

Review

Applications of network analysis to routinely collected health care data: a systematic review

Jason Cory Brunson and Reinhard C Laubenbacher

Center for Quantitative Medicine, UConn Health, Farmington, CT, USA

Corresponding Author: Jason Cory Brunson, Center for Quantitative Medicine, UConn Health, 263 Farmington Ave, Farmington, CT 06030-6033, USA. E-mail: brunson@uchc.edu; Phone: +1-860-679-1354

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ABSTRACT

Objective: To survey network analyses of datasets collected in the course of routine operations in health care settings and identify driving questions, methods, needs, and potential for future research.

Materials and Methods: A search strategy was designed to find studies that applied network analysis to routinely collected health care datasets and was adapted to 3 bibliographic databases. The results were grouped according to a thematic analysis of their settings, objectives, data, and methods. Each group received a methodological synthesis.

Results: The search found 189 distinct studies reported before August 2016. We manually partitioned the sample into 4 groups, which investigated institutional exchange, physician collaboration, clinical co-occurrence, and workplace interaction networks. Several robust and ongoing research programs were discerned within (and sometimes across) the groups. Little interaction was observed between these programs, despite conceptual and methodological similarities.

Discussion: We use the literature sample to inform a discussion of good practice at this methodological interface, including the concordance of motivations, study design, data, and tools and the validation and standardization of techniques. We then highlight instances of positive feedback between methodological development and knowledge domains and assess the overall cohesion of the sample.

Key words: network analysis, graph theory, secondary use, administrative data, EHR

BACKGROUND AND SIGNIFICANCE

As electronic information systems have increased in capacity, efficiency, and accessibility, digitized clinical recordkeeping has made routinely collected health care data (RCHD) of unprecedented depth, scope, and variability available to researchers. The computer science revolution behind this progress has also facilitated the development and implementation of rapid, accurate algorithms to perform calculations on mathematical graphs and sample from distributions. This has led to an explosion in applications of network analysis (NA), which have proved successful in many domains at extracting conceptual insights and predictive power from large and messy datasets. A recent systematic review of data acquisition and analysis in systems medicine identified RCHD such as electronic medical records and public databases as the most common sources of data and NA as the most common modeling paradigm.¹ In this article, we review the work being done at the interface of these tools.

OBJECTIVE

We set out to assess the motivations, substance, contributions, and needs of network analyses of routinely collected health care datasets (NARCHD): What problems have motivated this work, and what research programs have emerged? What has this research contributed to knowledge and methodology, and what further advances can be made? The paper provides a comprehensive survey of this literature and an evaluation of ongoing projects.

Our focus on methodologies complements several results-focused reviews that cover much of the same territory. Researchers seeking to build upon this knowledge base stand to benefit from a critical assessment of the methods in common use. By restricting our assessment to studies using data collected for nonresearch purposes, we showcase research designs that do not require collection of new data, which can be resource-intensive and require specialized expertise.

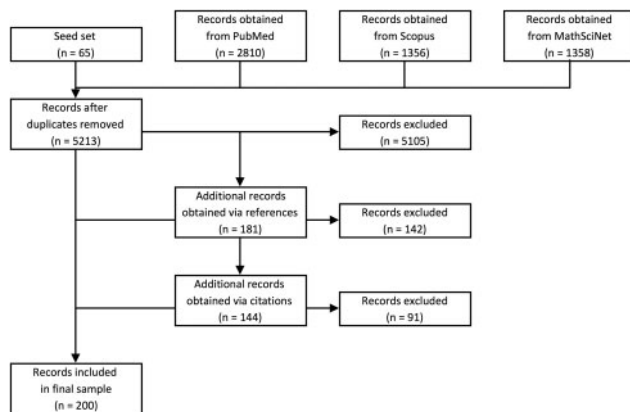


Figure 1. Search protocol and results. We based our keyword search on a “seed set” of publications that motivated our review, then adapted it to each database. Records were excluded based in most cases on title and abstract, and on full texts where necessary, though 8 desired full texts could not be found. Reference and citation chaining were performed twice in sequence (R, C, R, C).

MATERIALS AND METHODS

Search strategy

We operationalized our inclusion criteria as follows:

1. The study must have made use of
 - a. health care–related data
 - b. that were collected as part of routine operations
 - c. and were not collected or demarcated as part of an intervention.
2. These data must have been
 - a. modeled as mathematical graphs
 - b. that were themselves objects of study
 - c. investigated using tools from network analysis.

The search protocol is summarized in Figure 1 and detailed in the supplementary material. We omitted from consideration studies whose use of NA consisted in building artificial neural networks and Bayesian networks, which we felt were distinct subfields deserving separate treatment.

Analysis process

While reading the final sample studies, we grouped them by commonality of study design, with an emphasis on the setting in which data were collected and the techniques used to analyze them, and to a lesser extent the motivating questions. When a study employed multiple datasets or analytical frameworks, we focused on the stage we identified as NARCHD. We then identified and described coherent research programs within each group. In addition to our qualitative analysis, we performed a scientometric summary, reported in the supplementary material. Both informed our discussion of the sample. Table 1 defines network terminology used throughout the sample and in our discussion.

