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Intelligent Use and Clinical Benefits of Electronic Health Records in Rheumatoid Arthritis

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Abstract

In the last 10 years, electronic health records (EHRs) have had growing impact in clinical care. EHRs efficiently capture and reuse clinical information, which can directly benefit patient care by guiding treatments and providing effective reminders for best practices. The increased adoption has also lead to more complex implementations, including robust, disease-specific tools, such as for rheumatoid arthritis (RA). In addition, the data collected through normal clinical care is also used in secondary research, helping to refine patient treatment for the future. While few studies have directly demonstrated benefits for direct clinical care of RA, the opposite is true for EHR-based research – RA has been a particularly fertile ground for clinical and genomic research that have leveraged typically advanced informatics methods to accurately define RA populations. We discuss the clinical impact of EHRs in RA treatment, and their impact on secondary research, and provide recommendations for improved utility in future EHR installations.

Keywords

Rheumatoid Arthritis; Electronic Health Records; CPOE; Clinical Decision Support Systems; Pharmacogenetics

Introduction

The advent of electronic health records (EHRs) have been an important advance in clinical care and have seen both accelerated adoption and impact over the last five years. Clinicians and researchers have been seeking to design and implement electronic versions of the patient chart since the late 1960s[1]. Early electronic systems provided a common, up-to-date location for medical data that could be accessed by multiple providers at the same time. As early as the mid-1970s, researchers used EHRs to improve care quality through active interventions with the introduction of decision support[2,3]. As adoption of EHRs has become more widespread, studies have shown improvements in patient care with fewer errors[4], better guideline adherence[5], and reduced cost[6]. As a result of developments in

data standards and perceived financial incentives to optimize care, many healthcare systems have begun to share data across sites through Health Information Exchanges (HIE). However, EHRs are not a panacea - some studies have shown possible increases in mortality[7] or medication errors[8] associated with new EHR efforts, highlighting the need to consider and evaluate EHR interventions and new installations carefully.

Beyond clinical care, EHRs also provide a rich set of data for secondary research. One example of secondary use of EHR data is pharmacovigilance, mining records to check for previously unknown drug interactions or adverse events[9]. Institutions can also leverage EHR data for patient ascertainment for existing clinical trials[10]. Institutions are also beginning to utilize biobanks, most notably storing DNA, in order to augment the available phenotypic data[11,12].

In this review, we survey the clinical and research uses of EHR data within the context of rheumatology with a specific focus on rheumatoid arthritis (RA). Overall, data suggest that EHRs can improve the quality of care with some measures related to care for patients with rheumatologic diseases, though specific studies in RA are few. On the other hand, RA and other rheumatologic diseases have been fertile ground for secondary use, including with DNA biobanks. These trends seem likely to lead to improvements patient care, both through new discoveries and improved workflows.

Major Components of EHR Systems

A 2009 New England Journal of Medicine article by Jha, *et al.* included an expert consensus definition of EHR functionalities[13]. Included were two general classes of EHRs, “basic” and “comprehensive” that each had a list of criteria to characterize functionality. Basic EHR systems include demographic data, systems for capturing physician and nursing documentation, structured problem and medication lists, laboratory and radiologic results, and discharge summaries. They also must support “e-prescribing” tools that can electronically send prescriptions to pharmacies.[13] These tools typically represent electronic versions of paper based record systems.

Comprehensive EHRs include more features and provide potential advantages over paper-based records systems. Two primary examples are the use of Computerized Provider Order Entry (CPOE) and Clinical Decision Support (CDS)[13]. CPOE offers the ability for providers to electronically enter medications, laboratory tests, and radiology exams which improves order accuracy and also allows opportunities for CDS logic to examine the patient’s record and provide recommendations based on clinical evidence. For example, CDS can recommend dosing for medications with narrow therapeutic windows such as warfarin[14] and gentamycin[15], and alert clinicians to known drug-drug interactions[16]. Such CDS interventions have been shown to reduce preventable adverse drug event (ADEs) by 34% [17]. Leveraging the breadth of information available across a hospital system can additionally help in other areas, such as disease monitoring, where automated data retrieval can speed identification of potential outbreaks[18].

