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The Impact of Provider Networks on the Co-prescriptions of Interacting Drugs: A Claims-based Analysis

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Abstract

Introduction—Multiple provider prescribing of interacting drugs is a preventable cause of morbidity and mortality, and fragmented care is a major contributing factor. We applied social network analysis to examine the impact of provider patient-sharing networks on the risk of multiple provider prescribing of interacting drugs.

Methods—A retrospective analysis of commercial healthcare claims (years 2008–2011), including all non-elderly adult beneficiaries (n=88,494) and their constellation of care providers. Patient-sharing networks were derived based on shared patients, and care constellation cohesion was quantified using *care density*, defined as the ratio between the total number of patients shared by provider pairs, and the total number of provider pairs within the care constellation around each patient.

Results—2% (n=1,796) of patients were co-prescribed interacting drugs by multiple providers. Multiple provider prescribing of interacting drugs was associated with care density (odds ratio per unit increase in the natural logarithm of the value for care density, 0.78; 95% CI 0.74–0.83; p<0.0001). The effect of care density was more pronounced with increasing constellation size: when constellation size exceeded 10 providers, the risk of multiple provider prescribing of interacting drugs decreased by nearly 37% with each unit increase in the natural logarithm of care density (p<0.0001). Other predictors included increasing age of patients, increasing number of providers and greater morbidity.

Conclusion—Improved care cohesion may mitigate unsafe prescribing practices, especially in larger care constellations. There is further potential to leverage network analytics to implement large-scale surveillance applications for monitoring prescribing safety.

1 Introduction

The Institute of Medicine estimated that hospitalized patients are subject to at least one medication error per day [1]. Approximately 2 to 17 per 1000 outpatient visits in the U.S. were related to adverse drug events [2–5]. More than one in ten adverse drug events reported were caused by prescriptions of interacting drugs [6–7], many of which were preventable.

Multiple providers caring for individual patients often do not have accurate information about the medications their patients are taking [8–10]. A study of 120 elderly patients reported discrepancies between patients' medication lists and their physicians' list in 96% of patients [11]. In another study, discrepancies were present in 76% of 236 patients, with 51% of patients taking medications not recorded in their physician's record, and 29% of patients not taking a recorded medication [12]. The number of providers involved in the care of individual patients is frequently reported as one of the strongest predictors for inappropriate prescribing [13–17].

Indeed, many of the deficiencies in US health care are a consequence of the disjointed and poorly coordinated care that patients receive. With increased multidisciplinary approach to care provision, fostering collaboration among healthcare providers is challenging. In a recent study, we found that “stable” constellations of providers who care for a patient are exceedingly rare - it is uncommon for providers in a constellation to regroup together in the exact same configuration to care for more than one patient [18]. The Affordable Care Act seeks to foster the transition from siloed health care system to one that is better coordinated through the concept of Accountable Care Organizations (ACO) - a network of providers and hospitals that share financial and medical responsibility for providing coordinated care to patients [19–21]. However, the potential impact of provider networks remains under-studied.

Recent studies have begun to apply social network analysis to examine the impact of provider networks on patient care [22–24]. The approach builds on the premise that collaborative ties between physicians can be inferred based on the number of common patients shared, and these ties can impact care-decision making and behaviour. As physicians exchange information and establish rapport in the process of providing care to shared patients, physicians who share greater number of patients are likely to have stronger collaborative relationship [25]. Barnett et al showed that sharing of patients based on administrative data can indeed identify information sharing ties among physicians [26]. Comparing patient-sharing data from a claims dataset with survey of physicians, the study reported a positive correlation between the number of shared patients and the likelihood that a physician reported a relationship with another physician, thus lending credibility to the approach. The impact of these informal relationships on the quality and costs of care has been shown in a number of studies [27–29].

Here, we applied network analysis to measure the impact of patient-sharing networks on medication safety; specifically, multiple provider prescribing of medications with known drug-drug interactions (DDI). Multiple provider prescribing of interacting drugs often results from fragmented care. By capturing the collaborative patterns among providers, we hypothesized that patient sharing networks can predict the risk of multiple provider

prescribing of interacting drugs. Insights gained through this study will inform health care policies on the optimal organization of care constellations.

2 Methods

2.1 Study design and data

This is a retrospective analysis of commercial healthcare claims from the HealthCore Integrated Research Database (HIRDSM) [30], with a geographically diverse spectrum of longitudinal data across the US. Together, a total of 293 zip codes, located primarily in the urban areas of four mid-west and southern states were included, as characterized in a previous study [18]. Study participants included all non-elderly adult beneficiaries (>18 and <65 years of age) who were enrolled in a commercial health plan. Data spanned the years 2008 to 2011, and included patient demographics, outpatient visits, and prescription drugs dispensed. An independent Institutional Review Board used by HealthCore, Inc. approved the study, and the Committee on Clinical Investigation at Boston Children's Hospital determined it exempt.