RESULTS

Search

Our final sample comprised 138 journal articles, 52 conference presentations (papers and extended abstracts), 9 book sections, and 1 electronic preprint (see Figure 2). These 200 publications reported results from 189 distinct studies. In the sections below, we give an overview of each group and the major research programs within it, emphasizing projects that were primarily NARCHD.

Table 1. Common network analysis terminology used in this manuscript

Concept	Definition
<i>Network</i>	A system of <i>nodes</i> (members or parts) and <i>links</i> (relationships or connections) between them, usually modeled as a mathematical graph; links can be <i>directed</i> , <i>weighted</i> , or of different types, in which case the network is <i>multilayer</i>
<i>Motifs</i>	Small subgraphs consisting of a set of nodes and links among them, such as <i>dyads</i> (2 nodes) and <i>triads</i> (3 nodes)
<i>Neighborhood</i>	The set of nodes (<i>alters</i>) within a fixed number of <i>hops</i> along links, usually 1, from an index node (<i>ego</i>)
<i>Meso-structure</i>	Network structure that is not detectable locally (within neighborhoods) but does not require global information to detect, such as <i>community structure</i> (discerned from <i>community detection</i> , a family of node clustering methods for graphs) and distance effects
<i>Distance effects</i>	Phenomena that depend on hops along links through a network, such as <i>paths</i> (sequences of incident nodes and links), <i>cycles</i> (paths that end where they begin), <i>betweenness centrality</i> (the proportion of shortest paths on which a node lies), and <i>closeness centrality</i> (the reciprocal harmonic average distance from a node to other nodes)
<i>ERGM</i>	Exponential random graph (also p^*) model, a family of recursive logistic regression models developed to measure the effects of specific generative processes, such as assortativity (homophily), transitivity, and triad closure on the global structure of social networks

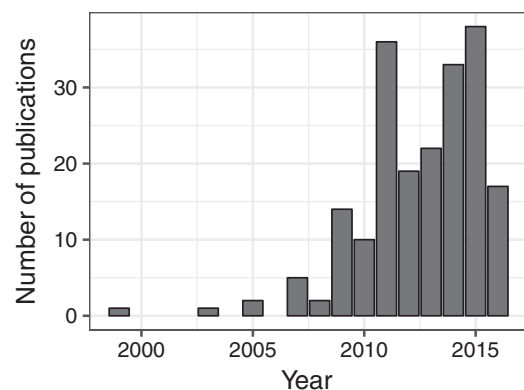


Figure 2. Number of publications each year in our sample, using the earliest date known to have been available.

Institutional exchange networks

Fifty studies analyzed interorganizational health care systems as institutional exchange networks, the most common instantiation of which were *patient-transfer* and *patient-sharing networks*. Most of these studies took a network flow approach,² focusing on the movement of information and resources between providers, though several emphasized that established transfer patterns are an important part of health care infrastructure.³ The studies sorted roughly into 2 investigative frameworks: interorganizational network analysis,⁴ which views institutions as competitors and coordinators in a health

care market and patient-sharing as a proxy for niche overlap or information exchange, and network epidemiology, which views patients as vectors for health care-associated infections.^{5,6} This is reflected in a methodological divide, with static models employed on the economical side and dynamic simulation on the epidemiological side.

Major programs

One research program within this group focused on the role of inter-hospital patient mobility in improving outcomes and increasing efficiency. Some studies sought to explain patient transfers in terms of resource and performance differentials, geography, and other factors.^{7–15} Others examined the structural positions of transfer partners^{7,11,12,16,17} and investigated transfer patterns that suggested inefficiencies.^{8,18} Another program tested theory-driven hypotheses of competitive interdependence, most notably similarities in performance between highly collaborative hospitals and in performance rankings between structurally equivalent ones.^{16,19–25} Some additional studies measured the impact of market-based incentives on administrative decisions.^{26,27} The largest program in the group examined how outbreaks spread through networks of patient transfer, referral, sharing, or interpersonal contact. Early observations that these networks had properties theorized to facilitate outbreaks^{7,28} were followed by several simulation^{29–36} and observational^{37–41} studies of the structural determinants of infection spread and the viability of surveillance^{42–45} and resource allocation^{46,47} strategies.