Studies of EHRs in the Treatment of RA

Few studies have directly studied EHR interventions in RA or other rheumatologic diseases. As of December 2014, a PubMed search for “Decision Support Systems, Clinical”[Mesh] returned 4843 results, yet a search also including “Arthritis, Rheumatoid”[Mesh] only included nine results[19–27]. Eight of these results were pertinent and are summarized in Table 1.

CDS is not the only way to impact the patient care. For instance, the use of automated audits using EHR data could be a valuable tool to ensuring quality of patient care in RA[28]. Similar investigation was performed into the identification of the American College of Rheumatology (ACR) quality indicators for RA patients in the EHR at Geisinger Health System[29]. These investigations at the VA and at Geisinger showed difficulty with identifying some of the subjective measures of patient information automatically in the EHR[28,29]. Selecting quality indicators that use the more typically codified data, e.g., lab tests and medication entries, is an easier solution, but additional complications related to the measuring of dates and filling status of prescriptions still remain[30].

One method of direct patient impact that has been investigated is the use of disease activity calculators. They are designed to help clinicians track patient status over time while encouraging detailed recording of the specific variables needed for calculation. One group of researchers designed and tested, both for accuracy and clinician response, a rheumatology-specific tool named “Rheumatology on Call” including Disease Activity Score on 28 joints (DAS28)[31,32]. It includes a graphical interface with trends for measurements and an image based joint exam summary. The physicians found the tool useful: at the end of the study, 12 of 13 physicians reported that use of the application improved patient care and that seeing a trend in DAS28 was useful. The tool itself, even in the absence of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) measurements at the time of the visit, was reported to be fairly accurate, especially in the extremes of disease activity[33]. Other tools, such as the ones mentioned in Table 1 above, have also approached this problem.

In addition, patient-facing techniques have been explored in RA. One example is from the Friction, *et al.* study in dental practices listed in Table 1. For patients who had a “medically complex” condition listed in their personal health record, the researchers sent a notification, by email or letter, before their dental visit encouraging them to discuss their condition and to review the individual’s personal care guidelines available in their record[20]. Another study used EHR data to provide a visualization of disease activity parameters over time to the patients[34]. In this randomized, controlled trial, patients who had the visualized feedback had significantly reduced DAS28 and significantly better medication adherence. In addition, the patients in the intervention group reported better quality of life markers in the final questionnaire. These works show the potential value of leveraging EHR data to inform and empower patients being treated for RA.

Secondary Use of EHR Data for Research

As institutions more widely implement EHRs, EHR data has been utilized more frequently in clinical research[35–37]. The accumulation of records over time has reached a critical mass where this data from institutions with early implementations of EHRs has captured sufficient patient data to investigate many hypotheses. Use of EHR data for research has revealed advantages and disadvantages compared to traditional case and control or other prospective studies[38].

In general, EHR-based studies use extant data and provide a broader and longer view of patient treatment when compared to a prospective clinical study. Prospective studies allow for more specific protocols, including well-defined time series measurements, e.g. tracking ESR over time, and tend to have less missing data compared to retrospective EHR studies. EHR studies tend to be biased towards certain populations as they are comprised of individuals already in contact with a particular health system; institutional policies and trends can also effect which tests and treatments are most commonly used. These tradeoffs between cost, cohort size, data specificity, and data reliability are important to effective study design. For instance, an EHR-based study may be cheaper and have more patients, but have irregular data collection[39]. This might increase the power to detect an association due to the sample size, but reduce the odds ratio due to the less reliable data[40].

