bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Learning and Mapping Lyme Disease Patient Trajectories from Electronic Medical Data for Stratification of Disease Risk and Therapeutic Response

Osamu Ichikawa[1,2*], Benjamin S. Glicksberg[1,3*], Brian Kidd[1], Li Li[1#], Joel T. Dudley[1#]

1. Department of Genetics and Genomic Sciences, Institute for Next Generation Healthcare, Icahn School of Medicine at Mount Sinai, 770 Lexington Ave., New York, NY 10065.
2. Drug Research Division, Sumitomo Dainippon Pharma. Co. Ltd., 3-1-98 Kasugade-naka, Konohana-ku, Osaka, 554-0022, Japan.
3. Institute for Computational Health Sciences, University of California, 550 16th St, San Francisco, California, 94158.

* These authors contributed equally to this work

Correspondence and requests for materials should be address to

Dr. Li Li (li.li@mssm.edu) or Dr. Joel Dudley (joel.dudley@mssm.edu)

Institute for Next Generation Healthcare

Icahn School of Medicine at Mount Sinai

770 Lexington Ave.

15th Floor

New York, NY 10065, USA

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

ABSTRACT (250 words)

Background

Lyme disease (LD) is an epidemic, tick-borne illness with approximately 329,000 incidences diagnosed each year in United States. Long-term use of antibiotics is associated with serious complications, including post-treatment Lyme disease syndrome (PTLDS). The landscape of comorbidities and health trajectories associated with LD and associated treatments is not fully understood. Consequently, there is an urgent need to improve clinical management of LD based on a more precise understanding of disease and patient stratification.

Methods

We used a precision medicine machine-learning approach based on high-dimensional electronic medical records (EMRs) to characterize the heterogeneous comorbidities in a LD population and develop systematic predictive models for identifying medications that influence the risk of subsequent comorbidities.

Findings

We identified 3, 16, and 17 comorbidities at broad disease categories associated with LD within 2, 5, and 10 years of diagnosis, respectively. At higher resolution of ICD-9 levels, we pinpointed specific co-morbid diseases on a timescale that matched the symptoms associated with PTLDS. We identified 7, 30, and 35 medications that influenced the risks of the reported comorbidities within 2, 5, and 10 years, respectively. These medications included six previously associated with the identified comorbidities and 29 new findings. For instance, the first-line antibiotic doxycycline exhibited a consistently protective effect for typical symptoms of LD, including 'backache Not Otherwise Specified (NOS)' and 'chronic rhinitis', but consistently increased the risk of 'cataract NOS', 'tear film insufficiency NOS', and 'nocturia'.

Interpretation

Our approach and findings suggest new hypotheses for precision medicine treatments regimens and drug repurposing opportunities tailored to the phenotypic profiles of LD patients.

Funding

The Steven & Alexandra Cohen Foundation

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

INTRODUCTION

Lyme disease (LD) is a vector-borne, infectious disease caused by the bacterium *Borrelia burgdorferi* that is transmitted to humans through tick bites. According to the US Centers for Disease Control and Prevention (CDC), around 329,000 LD cases occur annually and it becomes a major US public health problem that causes substantial use of health care resources. LD is most prevalent in the Northeast and upper Midwest, and 95% of all confirmed cases in 2015 were reported in 14 states [1]. The symptomology of LD is heterogeneous, although some general patterns have emerged. The first manifestation of LD is often an expanding annular lesion, called erythema migrans, near the bite location, but this sign is present in only 70–80% of patients [2]. The length of time for the rash to occur, along with the characteristics of the rash (e.g., composition and size) can also vary [3]. Other clinical features that often arise, singly or in combination, include fever, pain, arthritis, myopericarditis, neurological symptoms (e.g., facial nerve palsy), and satellite rashes. One explanation for this variability is that the genotype of the tick itself might affect aspects of pathogenesis, such as the probability of hematogenous dissemination [4,5]. The neurological manifestations in LD, reported in 3–12% of patients, are of greatest concern [6]. These phenomena, collectively called neuroborreliosis, are often associated with intense pain that can manifest either soon after infection or much later, from months to years afterward.

Accurate and precise diagnoses of LD present several challenges. Typically, laboratory testing of LD follows identification of cutaneous manifestations from visual inspection but these manifestations are not always present. Current guidelines recommend serologic testing, a two-phase process consisting of an enzyme immunoassay within 30 days of symptom onset, followed by Western blot after 30 days from symptom occurs [7,8] if the early test is active. Even together, this diagnostic strategy has poor sensitivity, particularly during the acute phase, with false-negative rates of up to 50% [9]. Other laboratory methods are specific for particular manifestations, e.g., testing of CSF for central nervous system involvement. Recent work has shown that incorporation of data from various wearable devices can detect early signs of LD and associated inflammatory responses. For example, variations in peripheral capillary oxygen saturation (SpO2), a marker associated with physiological macro-phenotypes such as fatigue, can be measured by portable biosensors to facilitate more accurate and rapid LD diagnosis from variations in these measurements and could be economically feasible for widespread use in the future. Currently, however, clinicians still have to rely on traditional measures to diagnose patients[10]. Furthermore, comorbid conditions can interfere with both diagnosis and treatment. For instance, other infections can be concurrently transmitted with LD [11], making differential diagnosis even more difficult and sometimes requiring specialized, alternative treatment strategies. Many studies have attempted to develop methods for differentiating LD from other similar syndromes, e.g., septic arthritis vs. LD of the knee in children [12].

Following successful diagnosis, LD is most commonly treated with antibiotics such as doxycycline, amoxicillin, cefuroxime axetil, and ceftriaxone. Although these medications have

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

high cure rates (~90%) [13], they are associated with serious complications and adverse events, especially under prolonged use [14,15 3,16]. Notably in this regard, one study showed that certain first-line treatments, specifically intravenous ceftriaxone followed by doxycycline for chronic LD patients were not effective compared to placebo forcing discontinuation of the trial [17]. Another study reported that repeated IV ceftriaxone treatment for Lyme encephalopathy resulted in only minor cognitive improvements, with high rates of relapse of cognitive symptoms [18]. These findings suggest that unknown factors are responsible for the high variability of treatment outcomes for patients with LD. Additionally, up to 20% of treated patients develop post-treatment Lyme disease syndrome (PTLDS), in which lingering symptoms such as fatigue, pain, or joint and muscle aches last for months or even years. The causes and frequencies of these symptoms remain unclear, and the issue is further confounded by the presence of concurrent diseases.

Several recent studies reveal the uncharacterized complexity of disease course and treatment response in LD. One study found certain first-line treatments, specifically intravenous ceftriaxone followed by doxyclycline, for chronic LD patients were not effective compared to placebo and were forced to discontinue their study[17]. Another study assessed the effects of repeated IV ceftriaxone treatment for Lyme encephalopathy and found only minor cognitive improvements with high rates of relapse in cognition issues [18]. Therefore, it seems that there are other factors at play that may explain the high variability of treatment outcomes for patients with LD. It is difficult to disentangle to what extent given treatment responses and disease sequelae are due to differences in individual immune responses, patient characteristics, disease burden, and treatment timing, or to the medications themselves. Indeed, it is very likely that response and outcome depend on a complex interplay between these factors, making clinicians' jobs extremely difficult. To address the diverse symptomology, imperfect diagnostic strategies, and variable treatment outcomes of LD, comprehensive study designs are required. For example, an investigation of risk factors for LD infection, such as behavioral and environmental risk factors, revealed that LD–positive serology is significantly associated with clinical and demographic features such as previous self-reported LD diagnosis and age, behavioral factors such as wearing protective clothing, and geographic/environmental factors such as shrub edge density in property location [19]. Another study evaluated the risks to individuals based on geographical features such as the suitability of the local habitat for ticks [20].

Although the aforementioned studies have provided a great deal of useful information, the variability in global risk profiles for LD pathogenesis remains incompletely understood, and there is an unmet need for personalized treatment recommendations that take into account individual characteristics such as demographics and disease burden. Electronic Medical Records (EMRs) from hospitals contain a wealth of longitudinal, patient-level data encompassing prior history of prescriptions and disease diagnoses, along with clinical outcomes, that can be exploited to investigate these issues in a data-driven fashion. To date there has been no systematic analysis of LD using EMR data, particularly from a hospital within a high-risk state. In

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

this study, we leverage an EMR data set representing over five million unique patients of diverse racial and ethnic backgrounds collected from a large academic medical center in New York City. Although not itself located adjacent to a wooded area, MSH caters to patients from all over the state. New York is one of the aforementioned 14 states reporting the vast majority of LD cases, and in 2017 had an incidence rate of 16.4 per 100,000 individuals (CDC), one of the highest in the country.

We hypothesized that EMR data from MSH could provide a rich framework for studying the heterogeneity of Lyme manifestation, as well as the quality and efficacy of treatment. Using various state-of-the-art statistical and machine learning methods, we sought to identify patterns of clinical outcomes in order to help physicians develop treatment strategies tailored to patients' disease profiles. Specifically, we investigated how demographic and clinical factors affect LD manifestations and clinical outcomes in the context of various treatments. Our main goals were to identify comorbidities associated with LD and develop a systematic predictive model for identifying medications that influence the risk of these conditions. As an alternative to one-size-fits-all strategies for treating LD, our methodology facilitates directing treatment recommendations and identifying possible repurposing opportunities tailored to the phenotypic profiles of Lyme patients. Our study is the first data-driven effort to prioritize medications for LD based on an individual's phenotype profile. We identified Lyme-associated comorbidities at the level of broad disease categories, pinpointed specific co-morbid diseases associated with LD over time, and used machine learning to predict medications that influence the risks of these comorbidities.

We expect that the novel framework and findings from this study can support current and future efforts to develop personalized treatment strategies for patients with LD, including efforts to provide physicians with a broader evidentiary foundation on which to base their treatment recommendations (e.g., selection of antibiotics) based on individual patients' disease risk profiles. Additionally, more precise knowledge of predicted adverse events would facilitate improvements in monitoring and management strategies.

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

METHODS

Patient population and standardization of clinical terminology

Patient cohort

We utilized Electronic Medical Records (EMRs) from the Mount Sinai Data Warehouse (MSDW), the largest comprehensive EMR system in New York City, which includes data from a racially and ethnically diverse patient base. Since 2000, more than 4.5 million unique patient records have been documented in this system. Disease diagnoses are encoded as International Classification of Diseases, 9th Revision (ICD-9) billing codes, which have been used extensively in EMR-related analyses [21]. In this study, we retrieved records from all patients diagnosed with Lyme disease (LD) with the ICD-9 code 088.81 (*n*=2,134). We restricted the data to records occurring between 2000 and 2015, allowing for up to 15-year follow-up. In accordance with Health Insurance Portability and Accountability (HIPAA) and Protected Health Information (PHI) guidelines, the ages of these patients were censored at 18 and 90. Finally, we only kept data from patients with defined age, self-reported sex, and self-reported race/ethnicity (referred to as "race" in this manuscript). For the total of 1,767 Lyme patients, there were 930 females (52.6%) and 837 males (47.4%), with an average age of 47.8 ± 19.7. The racial breakdown of the cohort is as follows: 1,201 Caucasian (70.0%), 49 African-American (2.8%), 34 Hispanic/Latino (1.9%), and 483 Others (27.3%). For these patients, we also retrieved all other available clinical variables from EMR, including prescriptions and other disease diagnoses. In addition, we retrieved IgM/IgG lab measurements pertinent to LD. IgM or IgG Western blot labs were available for 28 patients after or at the time of diagnosis (45 days window of diagnosis). Of those, 89% patients (25/28) were reported as either IgM or IgG Western blot–positive, confirming true positivity for Lyme. The remaining 11% of patients (3/28) were reported as IgM-negative, but all were positive for p23, an antigen specific to Lyme. In total, we compiled 3,936 diseases diagnosis and 5,723 prescriptions. We provide a schematic of our study design, approach, and patient selection criteria in Figure 1.

Clinical sources and term standardization

We categorized diseases using the Clinical Classifications Software (CCS) for ICD-9 diagnosis codes, developed by AHRQ [22], which aggregates and characterizes more than 14,000 ICD-9 codes into broader coherent disease categories. This strategy helps to avoid sample size limitation as a result of using ICD-9 codes alone. For categorization, we used the 'Single-Level Diagnosis' (CCS-single) level, which has a total of 283 different categories. We standardized medication data by mapping to the RxNorm ontology [23]. Specifically, we mapped these terms to ingredient codes, yielding 793 normalized medications. To ensure the robustness of our analyses, we required a sample size of > 20 patients for calculations of the significance of disease directionality and disease–medication association.