Physician collaboration networks

Another group of 33 studies modeled institutional and regional physician communities as physician collaboration networks. These studies frequently took a network architecture approach,² emphasizing the determinants and effects of patient-sharing ties and motifs among doctors. This reflects the wider physician collaboration literature, which seeks to identify patterns associated with higher-quality care and better outcomes^{48–50} and the dissemination of best practices.^{49,51}

Major programs

Several studies in this group addressed the accurate measurement and prediction of patient-sharing. One compared the concordance of physician recollection and billing records⁵² and others used demography, geography, affiliation, and attitudes at the physician or dyad level^{53–58} and sociostructural tendencies^{55,56,59} to account for shares and referrals. Another subset linked the motifs and meso-structure of patient-sharing networks to differences in physician practice,^{59–63} patient outcomes,^{56, 64–70} and health disparities.^{71,72}

Clinical co-occurrence networks

A distinctive group of 59 studies concerned relational models of clinical events mined from patient- or encounter-level health records (clinical co-occurrence networks) most often used to generate etiological hypotheses. Half of these studies investigated graph models of disease co-occurrence,^{73,74} often called *comorbidity networks*. Other studies investigated more general networks of diagnoses, lab tests, procedures, prescriptions, ingredients, and clinical terms mined from patient encounter notes.⁷⁵ Data mining and other exploratory methods dominated, with many techniques borrowed from other domains or developed ad hoc. Analyses were mostly local; only a handful invoked community structure or distance effects.

Major programs

Three coherent programs emerged from the studies on disease graphs. One used disease co-occurrence to identify candidate disease dependencies for lab research.^{76–82} Another assessed the ability of known genetic,^{78,79,83–86} proteomic,^{82,85} environmental, lifestyle,⁸⁷ or a combination of factors^{87–89} to account for co-occurrences. A third aggregated patient timelines into *temporal graphs*, directed graphs in which links encode time differentials, that were used to describe patient trajectories and predict future diagnoses.^{90–96} Several other studies employed clustering algorithms, in some cases to recapitulate formal disease ontologies,^{84,96,97} but in others to develop risk-predictive measures,⁹⁸ improve standard classifications,⁹⁹ and stratify patients.^{97,100,101}

Workplace interaction networks

The remaining 47 studies fit into a highly modular group investigating workplace interaction networks, including network models of *shared record access*, *interprovider communication*, *interpersonal contacts*, and *patient handoffs*. Most of these studies were institution-specific and drew from health information system access or process logs. Dominant research themes used signature NA methods, eg, process mining to model workflow.¹⁰² Some of these modules were integrated, by citation or common authorship, into 1 of the groups discussed previously. Most others lay within a larger literature on the social network analysis (SNA) of health care wards and teams.¹⁰³

Major programs

A unique program appearing in this group concerned anomaly detection. These studies used data from user access logs and focused on inappropriate access to patient records^{104–107} and fraud detection.¹⁰⁸ Another subset used similar datasets to model infection spread through contact networks. By incorporating patient-staff contact,^{109,110} surveillance cultures,¹⁰⁹ and spatial proximity,^{111,112} these studies extended the scope of the epidemiological studies discussed above. The largest program emerged from the process management literature. These studies used patient handoff data to characterize the interactions of care teams^{113–117} and ward staffs,^{118–122} and to identify prototypical clinical pathways.^{107,120,123–128}

DISCUSSION

The studies included in our sample took a wide range of approaches, summarized in Table 2, which reflected differences in their conceptual and material needs. In this section we document some strengths and weaknesses of these studies and suggest some standards of good practice. We focus on 2 fronts: the choice of framework and the model construction and validation. We then discuss several achievements and needs, focusing on the mutual benefits to knowledge and methodology and on the overall cohesion of the sample.

Framework assignments were subjective, and rare assignments were combined for ease of reference. Every study incorporated (social) network analysis conceptually and methodologically; when we identified no more specific framework, we listed “NA.”

Choice of framework

Every analysis decision requires justification, starting with the choice of framework. The network conceptual model is most illustratively called into question in the clinical co-occurrence setting:

Table 2. Summary of conceptual and methodological frameworks of journal articles in our sample

