

Comparative Effectiveness Research and Medical Informatics

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ABSTRACT

As is the case for environmental, ecological, astronomical, and other sciences, medical practice and research finds itself in a tsunami of data. This data deluge, due primarily to the introduction of digitalization in routine medical care and medical research, affords the opportunity for improved patient care and scientific discovery. Medical informatics is the subdiscipline of medicine created to make greater use of information in order to improve healthcare. The 4 areas of medical informatics research (information access, structure, analysis, and interaction) are used as a framework to discuss the overlap in information needs of comparative effectiveness research and potential contributions of medical informatics. Examples of progress from the medical informatics literature and the Veterans Affairs Healthcare System are provided.

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Medicine is an information-rich field with every interaction between patient and clinician producing hundreds, if not thousands, of data points. These data include information about symptoms, diagnoses of disease, laboratory tests and results, anatomical images, interventions, and responses to treatments over time. Acceleration of scientific innovation in medicine is also contributing to the medical data deluge. The National Library of Medicine's online database MEDLINE now contains >18 million records from 5,000-plus publications.¹ With the continuous introduction of new biological data (e.g., genomic, proteomic) in scientific analysis and its eventual inclusion in the patient record, the quantity of medical information produced will increase exponentially.

Despite the extraordinary amount of information produced and the rate with which it continues to grow, patients and

healthcare providers lack hard evidence to answer the most fundamental question of medicine: which treatments work best?² Our ability to answer this fundamental question of comparative effectiveness is tied directly to our ability to overcome several information-related obstacles. More specifically, understanding the comparative effectiveness of treatments requires methods of accessing relevant information from the mountains of information produced, structuring it to enable "apples-to-apples" comparisons, the discovery of meaningful findings, and the delivery of these findings to stakeholders.

The discipline created to address such information-related challenges is medical informatics. We highlight the overlap in the information needs of comparative effectiveness research (CER) and the focus of the field of medical informatics. To illustrate the challenges and opportunities facing CER and the potential contributions of medical informatics, examples are drawn from the medical informatics literature and from the authors' home institution, the Veterans Affairs (VA) Healthcare System.

FOCUS OF MEDICAL INFORMATICS

Interesting histories of the field have been written³ and numerous formal definitions proffered,⁴⁻⁶ but for this discussion medical informatics is defined as the field con-

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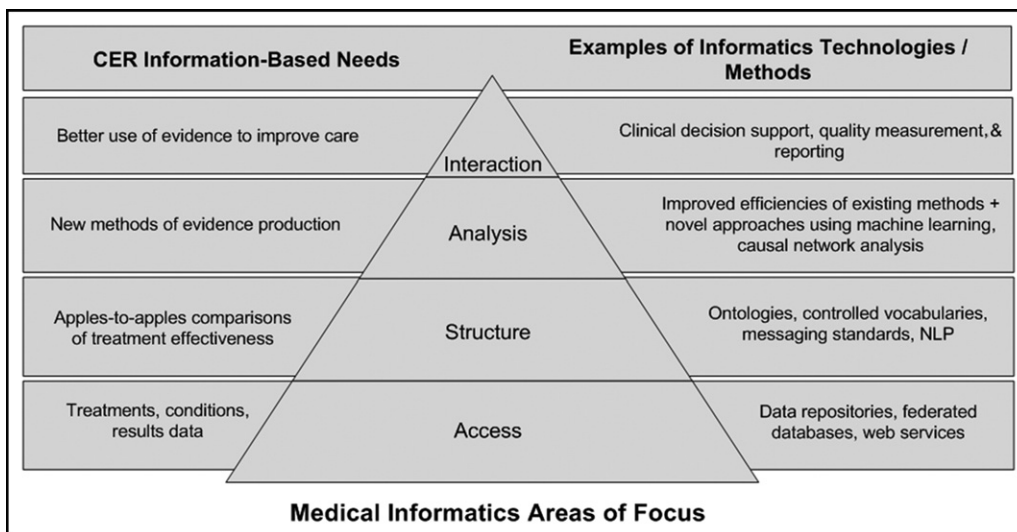


Figure 1 The areas of focus of medical informatics applied to the information-based needs of comparative effectiveness research (CER). NLP = natural language processing.

cerned with maximizing the utility of information to improve process and outcomes in medicine. Although the use of information technology is an important part of medical informatics, researchers employ both quantitative and qualitative methods to understand and improve the processes surrounding information use. At a high level, the study of these processes can be considered the areas of focus of the field of medical informatics research. Here we introduce 4 general categories of focus of informatics: information access, information structure, information analysis, and information interaction. These 4 categories and examples of CER information needs and medical informatics solutions are shown in Figure 1.

