziman (1980) estimated that the doubling time of medical knowledge from 1870 to 1980 was approximately 19 years—quite literally an exponential increase that may be showing acceleration.

Study of clinician problem solving indicates that in addition to having difficulty assimilating large amounts of data, clinician's tend to organize information into 'scripts' representing prototype patients that facilitate pattern matching, something that the human brain is well suited for (Schmidt et al. 1990). This approach coupled with the accumulation of experience leads to a decrease in hypothesis errors but an increase in identification and interpretation errors (Groves et al. 2003). This latter issue is likely due to inappropriate use of pattern matching combined with knowledge deficiencies and contributes to the observed variability of clinical practice. It is also recognized that recent experience receives more weight than

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distant experience which can inappropriately bias future decisions, a process known as selectionism (Zhang 2009). Genomic information will magnify these issues due to the sheer amount of data and the synthesis of the data elements being represented in probabilistic terms as opposed to patterns. This is a problem even with limited amounts of genomic data. An analysis of use of HIV genotype information delivered primarily in paper reports has shown that clinicians often made prescribing decisions that were contraindicated by the viral genotype, evidence that electronic management of genotype information combined with decisions support is necessary to ensure the long-term and appropriate use of genotypic information (Uy et al. 2007).

Aiding the management of knowledge by health care providers to improve patient care has been an area of intense interest. A major focus has been the use of information systems to aid clinician decision making. Information systems have the advantage of being able to handle many more discrete data elements than humans. In addition, information systems can be designed to use other problem solving approaches (such as Bayesianism). This can compensate for the weaknesses in adaptive learning outlined above in that a process such as Bayesianism can analyze data across all available diagnostic 'hypotheses' while selectionism focuses exclusively on the pre-selected hypothesis (Zhang 2009). In theory, creating a health care environment where clinicians can readily interact with sophisticated information systems could accelerate the translation of evidence-based personalized medicine into improved clinical care. At present, commercially available electronic medical record (EMR) systems have limited ability to perform these functions.

This article will present examples of how EMR systems can facilitate clinician information retrieval, enhance clinical decision making and outline what enhancements to current EMR systems are needed to fully realize personalized medicine.

Information retrieval

Questions frequently arise in clinical care. In primary care, it is estimated that two clinical questions arise for every three patients seen (Gorman and Helfand 1995). Analysis of the taxonomy of clinical questions revealed that three questions account for a significant portion of all questions: What is the drug of choice for condition X (11%); What is the cause of symptom X (6%); What test is indicated in situation X (6%) (Ely et al. 2000). Despite (or perhaps because of) the high frequency of clinical questions, it has been estimated that only 12–36% of questions are pursued (Sackett and Straus 1998; Ely et al. 1999). An analysis of obstacles encountered when attempting to answer a question identified 59 obstacles that could be organized according to five steps in asking and answering (Table 1) (Ely et al. 2002). Two other significant obstacles include not recognizing that a clinical question exists and believing that an answer to the clinical question does not exist.

Table 1 Five steps in asking and answering questions

Recognizing a gap in knowledge
Formulating a question
Search for relevant information
Formulate an answer
Use the answer to direct patient care

(Ely et al. 2002)

Given the explosion in information available electronically, it would seem that finding answers to clinical questions would be easier. Ely et al.(2005) analyzed the sources used to find answers and found that 63% of the time clinicians relied on colleagues or textbooks. Electronic resources represented only 18% of the sources and no single electronic resource accounted for more than 7% of use. Even if the use of electronic resources were to increase, the profusion of information available impacts the ability for a clinician to find a valid answer quickly—a problem represented by Slawson et al. (1994) as usefulness = relevance × validity/work to access. To illustrate this point, Lim and Ho (1999) compared internet and a standard textbook to find answers to 15 clinical questions. The textbook provided answers to 9 of the 15 questions compared to 13 of 15 questions for the internet, but the median time to find the answer to a single question in the textbook was 25 min compared to 110 min for the internet. Neither would meet the criteria of busy clinicians that a resource provide an answer within 2–3 min (Levy et al. 2008). While none of these problems are unique to genetics, it is important to recognize that general content collections used by clinicians have genetic content that is frequently incomplete or inaccurate (Levy et al. 2008).

There are strategies that can be used within an EMR to allow clinicians to answer questions in an expedited way during a clinical encounter.