Conceptual framework	Methodological framework	Studies
NA	NA	Anderson and Talsma (2011), ¹¹⁸ Hripcsak et al. (2011), ¹²⁹ Lee et al. (2011), ¹⁴ Lee et al. (2011) ¹³⁰
NA	ERGM	Moen et al. (2016) ⁵⁹
NA	Hypothesis generation	Hanauer et al. (2009), ⁷⁷ Hanauer and Ramakrishnan (2013) ⁹³
NA	Mixed methods	Barnett et al. (2012) ⁵⁷
NA	Regression	Boyer et al. (2005), ¹³ Landon et al. (2012) ⁵⁴
NA	Rule mining	Malin et al. (2011) ¹³¹
NA	Text mining	Finlayson et al. (2014) ¹³²
Care coordination	NA	Pham et al. (2009), ¹³³ Gray et al. (2010), ¹²¹ Siden and Urbanoski (2011), ¹¹³ Uddin and Hossain (2011), ¹¹⁴ Mandl et al. (2014), ¹³⁴ Uddin and Hossain (2014), ¹³⁵ Merrill et al. (2015), ¹²⁷ Soulaakis et al. (2015), ¹¹⁶ Uddin et al. (2015) ¹¹⁷
Care coordination	Mixed methods	Chen et al. (2014) ¹²²
Care coordination	Regression	Barnett et al. (2012), ⁶⁶ Pollack et al. (2013), ¹¹⁵ Spear (2014), ¹³⁶ Casalino et al. (2015), ⁶⁹ Ong et al. (2016), ⁶² Uddin (2016) ¹³⁷
Clinical ontology	NA	Aprile et al. (2008), ¹³⁸ Botsis et al. (2015) ¹³⁹
Clinical ontology	Complexity reduction	Lyalina et al. (2013), ¹⁴⁰ Jing and Cimino (2014) ¹⁴¹
Clinical ontology	Feature extraction	Chen et al. (2015) ¹⁴²
Collaboration and competition	Agent-based modeling	Mascia and Di Vincenzo (2013) ²⁴
Collaboration and competition	ERGM	Lomi and Pallotti (2012), ¹⁶ Pallotti et al. (2013) ²⁵
Collaboration and competition	Regression	Pallotti and Lomi (2011), ¹⁹ Mascia et al. (2012), ²³ Mascia et al. (2015), ¹⁷ Pallotti et al. (2015), ²² Lee et al. (2016), ²⁷ Tranmer et al. (2016) ²¹
Collaboration and competition	Stochastic modeling	Stadtfeld et al. (2016) ²⁶
Collaborative practice	NA	Manuel et al. (2011), ¹⁴³ Uddin et al. (2012), ⁶⁷ Landon et al. (2013), ¹⁴⁴ Lubloy et al. (2016) ⁶⁵
Collaborative practice	ERGM	Uddin et al. (2013), ¹⁴⁵ Paul et al. (2014) ⁵⁵
Collaborative practice	Feature extraction	Zhang et al. (2015) ¹²⁸
Collaborative practice	Mixed methods	Barnett et al. (2011) ⁵²
Collaborative practice	Regression	Pollack et al. (2014) ⁷⁰
Collaborative practice	Survival analysis	Lomi et al. (2014), ¹² Hussain et al. (2015) ⁶⁴
Comorbidity	NA	Kim et al. (2016), ¹⁴⁶ Liu et al. (2016) ¹⁴⁷
Comorbidity	Complexity reduction	Schafer et al. (2014) ¹⁴⁸
Comorbidity	Feature extraction	Sideris et al. (2016) ⁹⁸
Comorbidity	Natural language processing	Roque et al. (2011) ⁹⁷
Comorbidity	Software development	Moni and Lio (2015) ⁸⁷
Decision support	Natural language processing	Nikfarjam et al. (2013) ¹⁴⁹
Decision support	Process mining	Rossille et al. (2008) ¹²³
Decision support	Rule mining	Zhou et al. (2010) ¹⁵⁰
Decision support	Software development	Heer and Perer (2014), ¹⁵¹ Li et al. (2015), ¹⁵² Warner et al. (2015) ¹⁵³
Disease progression	NA	Chmiel et al. (2014), ¹⁵⁴ Jensen et al. (2014) ⁹⁰
Disease progression	Hypothesis generation	Hidalgo et al. (2009), ⁹² Kannan et al. (2016) ⁹⁵
Disease progression	Probabilistic modeling	Chen et al. (2009) ⁹¹
Disease progression	Survival analysis	Xu et al. (2015) ⁸⁹
Epidemiology	NA	Liljeros et al. (2007), ²⁸ Donker et al. (2010), ²⁹ Huang et al. (2010), ³⁸ Walker et al. (2012), ³⁹ Ohst et al. (2014), ³⁴ Geraci et al. (2016), ¹⁵⁵ Takahashi et al. (2016) ⁶³
Epidemiology	Agent-based modeling	Lee et al. (2011), ³⁰ Donker et al. (2012), ³¹ Lee et al. (2012), ⁴² Curtis et al. (2013), ¹¹¹ Bartsch et al. (2014), ³³ Donker et al. (2014), ³² van Bunnik et al. (2015) ⁴⁵
Epidemiology	Regression	Geva et al. (2011), ¹⁰⁹ Ke et al. (2012), ³⁷ Simmering et al. (2015), ⁴¹ Gibbons et al. (2016) ⁴⁰
Epidemiology	Stochastic modeling	Ueno and Masuda (2008), ¹¹⁰ Karkada et al. (2011), ⁴⁶ Lesosky et al. (2011), ³⁵ Cusumano-Towner et al. (2013), ¹¹² Ciccolini et al. (2014), ⁴³ van den Dool et al. (2016) ³⁶
Health surveillance	NA	Ball and Botsis (2011), ¹⁵⁶ Patel and Kaelber (2014), ¹⁵⁷ Scott et al. (2014), ¹⁵⁸ Franchini et al. (2015) ¹⁵⁹
Health surveillance	Text mining	Roitmann et al. (2014) ¹⁰¹
Inappropriate access	Anomaly detection	Chen et al. (2012), ¹⁰⁵ Chen et al. (2012), ¹⁰⁴ Zhang et al. (2013), ¹⁰⁷ Menon et al. (2014) ¹⁰⁶

(continued)