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Machine learning methods and analysis

Disease pair temporal directionality

For all patients with LD, we first assessed disease-pair connectivity patterns for comorbid diseases. Specifically, we determined whether the members of each pair exhibited a significant pattern in their temporal order, e.g., whether one preceded the other more often than expected by chance. We performed a cumulative binomial probability test to assess the temporal ordering of the associations between Lyme and all other diseases, assuming a 50% probability of either to occur before the other. We performed the following analysis on both broad and narrow disease categories. At the broader level, we analyzed representative CCS-single-level categories because this strategy could enhance signals that might be lost due to small sample size at the ICD-9 level. Second, we performed the analysis using standard ICD-9 codes in order to detect associations at a higher resolution for certain codes that may be more prevalent. Because these comorbid conditions can be either chronic or acute, we performed several iterations of this analysis over different time windows, specifically 2, 5, and 10 years. For each time window, we restricted collection of information for the comorbid diseases in both temporal directions, relative to the date of first Lyme diagnosis. For the 2-year window, for example, we only collected disease data for each patient 2 years before and 2 years after the date of Lyme diagnosis. For the CCS-single- and ICD-9–level analyses, we performed 275 and 3,639 tests for each window, respectively. Last, to determine whether disease pairs with significant temporal directionality were also significantly comorbid, we performed a logistic regression for each pair controlling for age, sex, and self-reported race. The outcome variable in this model was the disease that was shown to occur after the other in the temporal analysis (significant in the binomial assessment).

Definition of outcomes and covariates in the machine-learning model

To discover risk factors or new therapeutic options for LD sequelae, we focused on the new onset of disease comorbidities more than 7 days after the diagnosis of LD. Of the 1,767 LD patients in the overall cohort, we systematically assessed the comorbidities and medication associations for 1,196 patients who were followed up for more than 7 days and had at least one prescription record in MSH's EMR system. Like our disease-pair temporal directionality analysis, we set time windows of 2, 5, and 10 years. For each patient, we collected the diseases diagnosed within 2, 5, or 10 years after their first Lyme diagnosis date. We also retrieved medications prescribed within 1 year prior to and 2, 5, or 10 years after the first Lyme diagnosis. Outcome comorbidities were defined by ICD-9 code and categorized using CCS-single-level Diagnosis terms.

Feature selection

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

We considered many disease variables, coded by CCS-single-level categories, and medication variables, which were mapped to RxNorm ingredient codes. Accordingly, we adopted a feature selection method, penalized logistic regression with the adaptive LASSO (Eq. 1), to identify variables of the highest relevance that associated with ensuing comorbidities following LD diagnosis. The adaptive LASSO is an extension of the traditional LASSO [24] that uses coefficient-specific weights [25]. The adaptive LASSO estimator selects the zero coefficients of the true parameters are estimated as zero with probability tending to one, which is called sparsity property. And the non-zero components are estimated as if the true sparse model were known *a* prior, which is asymptotically normal [26]. Let $\mathcal{L}_n(\beta; Y, X)$ be the negative log-likelihood parametrized by β for a sample of size n. The adaptive LASSO estimator is defined as:

$$\hat{\beta} = argmin_{\beta} \{\mathcal{L}_n(\beta; Y, X) + \lambda_n \sum_{j=1}^{d} \widehat{\omega_j} |\beta_j|\} \quad (1)$$

where $\widehat{\omega_j} = |\widetilde{\beta_j}|^{-\gamma}$ is a coefficient specific weights vector, and λ_n is a regularization parameter. We set the positive constant γ as 1 according to Zou et al. [25], and obtained $\tilde{\beta}$ by the maximum likelihood estimate of Ridge regression. The $\lambda_n$value for minimum AUC was chosen by 10-fold cross validation. We used the R package *glmnet* [27] for these penalized regressions.

Logistic regression model

We used odds ratio (OR) from logistic regression (Eq. 2) to assess the risk of future comorbidity progression on each medication taken (i.e. either increased risk or protective effect). We analyzed the pairs of outcome disease comorbidity and the medications that were selected by the adaptive LASSO. In this model, we adjusted for age, sex, self-reported race, and the follow-up time frame.

$$log\left(\frac{P}{1-P}\right) = \beta_0 + \beta_m medication + \beta_a age + \beta_g gender + \beta_r race + \beta_p observered\ period \quad (2)$$

where *P* is the probability of a disease, medication is a binary variable, age is a continuous parameter, gender is a binary variable (Female/Male); race is a categorical variable (Caucasian, African American, Hispanic/Latino, or Other), and observed period is a continuous parameter. β coefficients for each covariate represent the effect size when controlling for all others.

Propensity score matching

To control for potential confounding factors due to imbalances of clinical characteristics, not limited to age and gender, we analyzed the temporal effects of medications after the propensity score matching to select an appropriate control cohort for the targeted case cohort [28]. Thus, we created comparable cohorts, consisting of groups treated or untreated with a

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

targeted medication, based on a set of covariates at the baseline time point, i.e., time zero for each patient. The baseline time point was defined as the first prescription day of the targeted medication or 7 days after LD diagnosis, whichever was later, because we observed disease comorbidities for more than 7 days after LD diagnosis.

The propensity scores of targeted prescriptions were predicted by a logistic regression model, including other significant medications and disease confounders selected by the adaptive LASSO with a 10-year time window, with patient demographics as covariates. Each patient prescribed a given medication was matched to a corresponding comparison patient (1:1 ratio) by nearest-neighbor matching. For instance, we analyzed association between doxycycline and 'backache Not Otherwise Specified (NOS)' (ICD-9 code: 724.5), 'chronic rhinitis' (472.0), 'tear film insufficiency (insuffic) NOS (375.15)', and 'cataract NOS (366.9)', and between amoxicillin and 'acute upper respiratory infection (URI) NOS (465.9)'. A total of 328, 330, 358, 370, and 115 subjects were selected for each medication-comorbidity pair in the propensity score-matched treated/untreated group. The R package *MatchIt* [29] was used for propensity score matching.

Survival analysis

We generated survival curves by the Kaplan–Meier method and examined differences in survival among subgroups by the log-rank test, with propensity score matching of cases and controls. We calculated hazard ratios using Cox proportional hazards models:

$$h(t) = h_0(t)\exp(\beta_m medication) \qquad (3)$$

where $h(t)$ is the expected hazard at time t, $h_0(t)$ is the baseline hazard, and medication is a binary variable. We verified the proportional hazards assumption by confirming that Schoenfeld residuals are independent of time (Schoenfeld test $p > 0.1$). We used the R packages *survival* and *survminer* for the survival analysis.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding authors had full access to all the data in this study and had final responsibility for the decision to submit for publication.

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

RESULTS

Identified comorbidities associated with Lyme disease, grouped as broader disease categories

We assessed the temporal ordering of the associations between Lyme disease (LD) and other diseases; specifically, we sought to determine whether a given comorbidity tended to occur before or after diagnosis of LD. We restricted our analysis to diseases with reported dates and only included the first reported encounter of a diagnosis, resulting in 41,713 disease-disease pairs, and analyzed their temporal ordering at the patient level. Specifically, for each comorbid disease pair (i.e. LD and another disease category), we tabulated the number of patients with both diseases and assessed which disease in the pair occurred first, or if they occurred at the same time, based on the visit dates. Overall, out of the 275 Lyme-comorbidity combinations for all time windows, 21 were nominally significant, with 5 diseases occurring prior to LD and 16 occurring after ($p < 0.1$; Table 1a). For the 2-year window, we identified three disease categories significantly associated with LD, with two prior and one after; for the 5-year window, 16 categories, with four prior and 12 after; and for the 10-year window, 17 categories with five prior and 12 after (Table 1a). We reconfirmed some previously reported Lyme comorbidities, including 'nutritional deficiencies' [p=0.069, probability (prob) =0.54 at 5 years; p=0.035, prob=0.55 at 10 years] [30,31], 'vision defect' (p=0.099, prob=0.57 at 5 years; p=0.076, prob=0.57 at 10 years) [32 33], and 'disorder of lipid metabolism' (p=0.036, prob=0.54 at 5 years; p=0.076, prob=0.57 at 10 years) [34]. Additionally, we identified several disease comorbidities not previously reported, including 'cataract' (p=0.0037, prob=0.65 at 5 years; p=0.033, prob=0.64 at 10 years), 'acute bronchitis' (p=0.094, prob=0.62 at 2 years; p=0.022, prob=0.64 at 5 years; p=0.034, prob=0.63 at 10 years), and 'nonmalignant breast conditions' (p=0.057, prob=0.58 at 5 years; p=0.066, prob=0.58 at 10 years). A complete list of disease categories is shown in Table 1a.

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Time (year)	Direction	Disease (CCS)	Lyme First	Disease First	Same Time	P value	Prob.
2	-	Coronary atherosclerosis and other heart disease	18	58	17	1.10E-02	0.62
2	-	Administrative/social admission	41	66	9	8.17E-02	0.57
2	+	Acute bronchitis	23	11	3	9.39E-02	0.62
5	-	HIV infection	2	21	9	5.51E-02	0.66
5	-	Coronary atherosclerosis and other heart disease	38	80	17	1.92E-02	0.59
5	-	Administrative/social admission	55	88	9	3.09E-02	0.58
5	-	Disorders of lipid metabolism	117	269	111	3.63E-02	0.54
5	+	Open wounds of extremities	24	6	0	7.15E-04	0.8
5	+	Open wounds of head; neck; and trunk	19	9	0	4.36E-02	0.68
5	+	Fracture of lower limb	16	8	0	7.58E-02	0.67
5	+	Cataract	57	21	10	3.67E-03	0.65
5	+	Fracture of upper limb	18	9	1	9.25E-02	0.64
5	+	Acute bronchitis	36	17	3	2.20E-02	0.64
5	+	Anal and rectal conditions	26	11	5	8.21E-02	0.62
5	+	Nonmalignant breast conditions	60	36	7	5.72E-02	0.58
5	+	Other eye disorders	75	41	14	4.76E-02	0.58
5	+	Neoplasms of unspecified nature or uncertain behavior	60	39	6	8.58E-02	0.57
5	+	Blindness and vision defects	58	33	11	9.89E-02	0.57
5	+	Nutritional deficiencies	219	141	47	6.85E-02	0.54
10	-	HIV infection	2	25	9	1.44E-02	0.69
10	-	Coronary atherosclerosis and other heart disease	44	91	17	9.18E-03	0.6
10	-	Administrative/social admission	61	97	9	2.20E-02	0.58
10	-	Disorders of lipid metabolism	121	301	111	1.59E-03	0.56
10	-	Essential hypertension	96	271	124	1.20E-02	0.55
10	+	Open wounds of extremities	28	7	0	2.54E-04	0.8
10	+	Maintenance chemotherapy; radiotherapy	14	5	1	5.77E-02	0.7
10	+	Cataract	64	26	10	3.32E-03	0.64
10	+	Occlusion or stenosis of precerebral arteries	22	10	3	8.77E-02	0.63
10	+	Acute bronchitis	37	19	3	3.37E-02	0.63
10	+	Poisoning by other medications and drugs	24	7	8	9.98E-02	0.62
10	+	Anal and rectal conditions	29	14	5	9.67E-02	0.6
10	+	Other eye disorders	87	43	14	7.69E-03	0.6
10	+	Nonmalignant breast conditions	65	41	7	6.60E-02	0.58
10	+	Blindness and vision defects	63	36	11	7.62E-02	0.57
10	+	Inflammation; infection of eye (except that caused by tuberculosis or sexually transmitteddisease)	78	39	20	6.19E-02	0.57
10	+	Nutritional deficiencies	228	143	47	3.51E-02	0.55