Electronic resources

Many EMRs have a link to electronic content collections within the patient record. These e-resources can contain external collections (both free and subscription) available to the user, links to the specific healthcare system's medical libraries and patient education resources, as well as internal resources including internally developed care guidelines, protocols, laboratory, formulary information and local genetics experts. In order to provide more access

to genetic resources, links can be added to external genetics resources such as GeneReviews, Genetics Home Reference (Mitchell et al. 2004) the National Office of Rare Diseases, or Online Mendelian Inheritance in Man as well as links to disease specific resources. Clicking any one of the links takes the user to the home page of the resource. The user must then enter search terms to identify the information required. While the link lowers the barrier to accessing information during a patient encounter (since this can be accessed directly from a patient's EMR), it still requires the user to search the targeted resource for information. If information is not identified, then the user would need to move to another resource and repeat the process either until the information is found, or the search ends from lack of time or frustration. Another issue is the accuracy of the information in the linked resources. It is critical that prospective resources are vetted by local content experts before linkages are created. Periodic review is necessary to insure that links remain active and content is updated.

Infobuttons

In order to address the problems noted above, informaticists began to explore the idea that where the physician is navigating in the patient EMR could provide context for the question being asked which allows the opportunity to "pre-search" content libraries. This would enable the physician to have a filtered set of resources that could facilitate getting to answers while minimizing search time (Cimino 2008). Infobuttons build and run queries against electronic resource collections based on patient data and clinical context in order to take the user to the most appropriate section(s) within a content collection with a minimum number of clicks. In EMRs with this capability, infobuttons or equivalent capabilities appear in locations relevant to the most commonly asked questions—usually the problem list, laboratory results and medication list (including medication ordering). To make this resource even more useful, the preferred content resource can be changed based on a determination by the knowledge managers about which resource is most likely to provide the best answer for a given question. In the case of an Infobutton in the problem list associated with the problem 'Diabetes' the preferred content could be internally developed best practice guidelines of the specific healthcare system, or a professional society. For genetic conditions such as Marfan syndrome, the preferred content could be Genetics Home Reference (a concise, simplified resource) or GeneReviews (more complete and detailed information but tailored more for genetics professionals) (Del Fiol et al. 2006). Alternatively, if the system had genetic content experts, these experts could create content specific to best care practices for the system. This has the potential to improve the appropriate use of genetic tests and assist with interpretation of genetic test results.

Neither of these approaches would be able to assist clinicians with questions about the cause of a particular sign or symptom or to assist with diagnosis. For these issues, more advanced forms of clinical decision support are needed.

Clinical decision support

Clinical decision support (CDS) "…refers broadly to providing clinicians and/or patients with clinical knowledge and patient-related information, intelligently filtered, or presented at appropriate times, to enhance patient care." (Osheroff et al. 2007). Decision support can be grouped into three general categories: passive, asynchronous, active. Passive decision support consists of non-mandatory resources available at the time of care. Electronic resources and infobuttons are examples of passive decision support. These have been discussed above and will not be considered further. Asynchronous and active decision support have the potential to address the issue of a clinician not being aware of an information need.

Asynchronous clinical decision support

Asynchronous CDS involves the system monitoring behaviors, perhaps assembling data that was not completely available at the time of clinician/patient interaction and recognizing a potential risk or need for further consideration. The output of asynchronous decision support can be an email to the inbox, a report summarizing patients that need a second look or other approaches. One example of this is a drug recall. When celecoxib (Celebrex®) was removed from the market because of safety concerns, it was important to identify patients on the medication and contact them to switch to a different medication. This would represent a nearly impossible task for a clinician using paper records, however with EMRs, a list of all patients on celecoxib with contact information sorted by clinician can be forwarded to each clinician's office, assuming the EMR maintains a medication list and assigns a primary provider. A genetic example involves duplicate genetic testing. A unique aspect of germline genetic testing is that the test only needs to be done once in a patient's lifetime. Riegert-Johnson et al. (2008) identified a significant issue with genetic tests being repeated, leading to wasted resources. An examination in our system looking at two thrombophilia tests (Factor V Leiden and Prothrombin G20210A) confirmed that roughly 5% of these tests represented duplicates (Williams et al. unpublished data). When additional data were examined in the course of a root