Table 2. continued

Conceptual framework	Methodological framework	Studies
Molecular biology of disease	NA	Park et al. (2009), ⁸³ Davis and Chawla (2011), ⁸⁴ Park et al. (2012), ⁸⁵ Paik et al. (2014) ⁸²
Molecular biology of disease	Hypothesis generation	Bagley et al. (2016) ⁷⁹
Molecular biology of disease	Probabilistic modeling	Rzhetsky et al. (2007), ⁷⁶ Blair et al. (2013) ⁸⁶
Molecular biology of disease	Rule mining	Chen and Xu (2014) ¹⁶⁰
Molecular biology of disease	Software development	Liu et al. (2014) ⁸⁸
Organizational effectiveness	NA	Minerba et al. (2008), ¹⁶¹ Iwashyna et al. (2009), ⁷ Iwashyna et al. (2009), ¹¹ Puggioni et al. (2011), ⁹ Abbasi et al. (2012), ¹⁶² Tighe et al. (2014) ¹¹⁹
Organizational effectiveness	Mixed methods	Veinot et al. (2012) ¹⁵
Organizational effectiveness	Process mining	Baumgart et al. (2009), ¹²⁰ Rebuge and Ferreira (2012) ¹²⁵
Organizational effectiveness	Regression	Iwashyna et al. (2010), ⁸ Butala et al. (2015) ¹⁶³
Population health	NA	Feldman et al. (2016), ¹⁶⁴ Glicksberg et al. (2016) ⁹⁴
Population health	Regression	Hollingsworth et al. (2015) ⁷¹
Population health	Rule mining	Holmes et al. (2011) ¹⁶⁵
Social capital and social influence	NA	Kwan et al. (2015) ¹⁶⁶
Social capital and social influence	ERGM	Fattore and Salvatore (2010) ¹⁶⁷
Social capital and social influence	Regression	Fattore et al. (2009), ¹⁶⁸ Pollack et al. (2012), ⁶⁰ Hackl et al. (2015), ⁵⁸ Pollack et al. (2015), ⁶¹ Geissler et al. (2016) ⁷²

There are widely recognized problems with collapsing co-occurrence data to unipartite network models, but few studies of the “diseaseome” addressed them. The most popular use of these models was visualization; indeed, several studies analyzed co-occurrence data geometrically, for instance by using hierarchical clustering rather than community detection, but visualized them as graphs.^{97,101,169} Force-directed layout algorithms exploit the binary nature of graphs and can place unlinked dyads at any distance and orientation from each other; for count data such as these, visualizations like correspondence analysis biplots that minimize distortion are arguably more appropriate.¹⁷⁰ Additionally, a defining element of NA is the conceptualization of transmission channels as links and of functional dependencies as motifs, which predicts distance effects between nonadjacent nodes and dependencies between node attributes and neighborhood characteristics. These concepts do not follow as naturally from disease co-occurrence as from, say, patient-sharing. Some studies demonstrated the utility of visualizations for electronic dashboards, though only at the neighborhood level.^{80,116,153} While a few studies made valuable use of distance effects^{81,90,91} or motif mining,⁸⁴ most were primarily dyadic. Thus, despite their conceptual popularity, disease networks themselves have received little analytic attention.

Once a framework is adopted, consequential considerations remain, among them concordance between the theoretical constructs of interest and the measures used to detect them. In the (S)NA setting, some constructs will be structural, and the corresponding measures should be theoretically grounded. For example, early epidemiological studies identified features of contact and transfer networks known from existing work to have implications for infection spread.^{11,28} Some studies employed network measures without specific motivation, eg, degree and betweenness centrality as possible social determinants of methadone treatment continuation.¹⁶⁶ In this case, a discernible effect of degree was given a reasonable interpretation, but an indiscernible effect of betweenness was not commented upon; had it been theoretically motivated, an account of this result would clearly be required. Occasionally, an SNA framing seemed incidental to the analysis being conducted. For example, the number of visits a doctor makes to a patient and the share of the

visit costs coming from hospital claims might be expected to predict total visit costs by indicating severity of illness or resource use; when termed “connectedness” and “tie strength,” they instead suggested a causal relationship with care team coordination.¹¹⁴ In this case, SNA theory seemed ill-suited to the hypotheses being tested.

Model construction and validation

Network models were constructed, with few exceptions, by linking nodes according to 3 data patterns: co-occurrence on records (physicians’ patients, patient diagnoses), sequential occurrence on chronological records (patient admissions and discharges, staff HIS access), and source/target designation on transmission records (patient transfers, staff handoffs). Higher-order multipartite structures were often reduced to simple graph models for conceptual or computational reasons. For example, early interorganizational analyses relied on network measures of collaboration and competition, for which chronological patient-hospital admission/discharge data were flattened to unipartite graphs.^{16,19,20,23,25} More recent contributions expanded their scope to multilevel models of organizations and activities²⁶ and of organizations and their departments,²¹ in both cases grounding the motifs of interest in theory and building statistical inference models around them.