To highlight the overlap of CER and medical informatics, consider the hypothetical but not atypical case of a cardiologist receiving an award to conduct comparative effectiveness research. The fictional Dr. Z was recently awarded a 3-year grant from the US National Institutes of Health (NIH) to conduct an observational study of the comparative effectiveness of drug A versus drug B for secondary prevention of vascular events in survivors of acute myocardial infarction (MI). Dr. Z's hypothetical study team has considerable expertise in vascular disease and some experience in statistical analysis. Yet to produce meaningful evidence on the comparative effectiveness of 2 drugs, Dr. Z's team will be responsible for overcoming a number of information-oriented challenges. We use the challenges faced by Dr. Z's team to highlight the overlap between the information-related obstacles to CER and the focus of medical informatics research.

AREAS OF MEDICAL INFORMATICS RESEARCH AND COMPARATIVE EFFECTIVENESS RESEARCH

Information Access

The first hurdle in CER is gaining access to the information required to conduct the study. The degree of information

access provided to Dr. Z will determine the size and representation of the cohort and the covariates and outcomes available for analysis. In other words, access is the prerequisite step upon which all others in her study are dependent. Despite its importance, any number of obstacles to gaining access may exist. The first obstacle is the potential lack of adoption of electronic medical record (EMR) systems. Some estimates place the rate of adoption of EMRs in the United States at <20%.⁷ Assuming that Dr. Z's home institution is among the 20% of facilities with EMRs, adoption of an EMR system is far from a guarantee of access to the information required for CER. The lack of interoperability between different EMR systems leads to gaps in documented care when patients have been treated at different institutions or facilities. In addition, EMR systems are designed to support 1-on-1 interactions between care providers, to provide a legal documentation of events, and to support financial reimbursement. As a result, they are neither well-suited for, nor maintained to facilitate research. Dr. Z may therefore have to negotiate access to EMR data with hospital information technology (IT) departments that do not have adequate resources to divert from clinical and administrative operations to research-related tasks. Adding to IT departments' potential reluctance is the highly sensitive nature of clinical data. This is particularly true of access to the free text portions of clinical records where any 1 of the 18 Health Insurance Portability and Accountability Act (HIPAA)-defined patient health identifiers can appear.

Assuming access can be negotiated, the databases of EMR systems are designed to support updates, inserts, and reads of individual data elements. Such "transactional" databases are optimized to ensure the integrity of the data, even when requests are being made from large numbers of users simultaneously. The result is data spread across thousands of tables that were not intended to be accessed outside of the mechanisms provided by the EMR system. Research-

ers intending to aggregate several variables must therefore identify relevant information across hundreds of tables and columns, often without the benefit of researcher-friendly data dictionaries or tools.

The American Recovery and Reinvestment Act's \$19 billion in incentives payable to physicians adopting EMRs over the next 5 years⁸ is likely to improve adoption rates at private hospitals significantly. Although greater adoption will make it possible to begin to utilize clinical data for CER in new ways, improved methods of access must be developed first. Several prominent informatics-driven efforts are under way to explore solutions to improved access, including the development of Regional Health Information Organizations and Health Information Exchanges.⁹ Technologies designed to facilitate access to clinical data are central to many of the NIH's ambitious programs to transform clinical science, including the National Center for Research Resources' Clinical and Translation Science Awards (CTSA),¹⁰ and the National Cancer Institute's multibillion dollar Cancer Biomedical Informatics Grid (caBIG).¹¹ Many of the projects emerging from these initiatives have explored the use of technologies to connect different information systems across and within institutions such as grid computing and federated databases,¹² clinical data warehouses or repositories,¹³ and communications protocols such as Web services.¹⁴ Coupled with workflows that provide role-based governance, these methods of data access have proved capable of facilitating requisite access while ensuring appropriate levels of security.¹⁵