Time (year)	Direction	Disease (CCS)	ICD9	Disease (ICD9)	Lyme First	Disease First	Same Time	p value (binomial)	Prob. (binomial)	p value (logistic regression)	OR (logistic regression)
5	-	HIV infection	V08	HIV positive NOS	0	21	8	1.21E-02	0.72	1.80E-05	2.17
5	-	Administrative/social admission	V20.2	Routin child health exam	16	49	4	3.18E-04	0.71	1.31E-02	2.08
5	+	Nutritional deficiencies	268.9	Vitamin D deficiency NOS	203	124	36	1.37E-02	0.56	1.20E-177	5.64
5	+	Cataract	366.9	Cataract NOS	40	18	7	4.08E-02	0.62	2.90E-30	4.27
5	+	Acute bronchitis	466.0	Acute bronchitis	36	16	3	1.50E-02	0.65	4.02E-21	3.56
5	+	Nonmalignant breast conditions	793.80	Unspecified abnormal mammogram	28	12	0	8.29E-03	0.70	8.92E-10	2.61
10	-	HIV infection	V08	HIV positive NOS	0	24	8	3.50E-03	0.75	1.80E-05	2.17
10	-	Disorders of lipid metabolism	272.0	Pure hypercholesterolem	84	159	50	8.04E-02	0.54	1.60E-30	2.22
10	-	Disorders of lipid metabolism	272.4	Hyperlipidemia NEC/NOS	97	187	64	9.01E-02	0.54	1.06E-18	1.78
10	-	Essential hypertension	401.9	Hypertension NOS	96	247	120	8.16E-02	0.53	9.83E-08	1.39
10	-	Administrative/social admission	V20.2	Routin child health exam	17	54	4	8.82E-05	0.72	1.31E-02	2.08
10	+	Nutritional deficiencies	268.9	Vitamin D deficiency NOS	211	124	36	4.67E-03	0.57	1.20E-177	5.64
10	+	Cataract	366.16	Senile nuclear cataract	17	2	1	1.29E-03	0.85	2.94E-03	1.97
10	+	Cataract	366.9	Cataract NOS	45	21	7	3.02E-02	0.62	2.90E-30	4.27
10	+	Inflammation; infection of eye (except that caused by tuberculosis or sexually transmitteddisease)	373.00	Blepharitis NOS	33	2	1	1.14E-07	0.92	2.27E-14	3.79
10	+	Other eye disorders	375.15	Tear film insuffic NOS	24	11	1	3.26E-02	0.67	4.44E-12	3.36
10	+	Acute bronchitis	466.0	Acute bronchitis	37	17	3	1.66E-02	0.65	4.02E-21	3.56
10	+	Nonmalignant breast conditions	793.80	Unspecified abnormal mammogram	31	12	0	2.70E-03	0.72	8.92E-10	2.61

Table 1 (a; top) Diseases associated with Lyme, analyzed as CCS-single-level categories (p value < 0.1). A total of 275 diseases were tested. (b; bottom) Diseases associated with Lyme, by ICD-9 category. A total of 3,639 diseases were tested. This table includes only the ICD-9 diseases that are classified into the CCS-single-level categories shown in (a), and a full list of associations is provided in Supplementary Table 1.

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Highlighted specific known or novel diseases associated with LD, analyzed at higher resolution

Although the CCS-single-level categories were helpful in identifying disease groups of relevance from a broader perspective, we also performed the same analysis at a higher granularity (Table 1b and S. Table 1). To this end, using the ICD-9 codes, we sought to determine which specific diseases drove the signal and whether the signal still persisted. A total of 3,639 Lyme–comorbidity combinations were analyzed using the ICD-9 codes. At the 2-year window, five pairs were nominally significant ($p<0.1$ due to the relatively small sample size, $N\geq20$ patients for Lyme first onset), with four prior to LD and one after (S. Table 1). For the 5-year window, we found 53 significant associations, with 49 prior to LD and 4 afterwards. For the 10-year window, we found 75 significant associations, with 67 prior to LD diagnosis and 8 after. The significance of all disease categories significantly associated with LD that we identified in the previous analysis persisted, including the four diseases that significantly occurred prior to LD: 'pure hypercholesterolemia' (p=0.080, prob=0.54 at 10 years), 'hyperlipidemia NEC/NOS' (p=0.090, prob=0.54 at 10 years), 'hypertension NOS' (p=0.082, prob=0.53 at 10 years), and 'coronary atherosclerosis (athero) NOS' (p=0.022, prob=0.61 at 5 years; p=0.075, prob=0.62 at 10 years). Nine sequelae diseases, namely 'vitamin D deficiency NOS' (p=0.014, prob=0.56 at 5 years; p=0.0047, prob=0.57 at 10 years), 'cataract NOS' (p=0.041, prob=0.62 at 5 years; p=0.030, prob=0.62 at 10 years), 'senile nuclear cataract' (p=0.0013, prob=0.85 at 10 years), 'tear film insufficiency (insuffic) NOS' (p=0.033, prob=0.67 at 10 years), 'acute bronchitis' (p=0.015, prob=0.65 at 5 years; p=0.017, prob=0.65 at 10 years), 'blepharitis NOS' (p=1.1E-7, prob=0.92 at 10 years), 'unspecified abnormal mammogram' (p=0.0083, prob=0.70 at 5 years; p=0.0027, prob=0.72 at 10 years), 'HIV positive NOS' (p=0.012, prob=0.72 at 5 years; p=0.0035, prob=0.75 at 10 years)' and 'routine child health exam' (p=3.2E-4, prob=0.71 at 5 years; p=8.8E-5, prob=0.72 at 10 years) drove the signal from the broad disease categories (Table 1b). Additionally, we reported LD comorbidities if other significant ICD-9 codes associated with LD with a list of comorbidities are not widely known, including 'insomnia Not Elsewhere Classifiable (NEC)' (p=0.042, prob=0.59 at 5 years; p=0.045, prob=0.58 at 10 years), 'obstructive sleep apnea' (p=0.085, prob=0.60 at 5 years; p=0.044, prob=0.62 at 10 years), 'cervicalgia' (p=0.073, prob=0.59 at 5 years; p=0.041, prob=0.60 at 10 years), and 'dysuria' (p=0.096, prob=0.59 at 5 years; p=0.034, prob=0.62 at 10 years).

We confirmed that the large majority of the comorbidity pairs were significantly associated with LD with concordant directionality by adjusting age, gender, and race by logistic regression ($p<0.1$). We provide a complete list of ICD-9 level disease associations that passed our significance threshold in both analyses Supplemental Table 1.

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Medications predicted to modulate risk of subsequent comorbidities in LD patients, analyzed as broader disease categories

To investigate how various prescribed medications influenced the risk of subsequent disease pathogenesis, we focused on comorbidities with onset after the first diagnosis of LD. Using the adaptive LASSO methodology and a logistic regression model, we investigated all medications prescribed to LD patients prior to the comorbidities. We found 3, 12, and 18 medications associated with disease comorbidities, classified by CCS-single-level categories, within 2, 5, and 10 years after Lyme diagnosis, respectively (S. Table 2, Figure 2a, Figure 2b). Four medication–Lyme comorbidity associations were supported by published studies [35-41], and we confirmed that these medications modulated the risks of Lyme comorbidities, including fluticasone–'cataract' (adjusted OR=1.94, p=0.072 at 5 years; adjusted OR=2.01, p=0.033 at 10 years) hydrochlorothiazide–'neoplasms of unspecified nature or uncertain behavior' (adjusted OR=2.23, p=0.031 at 5 years; adjusted OR=2.48, p=0.0092 at 10 years), metformin–'nutritional deficiencies' (adjusted OR=2.05, p=0.097 at 10 years), and esomeprazole–'nutritional deficiencies' (adjusted OR=1.75, p=0.093 at 10 years).

Five antibiotics, doxycycline, azithromycin, levofloxacin, clavulanate, and mupirocin, and one antiviral drug, valacyclovir, were predicted to modulate the risk of subsequent comorbidities. Doxycycline, a first-line antibiotic that was the most prescribed antibiotic in our EMR for patients with LD (39%, N=553), was associated with an elevated risk of eye disorders, including 'cataract' (adjusted OR=2.05, p=0.092 at 2 years; adjusted OR=1.70, p=0.067 at 10 years), 'blindness and vision disorders' (adjusted OR=2.05, p=0.016 at the 5 years; adjusted OR=1.95, p=0.019 at 10 years), and 'other eye disorders' (adjusted OR=1.81, p=0.024) (Figure 2a).

In regard to 'nutritional deficiencies', eleven medications were predicted to be risk factors and three to be protective. Among the 11 risk factor medications were two antibiotics, levofloxacin (adjusted OR=2.26, p=0.0093 at 5 years; adjust OR=2.77, p=7.0E-4 at 10 years) and clavulanate (adjusted OR=1.64, p=0.094 at 10 years), and one antiviral prophylactic, valacyclovir (adjusted OR= 2.56, p=0.014 at 5 years; adjusted OR=2.58, p=0.011 at 10 years). Additionally, two pain relievers, diclofenac and hydrocodone, and one anti-allergy medication, azelastine, were also risk factors for 'nutritional deficiencies' (respectively: OR=3.08, p=0.0015 at 5 years/adjusted OR=3.02, p=0.0014 at 10 years; adjusted OR=1.90, p=0.034 at 10 years; and adjusted OR=3.44, p=0.0037/adjusted OR=2.95, p=0.0094). Interestingly, we could identify new therapeutic options for the LD adjunctive treatment. Three medications, propofol, docusate, and heparin, consistently exhibited a protective effect against 'nutritional deficiencies' at 5 and 10 years after LD (respectively: adjusted OR=0.32, p=6.6E-4 at 5 years/adjusted OR=0.43, p=0.0044 at 10 years; adjusted OR=0.37, p=0.0039 at 5 years/adjusted OR=0.46, p=0.014 at 10 years; and adjusted OR=0.44, p=0.024 at 5 years/adjusted OR=0.41, p=0.014 at 10 years) (Figure 2). In addition, acetaminophen exhibited a protective effect at the early stage (2 years post-Lyme) with adjusted OR=0.44, p=0.0069 (S. Table 2).

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Medications predicted to modulate risk of subsequent comorbidities in LD patients, analyzed at the ICD-9 level

In the higher-resolution analysis using ICD-9 codes, we identified 7, 22, and 31 medications that were significantly associated with the disease comorbidities at 2, 5, and 10 years post-Lyme (S. Table 3, Figure 3a and 3b). Among these were previously reported risk associations [42-45]: for instance, steroid prednisone was a risk for 'pain in limb' with adjusted OR=2.16, p=0.030 at 5 years/adjusted OR=2.49, p=0.0063 at 10 years, and ciprofloxacin was a risk for 'joint pain-shoulder (shlder)' with adjusted OR=4.42, p=8.9E-5 at 5 years/ adjusted OR=4.39, p=3.1E-5 at 10 years. In addition, five of the side effects for four medications were reported in the SIDER database [46,47]. Two steroids, fluticasone and mometasone, and one pain reliever, hydrocodone, were associated with increased risk for 'acute upper respiratory infection (URI) NOS' in comparison with the placebo group (S table 3) and were rediscovered in our study (respectively: adjusted OR=2.92, p=5.2E-5 at 5 years/adjusted OR=3.44, p=4.7E-7 at 10 years; adjusted OR=2.86, p=0.0028 at 10 years; adjusted OR=4.01, p=4.1E-5 at 5 years/adjusted OR=4.45, p=1.8E-6 at 10 years). We also reconfirmed the risk associations between fluticasone and 'chronic rhinitis' (adjusted OR=4.70, p=1.4E-4 at 2 years/adjusted OR=4.78, p=6.5E-7 at 5 years/adjusted OR=4.86, p=4.4E-8 at 10 years) and diclofenac and 'pain in limb' (adjusted OR=3.43, p=0.0011 at 10 years).

Doxycycline exhibited a consistently protective effect against typical symptoms of LD, including 'backache NOS' (adjusted OR=0.44, p=0.018 at 5 years/adjusted OR=0.50, p=0.035 at 10 years) and 'chronic rhinitis' (adjusted OR=0.48, p=0.036 at 5 years/adjusted OR=0.48, p=0.024 at 10 years) (Figure 3a, 3b). Furthermore, seven antibiotics, doxycycline, amoxicillin, azithromycin, ciprofloxacin, levofloxacin, mupirocin, and sulfamethoxazole, and one antiviral drug, valacyclovir, modulated the risk of subsequent comorbidities. Doxycycline consistently increased the risk of 'cataract NOS' (adjusted OR=2.57, p=0.053 at 2 years/adjusted OR=1.89, p=0.058 at 10 years), 'tear film insuffic NOS' (adjusted OR=2.64, p=0.042 at 5 years/adjusted OR=2.37, p=0.050 at 10 years), and 'nocturia' (adjusted OR= 3.46, p=0.010 at 2 years) (Figure 3b). Amoxicillin, another antibiotic recommended for LD, increased the risk of 'acute URI NOS' (adjusted OR=3.01, p=6.5E-4 at 2 years/adjusted OR=2.41, p=8.4E-4 at 5 years/adjusted OR=2.60, p=1.3E-4 at 10 years). Furthermore, azithromycin was associated with an increased risk of urinary-related diseases such as 'nocturia' (adjusted OR=4.62, p=3.5E-5 at 5 years/adjusted OR=4.90, p=1.3E-5 at 10 years) and 'urinary (urin) tract infection NOS' (adjusted OR=2.18, p=0.0095 at 5 years), as well as respiratory diseases such as 'acute URI NOS' (adjusted OR=8.63, p=3.9E-12 at 2 years/adjusted OR=7.55, p=1.0E-16 at 5 years/adjusted OR=7.2, p=1.4E-17 at 10 years), 'acute bronchitis' (adjusted OR=5.15, p=5.9E-5 at 5 years/adjusted OR=4.75, p=1.1E-4 at 10 years), and 'chronic rhinitis' (adjusted OR=2.99, p=7.2E-4 at 5 years; adjusted OR=3.07, p=1.5E-4 at 10 years). Ciprofloxacin, a fluoroquinolone antibiotic, increased risk of 'nocturia' (adjusted OR=7.19, p=5.9E-6 at 5 years/adjusted OR=6.92, p=7.0E-6 at 10 years) and 'joint pain-shlder' (adjusted OR=4.42, p=8.9E-5 at 5 years/adjusted OR=6.92 and

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

p=7.0E-6 at 10 years). Mupirocin, an antibiotic used to treat skin infection, increased risk of skin disorders, including 'solar dermatitis NEC' (adjusted OR=12.93, p=6.9E-10 at 5 years/adjusted OR=13.96, p=3.0E-11 at 10 years) and 'scar & fibrosis of skin' (adjusted OR=11.52, p=6.9E-9 at 5 years/adjusted OR=12.46, p=1.0E-9 at 10 years) (Figure 3a, 3b).