Studies not strongly grounded in theory usually focused on machine learning–based prediction, using a wider range of motifs in higher-order incidence structures and developing efficient algorithms to mine for them. This is evident from several studies that mined these structures for recurring patterns indicative of standard protocols^{128,171} or for deviations suggestive of security breaches^{104,105} or fraudulent practices.^{108,172}

Studies collapsed higher-order incidence structures into more manageable graphs using various techniques, none of which have become domain standards. In the research program on physician patient-sharing, for example, different studies adopted different statistics and thresholds on 2 physicians’ shared patients for link determination, including raw counts,⁷⁰ mutual percentages,⁵⁵ caseload-relative thresholds,⁵⁴ and average numbers of visits by shared patients.⁵⁹ Graph properties are sensitive to these decisions,

as illustrated by 2 inaugural studies that sought to quantify the number of alters with whom an ego physician must coordinate care. Based on shared Medicare patients for whom either ego or alter was deemed primary, a representative sample of physicians in the United States were found to have typically hundreds of peers.¹³³ In contrast, based on ego and alter seeing common patients at $\geq 1\%$ each of their total visits, physicians within professional groups in Ontario had on average 2.2 peers.¹⁴³

A related concern is the dependence of graph models on data sources, each having its own scope, bias, and format. Comorbidity graphs were constructed using patient-level data from several institution-specific electronic health records (EHRs)^{77,79,80,84,147} and from both public and private billing claims,^{83,86,146,148,154,173} and using incident-level data from adverse event reports.⁷⁸ “Co-occurrence” itself ranged in meaning from a simple correlation⁹² or odds ratio¹⁴⁶ to cosine similarity^{97,101} to a statistical signal from a probabilistic model,⁷⁶ and the aggregated parts were not always dyads.^{78,148} These models, of the same theoretical construct, were never directly compared.

A few validation studies did address such concerns. An early study of physician collaboration networks estimated the accuracy with which the number of Medicare patients 2 physicians share predicts their self-reporting of a professional relationship, using different raw-number thresholds,⁵² and a follow-up study characterized physicians’ stated reasons for referring patients to their data-mined colleagues.⁵⁷ A similar study examined the decision process whereby clinical teams at sending hospitals maintained primary transfer relationships with recipient hospitals.¹⁵ A later study of health care worker interactions compared the relative likelihood that patients’ records would be accessed by staff in different departments with those staff members’ expectations.¹²² By drawing from nationwide patient admission datasets from 2 countries, 1 study of infection surveillance was able to report on the robustness of their optimal strategy to the difference between the health care systems.⁴³ With respect to disease graphs, 2 studies compared the sets of comorbid pairs identified using the same link determination rule on multiple datasets,^{79,86} and 1 matched observed comorbidities with co-occurrences in the medical literature.¹⁶⁵ Several additional studies discussed biases in their data and tested the sensitivity of their results to different sources and thresholds, but these efforts were far narrower than the breadth of methods used, and none discussed concomitant differences in the resulting network structure.

Knowledge gains and methods development

Several studies used (S)NA to advance knowledge in ways that other methods would not be expected to, eg, invoking distance effects and motifs. Here is a partial list:

- An investigation of hospital transfers identified “cascades” of inefficiencies, measured as temporal paths through a transfer network in which a transfer by one sending hospital to a nonprimary recipient apparently results in a primary sending partner of the recipient redirecting a transfer of its own, and so on.¹⁸
- One approach to accounting for population comorbidities using genetic commonalities was to perform a triad census on the multilevel network of population comorbidities and genetic overlaps.⁸⁴ Another was to select diseases of high betweenness with respect to 2 index diseases (obesity and colorectal cancer) and identify their shared genetic associations.⁸¹
- One application for co-occurring clinical text fields was to distinguish “phenotypic signatures” of mental illnesses, which pose difficulties for criteria-based diagnosis.¹⁴⁰

- A study of operating room staff interactions following a layout redesign observed a shift from sequential to parallel performance of perioperative tasks, suggesting new vulnerabilities to staffing changes.¹²⁰
- A study in a neonatal intensive care unit linked longer handoff cycles to lower reported patient satisfaction, suggesting a quantitative measure of care continuity.¹²¹

Despite its inherent limitations, RCHD was likewise often well-suited to a study’s needs. One instance was the rigorous testing of hypotheses about interorganizational collaboration and competition derived from economic theory, which was made possible in the health care sector by the exceptionally thorough and reliable documentation on both information and resource exchange (patient transfers) and quality of performance (discharge rates or lengths of stay) contained in administrative datasets.^{19,23} Another was the use of empirical data on institutional infection rates or individual cultures by several inter-^{29,31,34,37,40,45} and intraorganizational^{109,155} epidemiological modeling studies, respectively, to calibrate or validate their network models. Third, patient-sharing networks provided an exceptionally detailed setting in which the social diffusion of practice could be measured.^{59,61,62} These studies focused on relationships between structural and attributive variables, which often require considerable expense and effort to generate but are common elements of RCHD.