2.2 Physician network

Healthcare encounter data from 2008 to 2011 were used to define provider networks, including all ambulatory care providers involved in face-to-face encounters with patients. Providers in specialties not related to routine ambulatory care (e.g. pathology, anesthesia, radiology, emergency medicine) were excluded.

The presence of shared patients was used to infer a professional relationship between physicians. A network tie is formed between two physicians if they had an encounter with one or more common patients. We refer to the group of physicians caring for an individual patient as a *constellation*. In a social network, the extent to which a population is characterized by mutual ties may reflect the degree of cohesion and trust. Thus, the average strength of ties across all possible ties, a measure known as *network density*, provides a way of quantifying social cohesion [31]. Extending this concept to patient-sharing networks, we quantified constellation density using the measure of *care density* [28], defined as the ratio between the total number of patients shared by physician-pairs within a constellation, and the total number of physician-pairs within the constellation (Fig 1). To ensure that providers in our dataset had substantive participation in the health plan, we excluded those with less than 50 patients during the study period, since they were unlikely to be part of the healthcare network throughout the study period. On average, a provider in our study population encountered 109 patients during the study period.

2.3 Co-prescription of interacting drugs

We identified patients who were co-prescribed interacting drugs by multiple providers, using DDIs extracted from a commercial rule base system, Cerner MultumTM (2012) [32]. The vendor's rule base comprised 125,758 DDI rules, classified by severity that ranks from 1 being minor, to 3 being major DDI. To maximize specificity, we restricted our analysis to major DDIs (n=17,410). We further compared the significance of the DDIs detected in our dataset against the risk ratings and recommendations provided in the LexicompTM database

[33], the official drug reference for the American Pharmacists Association (APA). Two additional sensitivity analyses were conducted to examine specific DDIs: (1) the most prevalent DDI among our study population classified as critical by the APA; and (2) DDIs recommended against by the APA (either to avoid combination or consider therapy modification) involving a list of medication classes selected a priori, including antiepileptics, anticoagulants or antiplatelets, tricyclic antidepressants, immunosuppressants and HMG-CoA reductase inhibitors.

Since our goal was to assess the impact of provider networks on prescribing behavior, we considered only co-prescriptions of interacting drugs by different providers; interacting drugs prescribed by the same provider were disregarded. To ensure that overlapping prescriptions were not a result of a deliberate change in medication regimen, we considered only those that were repeated more than once during the study period, where each episode of co-prescription had an overlapping coverage of more than 14 days (Fig 2). As a sensitivity analysis, we performed an additional analysis using a less stringent outcome measure of having at least one overlapping co-prescription of interacting drugs. We defined the control population as patients who were not co-prescribed any interacting drug-pairs, with an overlapping coverage of one or more days during the study period.

2.4 Study outcomes

We examined the relationship between care density and multiple provider prescribing of interacting drugs. As a secondary outcome, the impact of care density on multiple provider prescribing of interacting drugs for varying constellation size was investigated, by stratifying the study population into three subgroups: patients with less than 5 providers (<50th percentile), those with 5 to 10 providers (>=50th percentile and <=90th percentile), and those with more than 10 providers (>90th percentile).

2.5 Statistical analysis

Baseline characteristics were reported as percentages for categorical variables, and means and medians for continuous variables. We used chi-square and analysis of variance to test for differences in baseline characteristics between patients who were, and those who were not, exposed to co-prescriptions of interacting drugs. Exposure was examined as a dichotomous variable, defined as true when a patient was co-prescribed interacting drugs by multiple providers, whereby the co-prescription of a specific drug-pair was repeated more than once, with each co-prescription episode having an overlapping coverage of more than 14 days.

Conditional logistic regression was used to estimate the association between the natural logarithm of care density and multiple exposures to interacting medications prescribed by different providers. Care density was examined both as a continuous variable (after logarithm transformation), and as a categorical variable by quartiles. The quartile variable was scored ordinally, according to the distribution of care density of the study population. In all analyses, risk was adjusted for age, Charlson's comorbidity index, the total number of providers within a patient's constellation, and the presence of a primary care physician (PCP) in the constellation. Charlson's comorbidity index provides an estimate of mortality risk based on comorbid conditions [34], and was ascertained based on comorbidities

identified in all inpatient and outpatient visits during the study period. To detect potential multicollinearities among variables in multivariate regression analyses, we measured the variance inflation factors (VIF) for each regression variable [35]. To compare the impact of care density among the three pre-defined constellation size categories, we modelled each category separately using logistic regression, as well as collectively through multi-level regression [36].