'Vitamin D deficiency NOS', common in patients with persistent LD[48], is a specific form of nutritional deficiency, a comorbidity identified earlier at the broader (CCS-single) level (Figure 2a, 2b). Several medications increased the risk of this condition, three at 5 years post-Lyme and five at 10 years. These included two anti-infective drugs, levofloxacin (adjusted OR=2.68, p=0.0012 at 10 years) and valacyclovir (adjusted OR=1.95, p=0.087 at 5 years/adjusted OR=2.01, p=0.065 at 10 years), azelastine (adjusted OR=3.37, p=0.0035 at 5 years/adjusted OR=2.92, p=0.0085 at 10 years), diclofenac (adjusted OR=2.75, p=0.0032 at 5 years/adjusted OR=2.75, p=0.0026 at 10 years), and simvastatin (adjusted OR=1.77, p=0.083 at 10 years). On the other hand, four medications protected against 'vitamin D deficiency NOS': docusate (adjusted OR=0.33, p=0.0015 at 10 years), propofol (adjusted OR=0.37, p=0.0015 at 10 years), fentanyl (adjusted OR=0.46, p=0.012 at 5 years), and acetaminophen (adjusted OR=0.39, p=0.0025 at 2 years) (Figure 3a, 3b).

Respiratory disease (Figure 3b) is a complication frequently reported after LD [49]. We identified 11 medications that increased risk for these conditions and two that exhibited protective effects. In addition to the three medications reported in SIDER database and amoxicillin and azithromycin above, the medications that conferred increased risk for 'acute URI NOS' were an antibiotic, levofloxacin (adjusted OR=3.18, p=9.1E-4 at 10 years), a steroid, methylprednisolone (adjusted OR=2.14, p=0.027 at 5 years/adjusted OR=2.31, p=0.0077 at 10 years), cyclobenzaprine (adjusted OR=3.21, p=0.0025 at 5 years/adjusted OR=2.91, p=0.0037 at 10 years), homatropine (adjusted OR=7.16, p=7.3E-7 at 10 years), atorvastatin (adjusted OR=2.67, p=0.0017 at 10 years), and aspirin (adjusted OR=1.80, p=0.073 at 10 years). By contrast, acetaminophen (adjusted OR=0.55, p=0.025 at 5 years/adjusted OR=0.62, p=0.050 at 10 years), and oxycodone (adjusted OR=0.49/p=0.021 at 10 years) were associated with protective effects against this disease.

Medications that modulate LD pathophysiology on different timescales

We identified 16 medications associated with disease comorbidities within 5 years post-LD, 81% (13/16) of which overlapped with those identified as associated 10 years post-Lyme by the CCS-single-level categorization. Specifically, five out of six anti-infective drugs, doxycycline, azithromycin, levofloxacin, mupirocin, and valacyclovir, appeared in both timeframes. Moreover, 22 medications were associated with the ICD-9–level disease comorbidities within 5 years after Lyme, 95% (21/22) of which were also identified in the 10-year post-Lyme analysis. Among those 21 medications, five are antibiotics (doxycycline, amoxicillin, azithromycin, ciprofloxacin, mupirocin) and one is an antiviral drug (valacyclovir). The four medications

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

associated with comorbidities exclusively in the 5 years post-Lyme, clavulanate, gabapentin, midazolam, and fentanyl, may impact relatively early Lyme comorbidities (S. Figure 1).
A total of 17 medications overlapped between the CCS-single and ICD-9 levels in either the 5-year or 10-year time windows. Five of them were anti-infective drugs, namely doxycycline, azithromycin, levofloxacin, mupirocin, and valacyclovir. In the 5-year time window, 16 medications were associated with comorbidities classified by CCS-single-level category, of which 50% (8/16) were also identified at the ICD-9 level. At 10 years post-Lyme diagnosis, we identified 21 significant associations between medications and comorbidities, of which 81% (17/21) were consistent with those identified at the ICD-9 level.

Survival analysis of first-line medications in propensity-matched populations

By the cross-sectional analysis described above, we demonstrated that certain medications increased risk or protected against disease comorbidities in patients with LD. At higher resolution (i.e., using ICD-9 codes) with 10-year follow up, we found that doxycycline, the most commonly used antibiotic for treatment of LD [13], protected against 'backache NOS' and 'chronic rhinitis', but increased risk of 'tear film insuffic NOS' and 'cataract NOS'. Another commonly used antibiotic, amoxicillin, was associated with elevated risk of 'acute URI NOS'.

Prior to propensity score matching, we identified significant differences in the distributions of demographic and clinical characteristics between the doxycycline/amoxicillin-treated and untreated groups before. The doxycycline-treated group was significantly older than the untreated group ($P < 0.007$), whereas the amoxicillin-treated group was significantly younger than the untreated group ($P=8.7E-4$). In addition, doxycycline was prescribed more frequently to male than female patients ($P < 0.03$). The doxycycline/amoxicillin-treated groups had higher prevalences of certain pre-existing comorbidities and a higher prescription rate of particular medications than the untreated groups (S. Table 4). Moreover, both the doxycycline/amoxicillin treated groups had higher propensity scores than the corresponding untreated groups ($P < 0.001$). To clarify the longitudinal effects of doxycycline and amoxicillin, we analyzed these associations by propensity-score-matched survival analyses. After propensity score matching, the control cohorts were well balanced with the treated groups in terms of observed covariates (S. Table 4).
This analysis revealed that the risk of 'backache NOS' (Figure 4a) and 'chronic rhinitis' (Figure 4b) was significantly lower in the doxycycline-treated cohort than in the untreated cohort (HR=0.42, p=0.020; HR=0.49, p=0.040, respectively; Table 3). Furthermore, Kaplan-Meier curves demonstrated that the cumulative probabilities of remaining free from 'cataracts NOS' and 'tear film insuffic NOS' were lower among doxycycline-treated patients ($p = 0.0672$ and 0.0608, respectively; Figures 4c and 4d). Cox regression analysis supported a statistically significant association between doxycycline usage and increased risk of both 'cataract NOS' and 'tear film insuffic NOS' (HR=1.90, p=0.072; HR=2.65, p=0.071). On the other hand, patients prescribed amoxicillin had significantly higher hazard ratios for 'acute URI NOS' (HR=2.26, p=0.0091; Figure

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

4e). Therefore, the effects of doxycycline and amoxicillin revealed by the cross-sectional analysis were confirmed by survival analyses using the propensity score-matched cohort (Table 3).

Medication	Disease (ICD9)	ICD9	P value (LogRank)	Hazard Ratio (90% CI)	P value (Cox)
Doxycycline	Tear film insuffic NOS	375.15	6.08E-02	2.65 (1.09-6.45)	7.13E-02
Doxycycline	Cataract NOS	366.9	6.72E-02	1.9 (1.06-3.42)	7.18E-02
Doxycycline	Chronic rhinitis	472.0	3.60E-02	0.49 (0.28-0.87)	3.99E-02
Doxycycline	Backache NOS	724.5	1.67E-02	0.42 (0.23-0.78)	2.03E-02
Amoxicillin	Acute URI NOS	465.9	7.41E-03	2.26 (1.35-3.78)	9.13E-03

Table 2 Survival analyses of first-line therapeutics for Lyme disease using a propensity-score-matched cohort.

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

DISCUSSION

Proper diagnosis, treatment, and management of Lyme Disease (LD) are difficult for a variety of reasons. In particular, the complex interplay between various treatments and current clinical status, including disease burden, can lead to a wide range of sequelae. This study represents the first data-driven effort to identify clinical factors that affect treatment of LD patients using large-scale EMR data. EMR systems contain information pertaining to patients' health over time, including treatments administered and clinical outcomes. Thus, one advantage of using these data in comparison with prospective clinical trial studies is the availability of longitudinal data spanning more than 10 years, increasing the likelihood of capturing long-term effects. We utilized statistical and machine learning analyses to identify associations between medications, including first-line treatments, and comorbidity pathogeneses. In contrast to one-size-fits-all strategies, our approach may facilitate the personalization of treatment regimens based on the clinical profiles of affected individuals. This strategic transition is essential in light of the tremendous variability in efficacy of antibiotics and the adverse events associated with these treatments.

We first identified all significant comorbidities of patients with LD before and after their Lyme infections. Next, we applied machine learning models to assess the effect of medication treatment on the risk of developing subsequent conditions. Our analyses identified known associations between medications and specific disease comorbidity outcomes, and also discovered connections between drugs and LD that could facilitate precision medicine aimed at tailoring treatments to affected individuals' Lyme symptom profile.

Our analysis identified co-morbid conditions that were typically present before LD infection. Although this disease clearly requires contact with the bacteria, certain physiological properties make individuals more or less susceptible to infection. For example, we found that individuals categorized as having ‘disorders of lipid metabolism’ were more likely have LD infection in the future. *Borrelia burgdorferi* requires cholesterol for growth; researchers have found that apolipoprotein E (apoE)-deficient and low-density lipoprotein receptor (LDLR)-deficient mice, which have high levels amounts of serum cholesterol, are more susceptible than wild-type mice to pathogenesis induced by this bacterium [34]. Additionally, patients with hypercholesterolemia could increase susceptibility to trigger tick bite for this vector borne disease due to body heat, CO2, and moisture which are key attractants similarly to mosquitoes [50 51], but this is beyond the scope of this analysis and needs to be further investigated. Additionally, we identified an association between HIV infection and LD. Specifically, our data showed that patients with HIV almost exclusively developed LD subsequent to the HIV diagnosis, suggesting that immune system alteration increases the risk of LD. A handful of case reports have indicated that HIV-positive immunocompromised patients develop more severe Lyme complications following infection [52-54]. Although the specific immunological mechanisms

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

driving this connection remain unclear, it seems reasonable to speculate that immunosuppression plays an important role [55].

We also identified conditions that are more likely to be present after a LD diagnosis than beforehand, consistent with the possibility that these diseases are side effects or complications arising from Lyme infection. Many of these associations are well documented, enhancing our confidence in our results. Specifically, we found that the categories 'nutritional deficiencies', 'cataract', 'acute bronchitis', 'other eye disorders', and 'Inflammation; infection of eye (except that caused by tuberculosis or sexually transmitted disease)' are more likely to occur after Lyme infection than beforehand or by chance.

The results of this analysis feed into our drug-comorbidity associations network and can be used to inform treatment regimens. The associations identified for first-line antibiotic treatments of LD have the most straightforward potential application. These agents act by killing *B. burgdorferi*, and thus prevent the development of many complications associated with prolonged exposure to the bacteria. However, while antibiotics are the most effective first-line treatments for LD, their efficacies are nonetheless limited; moreover, some symptoms may persist notwithstanding the use of antibiotics, and long-term exposure to these agents risks additional complications. Indeed, it is possible that even acute use (usually a month) of these treatments is associated with long-term complications of LD that yet to be determined. Even when treated, up to 20% of patients develop Post-Treatment Lyme Disease Syndrome (PTLDS), in which symptoms including fatigue or muscle pain last for months or years. Although the etiology of PTLDS is not yet known, better tailoring of treatment strategies to an individual's phenotypic profile could prevent or modulate the risk of developing these symptoms. We identified a number of comorbidities matching the symptoms aligned with PTLDS, including chronic pain, chronic rhinitis (Figures 3a and 3b). Notably in this regard, we also found that usage of steroid medications increases the risk of many symptoms common to PTLDS. Consistent with this, corticosteroid use is associated with poor outcomes for LD patients [43]. In particular, we found that prednisone was associated with elevated risk for 'backache NOS', 'pain in limb' and 'other abnormal glucose', defined at the ICD-9 level. Use of fluticasone was associated with elevated risk for 'chronic rhinitis', 'postnasal drip', 'cervicalgia', and 'acute URI NOS'; mometasone was also associated with elevated risk for 'acute URI NOS'; and methylprednisolone was linked to increased risk of 'chronic rhinitis', 'backache NOS', and 'acute URI NOS' as well. Steroids, which suppress patients' immune systems, might be particularly harmful to LD patients, allowing the bacteria to grow, rather than attacking the infections. These findings suggest that steroid use should be limited in LD patients, and that patients exposed to these drugs should be monitored carefully for complications.