The authors' home institution, the VA Healthcare System, addresses issues of access by providing both a nationally-connected EMR system and databases formatted specifically to support secondary analysis. Access to EMR data within the VA Healthcare System is provided by the Veterans Health Information Systems and Technology Architecture (Vista). Developed at the VA and now available as open source software, Vista is used at all of the VA's 1,500-plus clinics and hospitals. Tables 1 and 2 provide some insights into the amount of information available in Vista. The VA also has >100 patient registries that aggregate specific types of patient information for convenient access and reporting. Table 3 highlights a small sample of the diverse coverage of VA patient registries. While most existing VA repositories are disease- or data-type specific (e.g., diabetes registry, pharmaceutical registry), new initiatives such as the Veterans Informatics and Computing Infrastructure (VINCI) and the Medical Domain Web Services (MDWS) will enable access to the longitudinal treatment histories of >9 million patients, enabling the type of real-world analysis required for CER.

Another active area of medical informatics research that can provide a layer of patient privacy protection is the automated de-identification of free text, or the removal or replacement of personal health identifiers. Automated de-identification uses natural language processing (NLP) and pattern recognition algorithms from the field of computer science. Performance of such algorithms is unlikely to be

Table 1 US Department of Veterans Affairs (VA) Organization and Workflow in 2006

● Points of care	1,400+
● Patients treated	5.2 million
● Outpatient encounters	129 million
● Inpatient discharge	600,000
● Pharmacy refills	172 million
● Chemistry lab tests	250 million
● Radiology procedures	135 million

Table 2 US Department of Veterans Affairs (VA) Veterans Health Information and Technology Architecture (Vista) Data Volumes and Use through December 2006

	2006 Total Volume	Vista Use Per Workday
Text Documents (progress notes, discharge summaries, reports, etc.)	874 million	+638,000
Orders	1.65 billion	+955,000
Images	590 million	+884,000
Vital signs measurements	1.06 billion	+729,000

perfect, but it has proved capable of removing a large percentage of all personal identifiers.¹⁶

Information Structure

Having obtained access to the raw data required to conduct her analysis, Dr. Z must identify a number of variables to create her cohort and conduct her analysis. Her protocol clearly outlines the cohort characteristics and variables of interest. Unfortunately, the poor mathematical format and the heterogeneous nature of medical data can prohibit the types of apples-to-apples comparisons of patient conditions, interventions, and outcomes required. Identifying a population of patients with a history of MI will likely rely on use of very few data standards such as International Classification of Diseases (ICD)-9 codes for cohort identification. Unfortunately, ICD-9 codes are primarily assigned to ensure financial reimbursement and can be of dubious quality for other purposes.^{17,18} Key covariates, such as history of smoking, are often buried in the free text of clinical records. As a result, Dr. Z's study may have to exclude some variables or be limited to the resources available for manual chart review.

Developing and evaluating methods to structure clinical data is an important focus of medical informatics. There are 2 related areas of research on information structure: research on representations of information (e.g., standards, controlled vocabularies, etc.), and research on the algorithms used to map data to structured representations (e.g., NLP). Research on information structures involves the creation, use, and evaluation of domain-specific controlled

Table 3 A sampling of US Department of Veterans Affairs (VA) Registries Available to Researchers

Registry	Description
ASI	Provides centralized record keeping on substance abuse patients using VA medical facilities. Provides statistical information by medical center (e.g., treatment outcome measurements). Provides reports for evaluation of substance abuse patient care performance at each of the VAMCs.
BHIE	BHIE provides both the VHA and DoD physicians' access to clinical data for a patient regardless of the location of the data
CICSP	Demographic data is derived from the administrative packages and operative and outcome data from the surgical package. Provides information required to focus and direct internal quality improvement efforts and national cardiac surgery policy initiatives.
CJDLD	The CJDLD is dependent upon data input from individual VHA medical facilities that is used by the Infectious Diseases Program Office to update the CJDLD. The tracking system is an epidemiological tool to determine if patients in the dataset have an impact on VA CJD cases nationwide.
Drug accountability	Provides a national database containing information on drug dispensing at VAMCs. Provides reporting at local, regional, and national levels for VAMCs.
EPSC	Provides a central registry of all information relevant to the installation, model, and functioning of pacemakers implanted in VHA patients.
EPI	Provides data on emerging pathogens to VA headquarters without additional local data entry. Provides national SAS data sets for the Infectious Disease Program.
NPPD (prosthetics & sensory aids service)	Enhances prescription practices and research by providing a means for national utilization comparisons using HCPCS standardization. Provides a patient item history on main NPPD groups that are based on HC PCS codes.