Analyses were conducted using SPSS, version 23. All tests of statistical significance were 2-tailed and used an α level of $p < 0.05$.

3 Results

3.1 Baseline characteristics of the patients

A total of 88,494 individuals were included in our study (Table 1). Of these, 2.0% ($n=1,796$) were exposed to repeated co-prescriptions of interacting drugs by different providers, with each co-prescription having an overlapping coverage of more than 14 days, excluding co-prescriptions of interacting drugs by the same provider. In univariate analyses, exposures to multiple provider prescribing of interacting drugs were positively associated with several conventional risk factors, including increasing age, Charlson comorbidity index, and the number of providers involved in the care of a patient; the presence of a PCP in a patient's constellation reduced the risk of multiple provider prescribing of interacting drugs. There was no statistically significant relationship between gender and the risk of multiple provider prescribing of interacting drugs; patient's gender was therefore omitted from multivariate analyses. Compared with the unexposed group, patients exposed to multiple provider prescribing of interacting drugs had a lower mean care density and care density quartiles. Differences in care density between the exposed and unexposed groups increased with increasing quartiles.

3.2 Relationship between care density and multiple provider prescribing of interacting drugs

In the univariate model, repeated co-prescriptions of interacting drugs by multiple providers were significantly associated with care density (odds ratio per unit increase in the natural logarithm of the value for care density, 0.76; 95% confidence interval [CI], 0.72 to 0.79; $p < 0.0001$) (Table 2). After adjustment for age, Charlson comorbidity index, number of providers and the presence of PCP in constellation, the association remained strong (odds ratio, 0.78; 95% CI, 0.74 to 0.83; $p < 0.0001$) (Table 2, Multivariate Model 1).

Multicollinearity in the multivariate models was ruled out, since the calculated VIF for all regressor variables was less than 1.01.

The risk of repeated co-prescriptions of interacting drugs associated with increasing quartiles of care density was strong and graded ($p < 0.0001$) (Table 2, Multivariate Model 2). Moreover, when patients with care density below the first quartile was used as the reference group, the adjusted risk was reduced for patients with care density above the second (odds ratio, 0.84; 95% CI, 0.73 to 0.95; $p = 0.007$) and third quartiles (odds ratio, 0.49; 95% CI, 0.42 to 0.58; $p < 0.0001$). There was no reduction in risk for patients with care density above

the first quartile (odds ratio, 1.11; 95% CI, 0.98 to 1.25; $p=0.116$). Relaxing the outcome to one or more co-prescriptions of interacting drugs, instead of multiple repeated co-prescriptions, did not alter its association with care density. With each unit of increase in the natural logarithm of care density, the risk of one or more co-prescriptions of DDI decreased by 22% (odds ratio, 0.78; 95% CI, 0.75 to 0.82; $p<0.0001$).

3.3 The impact of constellation size

The strength of the association between care density and the risk of multiple provider prescribing of interacting drugs increased with increasing constellation size, while the effect of other risk factors, including the number of providers, age and Charlson comorbidity index, diminished but remained significant (Table 3). Application of multi-level regression also showed a significant association between care density and the risk of co-prescriptions of interacting drugs ($F\text{-ratio}=81.1$; $p<0.0001$) (see Electronic Supplementary Material Table S1). The presence of a PCP was not associated with the risk of multiple provider prescribing of interacting drugs. We further observed that on average, patients without a PCP had a smaller constellation size: almost two-thirds had a constellation size of less than 5 providers, the remaining one-third had 5 to 10 providers, and only 1.4% had more than 10 providers. In contrast, among those with a PCP, one-third had a constellation size of less than 5 providers, 56% had 5 to 10 providers, and 7.8% had more than 10 providers (see Electronic Supplementary Material Table S2).

To assess whether constellation size moderated the effect of care density on the risk of multiple provider prescribing of interacting drugs, an additional regression analysis was conducted whereby the product of constellation size and care density was included as a covariate. The results showed a small but significant interaction effect between constellation size and care density (OR 0.98; 95% CI 0.97 – 0.996; $p=0.012$); the independent effect of care density on DDI risk remained (OR 0.88; 95% CI 0.79 – 0.97; $p=0.012$) (Table 4). Pearson correlation analysis further confirmed that constellation size was negatively correlated with care density (-0.075 ; $p<0.0001$).