There has been a large growth in EHR research methods, made apparent in the growing number of secondary use publications and research networks, such as the Electronic Medical Records and Genomics network (eMERGE)[11], the Pharmacogenomics Research Network's (PGRN) PharmacoGenomics in large POPulations (PGPop) initiative[71Web], and the recently-formed Patient-Centered Outcomes Research Network (PCORnet), which will allow secondary uses studies covering at least one half of a percent of the US population[41]. These collaborations increase the sample size for investigators, allowing larger studies across regions, which can be valuable in exploring more phenotypes and diverse populations[42].

Identifying RA Patients in the EHR

RA has been well studied by researchers identifying phenotypes in the EHR. The identification of RA in the EHR is difficult in part due to the complex relationships between autoimmune disorders. An individual with one ICD9 billing code for RA was shown to have a confirmed clinical diagnosis of RA less than 50% of the time at three sites, and many of the individuals also had diagnosis codes for systemic lupus erythematosus (SLE), juvenile idiopathic arthritis, or psoriatic arthritis [43]. A study using the Veterans Health administration databases showed that of individuals with two RA codes six months apart only 30.9% had a clinical diagnosis of RA on review at the last available encounter[44].

The earliest methods for identifying RA sought to improve upon simple presence or absence of ICD9 billing codes by employing rule based approaches that identified cases based on the presence or absence of codes, medications, and text matches[44–46]. Later methods

developed include more complicated statistical and machine learning approaches to RA case identification[45,47].

Liao et al. identified RA patients using logistic regression across many attributes including codified data (e.g., ICD9 codes, electronic prescriptions, and anti-citrullinated protein antibodies (ACPAs) and rheumatoid factor (RF) laboratory values) and NLP results from narrative EHR data, including extracted disease diagnoses, medications, laboratory data, and radiology findings[45]. They began their algorithm with a filter requiring the presence of at least one ICD9 code for RA. The authors showed a dramatic improvement in PPV over just using ICD9 codes: 94% as compared to 56% for those individuals with three RA billing codes. They also highlighted the importance of including both codified and NLP data, as the PPVs for models including only each class of data were 88% and 89% respectively. A later study demonstrated that these methods are applicable to other institutions[43]. Another method applied support vector machines, a machine learning technique[48], to ICD9 codes, NLP results, and medication records with similar performance[47]. Another group of researchers has investigated non-diagnosis code lists and keywords in early identification of RA[49,50].

Newer research has focused on identifying more complex attributes of RA patients instead of simply case/control disease status. These further studies allow the investigation of more distinct phenotypes. One example is a study that compared the serotypes of non-RA controls to RA individuals. This study found that individuals with RA had a significantly increased likelihood of having antinuclear antibodies (ANAs), normally associated with SLE, as well as the expected ACPAs[51]. Work has also been done on identifying disease activity, which can be used for investigating treatment trends. Researchers were able to train a model using lab values and NLP concepts that could identify between the broad DAS28 groups moderate and high versus low and remission with an AUC of 0.83. This is comparable to the results of clinician chart review[52]. This work is similar to the DAS28 calculator discussed earlier, but retrieves some information from the free text clinical narratives that was collected in the disease calculator.

A group of researchers out of Australia investigated issues with disease control for RA patients using de-identified EHR data from 28 sites. These sites implemented a DAS28-ESR calculator that presented information to the treating clinician, and the study focused on identifying barriers preventing patients from reaching low disease activity or remission. From 584 records with no adjustment of disease modifying anti-rheumatic drug (DMARD) therapy and a moderate or high DAS28-ESR score (≥ 3.2), the authors identified irreversible joint damage as the most common barrier to treatment control (BTC) in almost 20% of records. Other common BTCs included patient-driven undertreatment (14.7%), rheumatologist-driven undertreatment (9.9%), noninflammatory musculoskeletal pain (9.2%), and insufficient time to assess response to recently initiated DMARD (9.2%)[53].

Researchers are also focusing on differences in treatment and ways to predict risk or benefit of different treatment options. One such example is a study in the VA [54]. The authors of this study identified risk factors for liver function test abnormalities in patients treated with methotrexate. This study is notable as it used only EHR data, and the researchers suggest a

risk score could be calculated in the EHR and presented to physicians to help inform treatment and liver function monitoring decisions.