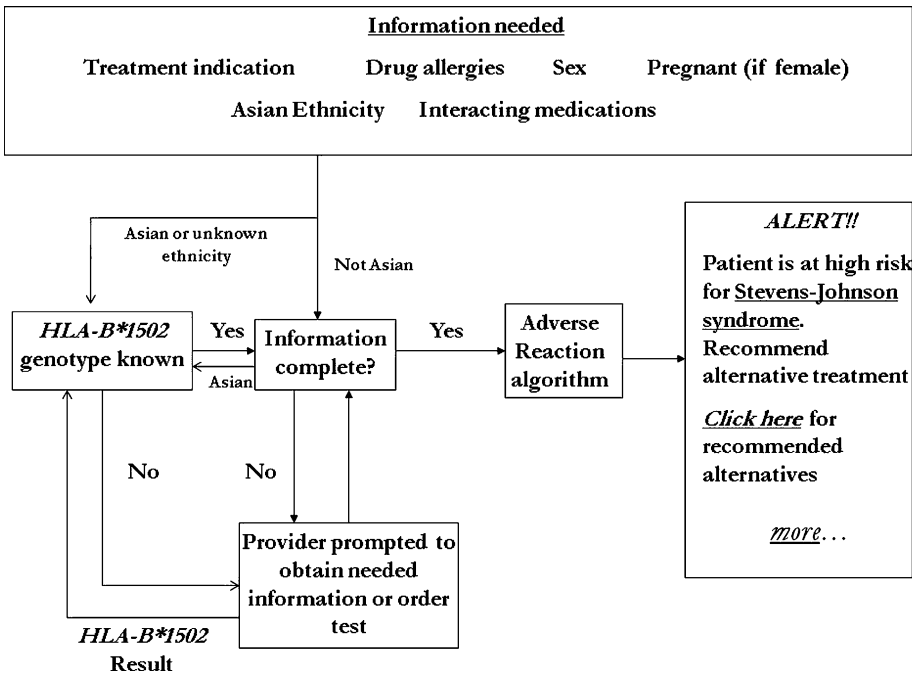

Fig. 1 Logic model for active CDS for carbamazepine pharmacogenomics adverse drug event algorithm. The *box* at the top represents all data elements needed to populate the decision model. If any data is missing, the clinician is prompted to supply it. HLA-B*1502 genotype information is only requested if the patient is of Asian ethnicity. If testing has been done previously, the result is obtained and the algorithm runs. If testing has not been done previously, the clinician is prompted to order the test. Once the result is obtained, the algorithm runs. If the patient does not have the HLA-B*1502 genotype, the prescription is filled. If the HLA-B*1502 genotype is present, the alert box at the *right* appears. There are two hyperlinks in the alert. The recommended alternative link presents alternative therapeutic choices based on the clinical indication and patient characteristics allowing the clinician to order an alternative with a minimum disruption of work. The 'more…' link takes the clinician to knowledge repositories with additional information explaining why the alert triggered supporting point-of-care, "just in time" education

cause analysis, a small number of providers were identified that were responsible for a disproportionate number of these duplicate tests. If these preliminary results are confirmed, asynchronous CDS can be used to inform and educate the providers who can be monitored prospectively to ensure that test ordering behavior has changed.

Active clinical decision support

Active (or synchronous) CDS is generally assumed to imply a workflow in which a clinician process, such as prescribing a medication, is monitored in real-time by rules logic and clinician behavior is influenced based on the logic embedded in a rule. The most widely recognized approach is pop-up alert window warning the user of a potentially risky decision, such as an allergy or drug–drug interaction. Other modalities are gaining favor (to avoid "alert fatigue"), including workflow logic in which warnings and alerts are embedded into the user navigation through the EMR application, for example, the contents of an application window may vary based on genetic risks or additional screening procedures may be added to order lists.

Pharmacogenomic testing for the drug carbamazepine (Tegretol®) demonstrates how active CDS can work. It is known that patients who carry a specific HLA type (B*1502) are at increased risk for an adverse drug reaction, specifically, Stevens–Johnson syndrome (Lim et al. 2008). This adverse event is rare, so a clinician may not be aware of this information, particularly if the clinician is not a frequent prescriber of this medication. If a clinician uses a computerized medication order entry system and chooses carbamazepine, an algorithm is run represented by the logic model in Fig. 1. The information in the top box is automatically collected by the program from various parts of the electronic data warehouse (EDW). In this case, the computer determines that the indication is psychomotor epilepsy. The weight is needed to determine the dose; sex is needed to determine if there is a risk of fetal exposure. If the patient is female over a predetermined age and the drug presents a risk to a fetus the clinician would be prompted to order a pregnancy test; allergy to carbamazepine or cross-reacting compounds is determined and medications with potential interactions are queried. The program also asks about ethnicity because of the increased risk for Stevens–Johnson syndrome or toxic epidermal necrolysis in patients