Conversely, though most studies used NA tools “out of the box,” several domain-specific research questions led to advances in methodology, attesting to the reciprocal value to network science of health care applications. The need to adapt individual-level epidemiological models to populated institutions led to fractional models of immunization,⁴⁷ and the simulation framework (and sometimes the software) developed for these studies was also used to test surveillance^{42–45} and resource allocation^{46,47} strategies. Predictive modeling of population comorbidity spurred the development of tools for exploration, link prediction, and stratification in multilayer disease networks combined from EHR and molecular data.^{84,87,88} Efforts to model disease progression and clinical workflow inspired several original aggregations of ordered pairs and longer chronological disease sequences into temporal graphs,^{90,91,128,174} a procedure still young in network science.¹⁷⁵ In the domain of interorganizational networks, the availability of exceptionally thorough and reliable documentation on patient admissions and transfers made health care a testing ground for novel graph-theoretical statistical inference methods, including new specifications of ERGMs,^{16,25} extensions to stochastic actor-oriented models,²⁶ and adaptations of multiple membership–multiple classification models to multilevel networks.²¹

Cohesion

While research at this interface shows no signs of slowing (Figure 2), a scientometric analysis (see supplementary material) showed that the literature is highly fragmented, roughly along the groups identified above. The research programs identified above often had “home journals” where several research teams published, for instance *Medical Care* for physician collaboration and *Infection Control and Hospital Epidemiology* for patient transfer epidemiology, but we found very little overlap in venues between programs, and no central hub for NARCHD. Several early publications that anticipated the approaches that later gained traction were not cited by any others in our sample,^{9,10,13,113,123,143,161,176,177} nor did they have any authors in common with them (until recently⁷⁹). Seldom, too, did active

teams form new collaborations.^{86,174,178} A stepwise ERGM of the graph of citations failed to explain the extent of fragmentation based on publication dates, common authorship, and simple generative processes.^{179,180}

This fragmentation is not so surprising from a young field, but is also in part an artifact of our review criteria. The cohesive research programs described above, as evidenced by several domain-focused reviews,^{5,6,48–51,74,75,102,103,181,182} are merely the contours along which much larger research programs intersect our sample. The vast majority of SNA in health care settings relies on original survey data,¹⁰³ and the scale of the health care environment amenable to network modeling far exceeds that of RCHD.¹⁸³ Our sample may therefore underestimate the cohesion of this research community.

We did observe several instances of corroborations and useful comparisons with previous work. Several regression and ERGM analyses (and some visual inspections) observed that patients tended to be transferred to target hospitals with more care-relevant resources^{7–10} and better patient outcomes,^{8,11–13} and the best-equipped and -performing target hospitals tended to be more central.^{7,11,17} Transfer partnerships were reliably associated with competitive interdependence, even after controlling for geography, attributive similarity, and generative processes.^{16,23,24} Several inter-organizational epidemiological studies corroborated associations between a hospital's in-degree and infection rate^{29–31,34,40,41} and between its overall connectedness and overall pathogen prevalence^{30,33,37} (with 1 exception³⁵).

Some applications saw interestingly inconsistent results: One study identified cohesive communities from the commonalities in conditions diagnosed by an institution's providers, which reflected departmental structure in some ways but not others.¹⁶¹ Another study mined access logs to produce a communication network dominated by multispecialty teams, more consistent with cohesive floor staff and service teams,¹²⁹ and a third observed from a similar dataset that collaboration was more prevalent within departments than between them.¹⁶² How best to identify and characterize cohesive units from institution HIS data appears to be an open question.

Yet researchers in different domains faced many similar challenges, and opportunities may have been missed to build upon each other's progress and to recombine techniques developed independently. A case in point is the aggregation of temporal sequences of clinical events into a directed graph. From a clinical informatics perspective, Patnaik et al.¹⁷⁴ explored a top-down approach starting with a partial order on a collection of diagnosis and procedure codes, before Hanauer and Ramakrishnan⁹³ (of the same team) adopted a bottom-up approach of statistically identifying individual temporal pairs. From a data security perspective, H. Zhang et al.¹⁰⁷ constructed a temporal graph from access logs for the purpose of characterizing routine behavior and identifying deviations from it, by aggregating all patient record-specific access sequences, analogous to Patnaik et al. At a more granular level, Nikfarjam et al.¹⁴⁹ developed a text-mining technique to encode clinical notes into encounter-level temporal graphs. From a prognosis perspective, Liu et al.¹²⁶ constructed similar patient-level temporal graphs from timelines of coded clinical events, which they clustered using feature extraction methods from linear algebra, and Jensen et al.⁹⁰ took the approach, an extension of Zhang et al.'s, of first clustering patient timelines and then aggregating these in each cluster into a cohort-level temporal graph. Meanwhile, more sophisticated tools to produce similar summary structures had been developed and implemented by business researchers for process management and applied to EHR process logs by a different community of

researchers.^{120,124,184–186} Y. Zhang et al.¹²⁸ proposed a clustering-based alternative to these standard tools, much in the spirit of Jensen et al., and Finney et al.¹⁸⁷ adopted an existing theoretical and methodological framework within which to contribute an efficient implementation. None of these studies cited those that came before (excluding the process mining studies).