EHR-Based RA Genomics Research

As early as 2010, replication of genetic associations with RA were shown using EHR derived data[46]. Two of the first four studies on EHR-based genetics studies included results on RA[46,55]. The ability to use EHR-derived phenotypes to identify genetic associations demonstrated in these and similar studies helped drive the utilization of EHR-linked biobanks for genetic research [11,12,56–58,72Web].

A 2011 study of RA using genomics data and EHR derived multiethnic cohort showed similar odds ratios to the published literature for many risk variants, as shown in Figure 1[59]. This study was further able to show connections between RA risk loci and ACPA status. In an analysis of 29 SNPs previously associated with RA, they found some significant differences in ORs for some SNPs when comparing results from studies with cases who were ACPA positive vs. those who were ACPA negative. They were also able to show similarity of RA risk SNPs across ethnicities[59]. This work was further expanded by investigating other autoantibodies and phenotypes in conjunction with RA status. The genetic risk score (GRS) models were able to show an association between more total RA risk alleles and more auto-antibodies[51]. EHR-derived samples also contributed to a large meta-analysis GWAS of 29,880 RA patients and 73,758 controls; this study identified 42 new genetic loci associated with RA[60]. Phenome-wide association studies of SNPs known associated with RA have demonstrated that some of these SNPs are also associated for type 1 diabetes and other autoimmune diseases, while others are not[40]. Table 2 presents a summary of EHR-based phenotyping and genetics studies.

Pharmacogenomics

Biobanks linked to EHRs are likely to continue to be important in many areas beyond simple disease associations, for example pharmacogenomics- finding associations between genes and drug metabolism, response, and toxicity[61]. A recent trend in CDS systems is the incorporation of complex genetic information into drug prescribing. One example is the Vanderbilt Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment (PREDICT) program[14,62]. In a study of the first 10,000 enrolled individuals, 91% had at least one actionable variant[63]. St. Jude's Children's Hospital has also integrated variant testing into their care[64]. We are not familiar with any such program for RA, but there are opportunities for this in the future. For instance, methotrexate treatment, the most commonly used treatment in RA, can lead to drug-induced liver injury[65]. There is an opportunity using EHRs and genetic data to further investigate the pathways behind this toxicity[66], which may lead to safer patient treatment in the future, perhaps through genetic risk profiling.

Due to the importance of early, aggressive treatment in RA, identifying genetic markers or other factors that may impact disease severity, complications, or the success of certain medication regimens could be very helpful. Studies have shown limited success thus far in identifying genetic factors related to anti-TNF treatment response[67], but larger studies

may have the power to find or confirm signals. Work has been done to predict disease activity groups retrospectively, which could be used to help plot patient trajectories for a treatment[68]. EHR biobanks and multi-site collaborations may provide the sample size needed to identify markers that may lead to more efficient, more tailored patient treatment.

Expert commentary

Many studies have demonstrated that EHRs can effectively improve clinical care, but there are relatively few studies investigating RA outcome improvements due to EHR interventions in clinical care. Thus, we suggest that the complex nature of RA care represents an opportunity for greater developed and research into EHR use. However, EHRs have proven a fertile environment for secondary research in RA, and the benefits of these studies are near to impacting clinical care.

In particular, EHRs are sought for the improvements that they can provide for patient health outcomes and the potential financial benefits provided. Often overlooked is their potential as a platform for development with real opportunities to provide clinicians with tools to simplify and improve their practice. Some of these tools do exist as mentioned earlier; however, many EHRs cannot support customization to allow implementation of external tools. As EHR adoption increases and more feature-rich EHRs spread, one can expect that the clinician-facing options will improve as well. One can compare this to the advent and adoption of smartphones: as smartphones have grown in capabilities, the user experience has improved and flexibility and available tools have increased. This growth in the platform has also provided for a much larger growth in the diversity and capability of the “apps”, magnifying the effects of wider adoption and growing features. Indeed, some such platforms are being developed today, including the Substitutable Medical Applications, Reusable Technologies (SMART)[69], which would exposure EHR data to a marketplace of replaceable and sharable “apps” much like on a smartphone.