ASI = Addiction Severity Index; BHIE = Bidirectional Health Information Exchange; CICSP = Continuous Improvement in Cardiac Surgery Program; CJD = Creutzfeldt-Jakob Disease; CJDLD = CJD Lookback Dataset; DoD = Department of Defense; EPI = Emerging Pathogens Initiative; EPSC = Eastern Pacemaker Surveillance Center Database; HCPCS = Health Care Financing Administration Common Procedure Coding System; NPPD = National Prosthetic Patient Database; SAS = Statistical Analysis System; VAMCs = VA Medical Centers; VHA = Veteran's Health Administration.

leading to often divergent representations. The result is well over 100 "standard" dictionaries of medical concepts, including the ICD, Medical Subject Headings (MeSH), Health Level 7 (HL7), the Systematized Nomenclature for Medicine–Clinical Terms (SNOMED-CT), and the Unified Medical Language System (UMLS). The second aspect of structure necessary for enabling comparisons of information is the development, use, and evaluation of algorithms for mapping the various representations or terms (e.g., heart attack, MI) to a standard format (e.g., UMLS Concept ID: C0027051).

Information retrieval and NLP algorithms have proved capable of facilitating CER. For example, information retrieval algorithms similar to those used to identify Web pages by search engines can retrieve relevant medical documents for analysis.¹⁹ Using these technologies, Dr. Z's team can sort through thousands of cases automatically, filtering out only those cases in which an MI event occurred. Once the appropriate records are identified, a number of informatics studies have demonstrated the ability to extract variables of interest from free text using NLP technologies. Of particular relevance to Dr. Z are the several systems created to automatically extract smoking status and diagnoses.^{20,21}

With billions of free text records available for analysis, the VA has become active in the area of NLP research, including sponsorship of the Consortium of Healthcare Informatics Research (CHIR). This 4-year, multimillion dollar research program is funding the development of NLP, machine learning, and information retrieval methods at >10 VA facilities and academic affiliates.

Information Analysis

In their reports on CER, both the Federal Coordinating Council and the Institute of Medicine cite limitations of existing study designs.^{22,23} Randomized controlled trials (RCTs) use primary data collection and randomization to produce high-quality evidence but can be costly, taking years to gather data and test a few hypotheses. Observational studies are less resource intensive, but must contend with limited data quality and issues of bias. Meta-analyses capitalize on the evidence usually produced through RCTs, but are limited to what has been already studied. Medical informatics can address some of these limitations through improved and novel methods of information analysis.

One way in which medical informatics can improve methods of analysis is through the development of scientific infrastructures. These shared infrastructures feature large databases containing millions of data points as well as supplying query tools, the ability to host or integrate with analysis tools (e.g., statistical software), and in some cases connectivity to third-party knowledge bases (e.g., the National Center for Biotechnology Information's Entrez search engine²⁴). Scientific infrastructures provide working environments that allow primary investigators to focus their content expertise on asking and answering scientific questions. This approach is central to the NIH Roadmap vision for the next generation of clinical science,²⁵ and early ex-

vocabularies, messaging protocols, and ontologies or definitions of concepts and their relationships to one another. Challenging the use of information structures is that each standard was created with a specific domain or use in mind,

amples of progress are emerging at caBIG and CTSA award sites. The availability of millions of data points introduces the opportunity of generating new hypotheses using data-mining approaches as well as the opportunity to incorporate biological data to explore the potential pharmacogenomic effects of drug A versus B. Importantly, the results of these analyses can be incorporated back into the infrastructure, creating a 'learning' system with value increasing with use.