In summary, the disconnectedness and inconsistency of this literature suggests the possible benefit to be gained from detailing how the motivating problems, study designs, data sources, and network tools reviewed here “hang together.”

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The authors have no competing interests to declare.

CONTRIBUTORS

JCB and RL conceived and designed the review. JCB designed and conducted the search. JCB and RL designed, and JCB performed, the synthesis. JCB designed and performed the scientometric analysis. JCB and RL contributed to the discussion, wrote and approved the final manuscript, and take responsibility for the integrity of the work.

SUPPLEMENTARY MATERIAL

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APPENDIX: CASE STUDIES

Institutional exchange networks

In an effort to structurally characterize hospitals that suffered the highest rates of methicillin-resistant *Staphylococcus aureus* (MRSA), Ohst et al. (2014)³⁴ drew upon a comprehensive regional dataset of care episodes to construct a contact network of care units based on patient transfers and to assign each unit a MRSA prevalence rate based on the observed frequency of positive tests. As candidate measures of each unit's structural position, the authors used 5 notions of centrality: in-degree and daily patient turnover (based on immediate contacts), weighted and unweighted betweenness (based on shortest paths), and PageRank (based on random walks). The contact network evolved over time, so units' centralities were calculated as of the time of each positive test. Averaging their results over the different strains of MRSA, the authors observed 2 paradoxical trends: more central units were more likely to have at least 1 positive test, but those that did had lower prevalence on average. This led the authors to conclude that the net relationship between centrality and prevalence has limited practical value. Simulations confirmed the

relationship and further showed that the measures based on immediate contacts outperformed those based on geodesics (betweenness) or walks (PageRank), and were themselves outperformed by the network-agnostic attribute of patient turnover.

Physician collaboration networks

Moen et al. (2016)⁵⁹ provide a richly detailed case study of physician collaboration, as reconstructed on the basis of patient-sharing observed in Medicare claims. The authors tailored their analysis, including the selection of comparison regions, the sample of beneficiaries and physicians, and the choice of network measures and models, to the question of why regional health care networks differ in their adherence to evidence-based defibrillator guidelines. Building upon a literature with mixed emphasis on physician-, hospital-, and region-level network structure, they incorporated effects of individual and structural attributes at the physician and hospital levels. Their multistage design used a patient-level logistic regression framework with physician-level and hospital-level random effects, and incorporated as predictors of interest the hospital referral region and several hospital-, physician-, and patient-level covariates. Among these were estimated effects of homophily by physician specialty, controlling for the distribution of colleague counts (degree distribution), and any of several measures of the centrality of hospitals within the region and of physicians within hospitals. Among other findings, they concluded that physicians' frequency of patient-sharing (node strength) and closeness centrality in their hospital-together accounted for much of the variation between hospital referral regions, indicating that the social positions of physicians among their colleagues is important to their institution's ability to articulate good practice.

Clinical co-occurrence networks

In an early contribution, Davis and Chawla (2011)⁸⁴ demonstrated that data-driven structural analysis could generate useful targets for experimental investigation. From the medical histories of patients served by a regional health system, they constructed a multimorbidity graph in which a link between 2 diseases was weighted by mutual information. Analogously, they constructed a disease graph whose links indicated shared genetic factors, based on gene-disease associations compiled from the experimental literature. (The most frequent database used for this purpose is the Online Mendelian Inheritance in Man, www.omim.org.) Their analysis of the combined multilayer disease network yielded several results: First, population-level co-occurrence ("phenotypic links") correlated strongly with known genetic overlap ("genetic links"), corroborating the genetic deterministic paradigm. Second, roughly the same subsets of nodes in both networks formed strongly linked communities, which recapitulated clinically meaningful disease groups. Finally, a probabilistic link prediction model, built on a generalization of the triad census, revealed that a combination of phenotypic and (known) genetic links achieved greater predictive accuracy of unknown genetic links than either source alone.

Workplace interaction networks

Zhang et al. (2013)¹⁰⁷ addressed a security problem that distinguishes EHRs from many other information systems: The frequency with which users will need to violate any manually curated set of access rules, in order to maintain patient care in hectic and unpredictable circumstances, makes postliminary auditing impractical. They proposed aggregating patient-specific sequences of EMR access into

temporal graph models, for which they derived statistics to measure the irregularity of a given access or access sequence with respect to the corpus. Whereas the temporal graphs would be constructed iteratively from continually generated access logs, this approach is learning-based but relies on an assumption that care processes are consistent over time. A test of the method on an institutional EHR revealed that rates of irregularity, and of the success of their approach, varied across hospital services, accentuating the need to carefully tailor anomaly detection methods.

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