of Asian ethnicity as HLA-B*1502 has a significantly higher prevalence in many Asian populations. It is now recommended that individuals of Asian ethnicity should be tested for this HLA type before initiating therapy with carbamazepine. If testing has been done previously and the patient carries the HLA-B*1502 allele, the clinician sees the alert represented in the right hand box of Fig. 1. If the 'more…' hyperlink is clicked the clinician is taken to the FDA alert's abstract where the entire report could be accessed with one more click. There is also a hyperlink to alternative medications. If this is clicked, the module will look at the indication for treatment as well as other factors built into the program and would propose clonazepam as the recommended alternative, given its equivalence to carbamazepine in the treatment of psychomotor seizures (with an Infobutton that would link to references that confirm this). Alternatively, if the HLA-B*1502 test had not been done previously the clinician would be alerted to order this test before prescribing carbamazepine with an Infobutton that would provide the rationale for the test. If the patient was not of Asian ethnicity, the query about the HLA-B*1502 would not have triggered and the prescribing would have proceeded with consideration of the other factors.

EMR enhancements needed to realize personalize medicine

In order to move toward the decision support scenarios described above, EMR systems will require a number of enhancements (Hoffman 2007). The legacy of EMRs traces back to early needs to better support administrative transactions, especially for billing purposes. These transaction oriented systems were not necessarily designed to enhance the care of individual patients. Before genetics and pharmacogenetics became synonymous with "personalized medicine", some EMR suppliers began to take a person-centric approach to their system architecture in the 1980s. This shift enabled users to more readily assemble an accurate picture of diagnostic and therapeutic events associated with a specific patient and was one of the first contributions of EMRs systems to personalized medicine.

Now that personalized medicine is increasingly synonymous with "genetically enabled medicine", EMR developers are actively assessing the innovations necessary to ensure that EMR systems can fully support the integration of genetic information into electronically enabled patient care. It is important to note that there are distinct categories of EMR developers. One category is the academic or large private institution model that has developed an EMR highly tailored to the unique needs of their institution, sometimes through a ground-up design of a unique system, sometimes through a highly customized integration of commercial systems. EMRs developed in this model have the benefit of agility, but the lessons learned in those contexts often prove difficult to disseminate outside of the system. The second broad category consists of EMRs developed through a commercial model for installation in a wide variety of settings. These systems must be flexible enough to meet the needs of a wide variety of organizations, must ensure that they meet the legal and regulatory requirements of a system that is distributed commercially and must enable information exchange of a subset of their data elements across platforms. Regardless of the development model, EMR developers have realized that improvements in foundational capabilities will enhance the ability to better support personalized medicine.

Discretely stored genetic test results

One foundational capability that is necessary to enable both asynchronous and synchronous decision support is the discrete storage of consistently codified genetic test results. The federally sponsored funding for implementation of EMRs through ARRA includes the requirement that systems highlight the discrete storage of laboratory results. While there are many interpretations of discrete data, this requirement will encourage all EMR developers to review their ability to store genetic data discretely. Many laboratory information systems (LIS) and EMR implementations have operated under the assumption that it was adequate to store genetic test reports as purely textual documents. While this is indeed useful in the context of a physician invoking the medical record of a patient, text documents are not yet a reliable basis upon which to build real-time decision support rules, despite the best advances in natural language processing. Discrete storage of genetic test results in a machine-readable format is an important pre-requisite to widespread availability of decision support based on genetic information.

In the academic EMR development model, Partners HealthCare has made strong progress toward discrete genetic data capture (M Ullman-Cullere personal communication). In the commercial EMR and LIS categories, Cerner has implemented a molecular diagnostics module for their LIS that stores genetic test results in a discrete format in tandem with the report that is utilized by the clinician. Discrete genetic data are important as a foundation for decision support, as a means of exchanging data between clinical organizations, whether reference labs and ordering physicians, or ultimately in the context of continuity of care across patient venues. Extension of these systems to manage DNA sequence results, both single gene and whole genome sequencing (WGS), is a likely progression of these efforts (Mitchell and Mitchell 2007).

Codification of genetic test results

In order to fully enable the exchange of genetic test results across EMR systems, genetic information should be associated with an appropriate standardized terminology to insure consistent meaning across venues. The Systematized Nomenclature of Medicine–Clinical Terms (SNOMED-CT) has a strong representation of clinical conditions, The Logical Observation Identifiers Names and Codes (LOINC) provides reasonable coverage of possible genetic test procedures and the Clinical Bioinformatics Ontology (CBO) provides a semantically structured vocabulary representing the physical observations of the diagnostic laboratory (variants observed, cytogenetic findings etc.) (Hoffman et al. 2005). For example, a clinician might order a cystic fibrosis screening panel that is associated with a LOINC code. The laboratory performing the testing can associate the presence or absence of the 87 mutations in the testing panel that they utilize with CBO concept codes. The final report confirming carrier status for cystic fibrosis or risk of congenital absence of the *vas deferens* might be associated with one or more SNOMED-CT codes.