3.4 Interacting drug pairs

We identified 9,246 episodes of multiple provider prescribing of interacting drugs, involving 1,094 different drug pairs and 324 drugs. The most common drug pair was amlodipine (a calcium-channel blocker) and simvastatin (a hypolipidemic drug) (see Electronic Supplementary Material Table S3). The most common drugs involved were the antidepressants bupropion and citalopram (see Electronic Supplementary Material Table S4).

Among the most prevalent DDIs detected in our dataset, the co-prescription of clopidogrel and omeprazole/esomeprazole had the greatest potential for serious harm (see Electronic Supplementary Table S3), based on the Lexicomp recommendations. The combined use of clopidogrel and omeprazole/esomeprazole inhibits the metabolism of clopidogrel, which in turn increases the risk of heart failure.

3.5 Sensitivity analyses

We conducted a subgroup analysis to assess the impact of care density on the co-prescriptions of clopidogrel and omeprazole/esomeprazole. Multivariate regression analysis showed that higher care density was associated with substantially lower co-prescriptions of this drug pair after adjusting for age, Charlson comorbidity index, and the number of providers (odds ratio per unit increase in the natural logarithm of the value for care density, 0.70; 95% CI, 0.50 to 0.97; $p=0.032$) (Table 5). Similar results were observed when we confined our analysis to the co-prescriptions of serious DDIs involving antiepileptics, anticoagulants or antiplatelets, tricyclic antidepressants, immunosuppressants and HMG-CoA reductase inhibitors. The association between care density and the co-prescriptions of these medications with another interacting drug remains significant (odds ratio per unit increase in the natural logarithm of the value for care density, 0.75; 95% CI, 0.62 to 0.92; $p=0.006$) (Table 5). In both analyses, the presence of PCP was also associated with a decreased risk of co-prescriptions of interacting drugs.

4 Discussion

We explored the relationship between provider patient-sharing networks and multiple provider prescribing of interacting drugs in the outpatient setting. Using a network-based approach to infer the collaborative relationships between providers based on the presence of shared patients, and quantifying the strength of the collaborative relationships using the measure of care density, we showed that repeated co-prescription of interacting drugs by multiple providers is reduced with higher care density. With each unit of increase in the natural logarithm of care density, the risk decreased by 12%. Furthermore, the risk of repeated co-prescriptions of interacting drugs was 51% lower among patients with care density above the 3rd quartile, compared with those with care density below the 1st quartile.

Our results can be interpreted in several ways. First, shared patients and care density reflect actual collaborative ties among providers, which led to better coordinated care thereby reducing the risk of multiple provider prescribing of interacting drugs. This interpretation is supported by an existing study demonstrating a positive correlation between shared patients and information ties between providers [26]. Our analysis also showed that the impact of care density became more pronounced with increasing constellation size, while the effects of other risk factors, including the number of providers and Charlson comorbidity index, diminished. This finding is clinically intuitive, as coordination of care across providers would tend to become more challenging with increasing constellation size; the opportunity for communication breakdown would be expected to increase exponentially, regardless of other risk factors. Landon et al further reported that physicians who shared patients tend to have similar patient panels in terms of race or illness burden [24]; this is consistent with the principle of “homophily” observed in many social networks, whereby people tend to form connections with others who are similar to them. Providers who were connected were also closer in geographic proximity and were more likely to be based at the same hospital [24]. All these factors may have contributed to improved awareness across providers of the actions of other constellation members.

An alternate explanation for the study results is that shared patients between providers merely reflect connections that emerge by chance, and do not actually capture information ties and care coordination among providers. Landon et al. showed that such ad hoc connections are more likely to occur when the number of shared patients between two providers is very low (e.g. one or less shared patient during the course of a year) [24]. In our study dataset, the average number of shared patients between providers across care constellations was 19.5. It is therefore unlikely that chance connections alone accounted for most of the ties identified. Nonetheless, caution should be taken in interpreting the meaning underlying the association, and more research is needed to validate the approach.

Our analyses further identified several patient subgroups with a high risk of being exposed to co-prescriptions of interacting drugs. These included older patients with greater comorbidity burden and patients who saw a greater number of providers, reflecting the complexity of caring for sicker patients and coordinating larger teams. The presence of PCP decreased the risk of clopidogrel and omeprazole/esomeprazole co-prescriptions, and other drug-pairs classified as critical by the APA. This is consistent with published evidence showing that the availability of primary care services leads to improved care quality [37–38]. However, we did not find an association between the presence of a PCP and safer prescribing behaviour in the primary analysis involving all critical DDIs identified in the Multum database. A likely explanation is that the significance of many of the DDIs defined by the Multum database are less firmly established, compared with those recommended against by the APA.