Other findings from our drug-comorbidity network might facilitate personalization of treatment regimens, with more favorable clinical outcomes for patients. For example, several anti-infectious drugs, pain relievers such as diclofenac and hydrocodone, and the anti-allergy medication azelastine were also associated with higher rates of 'nutritional deficiencies',

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

suggesting that physicians should consider recommending vitamin supplements for patients receiving these treatments.

Doxycycline is already associated with a range of side effects, including pain, increased pressure inside the skull [56], and gastrointestinal injury [57]. The nuances of these associations are not well understood. On the other hand, we also found that doxycycline use was associated with lower risk of 'backache NOS' and lower rates of 'chronic rhinitis'; the latter is to be expected, as it is a common symptom of chronic LD [11]. This medication increased the risk of many eye-related issues, such as 'cataract NOS', with the 2- and 10-year time windows, suggesting that it might exert both short-term and long-term side effects. We also found associations between this medication and elevated risk for 'tear film insuffic NOS' and 'blindness and vision disorders'.

The development of respiratory-related complications is a major concern for patients infected with LD. In one case study, secondary adult respiratory distress syndrome caused the death of a patient affected with LD during the course of her 2-month treatment [58]. The patient did not respond to conventional treatments, including antibiotics, salicylates, and steroids. In our study, we identified medications that are associated with elevated risk of respiratory-related diseases. Specifically, we found that the antibiotics amoxicillin, levofloxacin, and azithromycin all conferred increased risk of 'acute URI NOS'. In addition to the known risks of two steroids, prednisolone, and mometasone, reported in the SIDER database (S table 3), we found that another steroid, methylprednisolone, was also associated with increased risk for this disease. While we are unable to infer causation from our analyses, the associations we identified will hopefully inform physicians of the risks and encourage them to take the appropriate prophylactic measures. Particular attention should be paid to Lyme patients with respiratory complications because their immune systems are already weakened from Lyme infection, and certain medications (such as amoxicillin) are ineffective at treating these infections [59].

This study had several limitations. One issue is the relative low sample size, which is a consequence of the rarity of this disease although our hospital has the largest EMR system in NYC. Based on the available ELISA and Western blot lab tests specific for IgM and IgG, we found a great concordance for positive serology in patients with Lyme ICD codes, which enhanced our confidence of identifying true positive LD patients. Based on limited availability of these data, however, we had to use the ICD-9 code alone to select the patient cohort in this study. As tick bites are most likely to occur in surrounding rural locations in which forests are present, many patients may be initially diagnosed in a different facility, and then come to MSH for follow-up treatment. Another limitation is related to the close proximity of MSH to other medical centers in the area. Specifically, patients may seek treatment at other nearby hospitals, resulting in the loss of valuable information from our EMR system. Finally, because we do not have access to patients' historic EMR data from outside of MSH, our temporal analyses may not accurately capture the true timeline of acquisition of disease comorbidities. We are currently performing

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

an external replication analysis at another academic medical center, and the results of this effort may bolster our conclusions. Additionally, we are applying the findings from our current study in order to model explicit, optimal treatment recommendations at the patient level. From this work, we hope to enhance not only the success rates of treatment of LD, but also to facilitate preemptive strategies for managing high-risk ensuing conditions.

Our study is the first to investigate a comprehensive and racially diverse EMR with the aim of discovering the detailed clinical profiles of patients before and after diagnosis of LD. We identified a list of medications, including antibiotics recommended for treatment, which represent possible risk factors for chronic LD or PTLDS. In addition, we hope to investigate the contributions of genomics and genetic variants to differences pathophysiology. Our predictive medication–comorbidity models provide an evidence-based approach for treatment regimens that takes into account risk for Lyme comorbidities, with the ultimate goal of guiding precision medicine based on the individual clinical phenotypes of patients with LD.

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

CONTRIBUTORS

LL and JD were responsible for initial study design. LL was responsible for data collection. OI, BG, and LL were responsible for study implementation, interpreting the data, and ongoing management. OI and BG were responsible for statistical analysis, predictive models, literature review, and generating tables and figures. OI, BG, LL, and JD and wrote and edited manuscript. BK provided HIV insights and edits. LL and JD supervised the study.

DECLARATION OF INTERESTS

Dr. Dudley has received consulting fees or honoraria from Janssen Pharmaceuticals, GlaxoSmithKline, AstraZeneca, and Hoffman-La Roche; is a scientific advisor to LAM Therapeutics; and holds equity in NuMedii Inc., Ayasdi Inc., and Ontomics, Inc. Dr. Ichikawa is an employee of Sumitomo Dainippon Pharma Co., Ltd. The rest of authors declare no competing interests.

ACKNOWLEDGEMENTS

This study was funded by the Steven & Alexandra Cohen Foundation. We thank Savi Glowe and Francisco Santiago for administrative support. We thank Dr. Christopher Patil for providing scientific edits. We thank Mount Sinai Data Warehouse for supporting data access.

REFERENCES

1. Nelson CA, Saha S, Kugeler KJ, et al. Incidence of Clinician-Diagnosed Lyme Disease, United States, 2005-2010. *Emerg Infect Dis* 2015; **21**(9): 1625-31.

2. Steere AC. Lyme disease. *N Engl J Med* 2001; **345**(2): 115-25.

3. Shapiro ED. Clinical practice. Lyme disease. *N Engl J Med* 2014; **370**(18): 1724-31.

4. Wormser GP, Brisson D, Liveris D, et al. Borrelia burgdorferi genotype predicts the capacity for hematogenous dissemination during early Lyme disease. *J Infect Dis* 2008; **198**(9): 1358-64.

5. Hanincova K, Mukherjee P, Ogden NH, et al. Multilocus sequence typing of Borrelia burgdorferi suggests existence of lineages with differential pathogenic properties in humans. *PLoS One* 2013; **8**(9): e73066.

6. Kuehn BM. CDC estimates 300,000 US cases of Lyme disease annually. *JAMA* 2013; **310**(11): 1110.

7. Engstrom SM, Shoop E, Johnson RC. Immunoblot interpretation criteria for serodiagnosis of early Lyme disease. *J Clin Microbiol* 1995; **33**(2): 419-27.

8. Dressler F, Whalen JA, Reinhardt BN, Steere AC. Western blotting in the serodiagnosis of Lyme disease. *J Infect Dis* 1993; **167**(2): 392-400.

9. Wormser GP, Nowakowski J, Nadelman RB, Visintainer P, Levin A, Aguero-Rosenfeld ME. Impact of clinical variables on Borrelia burgdorferi-specific antibody seropositivity in

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

acute-phase sera from patients in North America with culture-confirmed early Lyme disease. *Clin Vaccine Immunol* 2008; **15**(10): 1519-22.

10. Li X, Dunn J, Salins D, et al. Digital Health: Tracking Physiomes and Activity Using Wearable Biosensors Reveals Useful Health-Related Information. *PLoS Biol* 2017; **15**(1): e2001402.

11. Berghoff W. Chronic Lyme Disease and Co-infections: Differential Diagnosis. *Open Neurol J* 2012; **6**: 158-78.

12. Baldwin KD, Brusalis CM, Nduaguba AM, Sankar WN. Predictive Factors for Differentiating Between Septic Arthritis and Lyme Disease of the Knee in Children. *J Bone Joint Surg Am* 2016; **98**(9): 721-8.

13. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; **43**(9): 1089-134.

14. Feder HM, Jr., Johnson BJ, O'Connell S, et al. A critical appraisal of "chronic Lyme disease". *N Engl J Med* 2007; **357**(14): 1422-30.

15. Halperin JJ. Prolonged Lyme disease treatment: enough is enough. *Neurology* 2008; **70**(13): 986-7.

16. Patel R, Grogg KL, Edwards WD, Wright AJ, Schwenk NM. Death from inappropriate therapy for Lyme disease. *Clin Infect Dis* 2000; **31**(4): 1107-9.

17. Klempner MS, Hu LT, Evans J, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N Engl J Med* 2001; **345**(2): 85-92.

18. Fallon BA, Keilp JG, Corbera KM, et al. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. *Neurology* 2008; **70**(13): 992-1003.

19. Finch C, Al-Damluji MS, Krause PJ, et al. Integrated assessment of behavioral and environmental risk factors for Lyme disease infection on Block Island, Rhode Island. *PLoS One* 2014; **9**(1): e84758.

20. Guerra M, Walker E, Jones C, et al. Predicting the risk of Lyme disease: habitat suitability for Ixodes scapularis in the north central United States. *Emerg Infect Dis* 2002; **8**(3): 289-97.

21. Denny JC, Bastarache L, Ritchie MD, et al. Systematic comparison of phenome-wide association study of electronic medical record data and genome-wide association study data. *Nat Biotechnol* 2013; **31**(12): 1102-10.

22. Healthcare Cost and Utilization Project (HCUP). HCUP Clinical Classifications Software (CCS) for ICD-9-CM. . Agency for Healthcare Research and Quality; 2017.

23. Nelson SJ, Zeng K, Kilbourne J, Powell T, Moore R. Normalized names for clinical drugs: RxNorm at 6 years. *J Am Med Inform Assoc* 2011; **18**(4): 441-8.

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

24. Tibshirani R. Regression shrinkage and selection via the lasso. *Journal of the Royal Statistical Society Series B (Methodological)* 1996: 267-88.

25. Zou H, Zhang HH. On the Adaptive Elastic-Net with a Diverging Number of Parameters. *Ann Stat* 2009; **37**(4): 1733-51.

26. Fan J, Li R. Variable selection via nonconcave penalized likelihood and its oracle properties. *Journal of the American statistical Association* 2001; **96**(456): 1348-60.

27. Friedman J, Hastie T, Tibshirani R. Regularization Paths for Generalized Linear Models via Coordinate Descent. *J Stat Softw* 2010; **33**(1): 1-22.

28. Little RJ, Rubin DB. Causal effects in clinical and epidemiological studies via potential outcomes: concepts and analytical approaches. *Annu Rev Public Health* 2000; **21**: 121-45.

29. Ho DE, Imai K, King G, Stuart EA. MatchIt: nonparametric preprocessing for parametric causal inference. *Journal of Statistical Software* 2011; **42**(8): 1-28.

30. Cantorna MT, Hayes CE. Vitamin A deficiency exacerbates murine Lyme arthritis. *J Infect Dis* 1996; **174**(4): 747-51.

31. Cristea V, Crisan M. Lyme disease with magnesium deficiency. *Magnes Res* 2003; **16**(4): 287-9.

32. Ormerod LD, Puklin JE, Giles CL. Chronic Propionibacterium acnes endophthalmitis as a cause of intermediate uveitis. *Ocul Immunol Inflamm* 1997; **5**(1): 67-8.

33. Heinz C, Schoonbrood S, Heiligenhaus A. Intermediate uveitis in children and young adults: differences in clinical course, associations and visual outcome. *Br J Ophthalmol* 2014; **98**(8): 1107-11.

34. Toledo A, Monzon JD, Coleman JL, Garcia-Monco JC, Benach JL. Hypercholesterolemia and ApoE deficiency result in severe infection with Lyme disease and relapsing-fever Borrelia. *Proc Natl Acad Sci U S A* 2015; **112**(17): 5491-6.

35. Wang JJ, Rochtchina E, Tan AG, Cumming RG, Leeder SR, Mitchell P. Use of inhaled and oral corticosteroids and the long-term risk of cataract. *Ophthalmology* 2009; **116**(4): 652-7.

36. Pottegard A, Hallas J, Olesen M, et al. Hydrochlorothiazide use is strongly associated with risk of lip cancer. *J Intern Med* 2017; **282**(4): 322-31.

37. Friedman GD, Udaltsova N, Chan J, Quesenberry CP, Jr., Habel LA. Screening pharmaceuticals for possible carcinogenic effects: initial positive results for drugs not previously screened. *Cancer Causes Control* 2009; **20**(10): 1821-35.

38. Niafar M, Hai F, Porhomayon J, Nader ND. The role of metformin on vitamin B12 deficiency: a meta-analysis review. *Intern Emerg Med* 2015; **10**(1): 93-102.