Exchange of genetic data across EMR systems

Discrete and codified genetic test orders and results enable better personalized medicine when integrated with clinical data exchange methods (Shabo 2005). Information exchange across provider settings supports personalized medicine by reducing the risk that a given provider may not have access to a significant insight about their patient. Health Language 7 (HL7) is the standard messaging protocol used to exchange information between clinical information systems. Using HL7, organizations can exchange information and reduce the likelihood of a clinician making a partially informed decision or ordering a duplicate test.

Family history

Unlike most other clinical data, genetic data has direct and lasting relevance to family members of the patient. While a variety of stand-alone pedigree generation and analysis applications have been available for quite awhile, integration of structured and machine-readable family history into EMR systems and workflows has been limited. The recent release of an electronic family history application by the US Surgeon General (Giovanni and Murray 2010) has generated renewed interest in integrating family history capability with both EMR and personal health records (PHR). Continued progress in this area, coupled with serious discussion and consideration of the complex ethical and legal issues related to cross-person data sharing, will eventually provide further foundations upon which to provide novel personalized medicine capabilities.

Collectively, these enhancements to EMR systems, regardless of development model, will provide a stronger foundation upon which to implement innovations in clinical decision support.

Extrinsic factors

The previous sections have for the most part focused on EMR enhancements that are under the control of a given health care system or vendor. In 2006, a strategic health information technology plan for the Department of Health and Human Services was developed (DHHS 2006). A large group of stakeholders, the American Health Information Community (AHIC) was convened to identify and propose solutions to eliminate interoperability barriers. Ten workgroups were created to address a number of issues including privacy and clinical decision support. The recognition that personalized medicine would be heavily dependent on fully functional EMR systems lead to empanelling of the AHIC Personalized Medicine Workgroup (PMW) of which both authors were participants. Many issues were identified that while having relevance for personalized medicine, were not unique to this area. Cross-cutting concerns include: privacy; construction of clinical decision support rules; defining the evidence base necessary to create rules or provide information in the EMR; communication between EMRs; external repositories of vetted decision rules, educational resources, curated mutation databases ideally associated with phenotypic or disease specific information; and data representation. The PMW identified significant deficiencies in data representation around concepts of family history, genotype and other molecular data as well as a lack of standards needed to communicate this information between EMRs. Several of these issues have been noted in the preceding sections. At the time of the AHIC sunset in 2008, the PMW had forwarded proposed standards for family history for certification to the Certification Commission for Health Information Technology (CCHIT) and had made significant progress on representation of molecular data elements and communication—work that is continuing in other groups such as the genomic workgroup of Health Level-7 an international health IT organization (HL7). For more details on these problems and solutions, the reader is referred to Downing et al. (2009).

The concept of a single source of evidence-based content for the application of genomic information during the delivery of patient care is appealing, but faces many challenges. While groups such as the Evaluation of Genomic

Applications in Practice and Prevention (EGAPP) have begun to systematically review evidence relating to genomics and personalized medicine, the volume of knowledge being generated outstrips the ability to use traditional evidence review methods to develop guidelines or even begin to define utility for many emerging tests. As noted above, responsibility at present falls to individual providers with content expertise to work on behalf of their organizations to vet the information and work with EMR specialists to best utilize the existing system to present information to providers and patients. While some national efforts such as the Genetic Testing Registry (GTR), the CCHIT workgroup on advanced clinical decision support, the Office of the National Coordinator for Health Information Technology and the National Library of Medicine are attempting to fill this gap, it will be some time before this problem will be solved.

Conclusion

Pauker and Kassirer (1987) proposed the following definition for personalized medicine, "Personalized medicine is the practice of clinical decision-making such that the decisions made maximize the outcomes that the patient most cares about and minimizes those that the patient fears the most, on the basis of as much knowledge about the individual's state as is available." The key elements of this definition are the need to represent all information of interest, including but not limited to genomic results and family history, in a coded and computable format within the EMR and the need to incorporate patient preferences regarding outcomes in clinical decision making. Only then will the dream of patient-centered personalized medicine become a reality.

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