Detailed analysis of the interacting drugs prescribed showed that psychoactive agents were responsible for a disproportionate share of potential DDIs. This is consistent with an existing study demonstrating that psychoactive agents accounted for more than half the adverse drug events in hospitalized patients [39]. The most common drug pairs involved were combinations of serotonergic agents; the additive effects of these agents expose patients to the risk of serotonin syndrome that can be potentially life-threatening. The increased use of serotonergic agents across multiple disciplines makes it likely that the prevalence of serotonin syndrome will rise. Caution should be used to avoid co-prescriptions of psychoactive agents, and in caring for mentally ill patients.

Our study is subject to several limitations. First, we ascertained physician relationships based on the presence of shared patients using claims data from a single commercial health plan. The results of this study may not generalize to other health plans. Furthermore, we may have missed patients and providers covered by other health plans. To mitigate this limitation, we chose regions with substantial market penetration by the health plan that provided the study data. Second, we could not assess whether the co-prescriptions of interacting drugs indeed stemmed from poor care coordination. Some drug combinations that are potentially risky may have been prescribed after careful consideration of the risk-benefit ratio, and with close surveillance in place. While we have sought to minimize this limitation by considering only drug combinations that are classified as serious interactions in the Multum database, there is often a lack of consensus on what constitutes clinically significant DDIs, therefore DDIs curated in drug reference databases may have varied relevance [40]. We attempted to address this by performing additional analyses on a subset of patients who were co-prescribed clopidogrel and omeprazole/esomeprazole, and those

who were co-prescribed other drug-pairs that are recommended against by the APA; both analyses also showed an association between care density and multiple provider prescribing of the drug pairs. Moreover, a study on emergency hospitalizations due to adverse drug events showed that relatively few adverse drug events resulted from medications typically designated as high-risk; rather, most were caused by a few commonly used medications [41]. Thus, low-risk DDIs are no less important. Third, we may not have recognized other DDIs of drugs that were prescribed, but not filled, as a result of deliberate interventions by pharmacists, especially as pharmacy clinical decision-support systems are increasingly used for detecting the prescriptions of interacting drugs. However, studies have consistently shown that these systems are less than optimal in identifying potential drug interactions [42–44], with one study showing only 28% of commercial information systems in ambulatory pharmacies capable of identifying critical DDIs [42]. Lastly, many potential drug interactions never lead to an actual clinical effect. The above prevalence rates might, therefore, overestimate the true clinical significance of the problem. However, since we seek to assess providers' prescribing behavior, prescription of interacting drugs represent inappropriate prescribing behaviour, regardless of whether it leads to an actual adverse event.