39. Ho JM, Juurlink DN. Considerations when prescribing trimethoprim-sulfamethoxazole. *CMAJ* 2011; **183**(16): 1851-8.

40. Audebert A, Zittoun J, Zittoun R, Bousser J. [Macrocytic animia due to the combination trimethoprim-sulfamethoxazole]. *Sem Hop* 1975; **51**(4): 243-5.

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

41. Heidelbaugh JJ. Proton pump inhibitors and risk of vitamin and mineral deficiency: evidence and clinical implications. *Ther Adv Drug Saf* 2013; **4**(3): 125-33.

42. Straubinger RK, Straubinger AF, Summers BA, Jacobson RH. Status of Borrelia burgdorferi infection after antibiotic treatment and the effects of corticosteroids: An experimental study. *J Infect Dis* 2000; **181**(3): 1069-81.

43. Jowett N, Gaudin RA, Banks CA, Hadlock TA. Steroid use in Lyme disease-associated facial palsy is associated with worse long-term outcomes. *Laryngoscope* 2017; **127**(6): 1451-8.

44. Stahlmann R, Lode H. Safety considerations of fluoroquinolones in the elderly: an update. *Drugs Aging* 2010; **27**(3): 193-209.

45. Gultuna S, Koklu S, Arhan M, Aydin F, Mesci P, Uskudar O. Ciprofloxacin induced tendinitis. *J Clin Rheumatol* 2009; **15**(4): 201-2.

46. Kuhn M, Campillos M, Letunic I, Jensen LJ, Bork P. A side effect resource to capture phenotypic effects of drugs. *Mol Syst Biol* 2010; **6**: 343.

47. Kuhn M, Letunic I, Jensen LJ, Bork P. The SIDER database of drugs and side effects. *Nucleic Acids Res* 2016; **44**(D1): D1075-9.

48. Donta ST. Issues in the diagnosis and treatment of lyme disease. *Open Neurol J* 2012; **6**: 140-5.

49. Abbott RA, Hammans S, Margarson M, Aji BM. Diaphragmatic paralysis and respiratory failure as a complication of Lyme disease. *J Neurol Neurosurg Psychiatry* 2005; **76**(9): 1306-7.

50. Enserink M. What mosquitoes want: secrets of host attraction. *Science* 2002; **298**(5591): 90-2.

51. Kim YM, Kim S, Cheong HK, Ahn B, Choi K. Effects of heat wave on body temperature and blood pressure in the poor and elderly. *Environ Health Toxicol* 2012; **27**: e2012013.

52. Gugliotta JL, Goethert HK, Berardi VP, Telford SR, 3rd. Meningoencephalitis from Borrelia miyamotoi in an immunocompromised patient. *N Engl J Med* 2013; **368**(3): 240-5.

53. Bremell D, Sall C, Gisslen M, Hagberg L. Lyme neuroborreliosis in HIV-1 positive men successfully treated with oral doxycycline: a case series and literature review. *J Med Case Rep* 2011; **5**: 465.

54. van Burgel ND, Oosterloo M, Kroon FP, van Dam AP. Severe course of Lyme neuroborreliosis in an HIV-1 positive patient; case report and review of the literature. *BMC Neurol* 2010; **10**: 117.

55. Elsner RA, Hastey CJ, Olsen KJ, Baumgarth N. Suppression of Long-Lived Humoral Immunity Following Borrelia burgdorferi Infection. *PLoS Pathog* 2015; **11**(7): e1004976.

56. Lochhead J, Elston JS. Doxycycline induced intracranial hypertension. *BMJ* 2003; **326**(7390): 641-2.

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

57. Affolter K, Samowitz W, Boynton K, Kelly ED. Doxycycline-induced gastrointestinal injury. *Hum Pathol* 2017; **66**: 212-5.

58. Kirsch M, Ruben FL, Steere AC, Duray PH, Norden CW, Winkelstein A. Fatal adult respiratory distress syndrome in a patient with Lyme disease. *JAMA* 1988; **259**(18): 2737-9.

59. Little P, Stuart B, Moore M, et al. Amoxicillin for acute lower-respiratory-tract infection in primary care when pneumonia is not suspected: a 12-country, randomised, placebo-controlled trial. *Lancet Infect Dis* 2013; **13**(2): 123-9.

60. Wei WQ, Mosley JD, Bastarache L, Denny JC. Validation and enhancement of a computable medication indication resource (MEDI) using a large practice-based dataset. *AMIA Annu Symp Proc* 2013; **2013**: 1448-56.

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Figure legends

Figure 1 Workflow of the study, outlining steps from data organization to statistical methodologies.

Figure 2 Medication–Lyme disease comorbidity network, analyzed by CCS-single-level categories, in time windows of 5 years (a) and 10 years (b). Significant associations between medications (cyan) and comorbidities (magenta) are connected by red or blue lines ($p < 0.1$). Red lines indicate risk associations (OR > 1), and blue lines indicate protective associations (OR < 1). Medications and indications (green) were connected based on information in the public knowledgebase MEDI [60].

Figure 3 Medication–Lyme disease comorbidity network at the ICD-9 levels in time windows of 5 years (a) and 10 years (b). Significant associations between medications (cyan) and comorbidities (magenta) are connected by red or blue lines ($p < 0.1$). Red lines indicate risk associations (OR > 1), and blue lines indicate protective associations (OR < 1).

Figure 4 Kaplan–Meier plot of propensity-score-matched survival analysis (a) doxycycline–'backache NOS' (ICD-9 code: 724.5), (b) doxycycline–'chronic rhinitis' (472.0), (c) doxycycline–'cataract NOS' (366.9), (d) doxycycline–'tear film insuffic NOS' (375.15), and (e) amoxicillin–'acute URI NOS' (465.9).

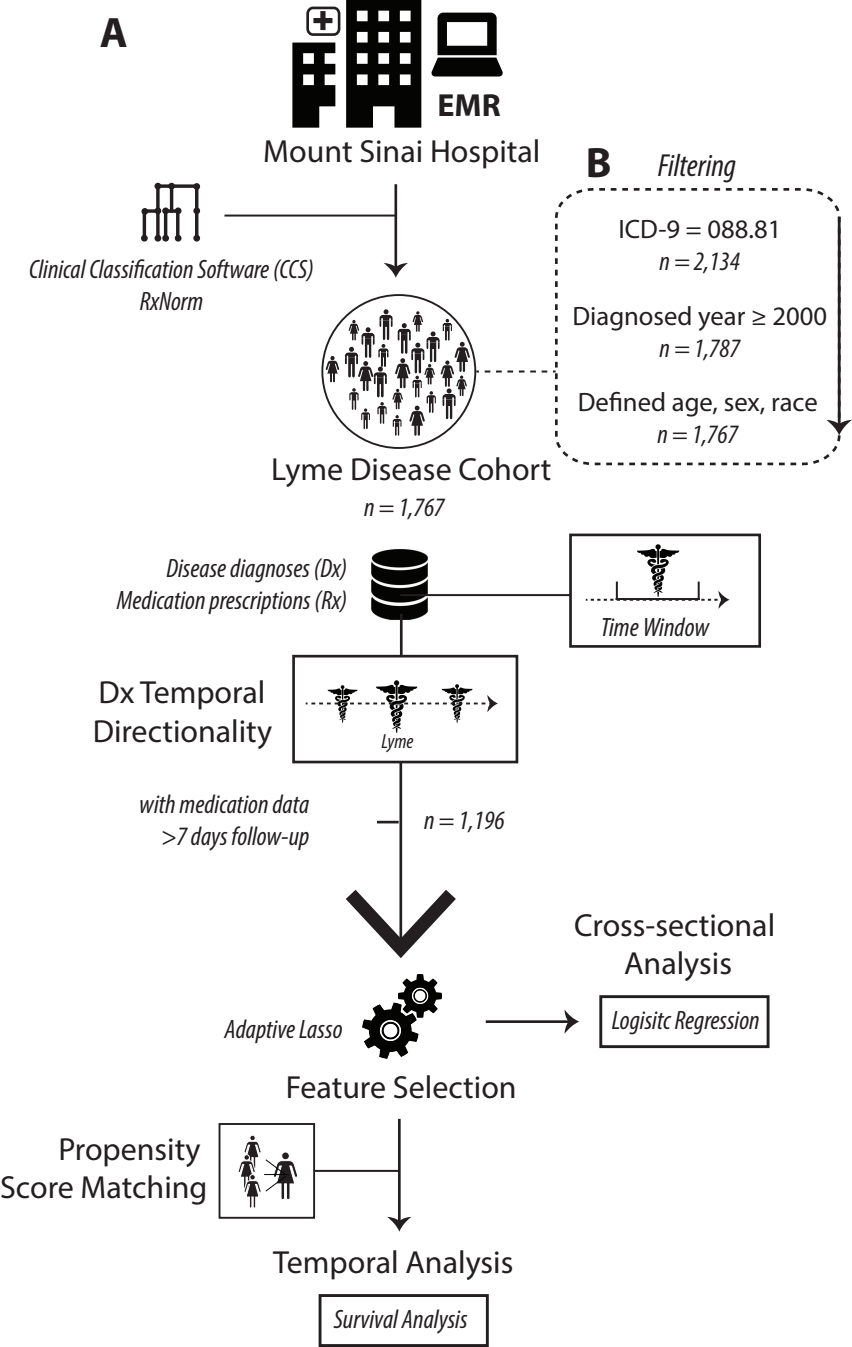
Supplementary figure 1 Venn diagram of the medications that significantly associated with at least one disease comorbidity in the 5- and 10-year time windows. (a) CCS-single-level categories. (b) ICD-9 level.

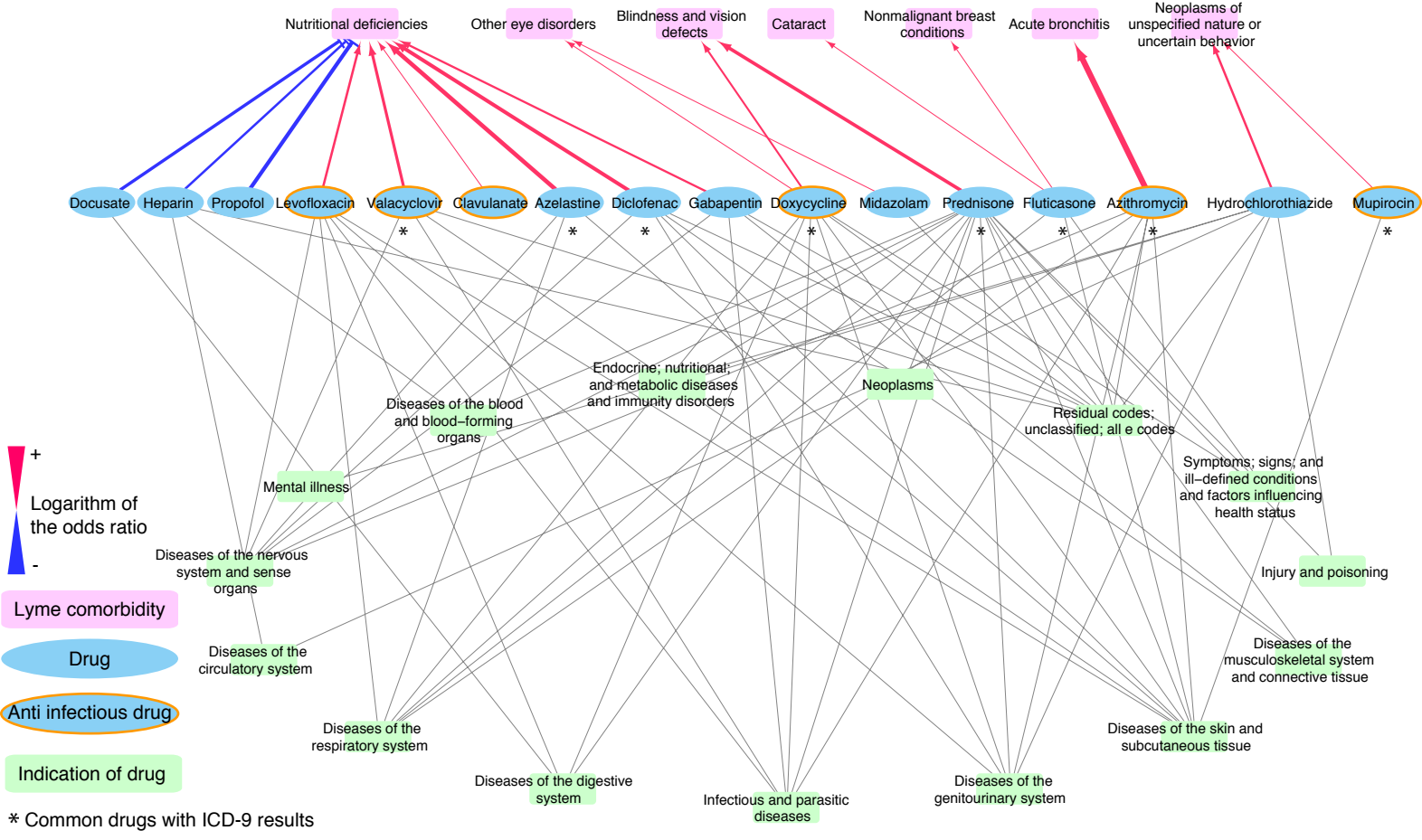
Supplementary table S1 All diseases associated with Lyme, by ICD-9 category (p value < 0.1).