EHR-based research in RA has provided some insights into the nature of the disease, genetic risks, and prediction of its severity. The genetic risk SNPs identified for RA do not provide much direct clinical benefit at this time - even if one knew an individual was at high genetic risk for RA, it is unlikely to change anything about their treatment or lifestyle choices as there are no proven preventative strategies for RA. Understanding the underlying biology could perhaps lead to new therapeutic targets and drug repurposing; indeed one study has used genetic results to suggest new drugs that might have efficacy in RA[60]. The larger, more immediate clinical benefit of genetic discovery will likely come from pharmacogenomics studies, which are becoming more common. Predicting which individuals are likely to respond and not have adverse effects from a given treatment would have a very practical impact on patient treatment in the near term. Such studies have been implemented in cardiology[14] and oncology[70] but not yet in rheumatology. These types of investigations can be well suited to the data available in EHRs and biobanks now instituted around the world. Indeed, collecting cohorts of patients with adverse drug events take very large patient populations, which may be more easily and inexpensively accrued as a byproduct of health care than a clinical trial.

Five Year View

EHRs will continue to gain in both clinical adoption and their robustness for the near future. Growth in EHRs provides opportunities for improved care in RA while simultaneously providing a platform for reuse for clinical and genetic research. Opportunities to integrate the existing tools to track RA disease status can assist clinicians in care and would likely also provide more structured data for secondary clinical and biological research. HIE implementation is likely to expand as well; benefits may include physician knowledge of DMARD treatment in emergency room visits for trauma where infections may be a concern.

Pharmacogenomics is an important and growing area of research, and EHR-based biobanks may be ideal for studies of rare outcomes and efficacy if the necessary data can be captured through the course of clinical care. Studying RA drug response and toxicity phenotypes in the EHR will be easier as methods develop, data in EHRs expand, and consortia grow. In particular, the identification of treatment patterns may help researchers and clinicians identify factors that lead to better response or avoid adverse reactions.

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Abbreviations

ACPAs	Anti–Citrullinated Protein Antibodies
ACR	American College of Rheumatology
ADEs	Adverse Drug Event
ANAs	Antinuclear Antibodies
BTC	Barrier to Treatment Control
CDS	Clinical Decision Support
CPOE	Computerized Provider Order Entry
DAS28	Disease Activity Score on 28 Joints
DMARD	Disease-Modifying Antirheumatic Drug
EHRs	Electronic Health Records
ESR	Erythrocyte Sedimentation Rate
HIE	Health Information Exchanges
NLP	Natural Language Processing
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
SLE	Systemic lupus erythematosus

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Key points

- 1) EHRs are growing in adoption and complexity due in part to national incentives for adoption. EHR use is typically associated with improved outcomes and reduced cost, though specific studies in RA are lacking.
- 2) RA specific tools exist to help track and use patient disease activity[21,22,24,32,33,49].
- 3) CDS is available to help clinicians treat patients, including assisting in dosing and alerting for possible drug-drug interactions.
- 4) Identifying quality indicators and disease activity scores are helped by codified data, e.g. joint counts, and EHRs are moving to collect more of this information.
- 5) RA has been an active area for secondary clinical and genetic research using EHR data. Genetic studies in EHR have demonstrated results in multiethnic cohorts, evaluated the role of genetics to predict autoantibody status, and contributed to finding new RA genetic loci.
- 6) Rule-based and machine learning methods exist for identifying RA patients and their disease activity automatically from the EHR[43–47,52]. These available algorithms can be used to create cohorts for research or surveillance.
- 7) Research networks provide opportunities for collaborations in studying hypotheses. Growing populations of EHR-linked biobanks will enable greater RA and RA pharmacogenetic research.