5 Conclusion

We find an association between the collaborative patterns of providers and multiple provider prescribing of interacting drugs. Additionally, we demonstrate the feasibility of applying network analysis to study the impact of physician relationships on patient care. Addressing quality in healthcare will require deeper understanding of the dynamics of healthcare interactions. Network-based approaches provide a way to characterize and quantify these interactions. Properties of such networks elucidate the collective behaviors of healthcare providers and the implications on patient care, which cannot be easily observed by studying individual providers alone. While we focused on multiple provider prescribing of interacting drugs, our approach can be easily extended to study other patient outcomes. There is further potential to leverage the technique to implement large-scale surveillance applications for monitoring the safety and quality of patient care. We used care density as the primary measure of provider interactions. Future research should consider methods to capture team structures that are most conducive to care cohesion. Efforts in developing such methods are already underway: Uddin et al showed that micro-level structures of provider networks are linked to hospitalization cost and hospital readmission rate [45]. There is also a need for further research into the drivers underlying care team structures, so as to guide interventions to prevent care fragmentation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Aspden, P., Wolcott, J., Bootman, JL., Cronenwett, LR. Preventing medication errors: quality chasm series. National Academies Press; 2006.
2. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients. JAMA. 1997; 277(4):301–6. [PubMed: 9002492]
3. Bourgeois FT, Mandl KD, Valim C, Shannon MW. Pediatric adverse drug events in the outpatient setting: an 11-year national analysis. Pediatrics. 2009; 124(4):e744–50. [PubMed: 19786435]
4. Cohen AL, Budnitz DS, Weidenbach KN, Jernigan DB, Schroeder TJ, Shehab N, et al. National surveillance of emergency department visits for outpatient adverse drug events in children and adolescents. J Pediatr. 2008; 152(3):416–21. [PubMed: 18280852]
5. Bourgeois FT, Shannon MW, Valim C, Mandl KD. Adverse Drug Events in the outpatient setting: An 11-Year National Analysis. Pharmacoepidemiol Drug Saf. 2010; 19(9):901–910. [PubMed: 20623513]
6. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18820 patients. BMJ. 2004; 329(7456):15–9. [PubMed: 15231615]
7. McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. Ann Pharmacother. 2002 Sep; 36(9):1331–6. [PubMed: 12196047]
8. Price D, Cooke J, Singleton S, Feely M. Doctors' awareness of the drugs their patients are taking. A major cause of overprescribing? Br Med J. 1986; 292:101. [PubMed: 3080075]
9. Claoué C, Elkington AR. Informing the hospital of patients' drug regimens. Br Med J. 1986; 292:101. [PubMed: 3080075]
10. Frank C, Godwin M, Verma S, Kelly A, Birenbaum A, Seguin R, et al. What drugs are our frail elderly patients taking? Do drugs they take or fail to take put them at increased risk of interactions and inappropriate medication use? Can Fam Physician. 2001 Jun; 47:1198–204. [PubMed: 11421047]
11. Bedell SE, Jabbour S, Goldberg R, Glaser H, Gobble S, Young-Xu Y, et al. Discrepancies in the use of medications. Their extent and predictors in an outpatient practice. Arch Intern Med. 2000; 24:2129–34.
12. Fisher ES, Staiger DO, Bynum JP, Gottlieb DJ. Creating Accountable Care Organizations: the extended hospital medical staff. Health Aff. 2007; 26(1):w44–57.
13. Boockvar K, Fishman E, Kyriacou CK, Monias A, Gavi S, Cortes T. Adverse events due to discontinuation in drug use and dose changes in patients transferred between acute and long-term care facilities. Arch Intern Med. 2004; 164(5):545–550. [PubMed: 15006832]
14. Tamblyn RM, McLeod PJ, Abrahamowicz M, Laprise R. Do too many cooks spoil the broth? Multiple physician involvement in medical management of elderly patients and potentially inappropriate drug combinations. CMAJ. 1996; 154:1177–1184. [PubMed: 8612253]
15. Green JL, Hawley JN, Rask KJ. Is the number of prescribing physicians an independent risk factor for adverse drug events in an elderly outpatient population? Am J Geriatr Pharmacother. 2007; 5:31–39. [PubMed: 17608245]
16. Olsson J, Bergman A, Carlsten A, Oke T, Bernsten C, Schmidt IK, et al. Quality of drug prescribing in elderly people in nursing homes and special care units for dementia: a cross-sectional computerized pharmacy register analysis. Clin Drug Investig. 2010; 30:289–300.
17. Beers MH, Munekata M, Storrie M. The accuracy of medication histories in hospital medical records of elderly persons. J Am Geriatr Soc. 1990; 38:1183–7. [PubMed: 2246454]
18. Mandl KD, Olson KL, Mines D, Liu C, Tian F. Provider collaboration: cohesion, constellations, and shared patients. J Gen Intern Med. 2014; 29:1499–1505. [PubMed: 25060655]
19. Devore S, Champion RW. Driving population health through Accountable Care Organizations. Health Aff. 2011 Jan; 30(1):41–50.