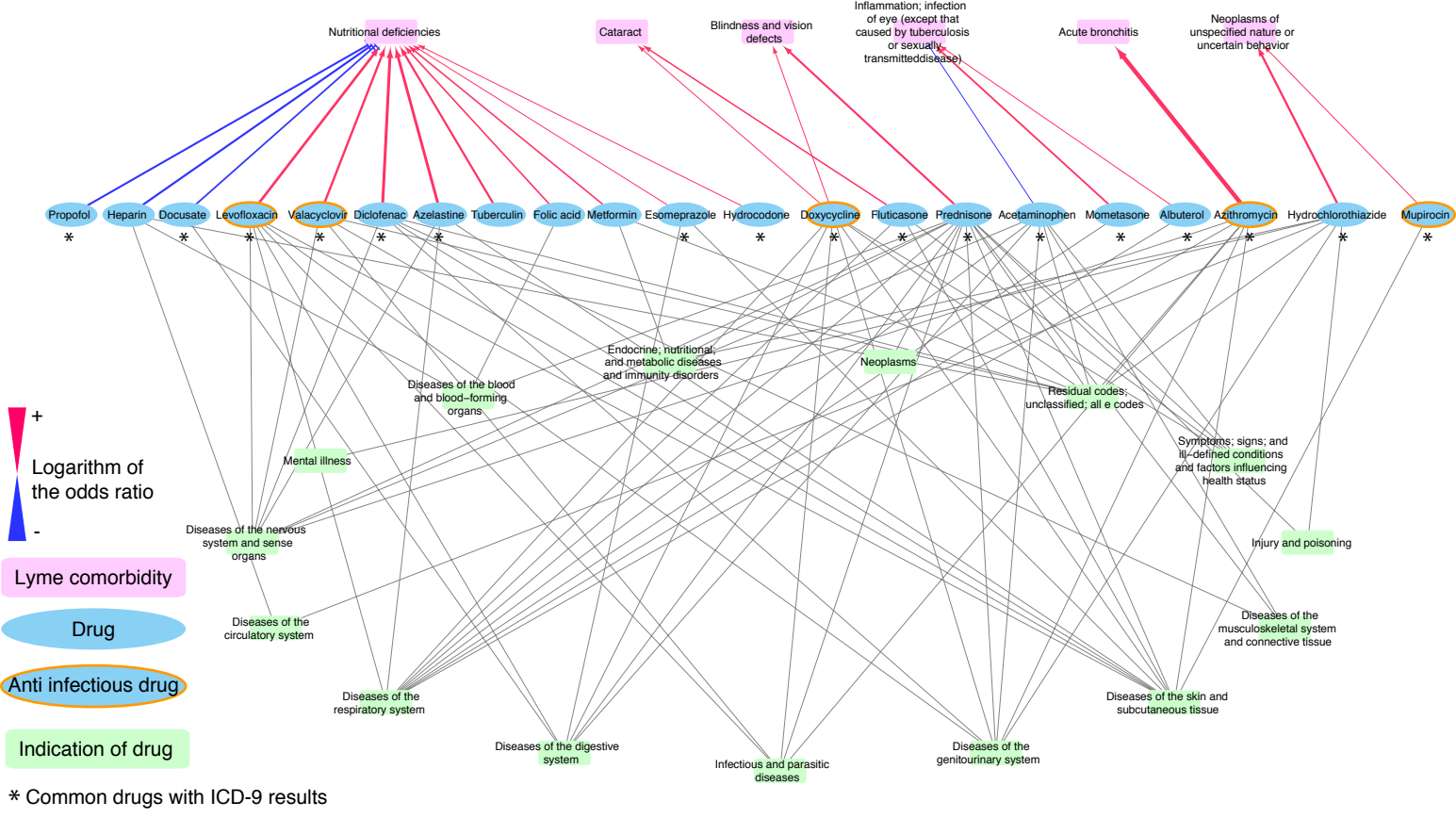
Supplementary table S3 Medications predicted to modulate risk of disease comorbidities, by CCS-single-level category (p value < 0.1).

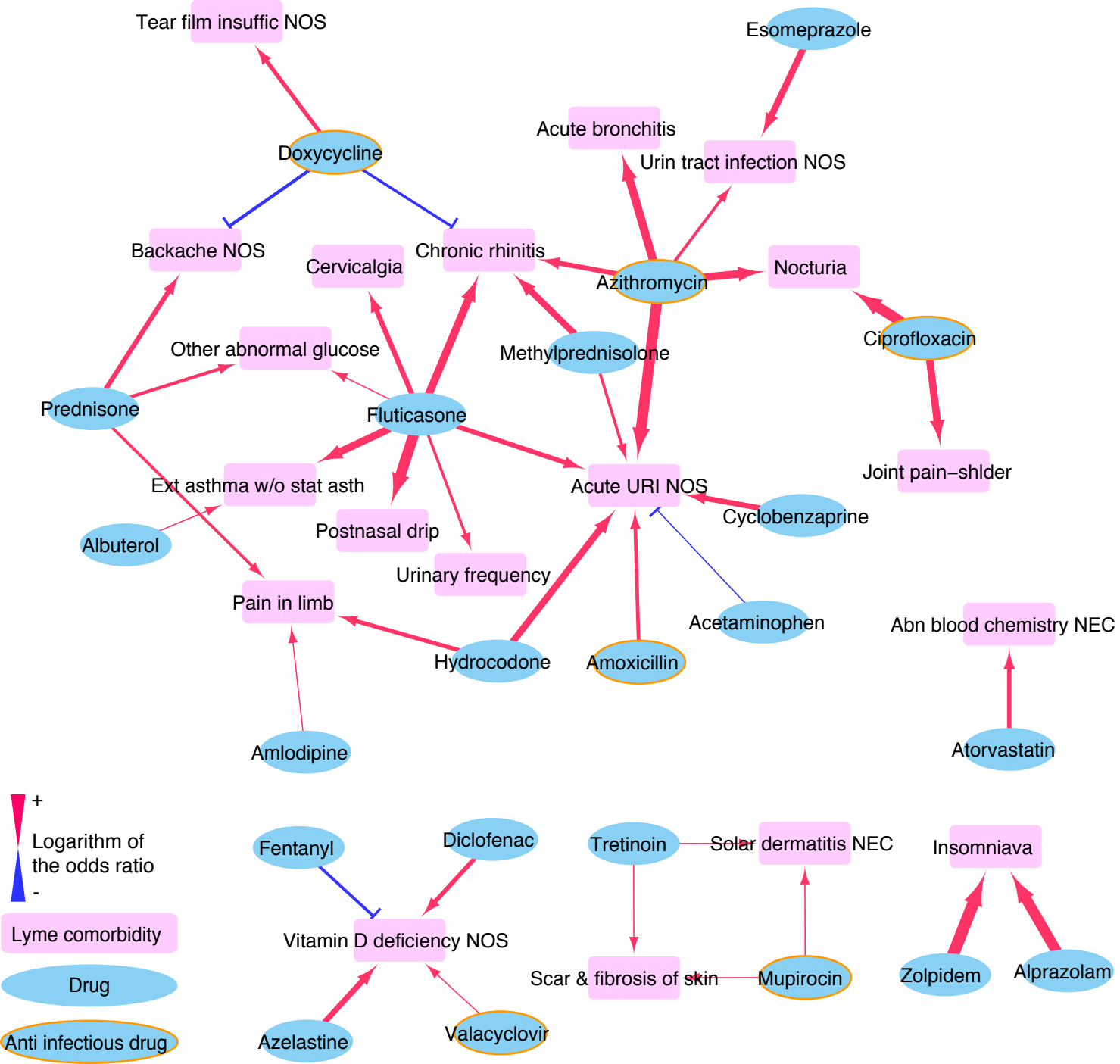
Supplementary table S4 Medications predicted to modulate risk of disease comorbidities, by ICD-9 category (p value < 0.1).

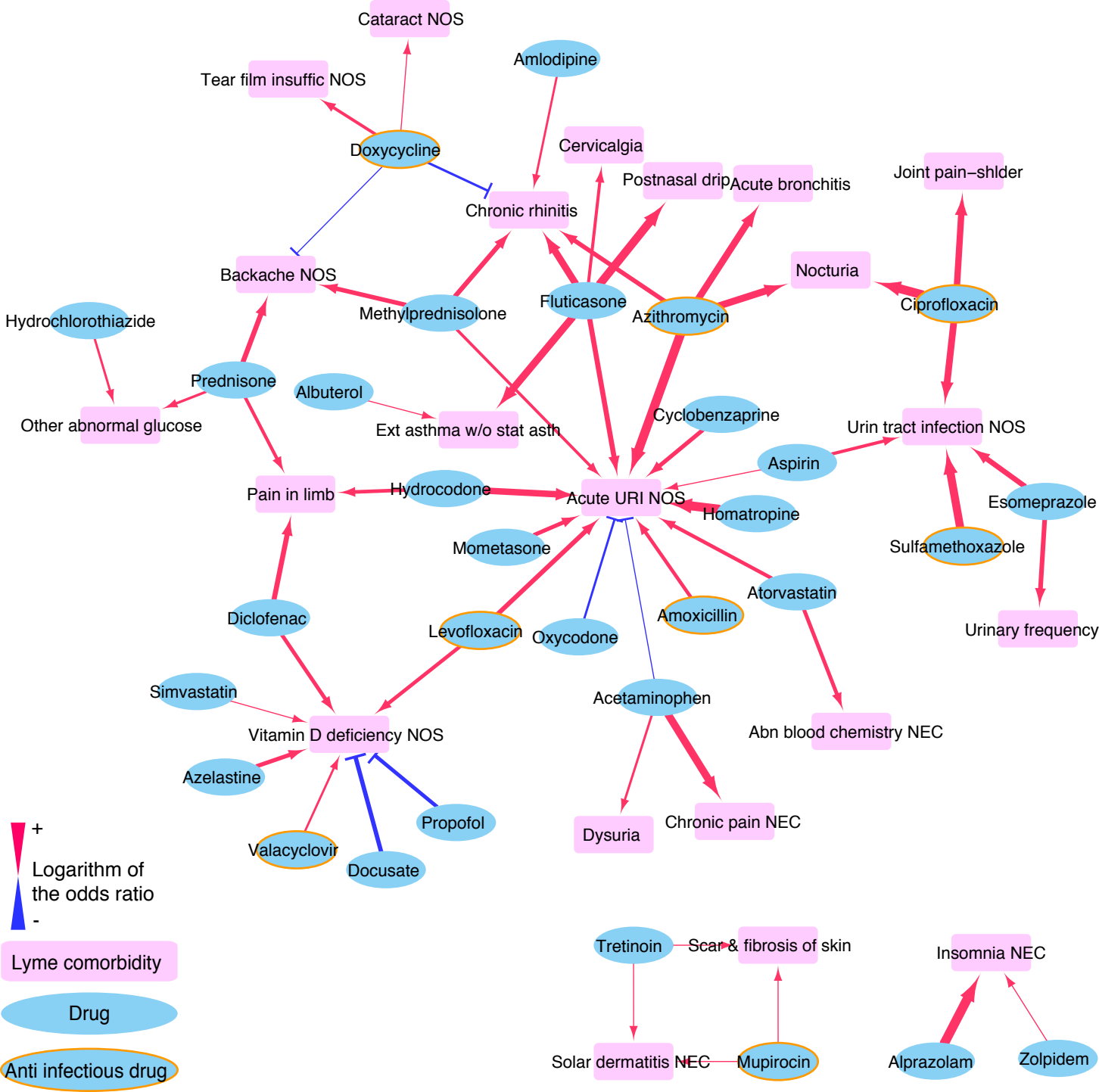
Supplementary table S5 The balance of covariates before and after propensity score matching.