Examples of scientific infrastructures at the VA include the previously described VINCI for hosting clinical data and the VA Genomic Information System for Integrative Science (GenISIS). GenISIS will combine EMR data with basic environmental/behavioral data and biological data, starting with single nucleotide polymorphisms from DNA. GenISIS will be populated with data from the Million Veteran Program, an observational cohort made available to VA-affiliated researchers.

Another novel mechanism for information analysis is the integration of studies into the EMR. For example, the VA Cooperative Studies Program has begun to pilot point-of-care clinical trials (POC-CT). POC-CT involves the use of randomized assignment of interventions within the EMR system to compare the effectiveness of treatments. POC-CT uses integration with the EMR system (in this case VistA) to flag cases of patients hospitalized with hyperglycemia, capture patient consent for participation, randomize the patient into a particular arm of treatment, and then track patient outcomes longitudinally. If successful, POC-CT will offer a new model for CER, providing the cost benefits of an observational study while capitalizing on the scientific strength of randomization. Importantly, integration with the EMR means the resulting real-world evidence base can be more easily converted to EMR-based clinical decision support.

Information Interaction

After 3 years of diligent work, Dr. Z's team has discovered that drug A does a significantly better job at preventing vascular events than does drug B. Unfortunately, this finding will do little more than boost Dr. Z's academic credentials until stakeholders can interact with relevant evidence at the point of care. With 14,716 new records added to MEDLINE between January 11 and 14 of 2010,²⁶ and no anticipated leaps in brain storage capacity in the near future, one cannot assume the average healthcare provider will learn of and remember Dr. Z's finding.

Medical informatics research in the area of information interaction addresses a number of issues of import for making use of CER findings. First, a thorough understanding of the complex workflows in which information is used is essential to translating the results of CER. Medical informatics researchers pull from a number of other disciplines to study information interaction, including the field of human computer interaction (HCI),²⁷ study of the effects of cognition on information interpretation and use,²⁸ and analysis of clinical workflows and information use.²⁹ Some informatics research facilities such as the Roudebush VA

Medical Center in Indianapolis have created HCI laboratories to conduct simulations and facilitate studies of user acceptance.³⁰ Work has also been done on some of the unintended consequences of implementing systems in healthcare that emphasizes the importance of understanding all of the ways, intended or otherwise, in which systems may be used in clinics.³¹

A number of informatics studies have focused on retrieving relevant evidence at the point of care using algorithms, some of which incorporate the context provided by the EMR.³² Researchers have shown that clinical decision support that integrates evidence at the point of care can reduce medical errors and improve physician performance.³³ The VA has a long history of using VistA to provide clinical decision support in the form of a national program of clinical reminders and research on guideline-based decision support.³⁴

SUMMARY

The field of medicine is entering a period of unprecedented opportunity. With the digitization of medical and biological information and an influx of support for CER, we appear to be closer than ever to finally providing healthcare's stakeholders with evidence of the comparative effectiveness of treatments. It is important, however, to recognize that recent infusions of support for CER and related technologies can only jump-start progress in these areas. One cannot expect healthcare institutions and providers to continue to invest millions of dollars developing and supporting evidence bases of comparative effectiveness and information systems without larger systemic change occurring.

While the economic incentives in healthcare are designed to reward the amount of care provided, both CER and the technologies described here will remain costly luxuries afforded primarily by researchers at few institutions. The current notion of clinical research and clinical care as 2 loosely related subdisciplines of medicine will persist, information will remain inaccessible and of poor quality for secondary use, and we will continue to suffer years-long lags between the conduct of scientific research and the implementation of its findings. If instead, the current trend continues toward incorporating the effectiveness of care in providers' reward systems, CER will be considered a foundation for improvement and the described technologies as necessary investments. It is therefore critical that those interested in advancing the sciences of CER and medical informatics capitalize on this window of opportunity to demonstrate the value of using information to its fullest potential to understand and improve upon clinical care.

AUTHOR DISCLOSURES

The authors who contributed to this article have disclosed the following industry relationships:

Leonard W. D'Avolio, PhD, reports no relationships to disclose with any manufacturer of a product or device discussed in this article.

Wildon R. Farwell, MD, MPH, reports no relationships to disclose with any manufacturer of a product or device discussed in this article.

Louis D. Fiore, MD, MPH, reports no relationships to disclose with any manufacturer of a product or device discussed in this article.

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