20. Kocher R, Sahni NR. Physicians versus hospitals as leaders of Accountable Care Organizations. *N Engl J Med*. 2010 Dec 30; 363(27):2579–82. [PubMed: 21067374]
21. Berwick DM. Launching Accountable Care Organizations – the proposed rules for the Medicare Shared Savings Program. *N Engl J Med*. 2011; 364(16):e32. [PubMed: 21452999]
22. Barnett ML, Christakis NA, O'Malley J, Onnela JP, Keating NL, Landon BE. Physician patient-sharing networks and the cost and intensity of care in US hospitals. *Med Care*. 2012; 50(2):152–60. [PubMed: 22249922]
23. Pollack CE, Weissman G, Bekelman J, Liao K, Armstrong K. Physician social networks and variation in prostate cancer treatment in three cities. *Health Serv Res*. 2012 Feb; 47(1 Pt 2):380–403. [PubMed: 22092259]
24. Landon BE, Keating NL, Barnett ML, Onnela JP, Paul S, O'Malley AJ, et al. Variation in patient-sharing networks of physicians across the United States. *JAMA*. 2012; 308(3):265–73. [PubMed: 22797644]
25. Bynum JP, Ross JS. A measure of care coordination? *J Gen Intern Med*. 2013; 28:336–338. [PubMed: 23179970]
26. Barnett ML, Landon BE, O'Malley AJ, Keating NL, Christakis NA. Mapping physician networks with self-reported and administrative data. *Health Services Research*. *Health Serv Res*. 2011; 46(5):1592–609. [PubMed: 21521213]
27. Ong MS, Olson KL, Cami A, Liu C, Tian F, Selvam N, et al. Provider patient-sharing networks and multiple-provider prescribing of benzodiazepines. *J Gen Intern Med*. 2016; 31(2):164–71. [PubMed: 26187583]
28. Pollack CE, Weissman GE, Lemke KW, Hussey PS, Weiner JP. Patient sharing among physicians and costs of care: A network analytic approach to care coordination using claims data. *J Gen Intern Med*. 2013; 28(3):459–65. [PubMed: 22696255]
29. Uddin S, Hossain L, Kelahe M. Effect of physician collaboration network on hospitalization cost and readmission rate. *Eur J Public Health*. 2012; 22(5):629–33. [PubMed: 22037593]
30. HealthCore Inc. <http://healthcore.com/research-environment>. Accessed 2 Jan 2015
31. Wasserman, S., Faust, K. Social network analysis: methods and applications. Vol. 181. Cambridge University Press; 1999.
32. Cerner Multum. <http://www.multum.com>. Accessed 2 Jan 2016
33. Lexicomp. <http://www.wolterskluwer.com>. Accessed 2 Jan 2016
34. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis*. 1987; 40(5):373–83. [PubMed: 3558716]
35. Mansfield ER, Helms BP. Detecting multicollinearity. *The American Statistician*. 1982; 36:158–60.
36. Uddin S. Exploring the impact of different multi-level measures of physician communities in patient-centric care networks on healthcare outcomes: A multi-level regression approach. *Sci Rep*. 2016; 6:20222. [PubMed: 26842548]
37. Tamblyn RM, McLeod PJ, Abrahamowicz M, Laprise R. Do too many cooks spoil the broth? Multiple physician involvement in medical management of elderly patients and potentially inappropriate drug combinations. *CMAJ*. 1996; 154:1177–1184. [PubMed: 8612253]
38. Druss BG, Rosenheck RA, Desai MM, Perlin JB. Quality of preventive medical care for patients with mental disorders. *Med Care*. 2002; 40:129–136. [PubMed: 11802085]
39. Gandhi TK, Weingart SN, Borus J, Seger AC, Peterson J, Burdick E, et al. Adverse drug events in ambulatory care. *N Engl J Med*. 2003 Apr 17; 348(16):1556–64. [PubMed: 12700376]
40. Phansalkar S. Criteria for assessing high-priority drug-drug interactions for clinical decision support in electronic health records. *BMC Med Inform Decis Mak*. 2013; 13(1):65. [PubMed: 23763856]
41. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med*. 2011; 365(21):2002–12. [PubMed: 22111719]
42. Saverno KR, Hines LE, Warholak TL, Grizzle AJ, Babits L, Clark C, et al. Ability of pharmacy clinical decision-support software to alert users about clinically important drug-drug interactions. *J Am Med Inform Assoc*. 2011; 18(1):32–37. [PubMed: 21131607]

43. Doan J, Zakrzewski-Jakubiak H, Roy J, Turgeon J, Tannenbaum C. Prevalence and risk of potential Cytochrome P450-mediated drug-drug interactions in older hospitalized patients with polypharmacy. *Ann Pharmacother*. 2013; 47(3):324–32. [PubMed: 23482734]
44. Ojeleye O, Avery AJ, Boyd MJ. Assessing the safety features of electronic patient medication record systems used in community pharmacies in England. *Br J Clin Pharmacol*. 2014; 78(2):401–9. [PubMed: 24528252]
45. Uddin S, Hamra J, Hossain L. Mapping and modeling of physician collaboration network. *Statistics in Medicine*. 2013; 32(20):3539–3551. [PubMed: 23468249]

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Key Points

- We applied social network analytics to characterize provider networks, and showed that collaborative patterns among providers can predict the risk of multiple provider prescribing of medications with known drug-drug interactions.
- Understanding the network dynamics of healthcare providers' prescribing behavior may help avoid adverse drug events.

Fig 1.
Graphical representation of patient-sharing network

Fig 2. Identification of multiple provider prescribing of interacting drugs, defined as co-prescriptions of interacting drugs by different providers that were repeated more than once, where each episode of co-prescription had an overlapping coverage of more than 14 days

Table 1

Baseline characteristics of study population, and comparison between patients who were, and were not, exposed to multiple provider prescribing of interacting drugs

Characteristics	Overall (n=88,494)	Exposed (n=1,796)	Unexposed (n=87,368)	p-value*
Age, mean	45.8	51.9	45.7	<0.0001
Gender (female), n (%)	53,497 (60.5)	1,061 (59.1)	52,436 (60.5)	0.223
Charlson index, mean	0.23	0.73	0.22	<0.0001
Number of providers, mean	6.0	8.4	5.9	<0.0001
Presence of PCP, n (%)	85,032 (96.1)	1,749 (97.4)	83,283 (96.1)	0.005
Care density, mean	19.5	12.1	19.6	<0.0001
Care density, quartile	–	–	–	<0.0001 [^]
1 st quartile (25 th percentile)	4.7	4.3	4.8	–
2 nd quartile (50 th percentile)	9.3	7.3	9.3	–
3 rd quartile (75 th percentile)	21.0	13.2	21.3	–

* The p-value is for the comparison between groups (exposed vs unexposed), and is based on the chi-square test of independence for categorical variables (gender, presence of PCP) and the analysis of variance for continuous variables (age, Charlson index, number of providers, care density);

[^] the p-value based on the analysis of variance across quartiles of care density.