A
EMR
Mount Sinai Hospital
B
Filtering
ICD-9 = 088.81
n = 2,134
Diagnosed year ≥ 2000
n = 1,787
Defined age, sex, race
n = 1,767
Clinical Classification Software (CCS)
RxNorm
Lyme Disease Cohort
n = 1,767
Disease diagnoses (Dx)
Medication prescriptions (Rx)
Time Window
Dx Temporal Directionality
Lyme
with medication data
>7 days follow-up
n = 1,196
Cross-sectional Analysis
Adaptive Lasso
Logisitc Regression
Feature Selection
Propensity Score Matching
Temporal Analysis
Survival Analysis


Nutritional deficiencies
Other eye disorders
Blindness and vision defects
Cataract
Nonmalignant breast conditions
Acute bronchitis
Neoplasms of unspecified nature or uncertain behavior
Docusate
Heparin
Propofol
Levofloxacin
Valacyclovir
Clavulanate
Azelastine
Diclofenac
Gabapentin
Doxycycline
Midazolam
Prednisone
Fluticasone
Azithromycin
Hydrochlorothiazide
Mupirocin
*
Endocrine; nutritional; and metabolic diseases and immunity disorders
Neoplasms
Diseases of the blood and blood–forming organs
Residual codes; unclassified; all e codes
Mental illness
Symptoms; signs; and ill–defined conditions and factors influencing health status
Diseases of the nervous system and sense organs
Injury and poisoning
Diseases of the circulatory system
Diseases of the musculoskeletal system and connective tissue
Diseases of the respiratory system
Diseases of the skin and subcutaneous tissue
Diseases of the digestive system
Infectious and parasitic diseases
Diseases of the genitourinary system
+
Logarithm of the odds ratio
-
Lyme comorbidity
Drug
Anti infectious drug
Indication of drug
* Common drugs with ICD-9 results

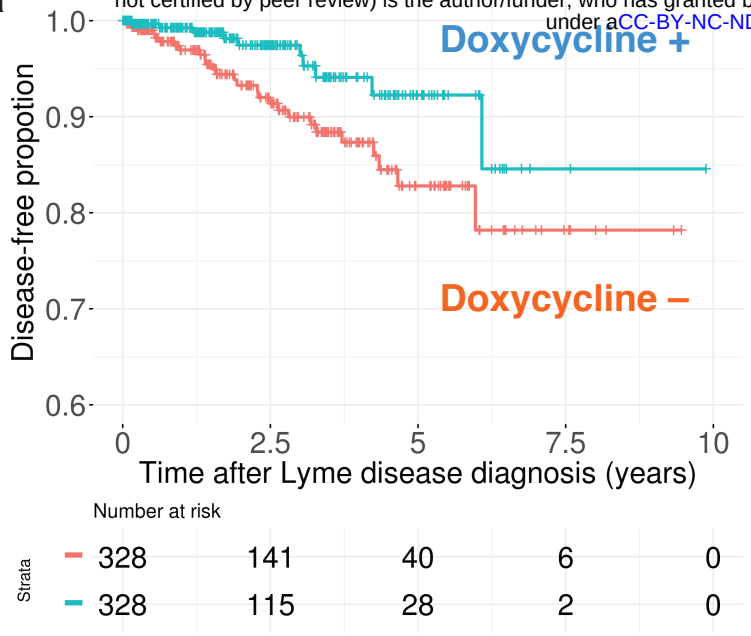

Nutritional deficiencies
Cataract
Blindness and vision defects
Inflammation; infection of eye (except that caused by tuberculosis or sexually transmitteddisease)
Acute bronchitis
Neoplasms of unspecified nature or uncertain behavior
Propofol
Heparin
Docusate
Levofloxacin
Valacyclovir
Diclofenac
Azelastine
Tuberculin
Folic acid
Metformin
Esomeprazole
Hydrocodone
Doxycycline
Fluticasone
Prednisone
Acetaminophen
Mometasone
Albuterol
Azithromycin
Hydrochlorothiazide
Mupirocin
Endocrine; nutritional; and metabolic diseases and immunity disorders
Neoplasms
Diseases of the blood and blood−forming organs
Residual codes; unclassified; all e codes
Symptoms; signs; and ill−defined conditions and factors influencing health status
Mental illness
Diseases of the nervous system and sense organs
Injury and poisoning
Diseases of the circulatory system
Diseases of the musculoskeletal system and connective tissue
Diseases of the respiratory system
Diseases of the skin and subcutaneous tissue
Diseases of the digestive system
Diseases of the genitourinary system
Infectious and parasitic diseases
+
Logarithm of the odds ratio
-
Lyme comorbidity
Drug
Anti infectious drug
Indication of drug
* Common drugs with ICD-9 results


Tear film insuffic NOS
Esomeprazole
Doxycycline
Acute bronchitis
Urin tract infection NOS
Backache NOS
Chronic rhinitis
Cervicalgia
Azithromycin
Nocturia
Ciprofloxacin
Other abnormal glucose
Methylprednisolone
Prednisone
Fluticasone
Joint pain–shlder
Ext asthma w/o stat asth
Acute URI NOS
Cyclobenzaprine
Albuterol
Postnasal drip
Urinary frequency
Pain in limb
Acetaminophen
Abn blood chemistry NEC
Hydrocodone
Amoxicillin
Atorvastatin
Amlodipine
+
Logarithm of the odds ratio
-
Lyme comorbidity
Drug
Anti infectious drug
Fentanyl
Diclofenac
Tretinoin
Solar dermatitis NEC
Insomniava
Vitamin D deficiency NOS
Scar & fibrosis of skin
Mupirocin
Zolpidem
Alprazolam
Azelastine
Valacyclovir

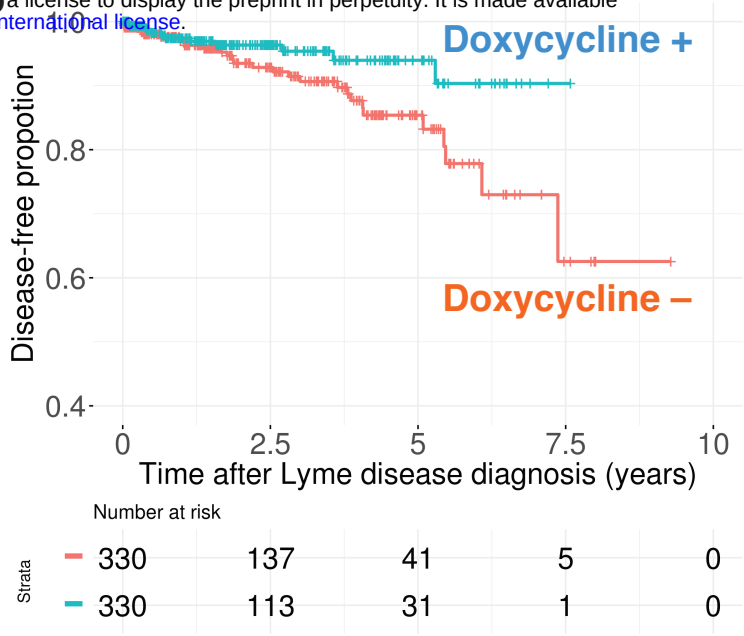

Cataract NOS
Amlodipine
Tear film insuffic NOS
Doxycycline
Cervicalgia
Postnasal drip
Acute bronchitis
Joint pain–shlder
Chronic rhinitis
Backache NOS
Nocturia
Hydrochlorothiazide
Methylprednisolone
Fluticasone
Azithromycin
Ciprofloxacin
Prednisone
Albuterol
Cyclobenzaprine
Other abnormal glucose
Ext asthma w/o stat asth
Urin tract infection NOS
Aspirin
Pain in limb
Hydrocodone
Acute URI NOS
Homatropine
Esomeprazole
Mometasone
Sulfamethoxazole
Atorvastatin
Diclofenac
Levofloxacin
Oxycodone
Amoxicillin
Urinary frequency
Simvastatin
Acetaminophen
Vitamin D deficiency NOS
Abn blood chemistry NEC
Azelastine
Propofol
Dysuria
Chronic pain NEC
Valacyclovir
Docusate
+
Logarithm of the odds ratio
-
Lyme comorbidity
Drug
Anti infectious drug
Tretinoin
Scar & fibrosis of skin
Insomnia NEC
Solar dermatitis NEC
Mupirocin
Alprazolam
Zolpidem

bioRxiv preprint doi: https://doi.org/10.1101/239020; this version posted December 23, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

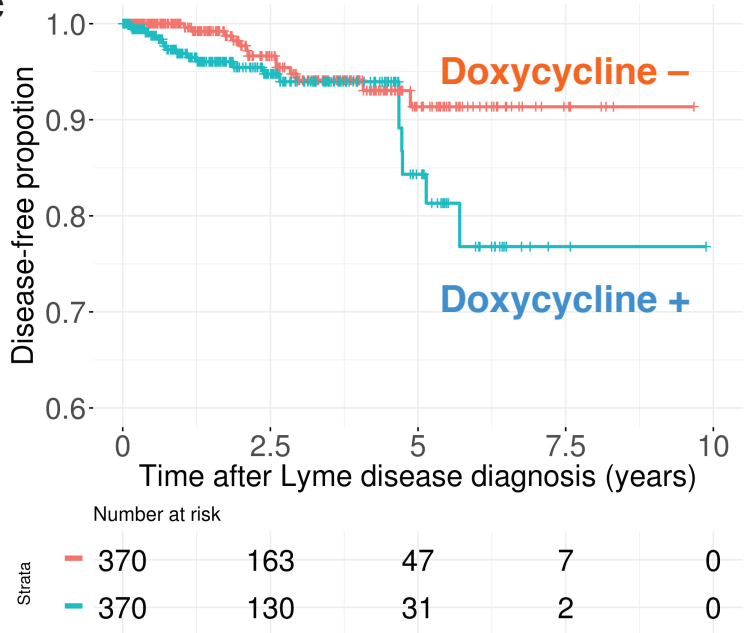
a



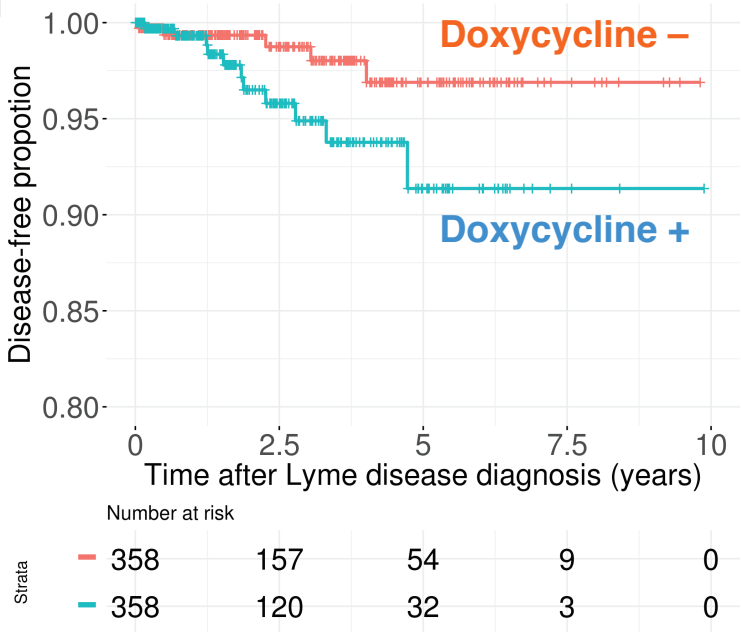
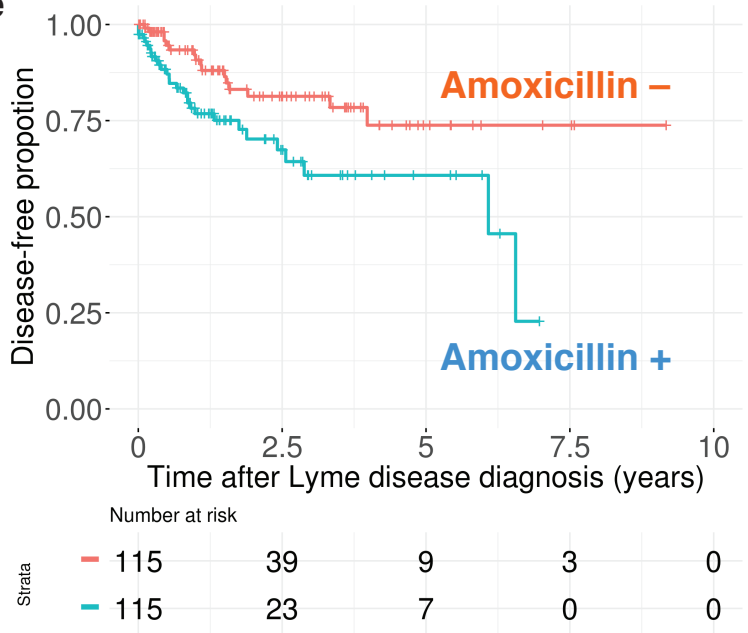
b



c



d



e