Figure 1.

Odds ratios and 95% CIs compared between a traditional GWAS meta-analysis and an EHR-derived cohort. The EHR cohort is comprised of European, ACPA+ individuals. Reprinted with permission from Elsevier [61,73].

ACPA: anti-citrullinated protein antibodies; EHR: Electronic health records; GWAS: Genome-wide association study.

Table 1

PubMed articles for clinical decision support and rheumatoid arthritis.

Citation	Topic and Significance
Friction <i>et al.</i> [20]	Electronic dental record alerts and patient portals to helped compliance with clinical guidelines for medically complex patients, including RA, across 102 providers at six months after implementation. At the 18-month mark, utilization of the resource returned to baseline levels.
Matsui and Tohma * [21]	An article in the Japanese Journal of Clinical Medicine, listed in PubMed as a review, covering a “support system”.
Kolarz <i>et al.</i> * [22]	An Austrian group describes an expert system that assists in capture of signs and findings in rheumatic disease, as well as knowledge-based support for differential diagnosis in rheumatic diseases.
Palmer and El Miedany [24]	The authors present a tool for recording visit data in inflammatory arthritis, including disease activity calculations.
Fransen <i>et al.</i> [25]	This article includes describes a suggested randomized controlled study for evaluating any type of CDS used to benefit RA patients.
van der Wilt <i>et al.</i> [26]	Researchers used a Bayesian approach to estimate probability of response to MTX treatment by modeling changes in a health assessment questionnaire scores between baseline and three months.
Dahlström <i>et al.</i> [27]	Researchers used heuristic models based on expert knowledge to cluster patients into prognostic groups, which showed improvement over the basic data mining methods.
de Vries-Bouwstra[19]	This study attempted to use a collection of patient attributes (age, gender, joint count, and more) to predict progression of radiologic damage at one year as measured by Sharp-van der Heijde (SH) score. The authors found a need for better prognostic variables.

* An English translation for this complete article was not identified for review.

CDS: Clinical Decision Support; MTX: Methotrexate; RA: Rheumatoid arthritis; SH: Sharp-van der Heijde.

Table 2

List of electronic health record-based rheumatoid arthritis identification and discovery research.

	Citation	Topic and Significance
RA Phenotyping	Liao et al. [45]	Designed a logistic regression model to identify RA. Demonstrates value of billing codes, text, lab, and medication attributes.
	Carroll et al. [47]	Designed a support vector machine to identify RA. Discusses training set size requirements and the benefit of using expert-selected features.
	Carroll et al. [43]	Shows portability of complex algorithms across three sites to identify RA.
	Ng et al. [44]	Uses VA administration data to identify RA.
	Lin et al. [52]	Calculates an estimate for disease activity groups from EHR notes and associated lab values.
	Nicholson et al. [49]	Identifies markers of RA that appear before a coded diagnosis.
	Ford et al. [50]	Compares RA keywords and information that appears in coded data to free text data, finding missing data in the coded information.
	Schmajuk et al. [54]	Identifies risk factors for abnormal liver function tests in patients treated with methotrexate.
RA EHR Genetics	Ritchie et al. [46]	Replicated known RA genetic associations using cohorts identified using an EHR algorithm.
	Kurreeman et al. [59]	Uses a large, EHR derived RA cohort to investigate genetic associations. Demonstrates similar genetics across ethnicities divided into subsets based on ACPA status.
	Liao et al. [51]	Compares genetics, autoantibodies, and diagnoses in an EHR cohort. Showed an association between more auto-antibodies and higher genetic risk for RA.
	Denny et al. [55]	Demonstrated the feasibility of phenome-wide association studies, in part, by replicating a known association with RA.

ACPA: Anti-citrullinated protein antibodies; EHR: Electronic health records; RA: Rheumatoid arthritis; VA: Veterans Administration.