Table 2

Regression analyses of risk factors for multiple co-prescriptions of interacting drugs by different providers, where each overlapping coverage was more than 14 days

Risk factor	Univariate Model *		Multivariate Model 1 *		Multivariate Model 2 +	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.06 (1.05 – 1.06)	<0.0001	1.04 (1.04 – 1.05)	<0.0001	1.05 (1.04 – 1.05)	<0.0001
Charlson index	1.47 (1.43 – 1.52)	<0.0001	1.30 (1.25 – 1.34)	<0.0001	1.30 (1.26 – 1.34)	<0.0001
Number of providers	1.19 (1.17 – 1.20)	<0.0001	1.17 (1.16 – 1.18)	<0.0001	1.17 (1.16 – 1.18)	<0.0001
Presence of PCP	1.52 (1.14 – 2.04)	0.005	1.26 (0.94 – 1.70)	0.124	1.25 (0.93 – 1.68)	0.149
Care density	0.76 (0.72 – 0.79)	<0.0001	0.78 (0.74 – 0.83)	<0.0001	0.83 (0.79 – 0.87)	<0.0001

* Care density was examined as a continuous variable (after logarithm transformation)

+ Care density was categorized into quartiles, and examined as a continuous variable

Table 3

Regression analyses of risk factors for multiple co-prescriptions of interacting drugs by different providers for varying constellation size.

Risk factor	<5 providers (n=32,944)		5 to 10 providers (n=48,901)		>10 providers (n=6,649)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.05 (1.04 – 1.06)	<0.0001	1.05 (1.04 – 1.05)	<0.0001	1.03 (1.02 – 1.04)	<0.0001
Charlson index	1.43 (1.32 – 1.56)	<0.0001	1.30 (1.24 – 1.36)	<0.0001	1.22 (1.15 – 1.30)	<0.0001
Number of providers	1.44 (1.14 – 1.82)	0.002	1.24 (1.19 – 1.29)	<0.0001	1.10 (1.07 – 1.13)	<0.0001
Presence of PCP	1.16 (0.72 – 1.89)	0.545	1.14 (0.76 – 1.72)	0.517	1.07 (0.37 – 3.08)	0.900
Care density	0.85 (0.76 – 0.94)	0.002	0.80 (0.74 – 0.86)	<0.0001	0.63 (0.55 – 0.72)	<0.0001

Table 4

Regression analyses of risk factors for multiple co-prescriptions of interacting drugs by different providers, accounting for the interaction effect between care density and the number of providers in a care constellation

Risk factor	OR (95% CI)	p-value
Age	1.04 (1.04 – 1.05)	<0.0001
Charlson index	1.29 (1.25 – 1.33)	<0.0001
Number of providers	1.21 (1.18 – 1.25)	<0.0001
Presence of PCP	1.23 (0.91 – 1.65)	0.179
Care density	0.88 (0.79 – 0.97)	0.012
Care density × Number of providers	0.98 (0.97 – 0.996)	0.012

Table 5

Regression analyses of risk factors for multiple co-prescriptions of clopidogrel and omeprazole or esomeprazole by different providers, where each overlapping coverage was more than 14 days.

Risk factor	Co-prescriptions of clopidogrel and omeprazole/ esomeprazole		Co-prescriptions of drugs interacting with antiepileptics, anticoagulants/antiplatelets, tricyclic antidepressants, immunosuppressants or HMG-CoA reductase inhibitors	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.11 (1.07 – 1.15)	<0.0001	1.04 (1.02 – 1.06)	<0.0001
Charlson index	1.20 (1.001 – 1.43)	0.049	1.19 (1.05 – 1.35)	0.005
Number of providers	1.13 (1.80 – 1.19)	<0.0001	1.13 (1.10 – 1.17)	<0.0001
Presence of PCP	0.34 (0.13 – 0.88)	0.026	0.36 (0.17 – 0.75)	0.006
Care density	0.70 (0.50 – 0.97)	0.032	0.75 (0.62 – 0.92)	0.006